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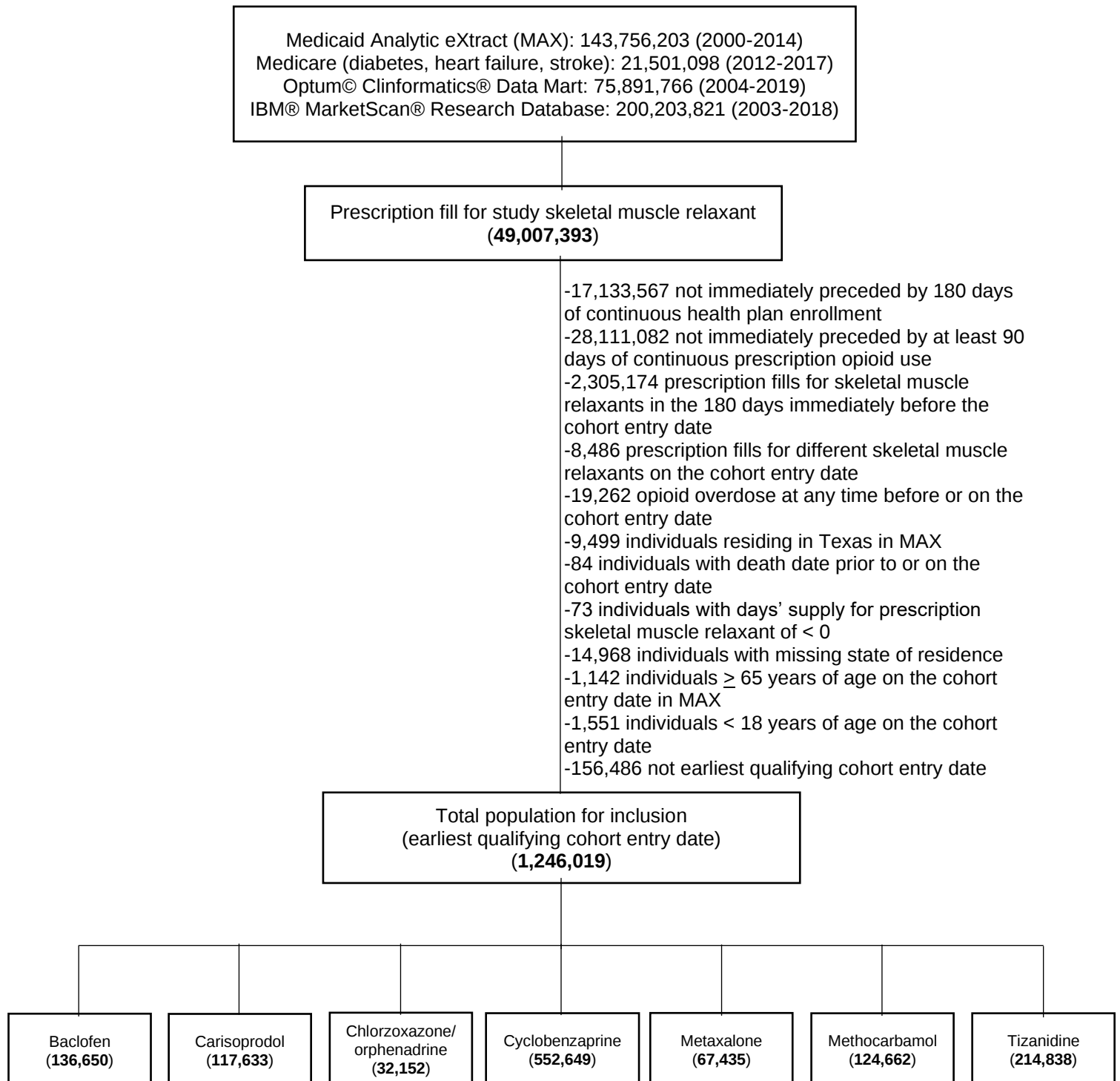
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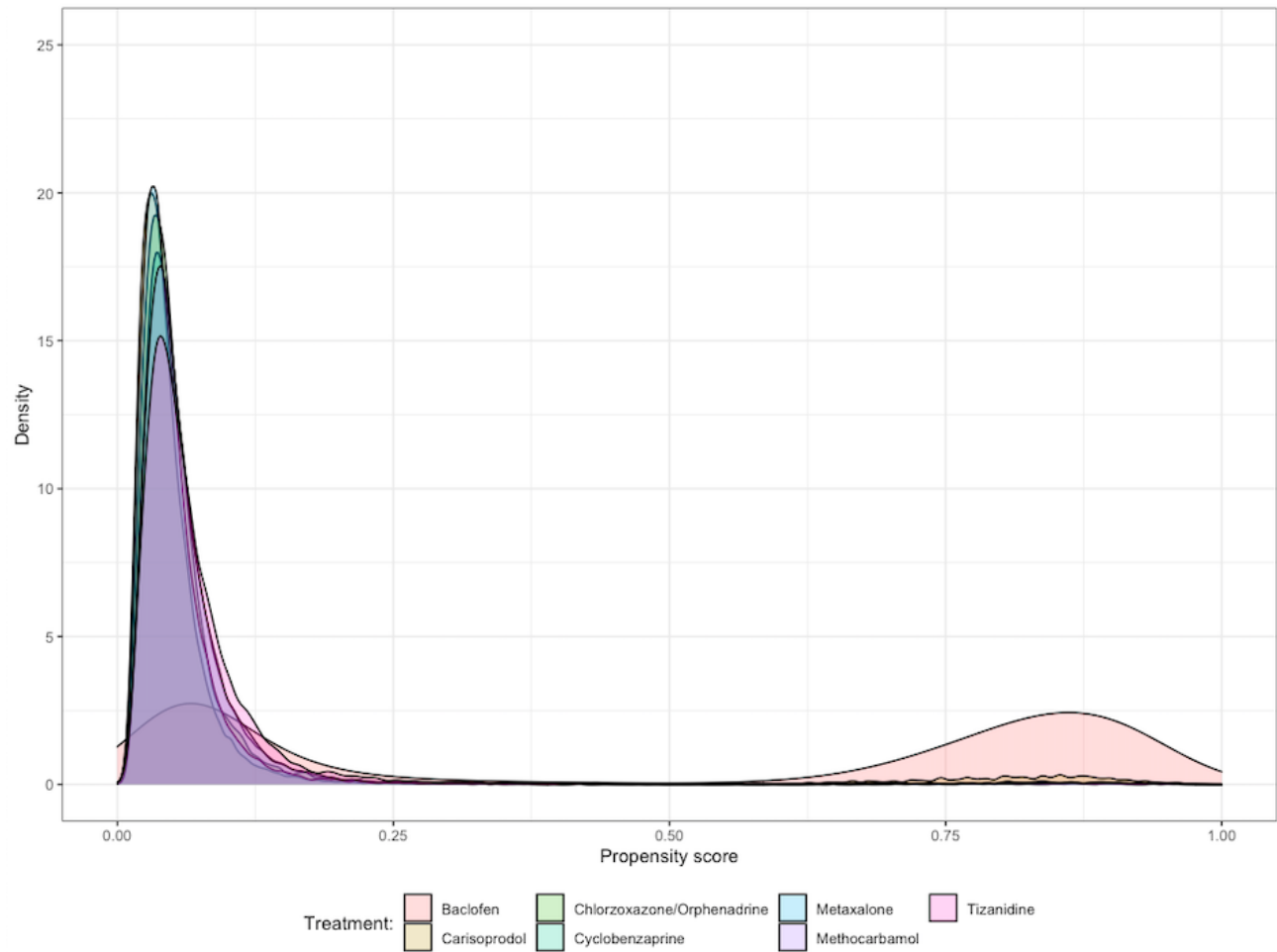
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**eFigure 1. Eligibility criteria for inclusion in active comparator cohort study design**

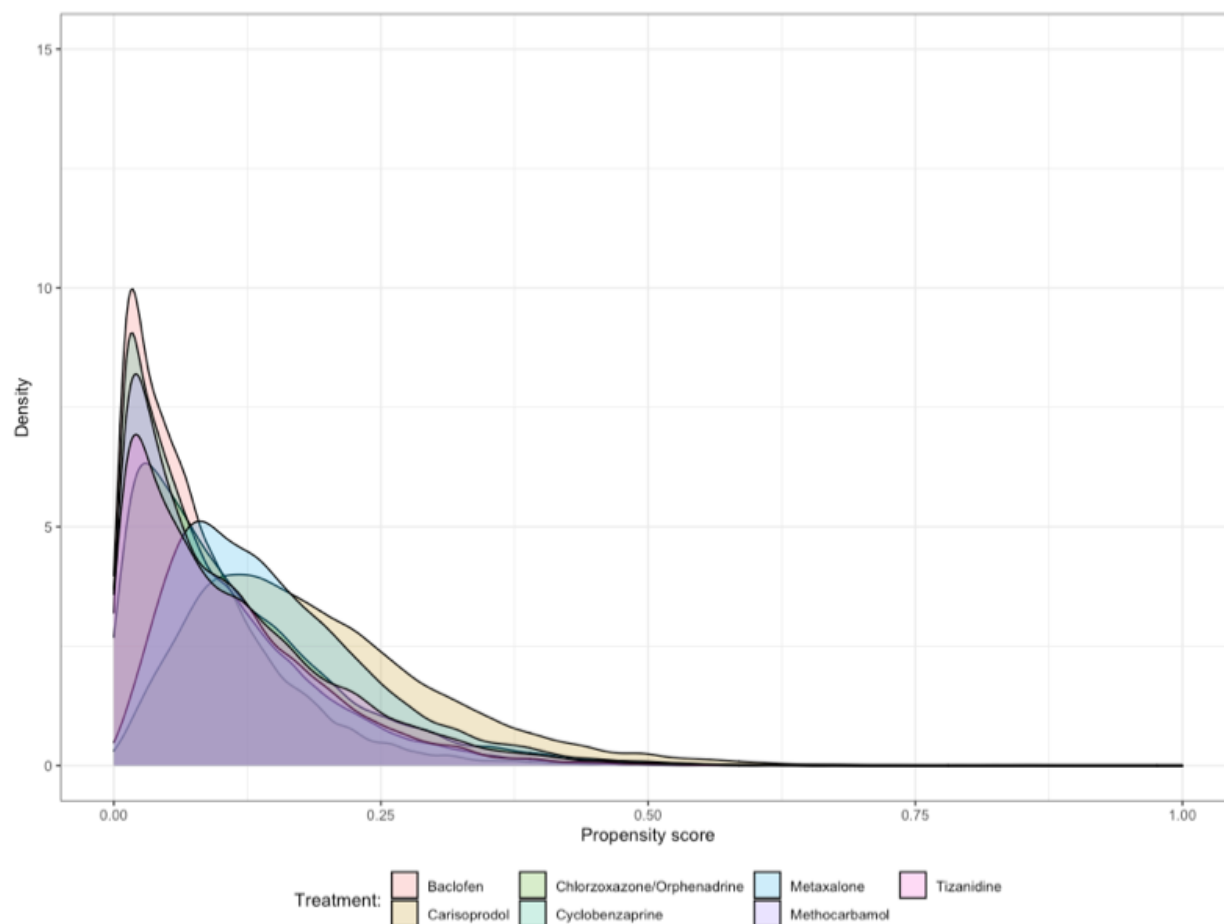


**eFigure 2A. Propensity score distributions for treatment with baclofen before matching weights in Medicaid Analytic eXtract (MAX)**



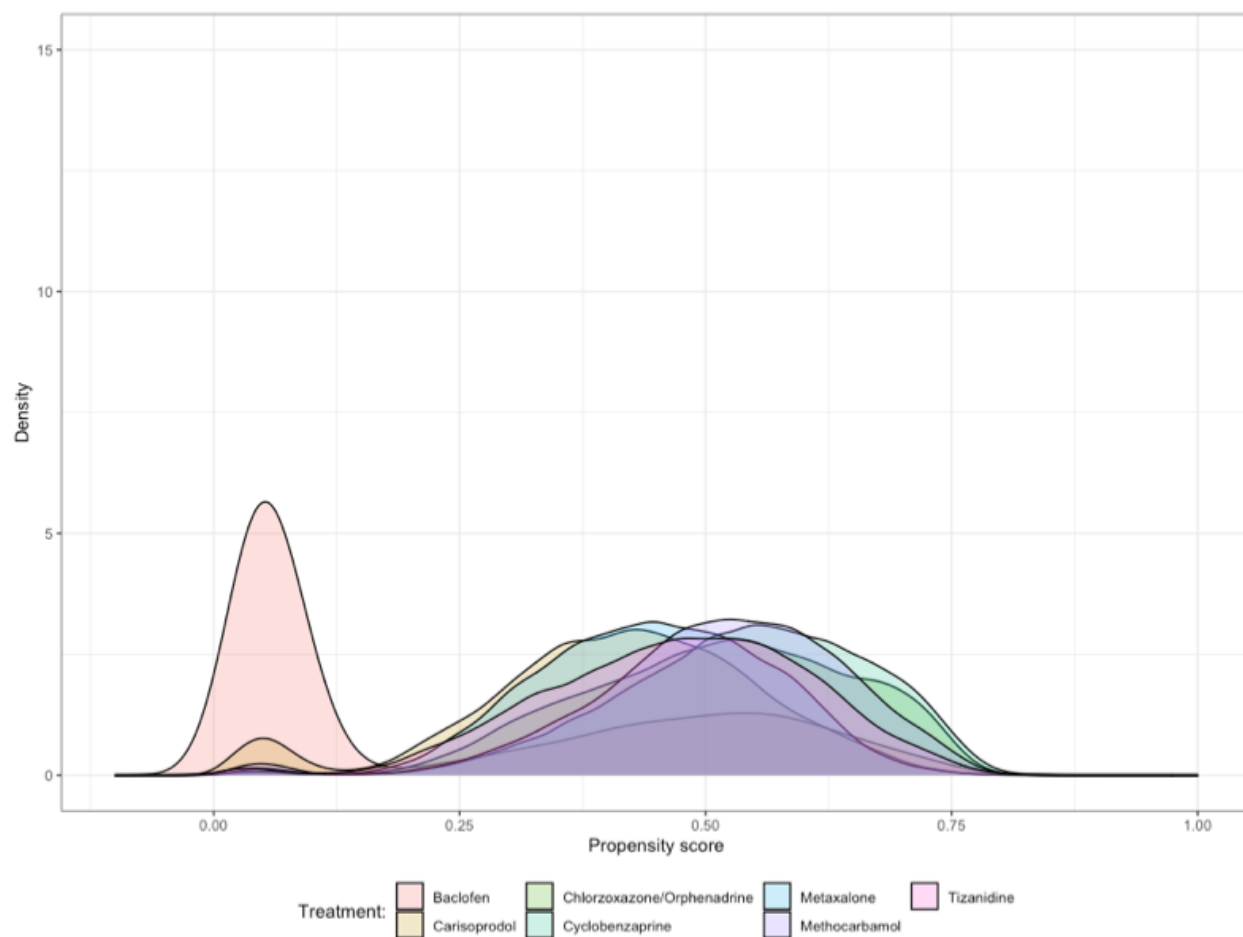
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 2B. Propensity score distributions for treatment with carisoprodol before matching weights in Medicaid Analytic eXtract (MAX)**



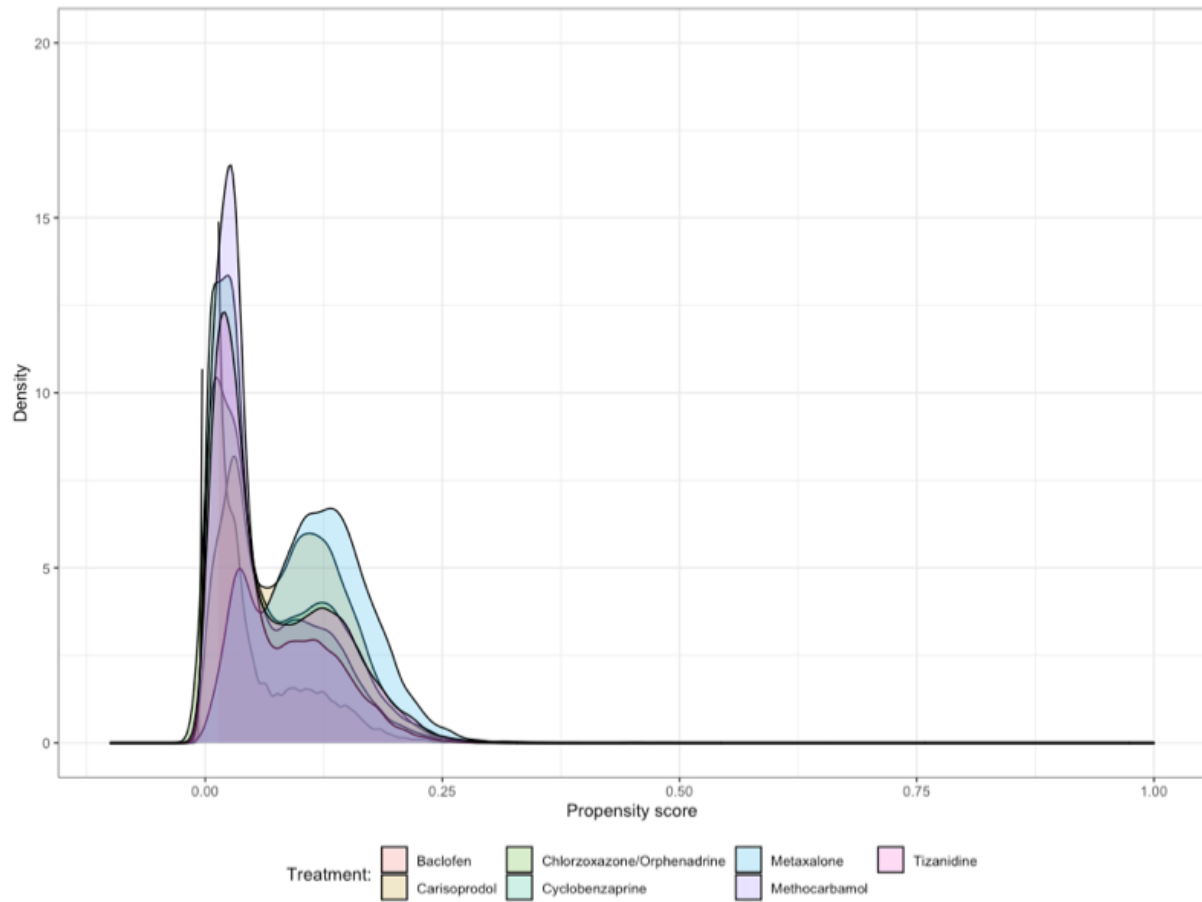
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 2C. Propensity score distributions for treatment with cyclobenzaprine before matching weights in Medicaid Analytic eXtract (MAX)**



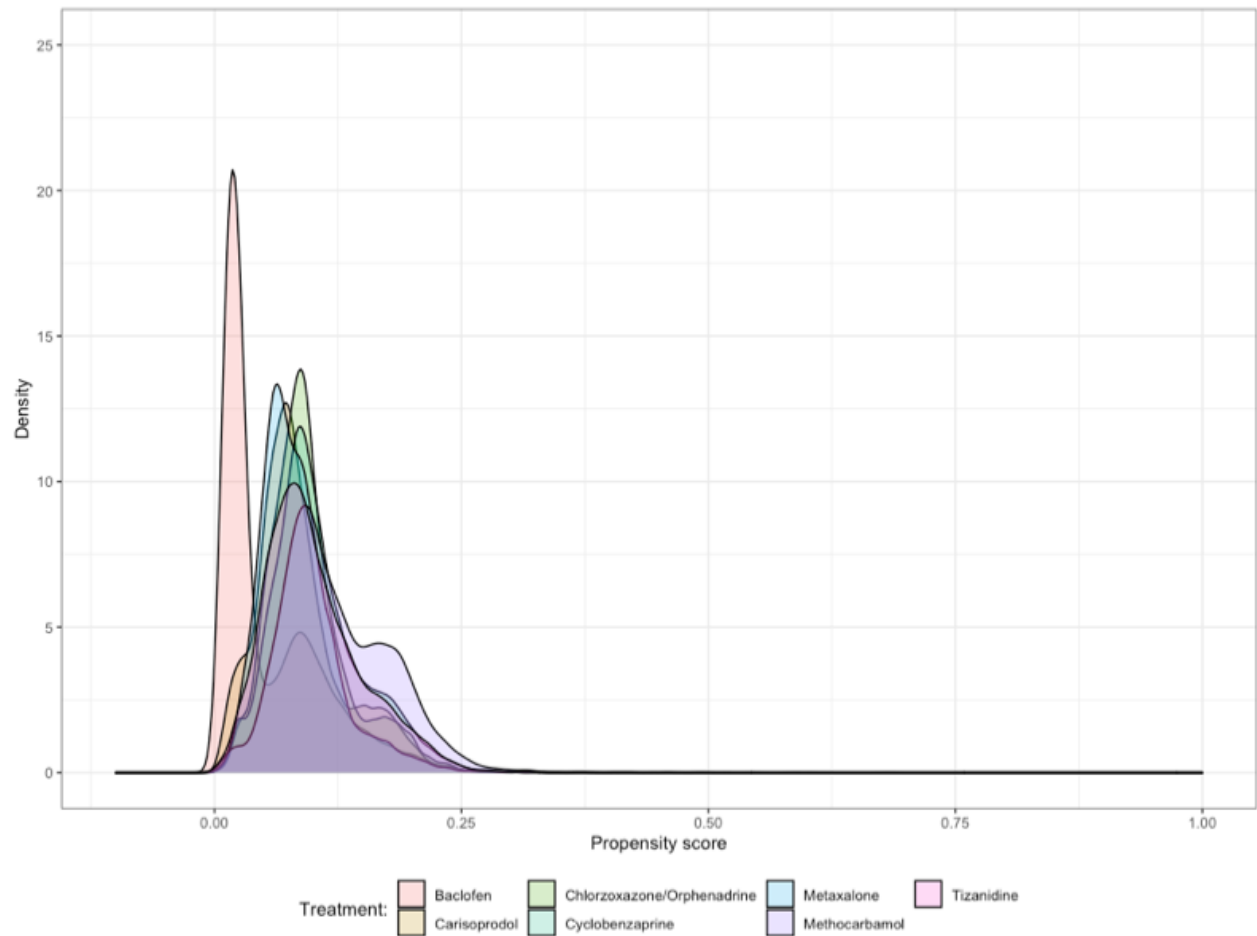
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 2D. Propensity score distributions for treatment with metaxalone before matching weights in Medicaid Analytic eXtract (MAX)**



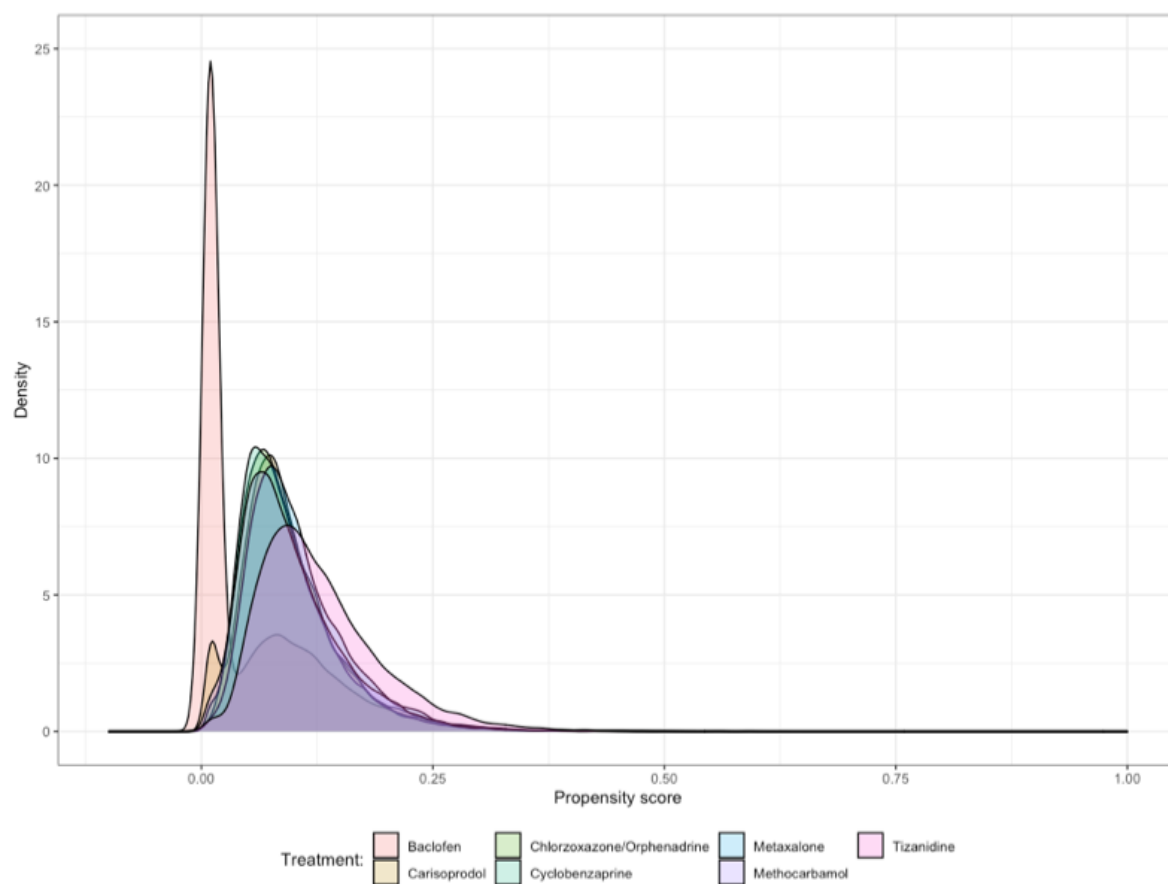
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 2E. Propensity score distributions for treatment with methocarbamol before matching weights in Medicaid Analytic eXtract (MAX)**



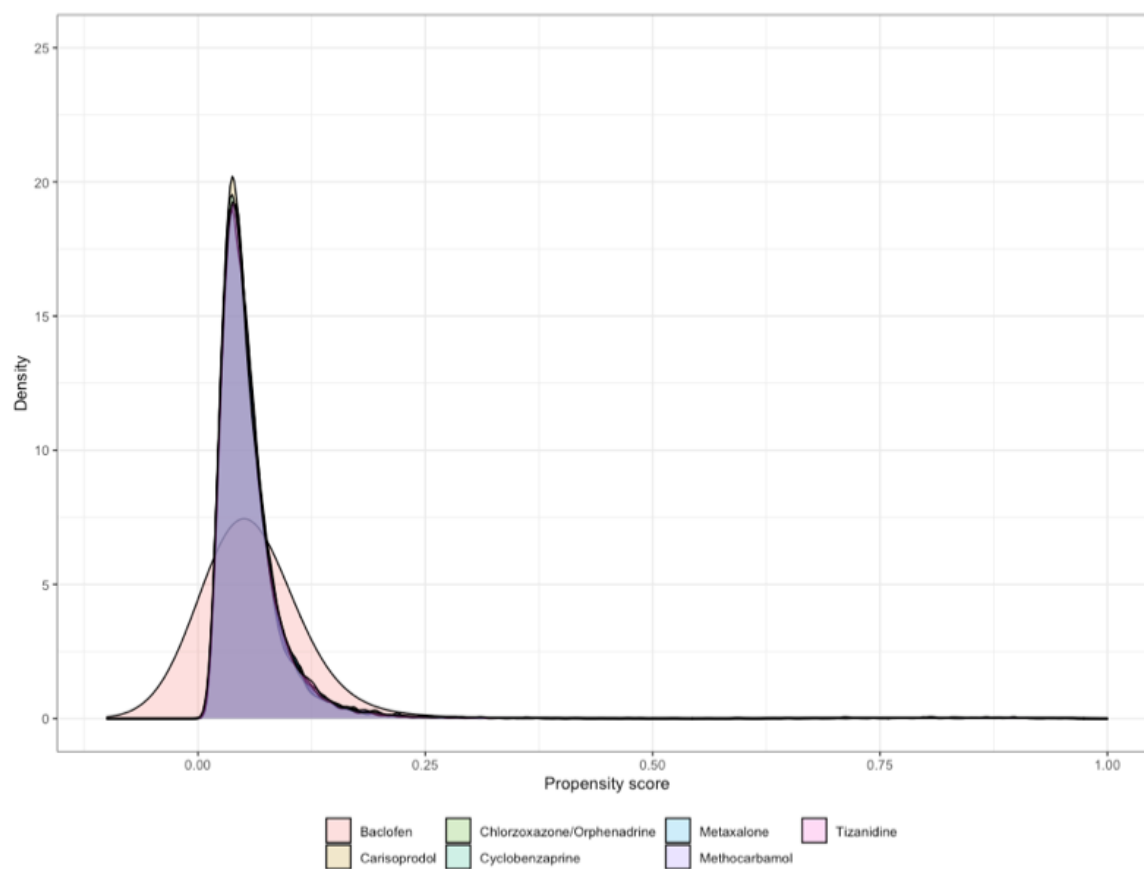
\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 2F. Propensity score distributions for treatment with tizanidine before matching weights in Medicaid Analytic eXtract (MAX)**



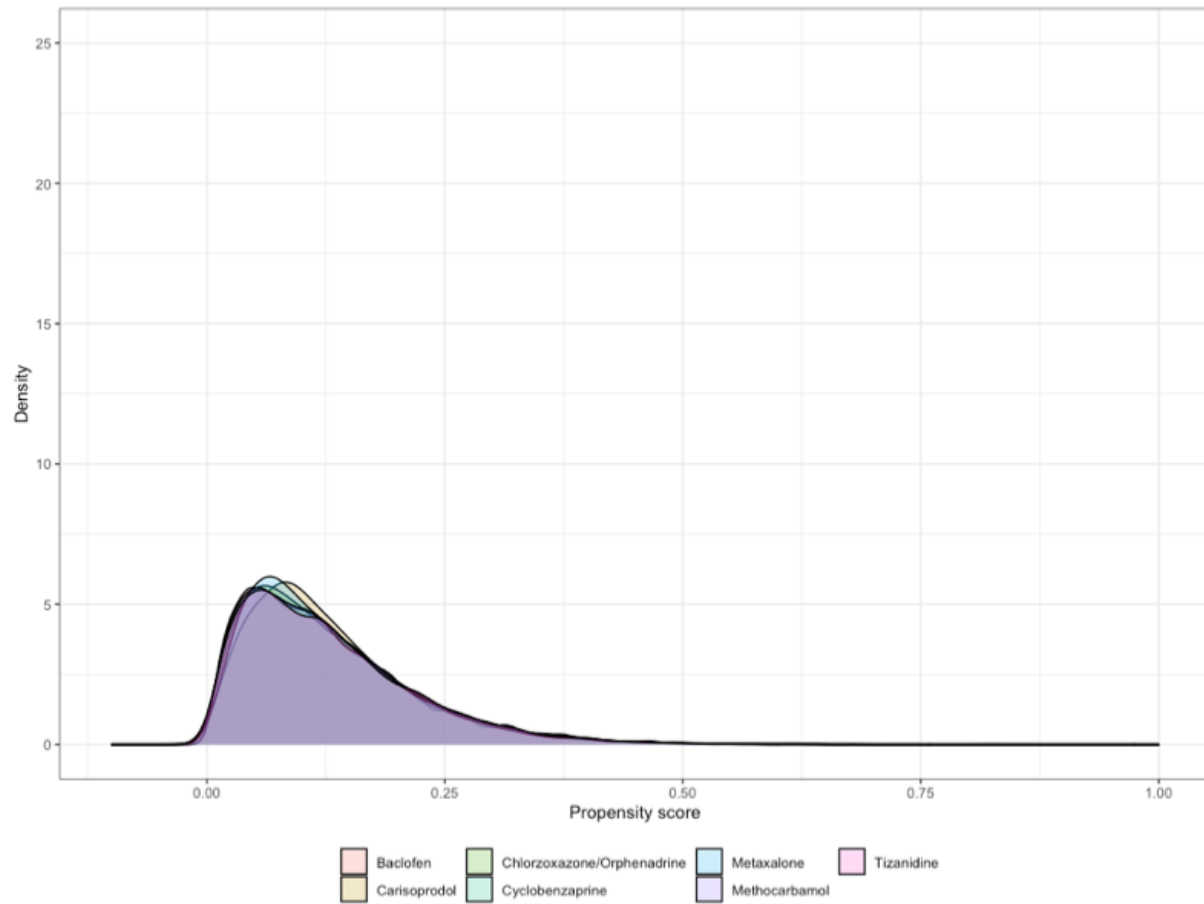
\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eFigure 3A. Propensity score distributions for treatment with baclofen after matching weights in Medicaid Analytic eXtract (MAX)**



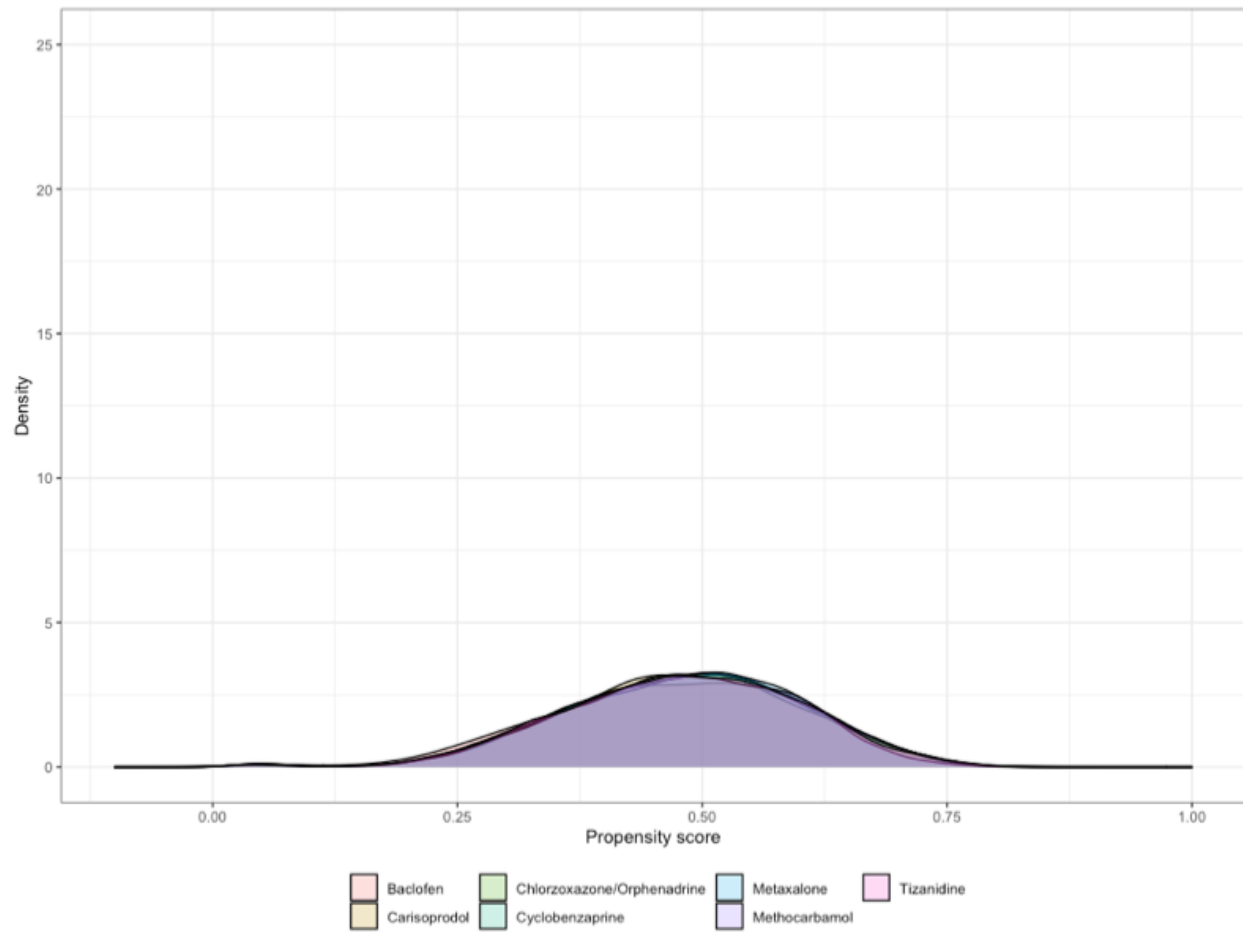
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 3B. Propensity score distributions for treatment with carisoprodol after matching weights in Medicaid Analytic eXtract (MAX)**



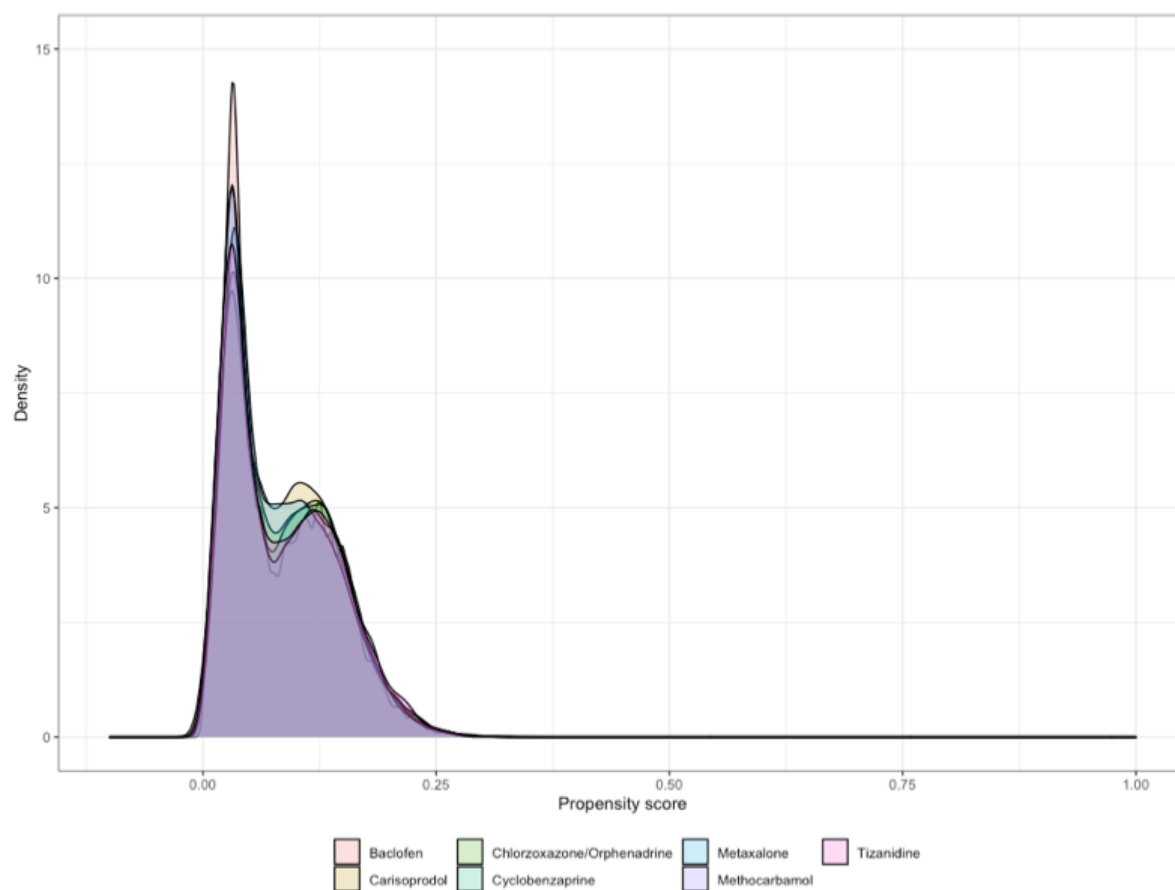
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 3C. Propensity score distributions for treatment with cyclobenzaprine after matching weights in Medicaid Analytic eXtract (MAX)**



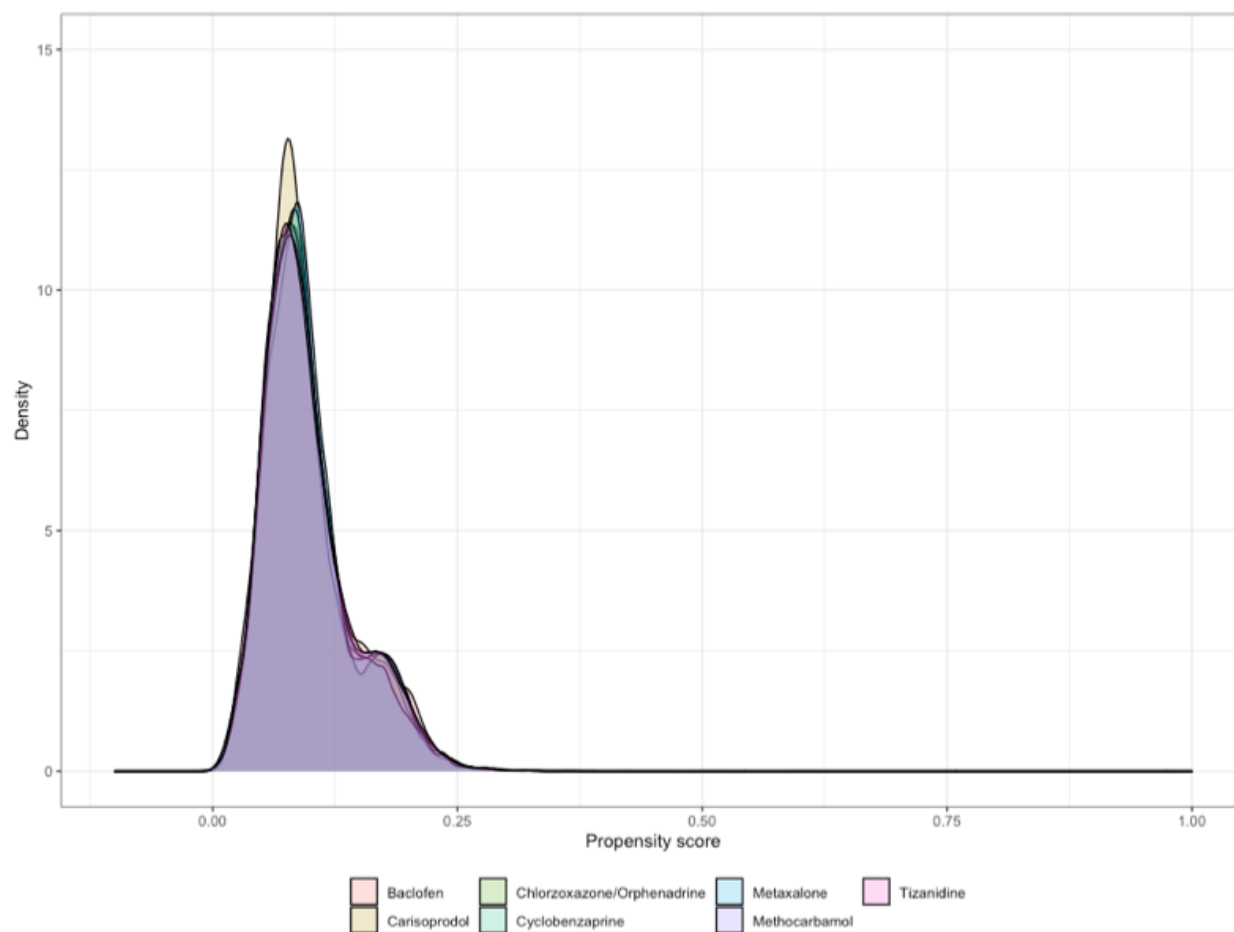
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 3D. Propensity score distributions for treatment with metaxalone after matching weights in Medicaid Analytic eXtract (MAX)**



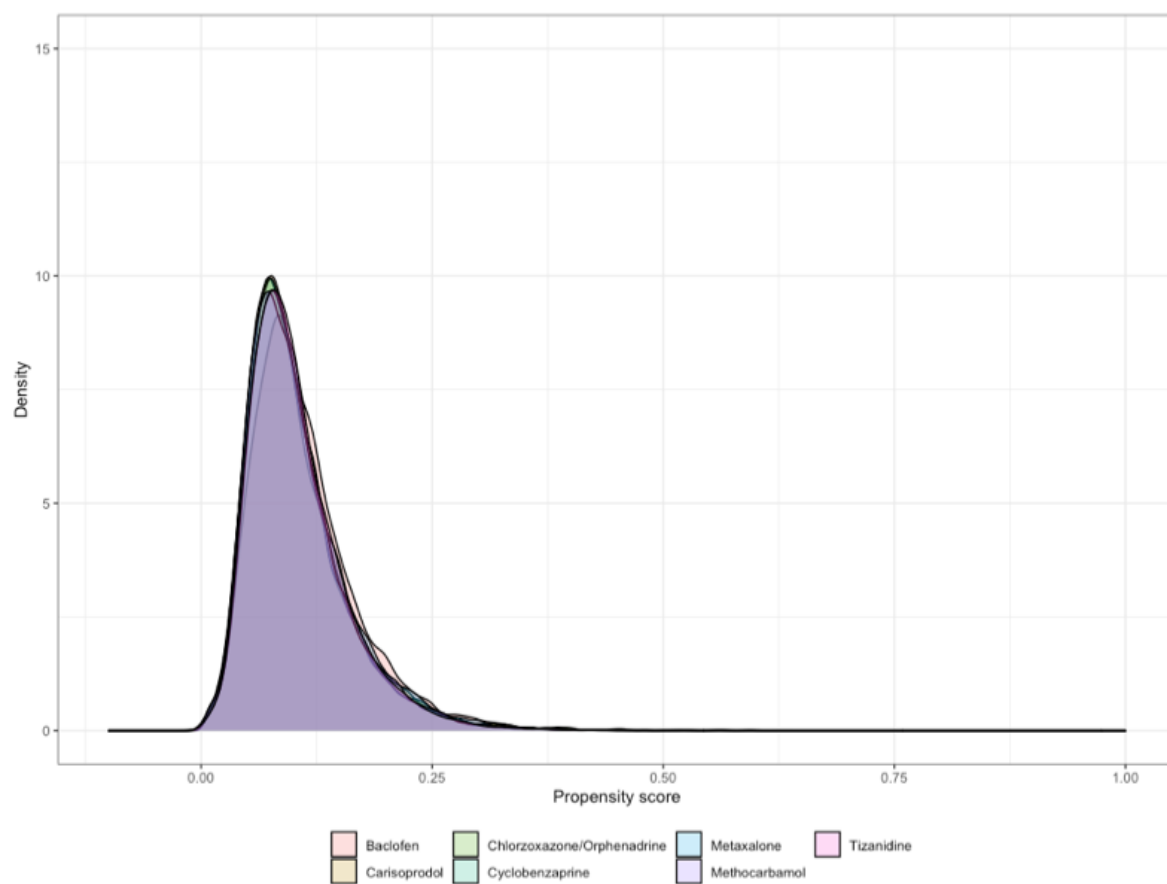
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 3E. Propensity score distributions for treatment with methocarbamol after matching weights in Medicaid Analytic eXtract (MAX)**



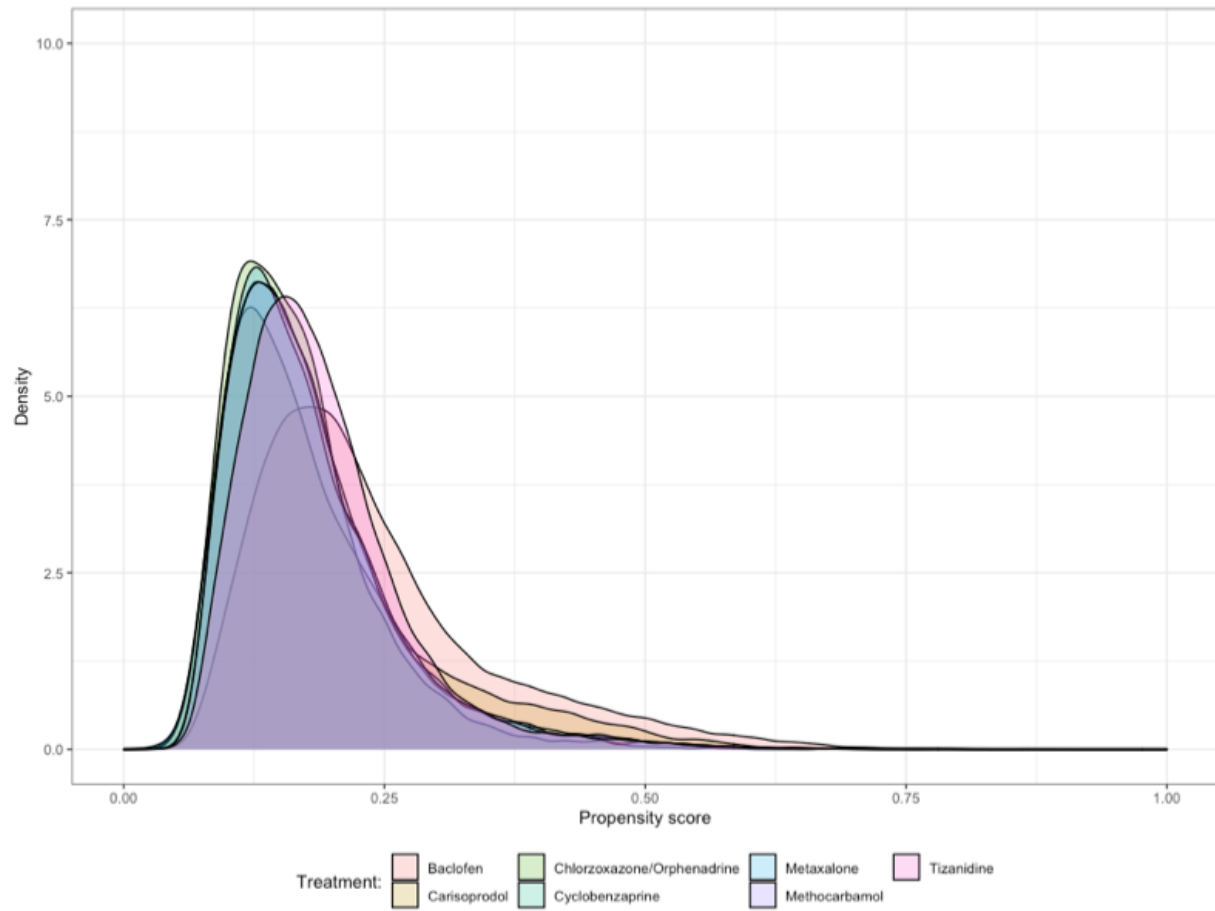
\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 3F. Propensity score distributions for treatment with tizanidine after matching weights in Medicaid Analytic eXtract (MAX)**



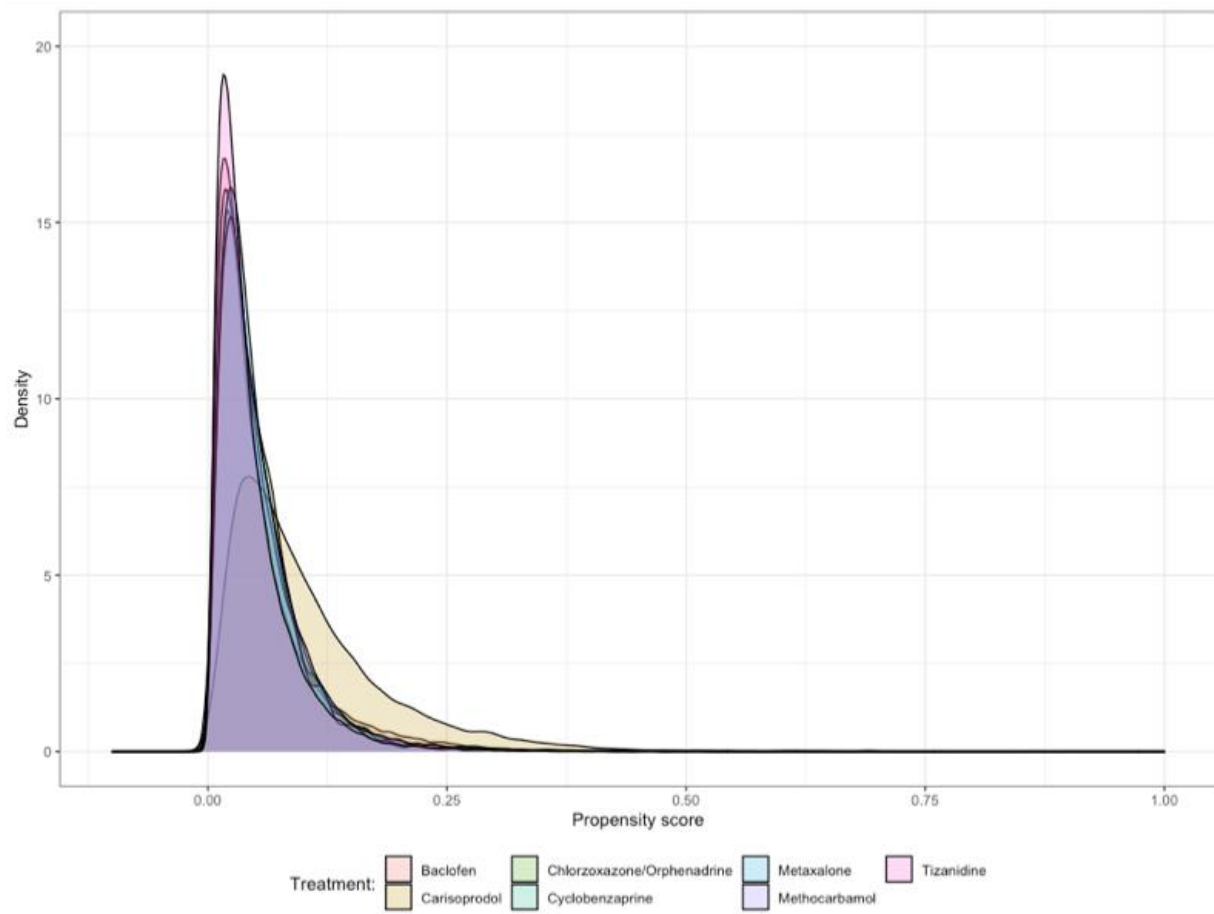
\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eFigure 4A. Propensity score distributions for treatment with baclofen before matching weights in Medicare (diabetes, heart failure, and stroke)**



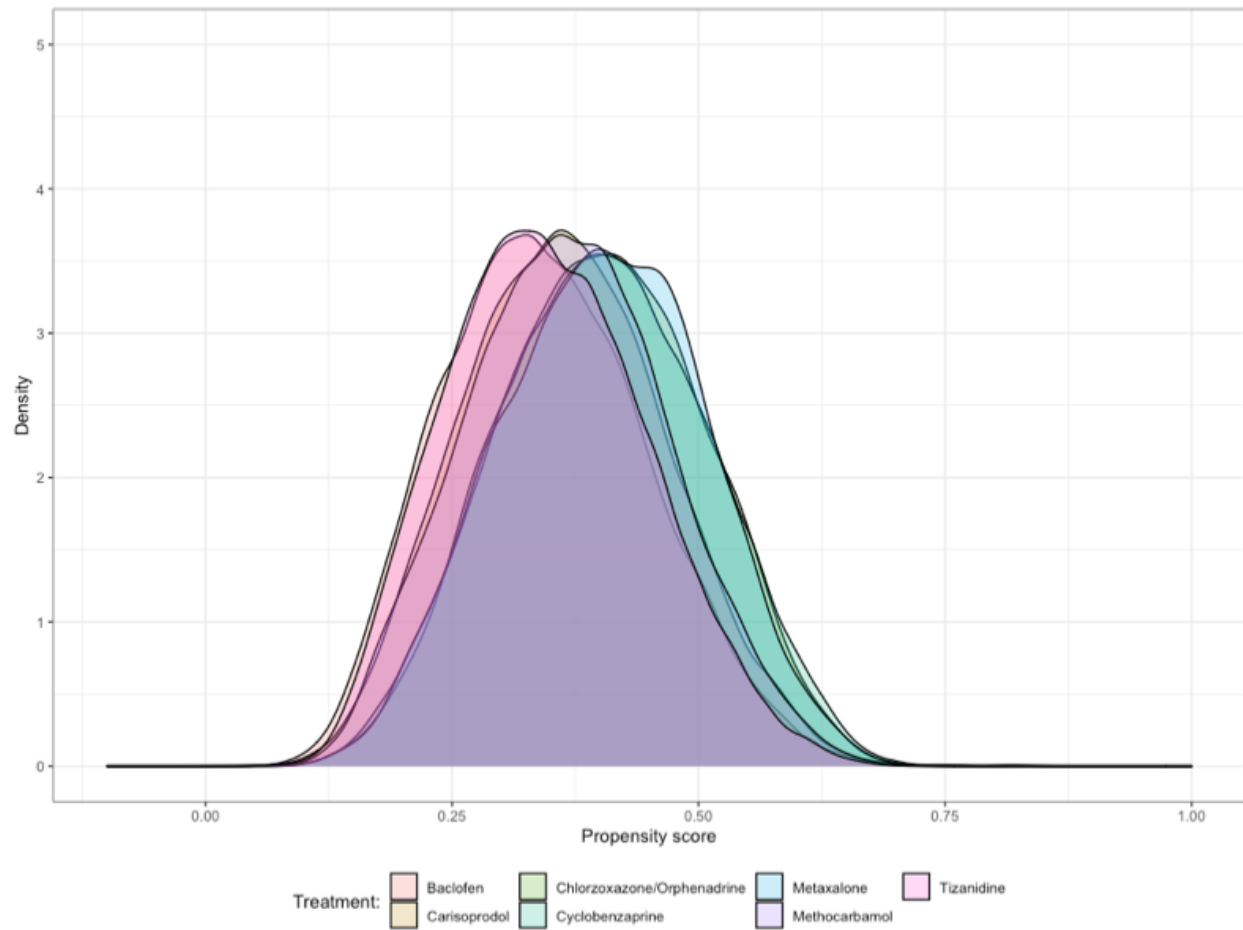
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 4B. Propensity score distributions for treatment with carisoprodol before matching weights in Medicare (diabetes, heart failure, and stroke)**



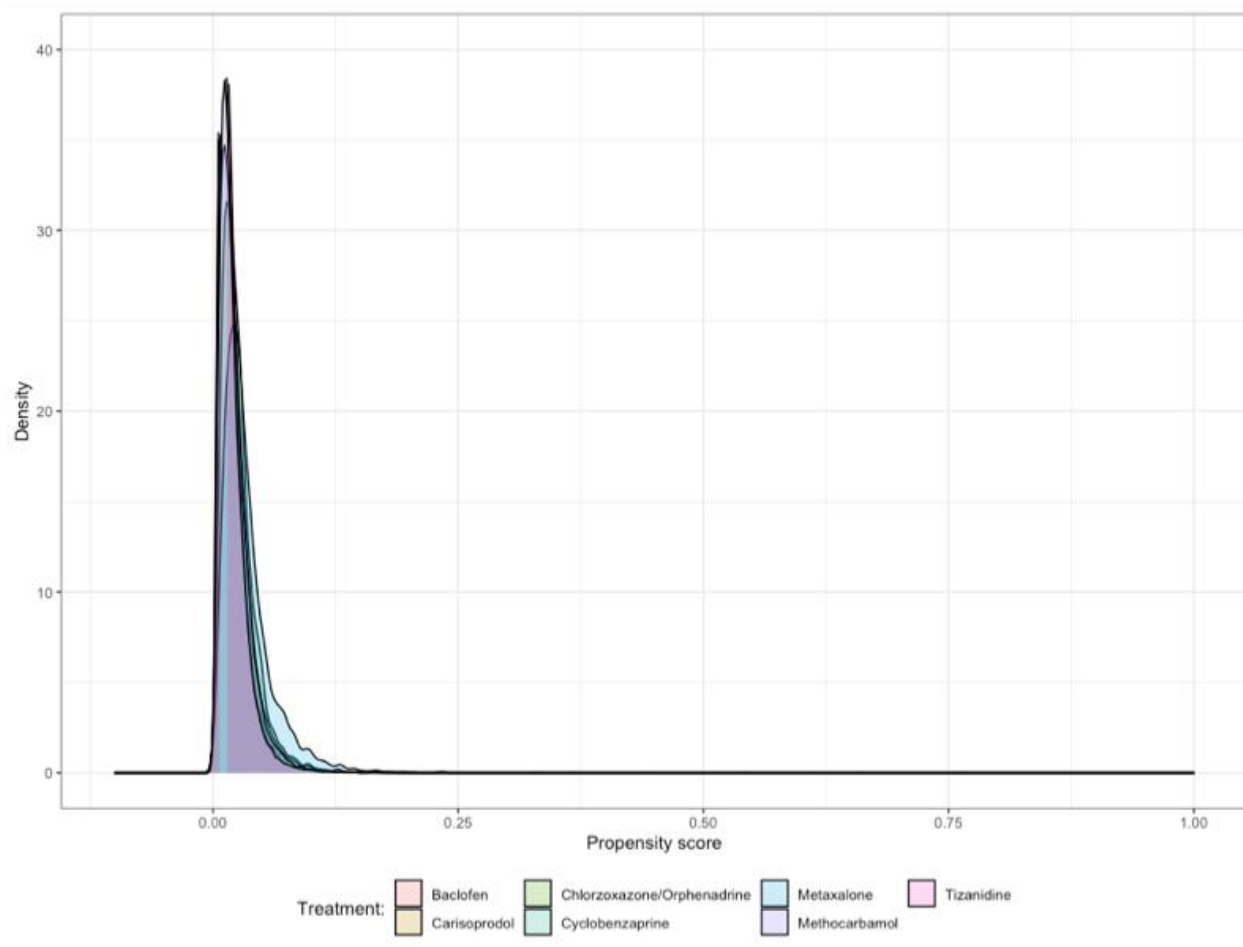
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 4C. Propensity score distributions for treatment with cyclobenzaprine before matching weights in Medicare (diabetes, heart failure, and stroke)**



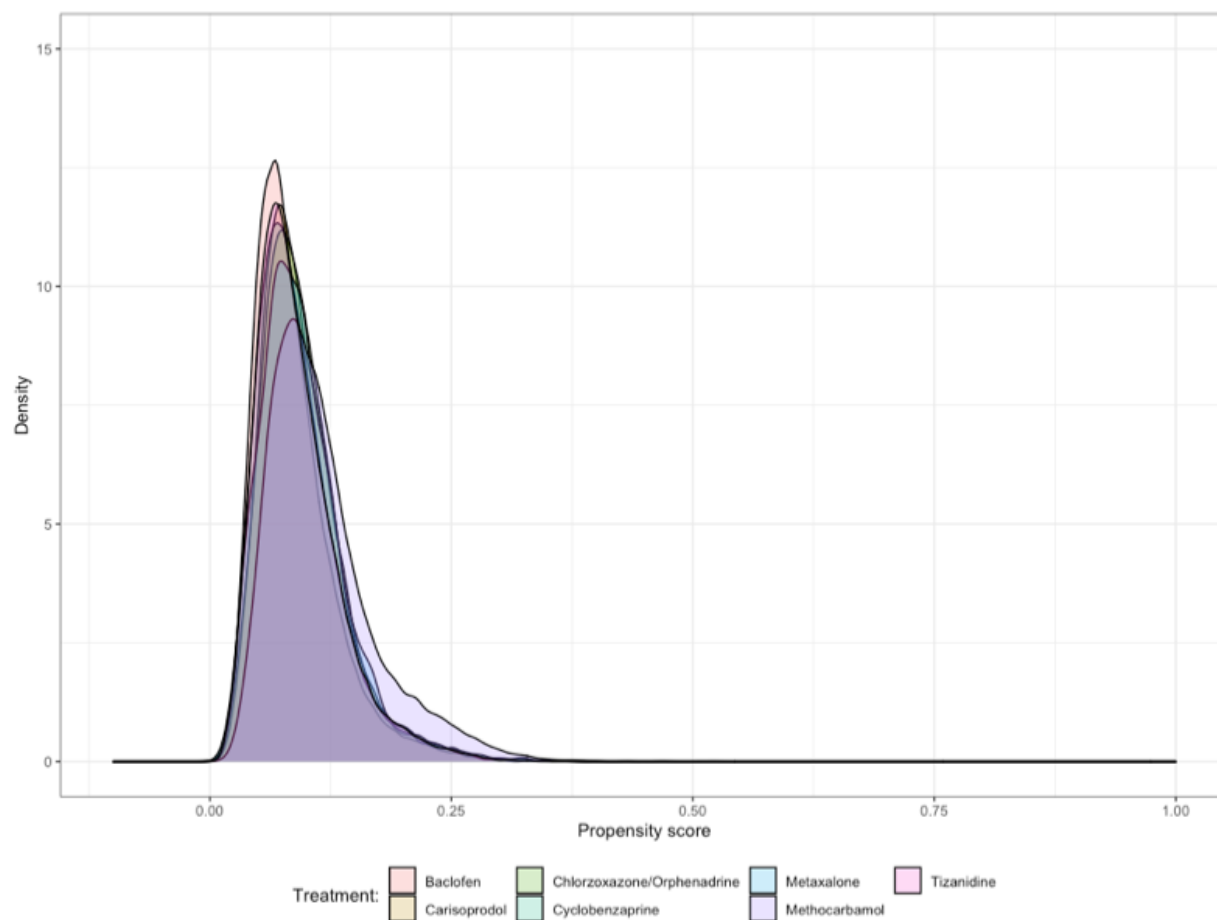
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 4D. Propensity score distributions for treatment with metaxalone before matching weights in Medicare (diabetes, heart failure, and stroke)**



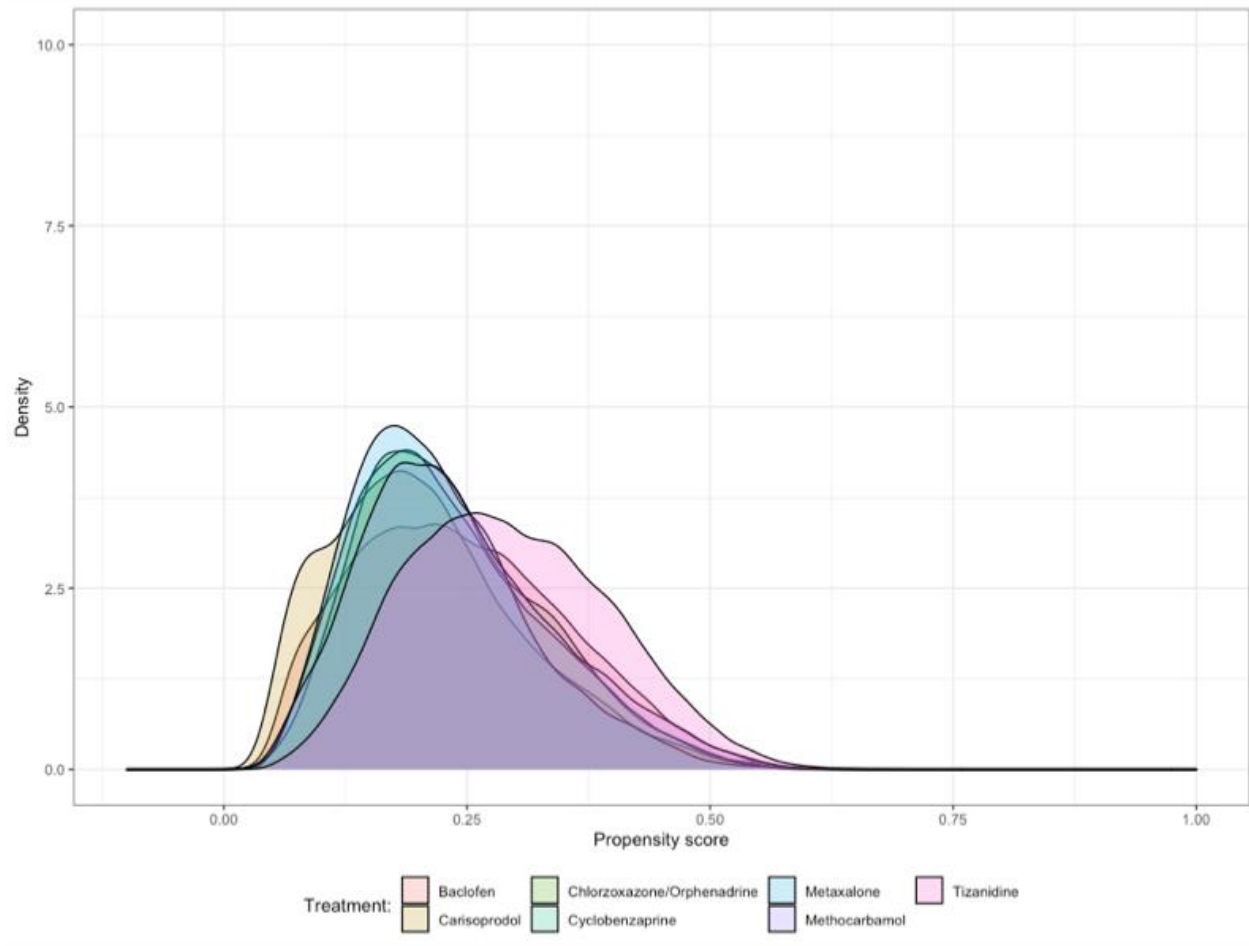
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 4E. Propensity score distributions for treatment with methocarbamol before matching weights in Medicare (diabetes, heart failure, and stroke)**



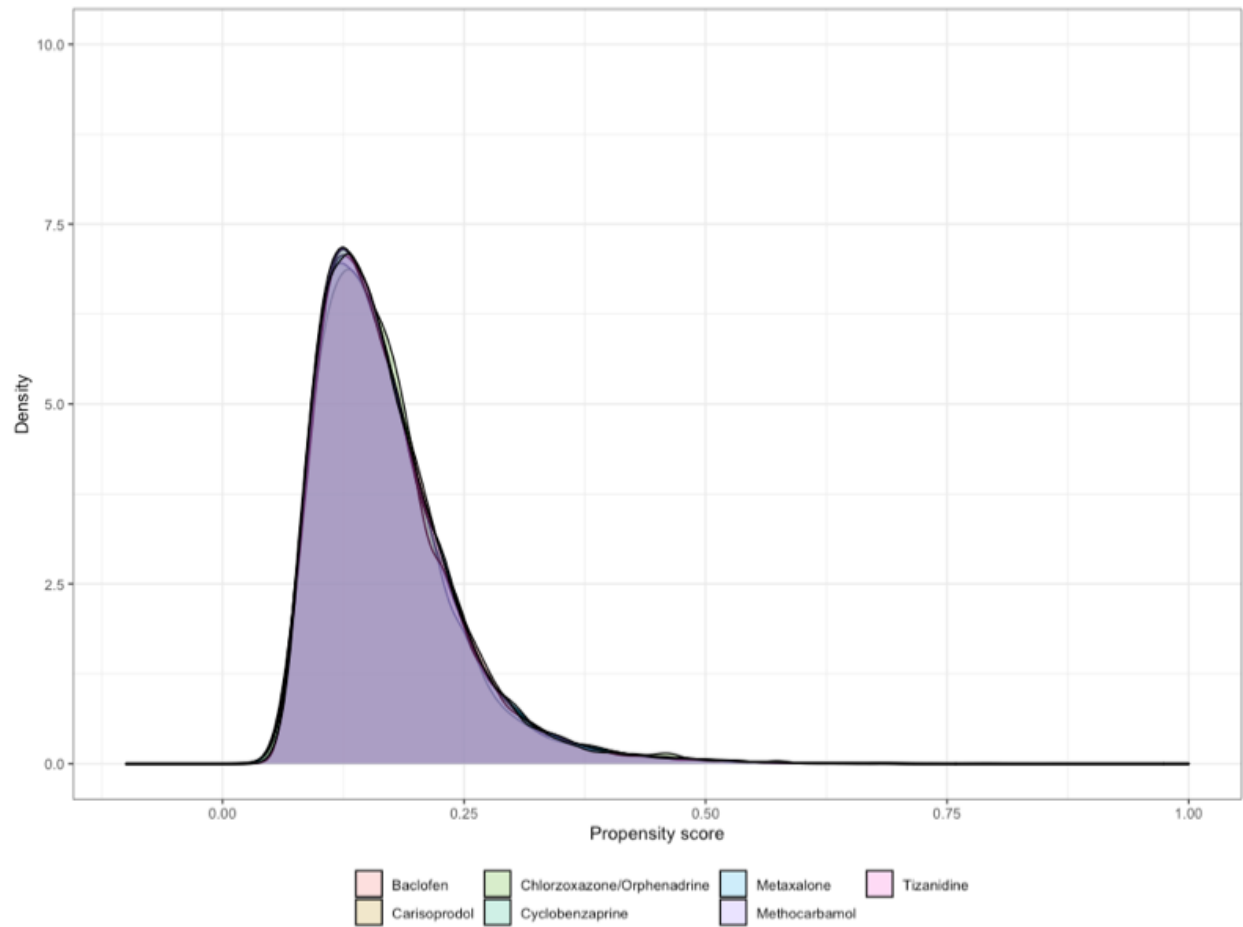
\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 4F. Propensity score distributions for treatment with tizanidine before matching weights in Medicare (diabetes, heart failure, and stroke)**



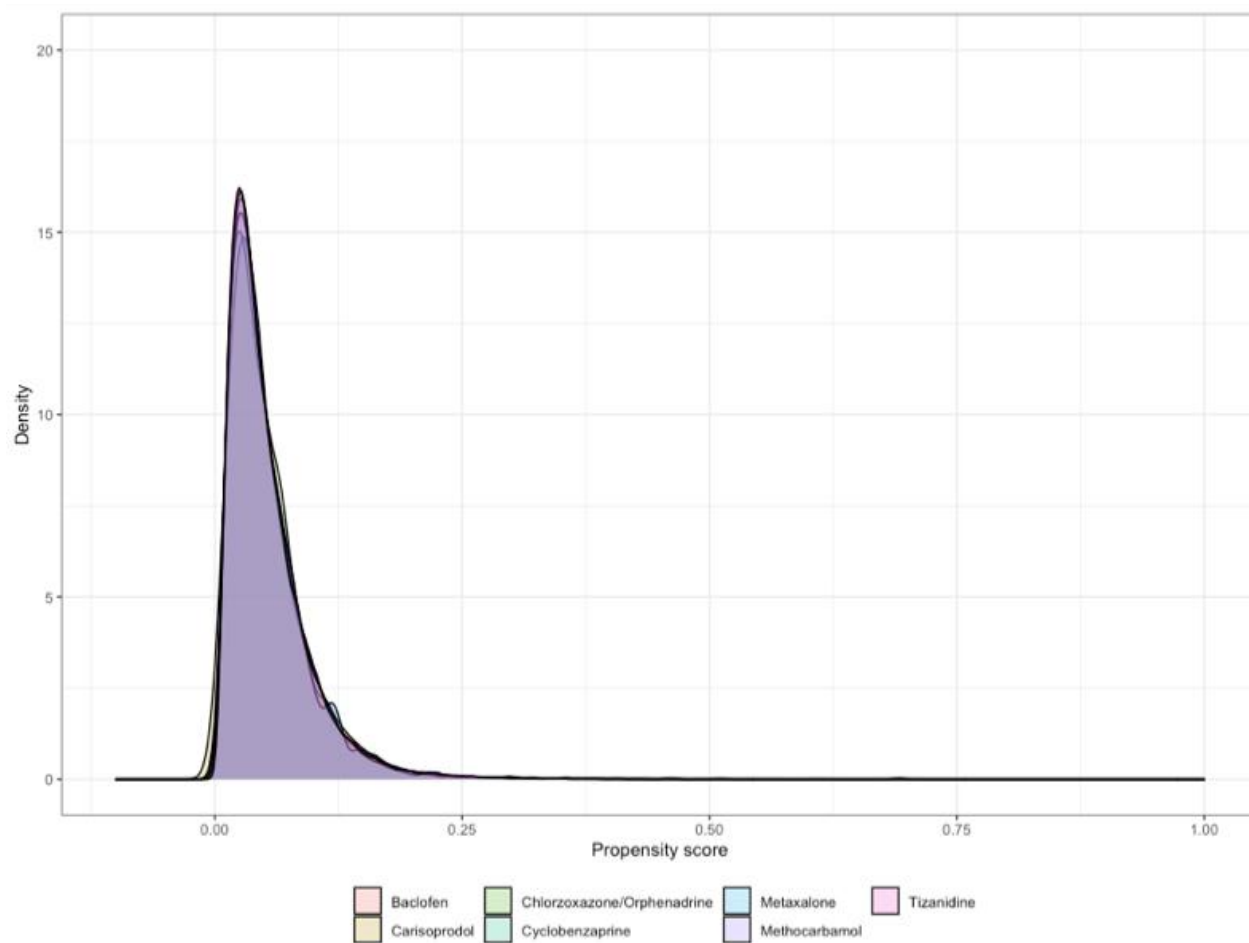
\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eFigure 5A. Propensity score distributions for treatment with baclofen after matching weights in Medicare (diabetes, heart failure, and stroke)**



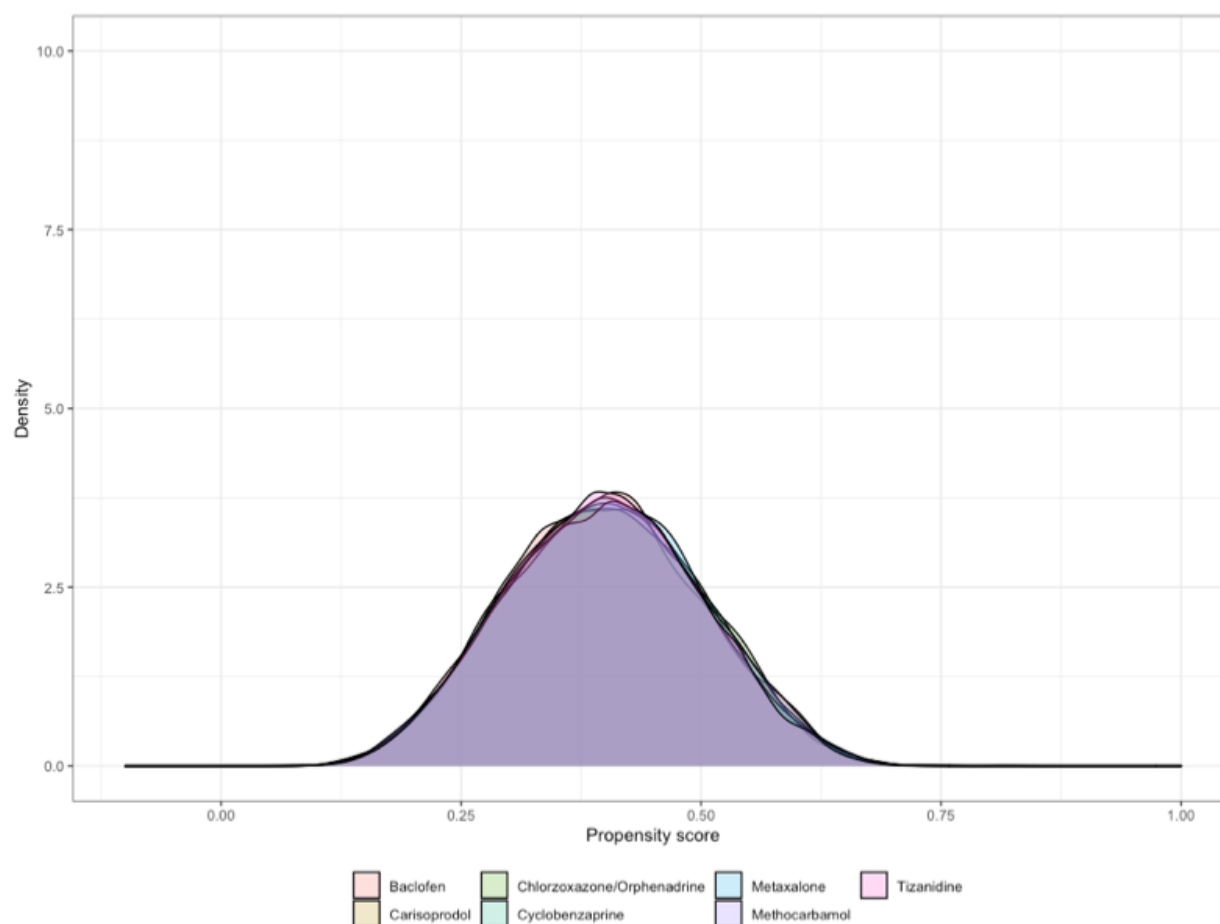
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 5B. Propensity score distributions for treatment with carisoprodol after matching weights in Medicare (diabetes, heart failure, and stroke)**



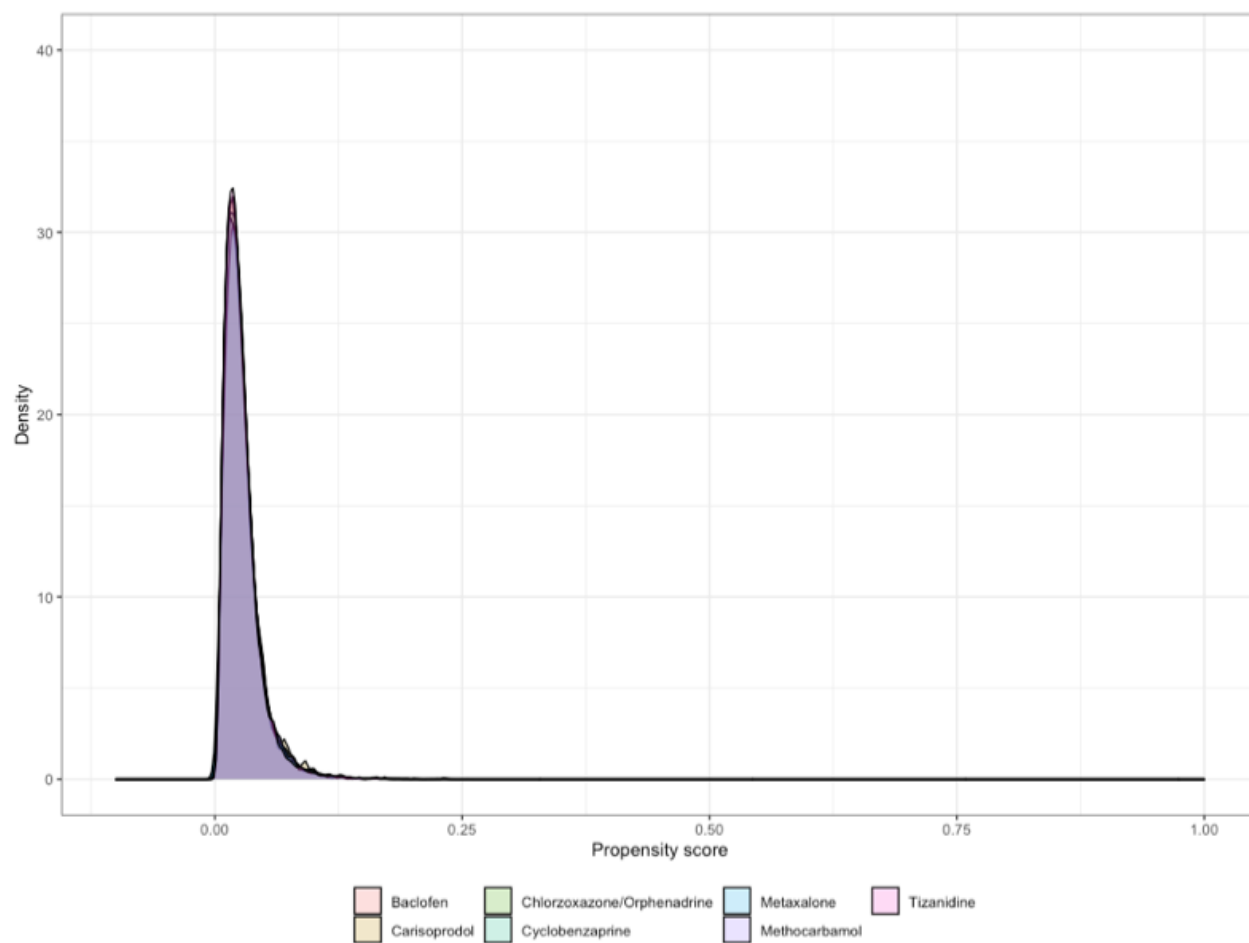
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 5C. Propensity score distributions for treatment with cyclobenzaprine after matching weights in Medicare (diabetes, heart failure, and stroke)**



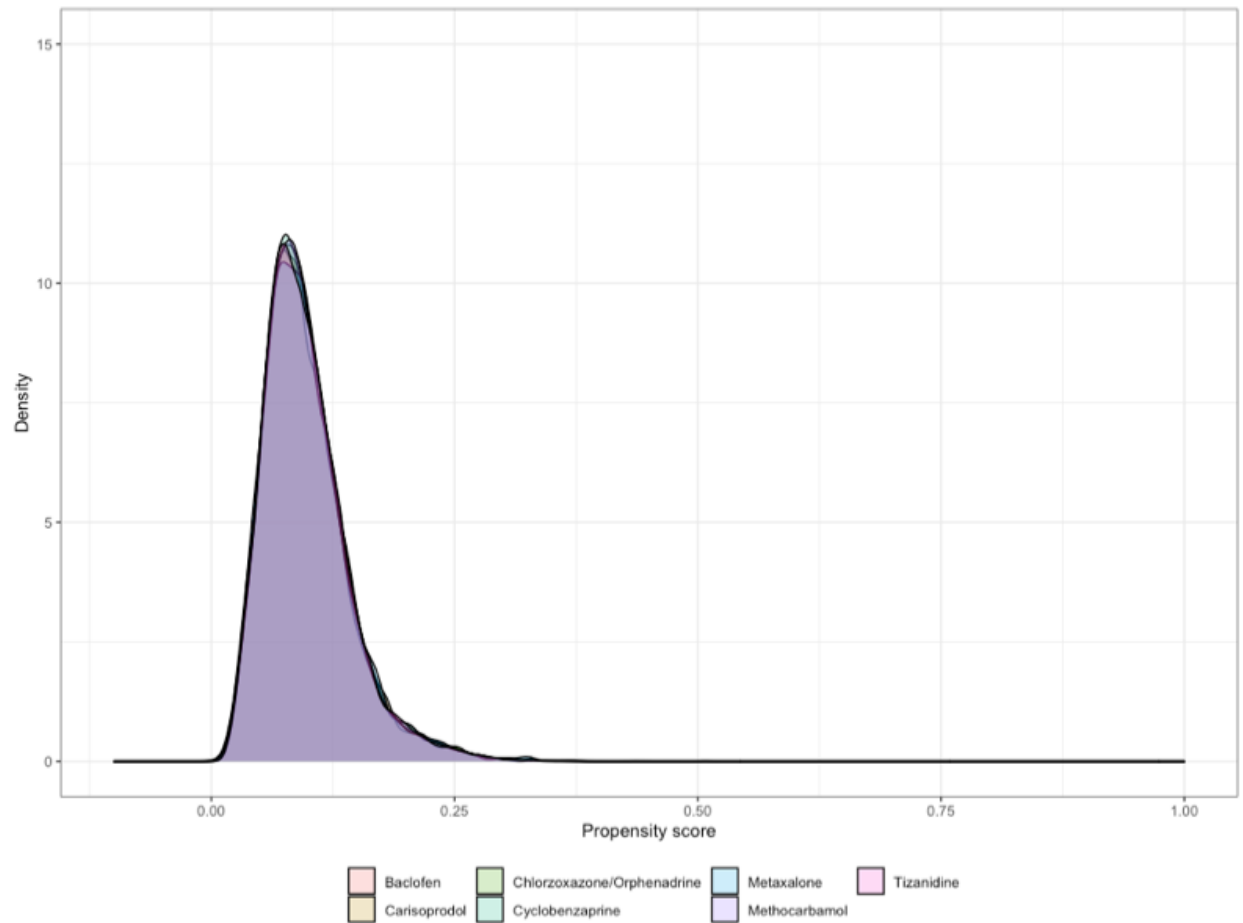
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 5D. Propensity score distributions for treatment with metaxalone after matching weights in Medicare (diabetes, heart failure, and stroke)**



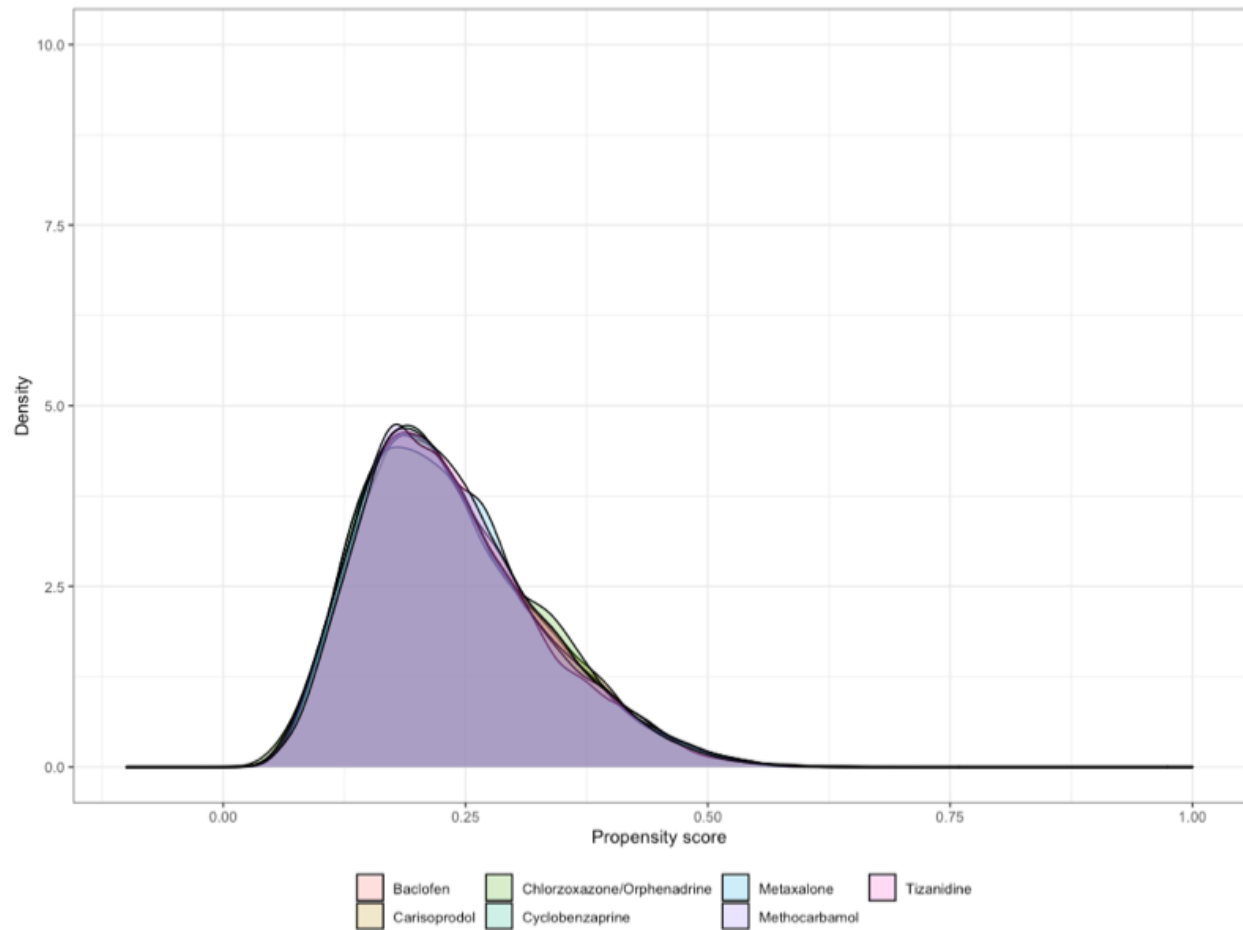
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 5E. Propensity score distributions for treatment with methocarbamol after matching weights in Medicare (diabetes, heart failure, and stroke)**



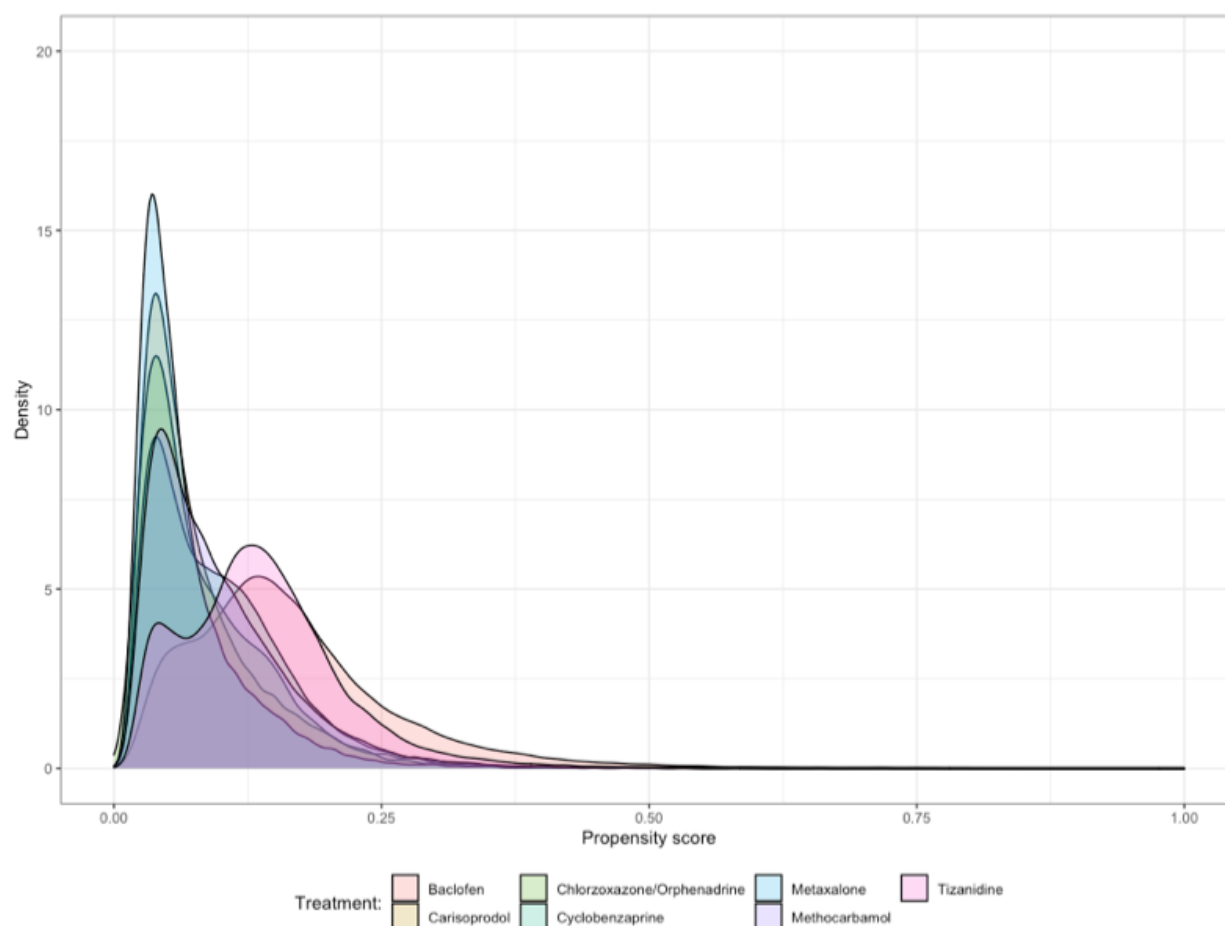
\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 5F. Propensity score distributions for treatment with tizanidine after matching weights in Medicare (diabetes, heart failure, and stroke)**



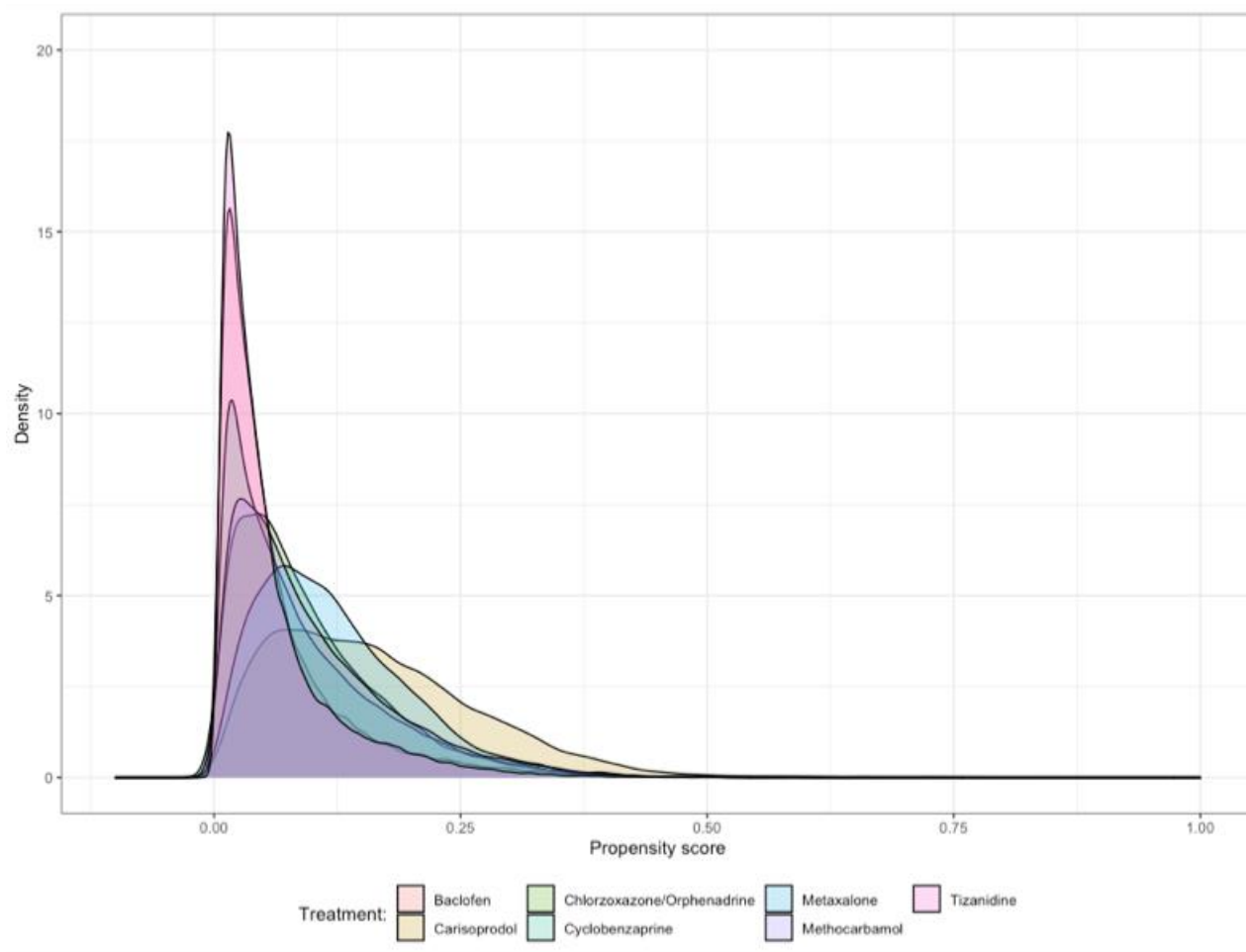
\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eFigure 6A. Propensity score distributions for treatment with baclofen before matching weights in Optum© Clinformatics® Data Mart**



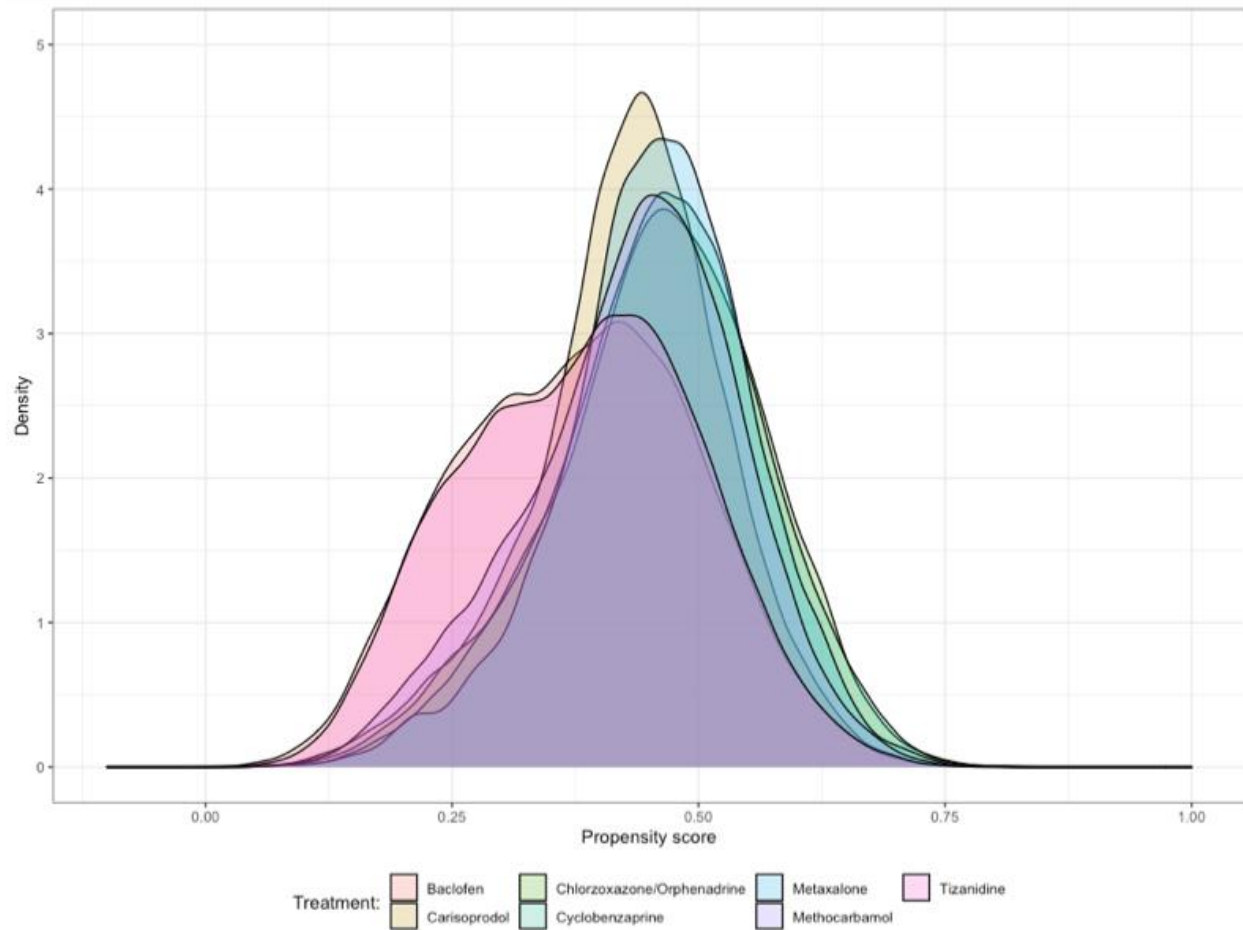
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 6B. Propensity score distributions for treatment with carisoprodol before matching weights in Optum© Clinformatics® Data Mart**



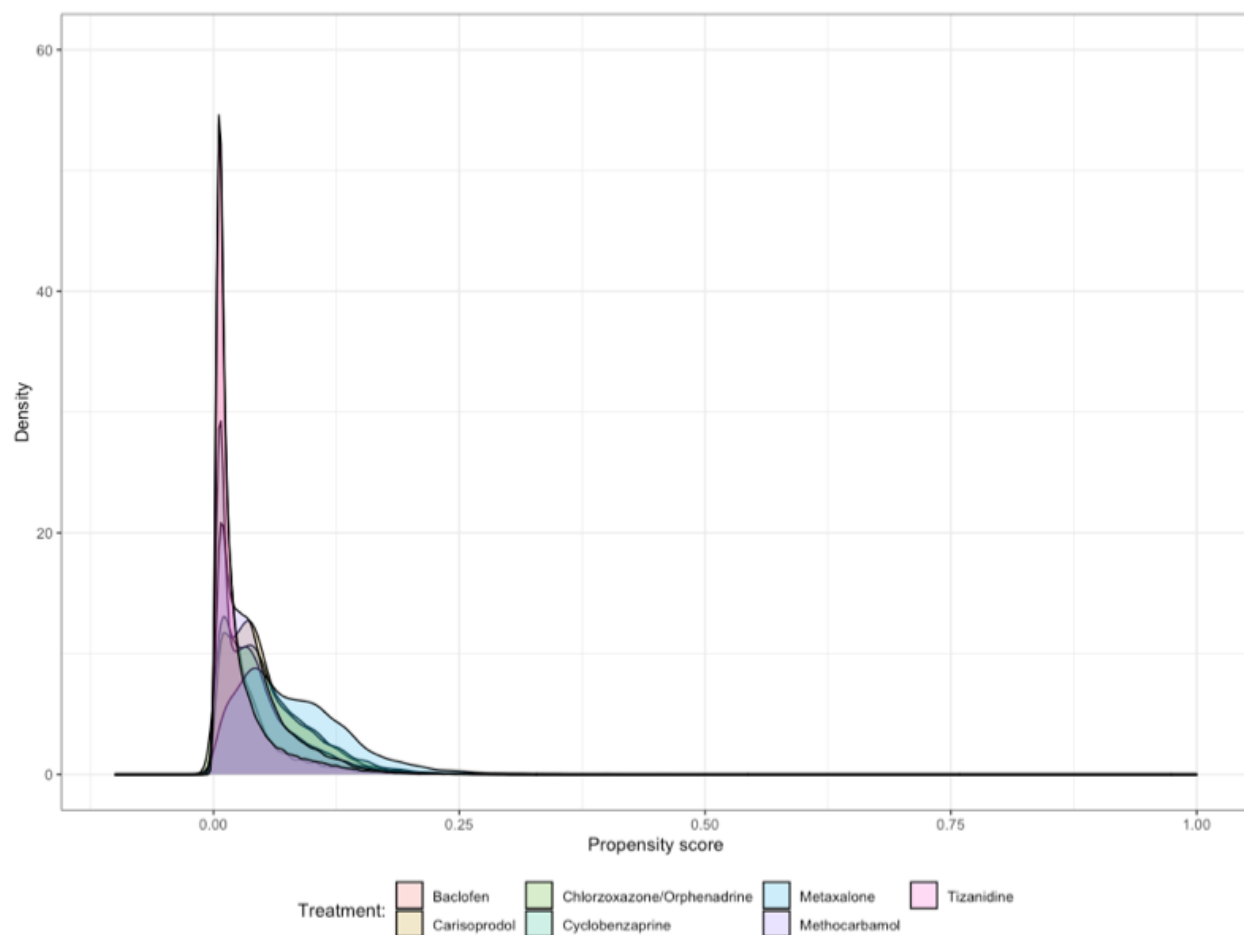
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 6C. Propensity score distributions for treatment with cyclobenzaprine before matching weights in Optum© Clinformatics® Data Mart**



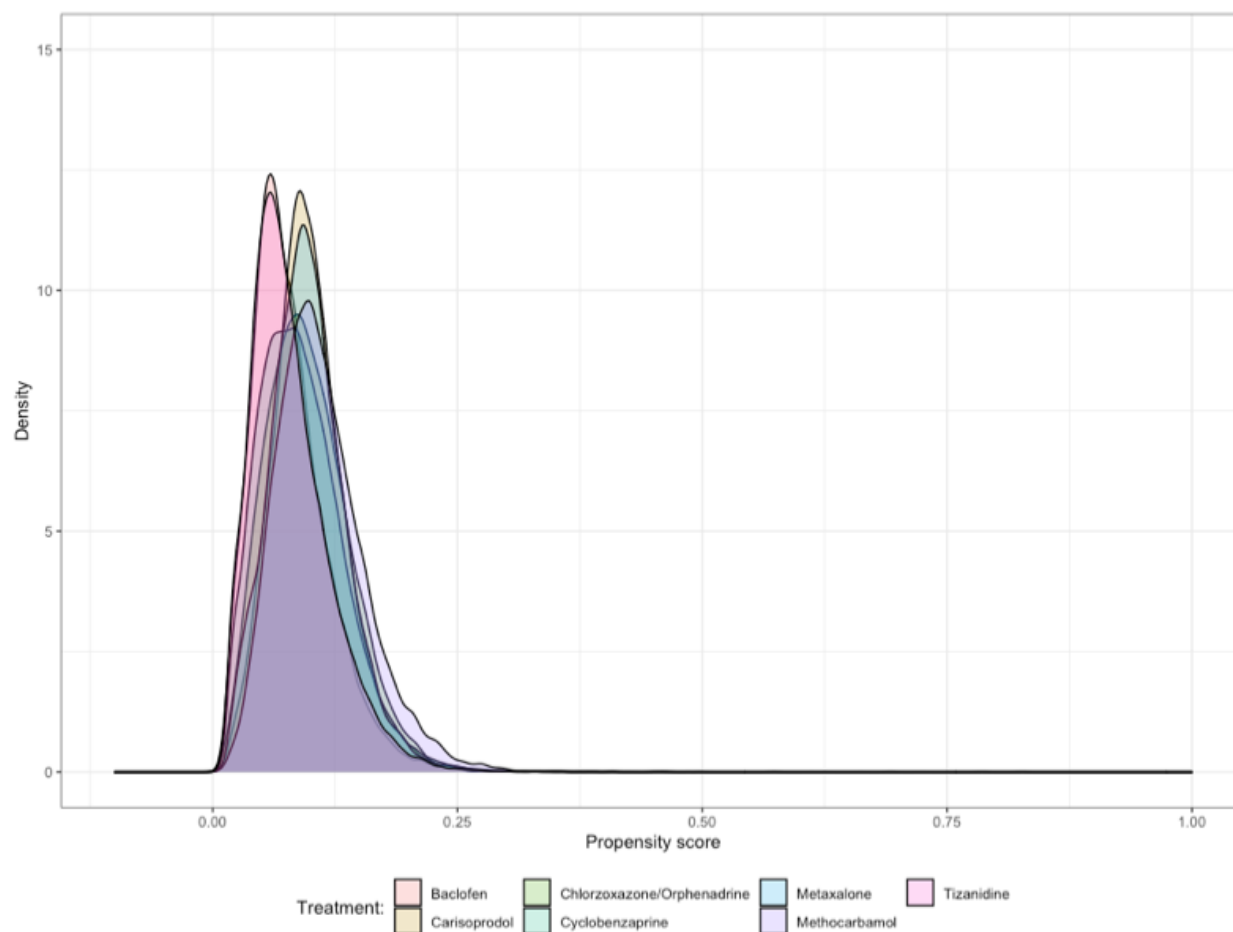
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 6D. Propensity score distributions for treatment with metaxalone before matching weights in Optum© Clinformatics® Data Mart**



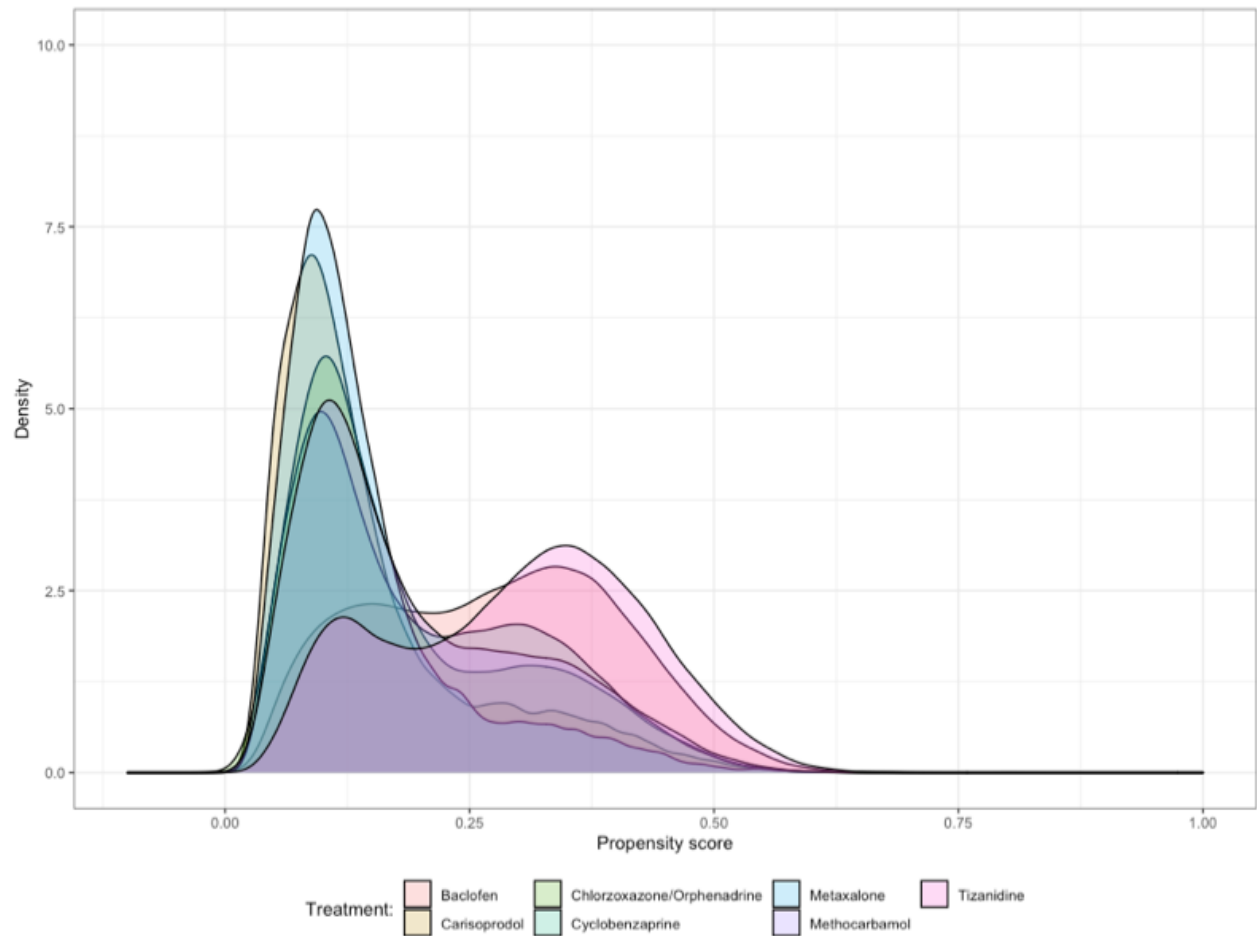
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 6E. Propensity score distributions for treatment with methocarbamol before matching weights in Optum© Clinformatics® Data Mart**



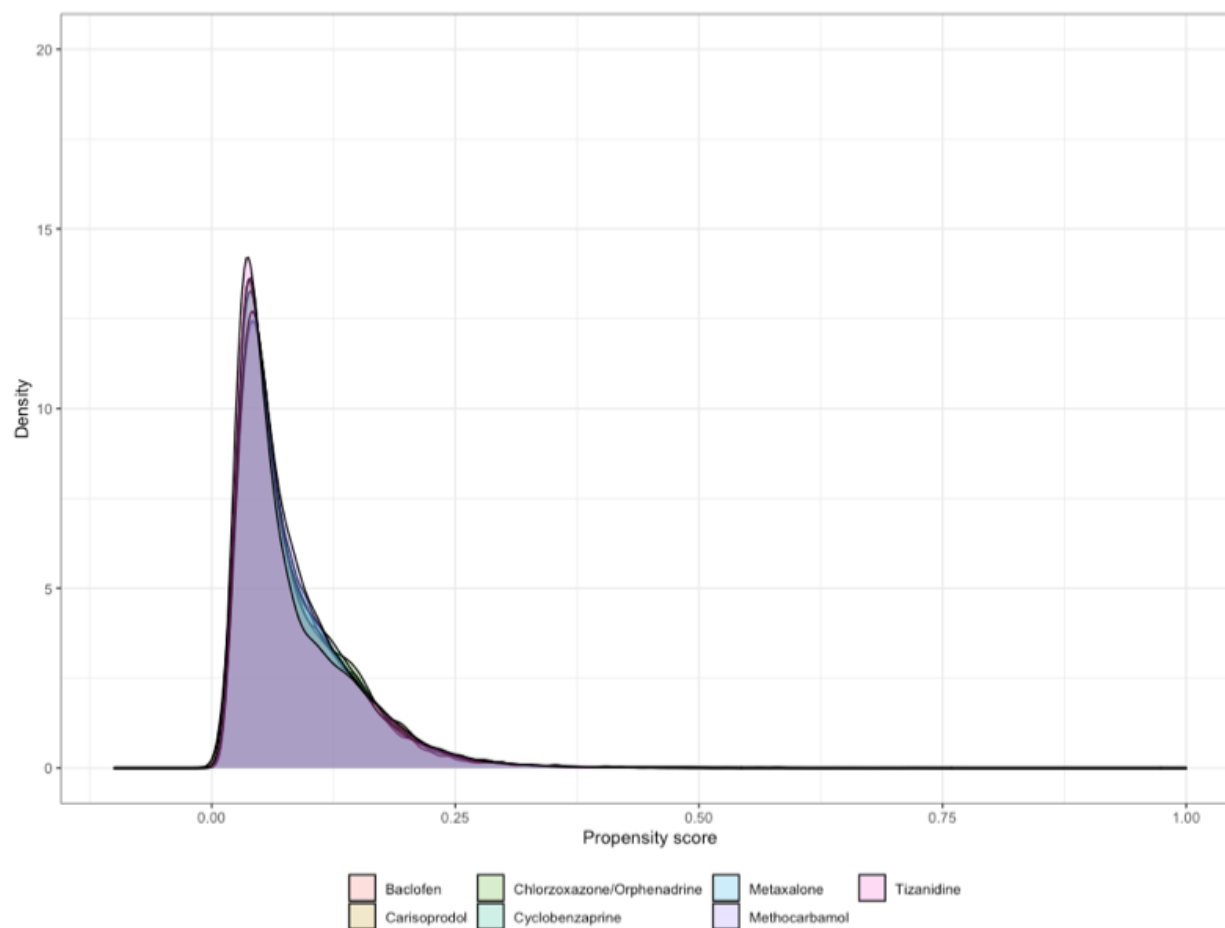
\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 6F. Propensity score distributions for treatment with tizanidine before matching weights in Optum© Clinformatics® Data Mart**



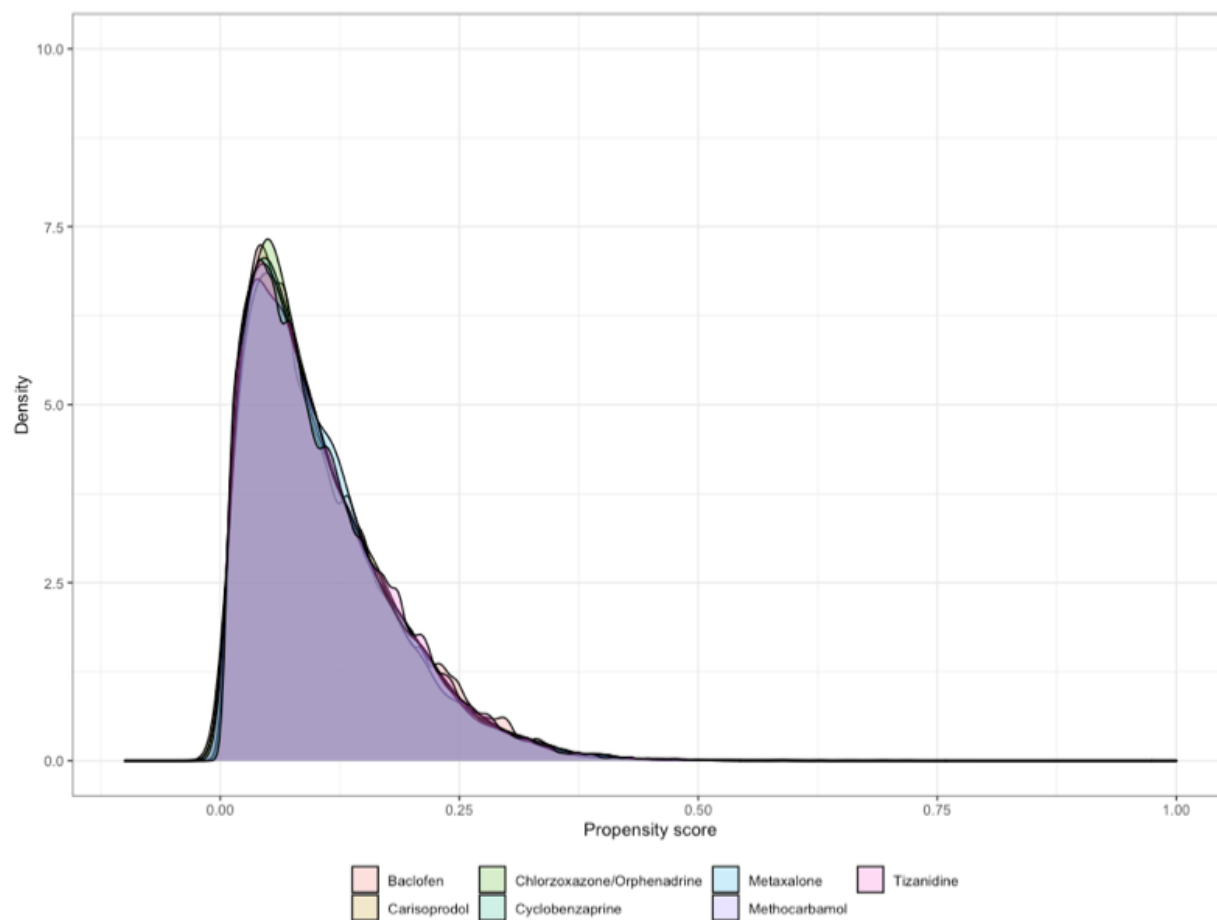
\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eFigure 7A. Propensity score distributions for treatment with baclofen after matching weights in Optum© Clinformatics® Data Mart**



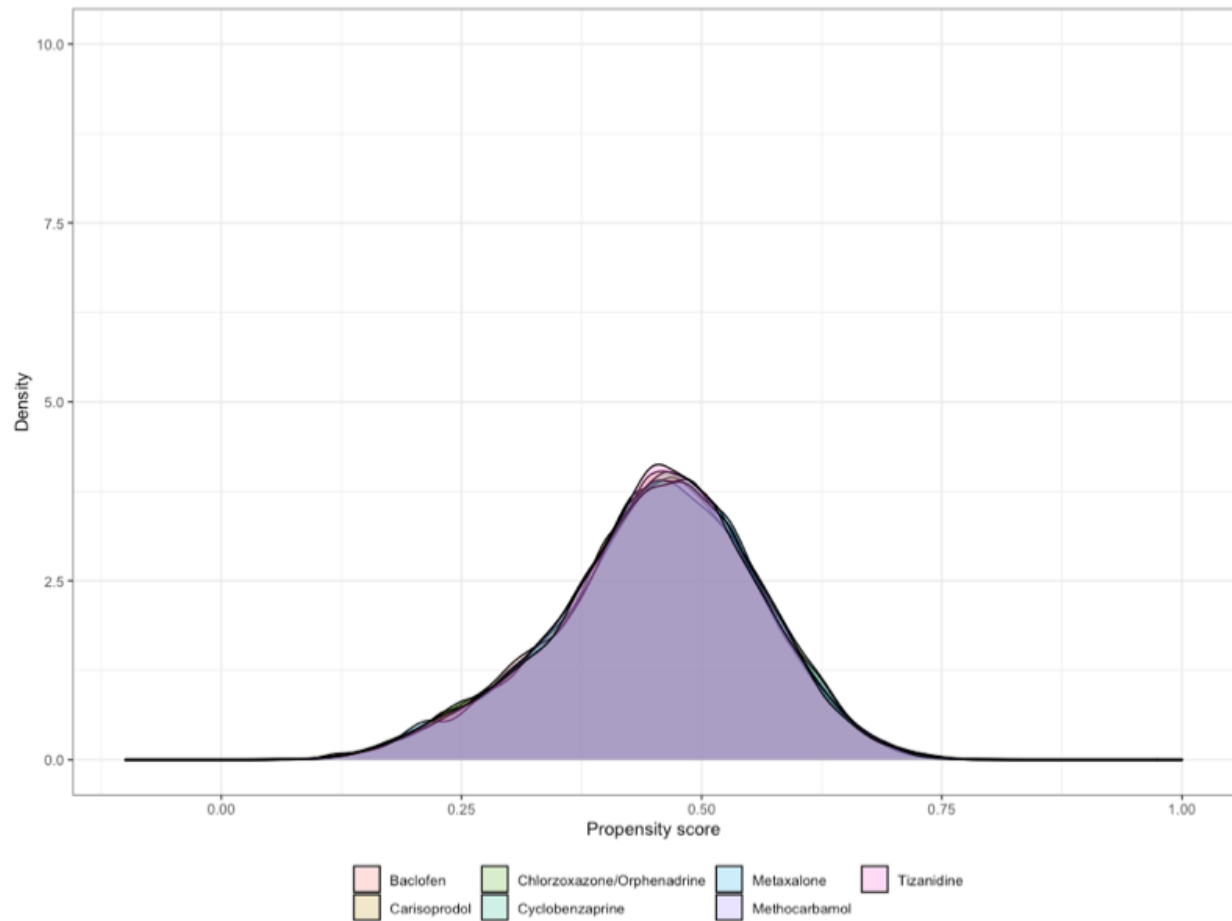
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 7B. Propensity score distributions for treatment with carisoprodol after matching weights in Optum© Clinformatics® Data Mart**



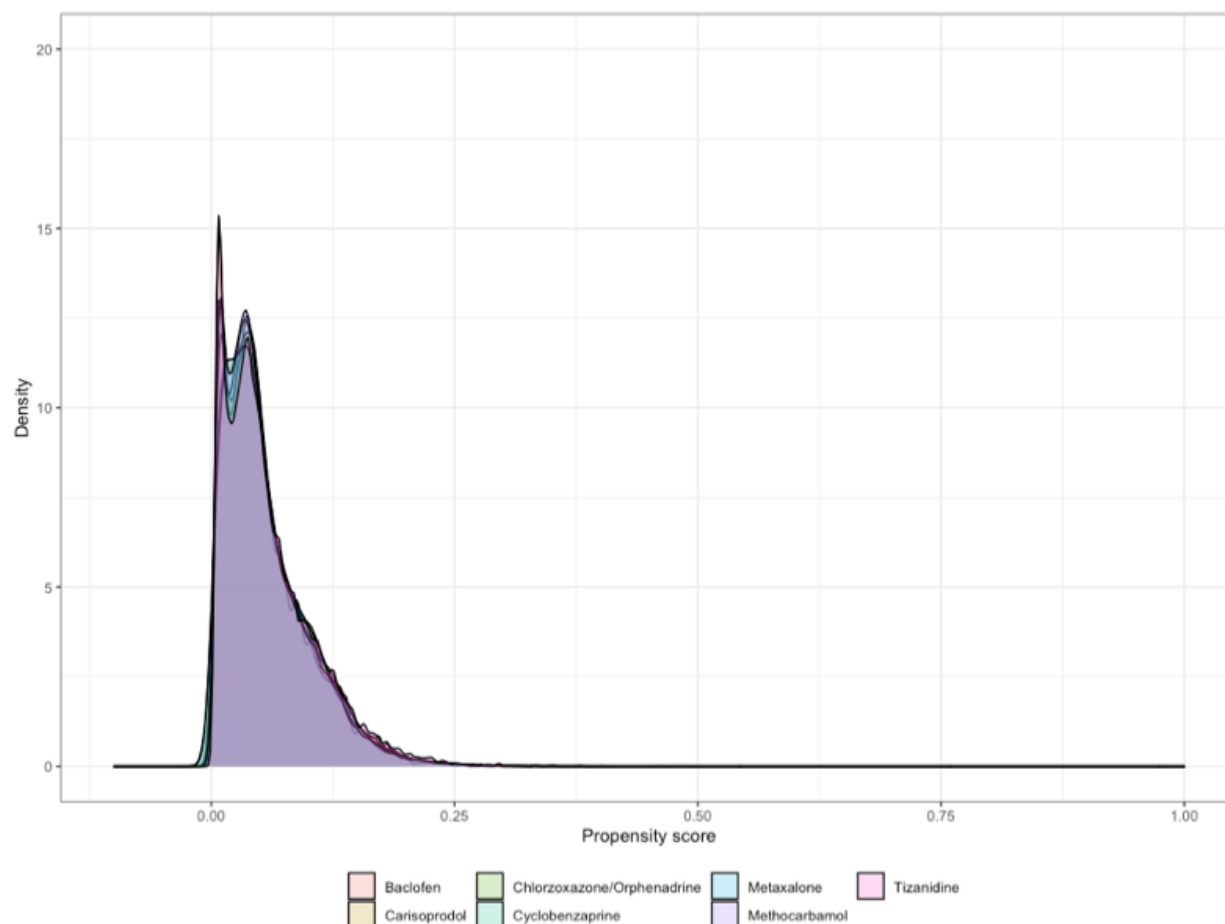
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 7C. Propensity score distributions for treatment with cyclobenzaprine after matching weights in Optum© Clinformatics® Data Mart**



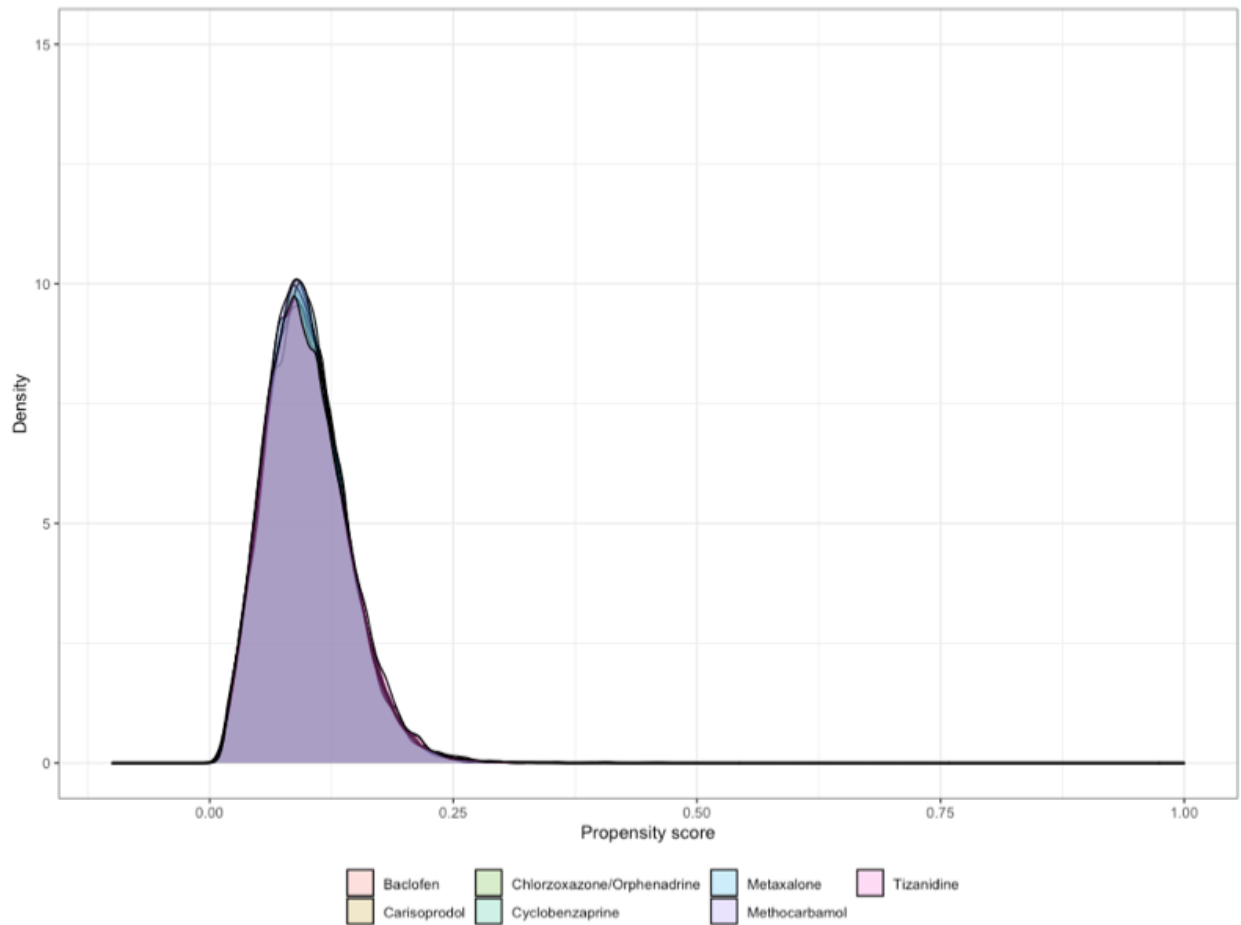
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 7D. Propensity score distributions for treatment with metaxalone after matching weights in Optum© Clinformatics® Data Mart**



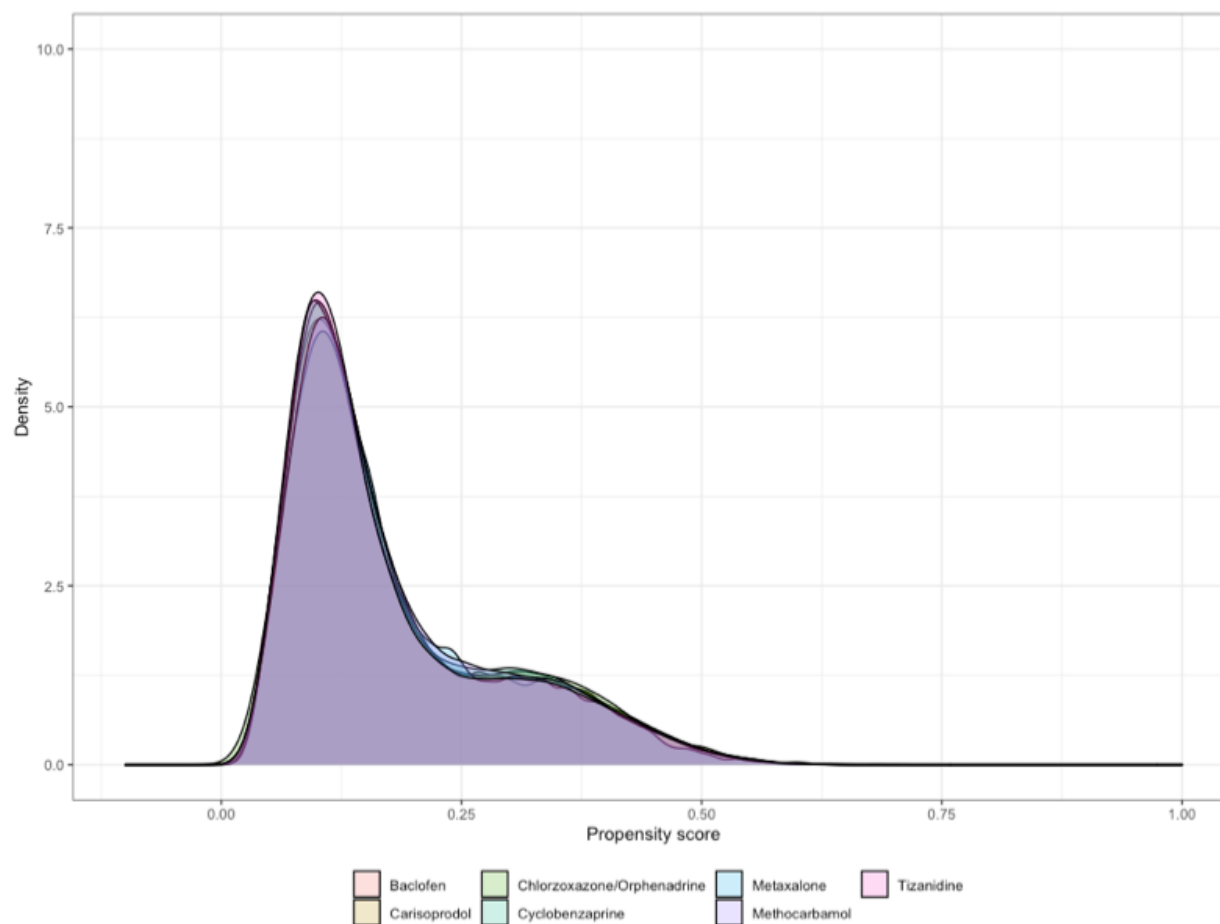
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 7E. Propensity score distributions for treatment with methocarbamol after matching weights in Optum© Clinformatics® Data Mart**



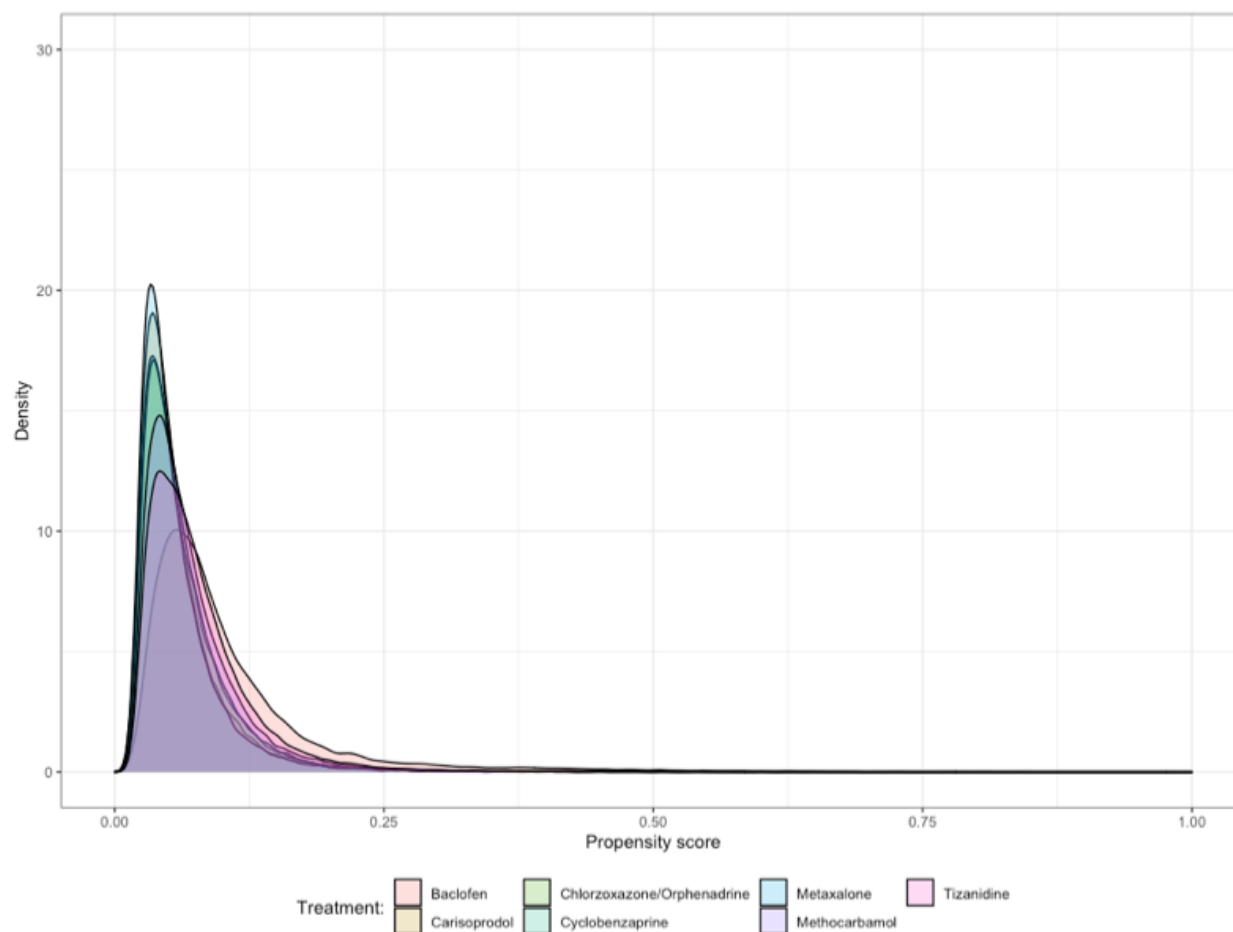
\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 7F. Propensity score distributions for treatment with tizanidine after matching weights in Optum© Clinformatics® Data Mart**



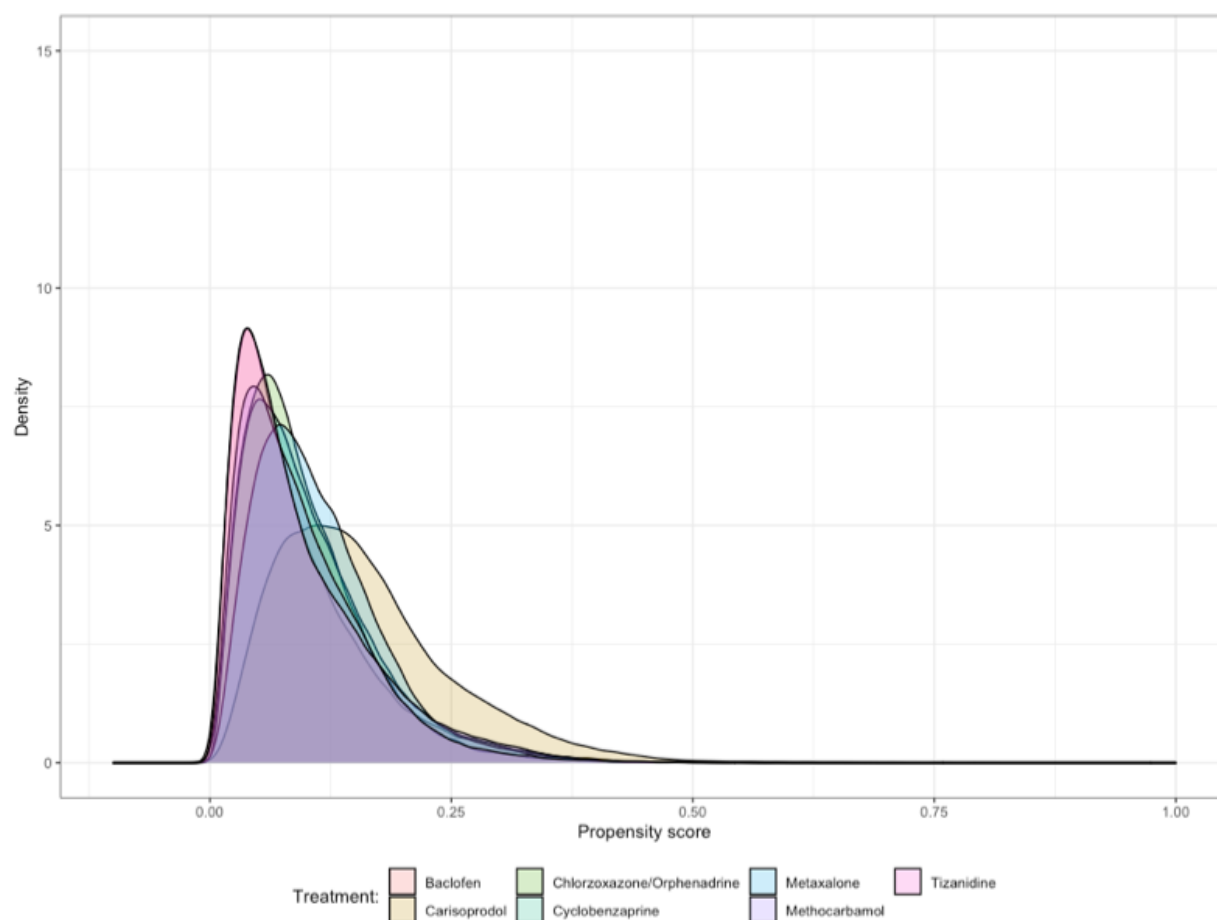
\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eFigure 8A. Propensity score distributions for treatment with baclofen before matching weights in IBM® MarketScan® Research Database**



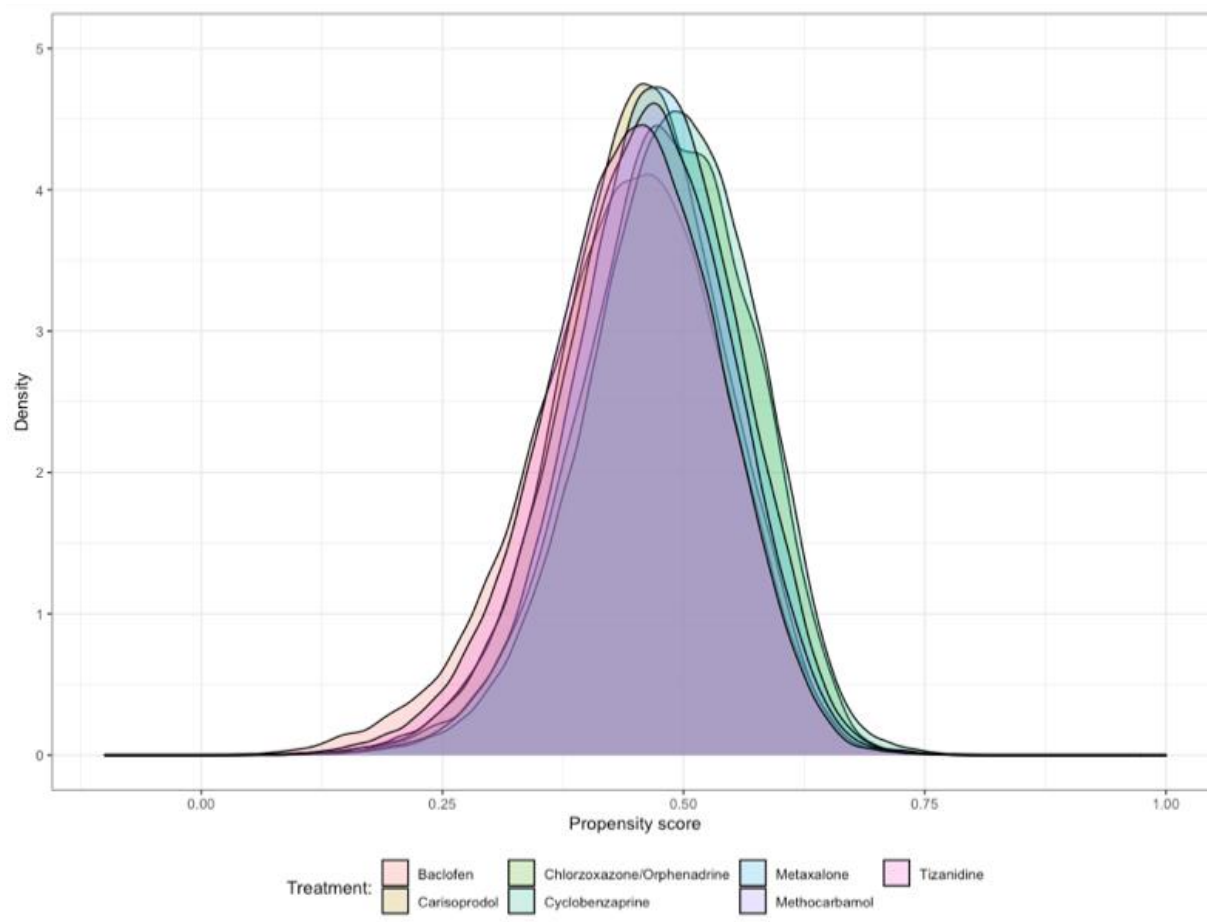
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 8B. Propensity score distributions for treatment with carisoprodol before matching weights in IBM® MarketScan® Research Database**



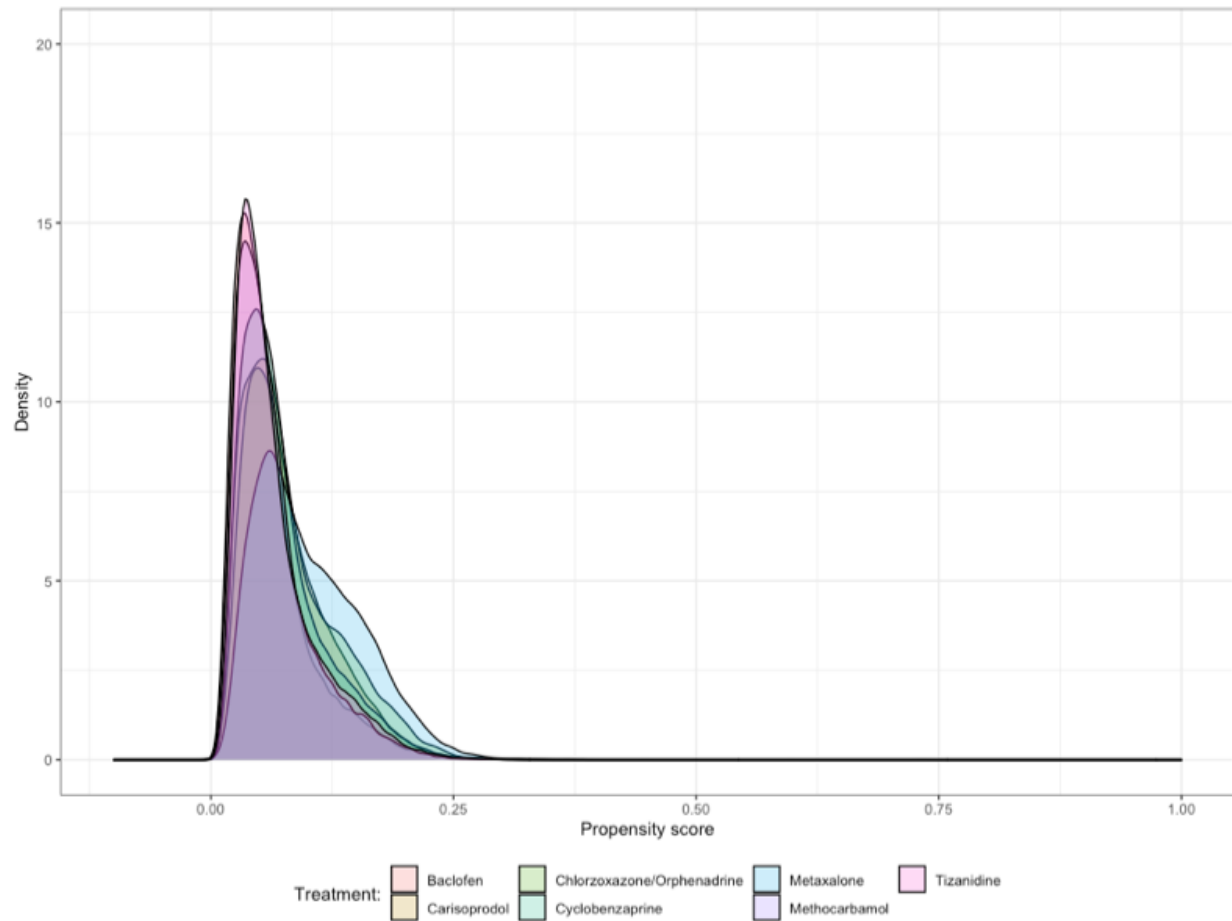
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 8C. Propensity score distributions for treatment with cyclobenzaprine before matching weights in IBM® MarketScan® Research Database**



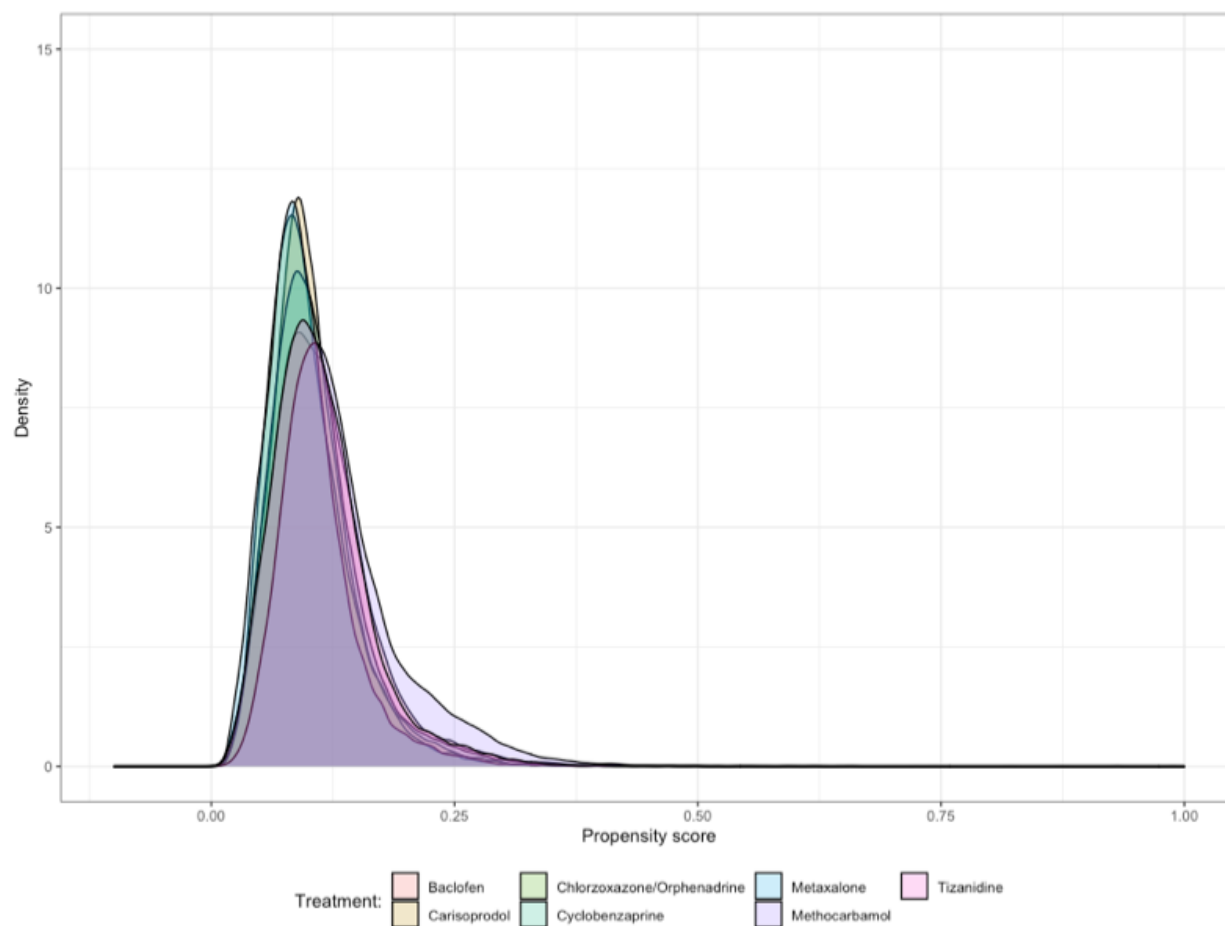
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 8D. Propensity score distributions for treatment with metaxalone before matching weights in IBM® MarketScan® Research Database**



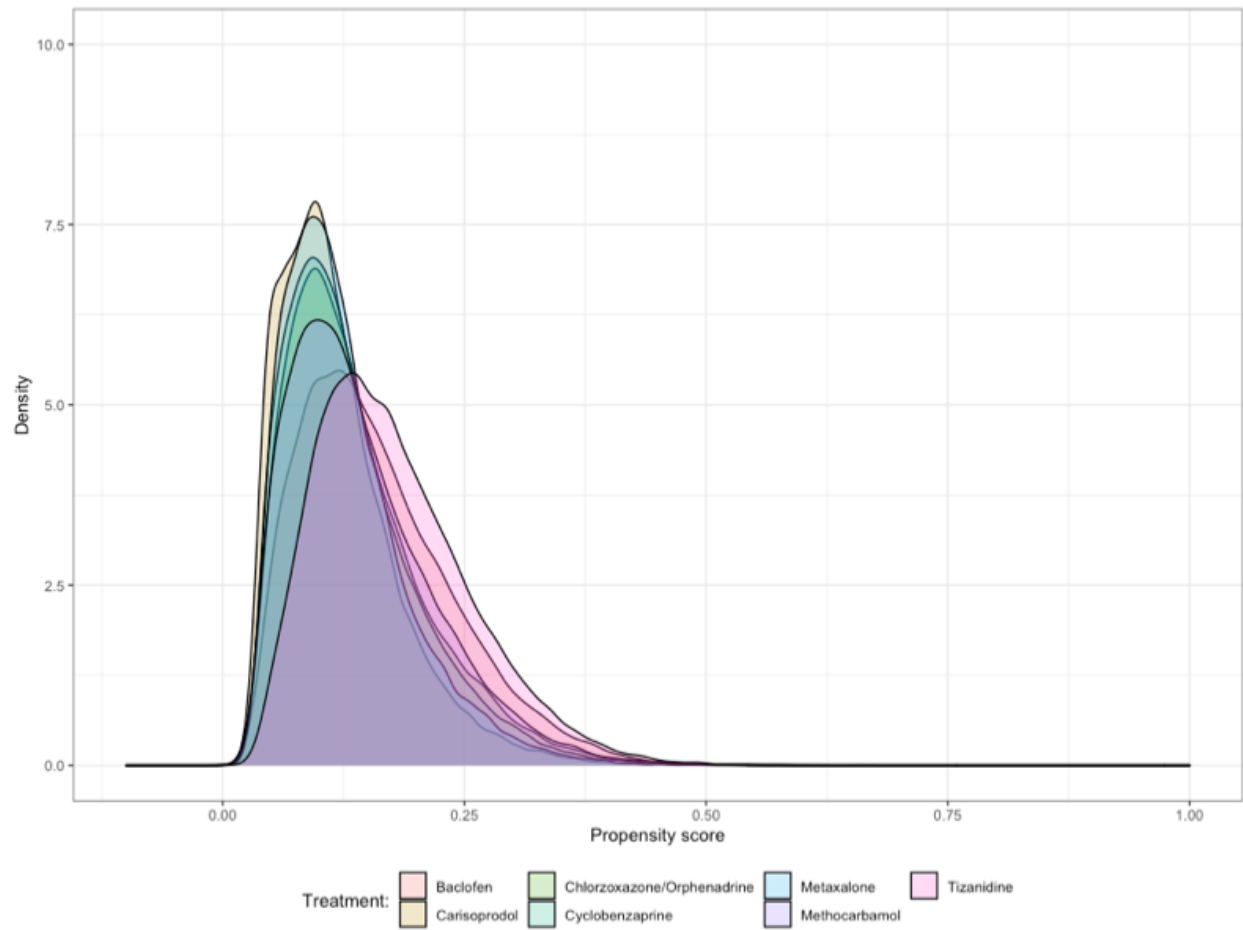
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 8E. Propensity score distributions for treatment with methocarbamol before matching weights in IBM® MarketScan® Research Database**



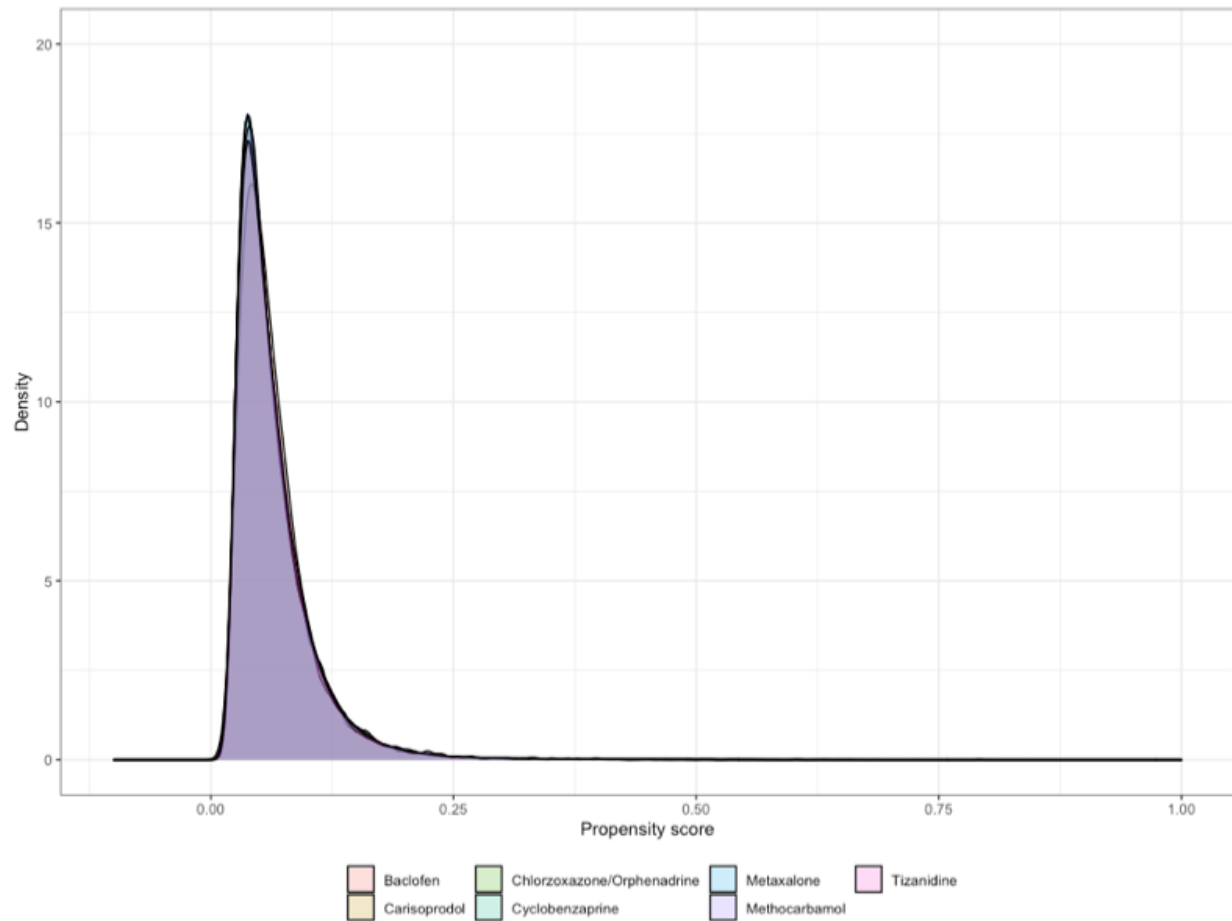
\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 8F. Propensity score distributions for treatment with tizanidine before matching weights in IBM® MarketScan® Research Database**



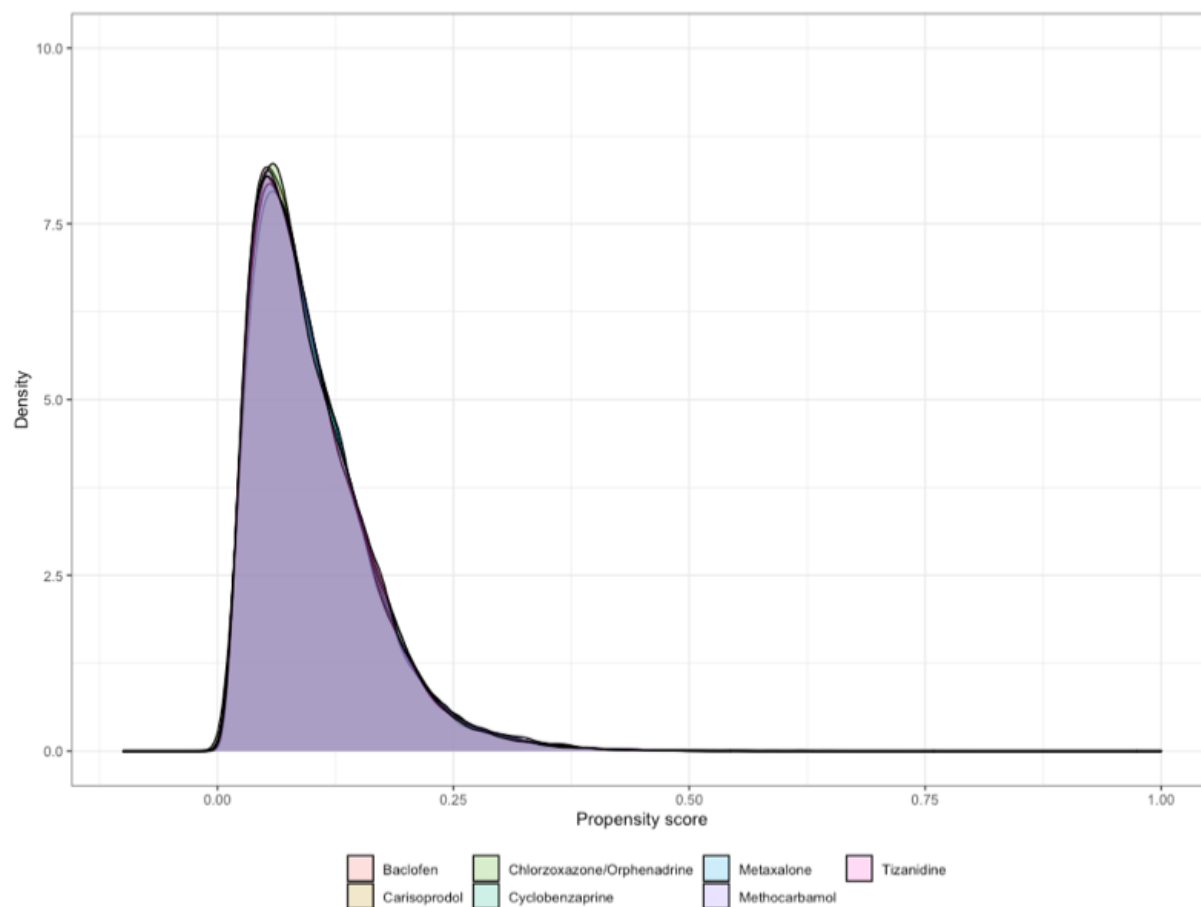
\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eFigure 9A. Propensity score distributions for treatment with baclofen after matching weights in IBM® MarketScan® Research Database**



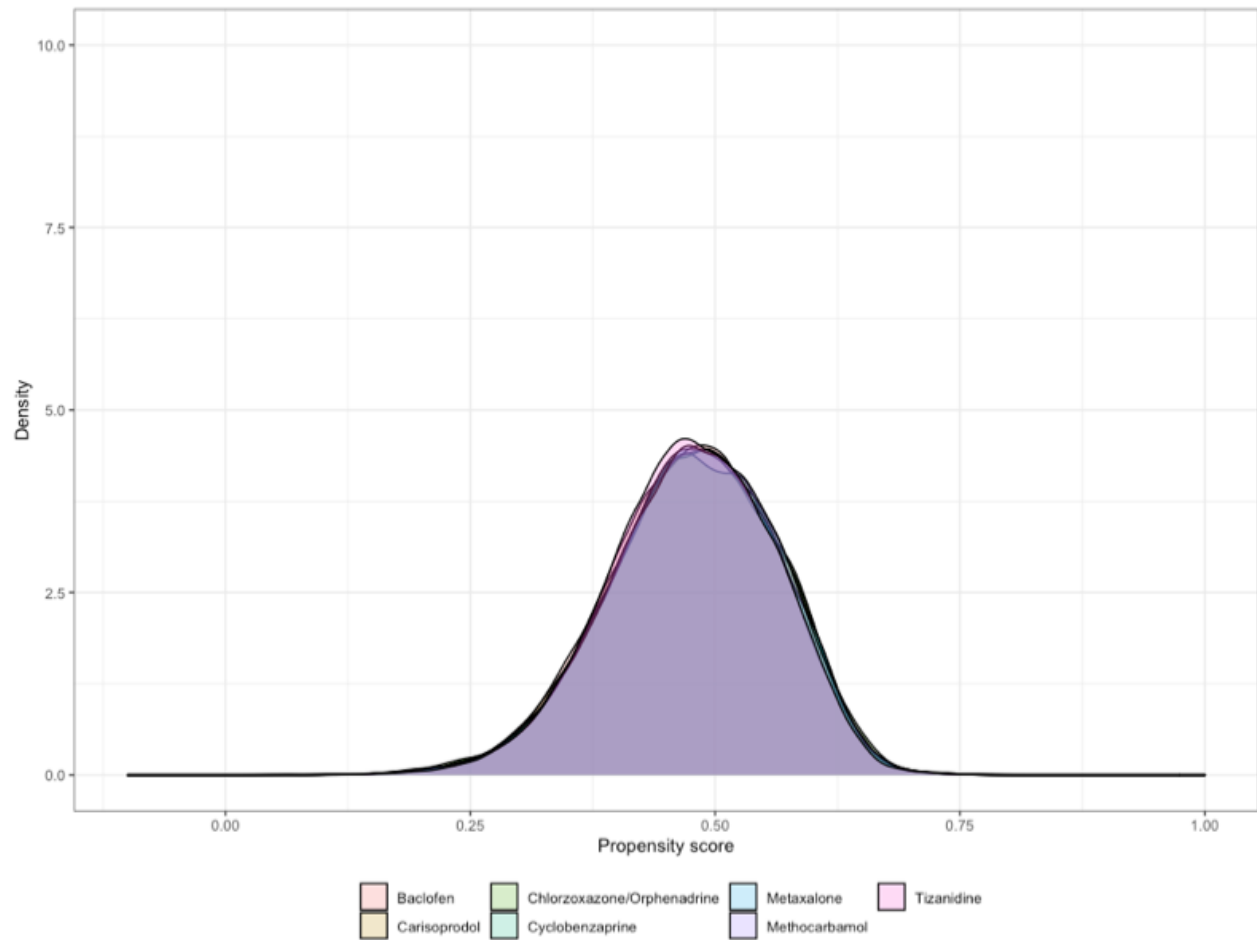
\*Plotted curves show the probability of receiving treatment with baclofen for each treatment group.

**eFigure 9B. Propensity score distributions for treatment with carisoprodol after matching weights in IBM® MarketScan® Research Database**



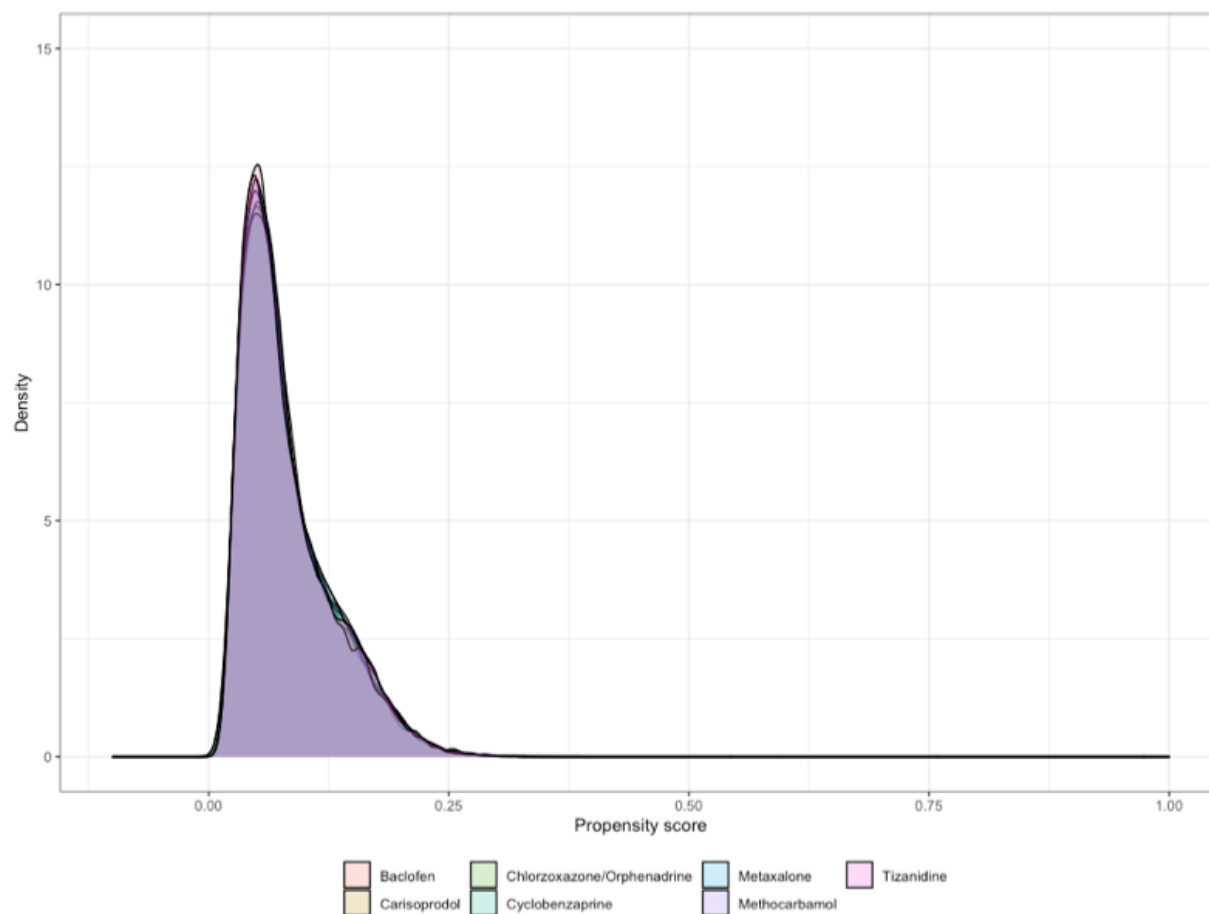
\*Plotted curves show the probability of receiving treatment with carisoprodol for each treatment group.

**eFigure 9C. Propensity score distributions for treatment with cyclobenzaprine after matching weights in IBM® MarketScan® Research Database**



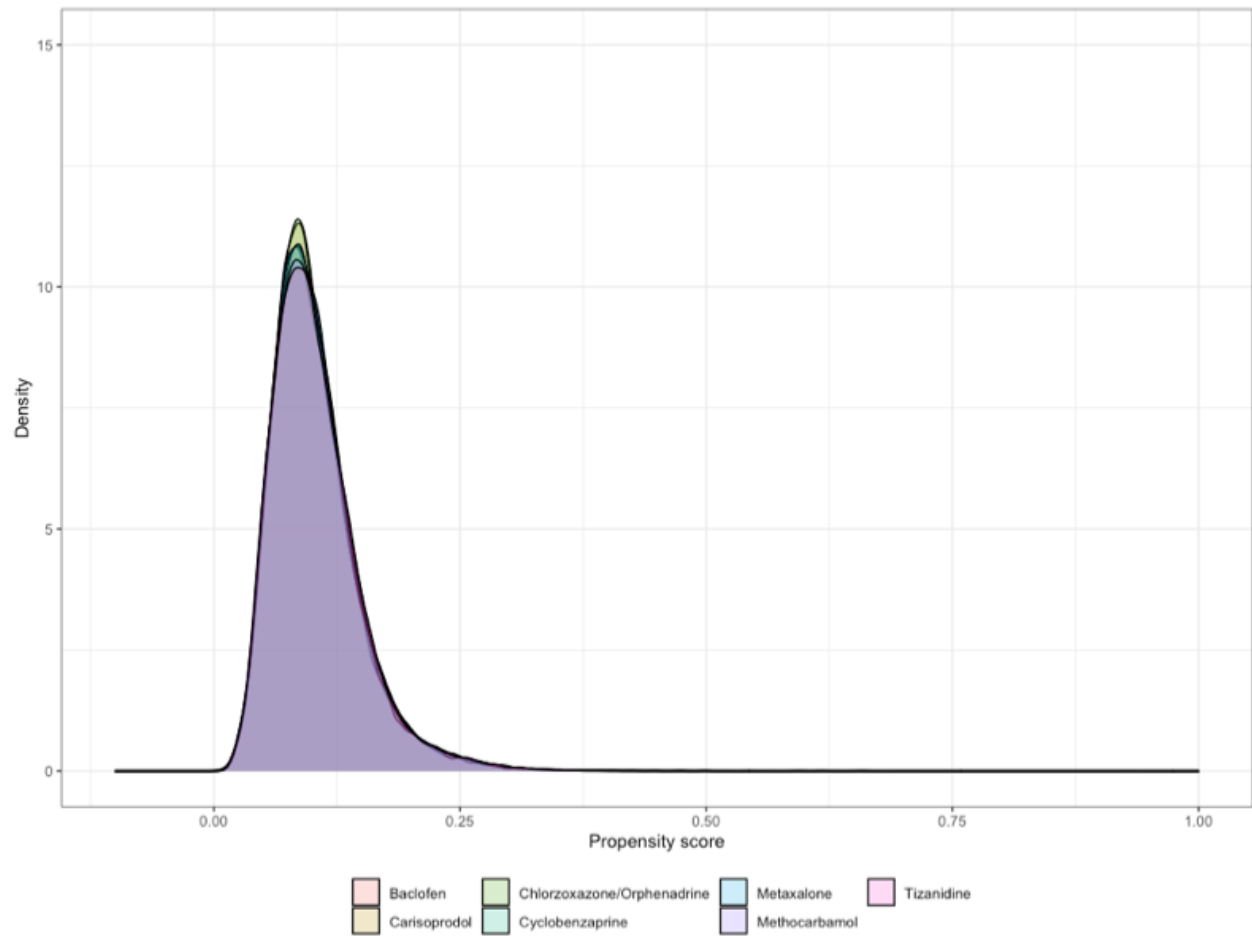
\*Plotted curves show the probability of receiving treatment with cyclobenzaprine for each treatment group.

**eFigure 9D. Propensity score distributions for treatment with metaxalone after matching weights in IBM® MarketScan® Research Database**



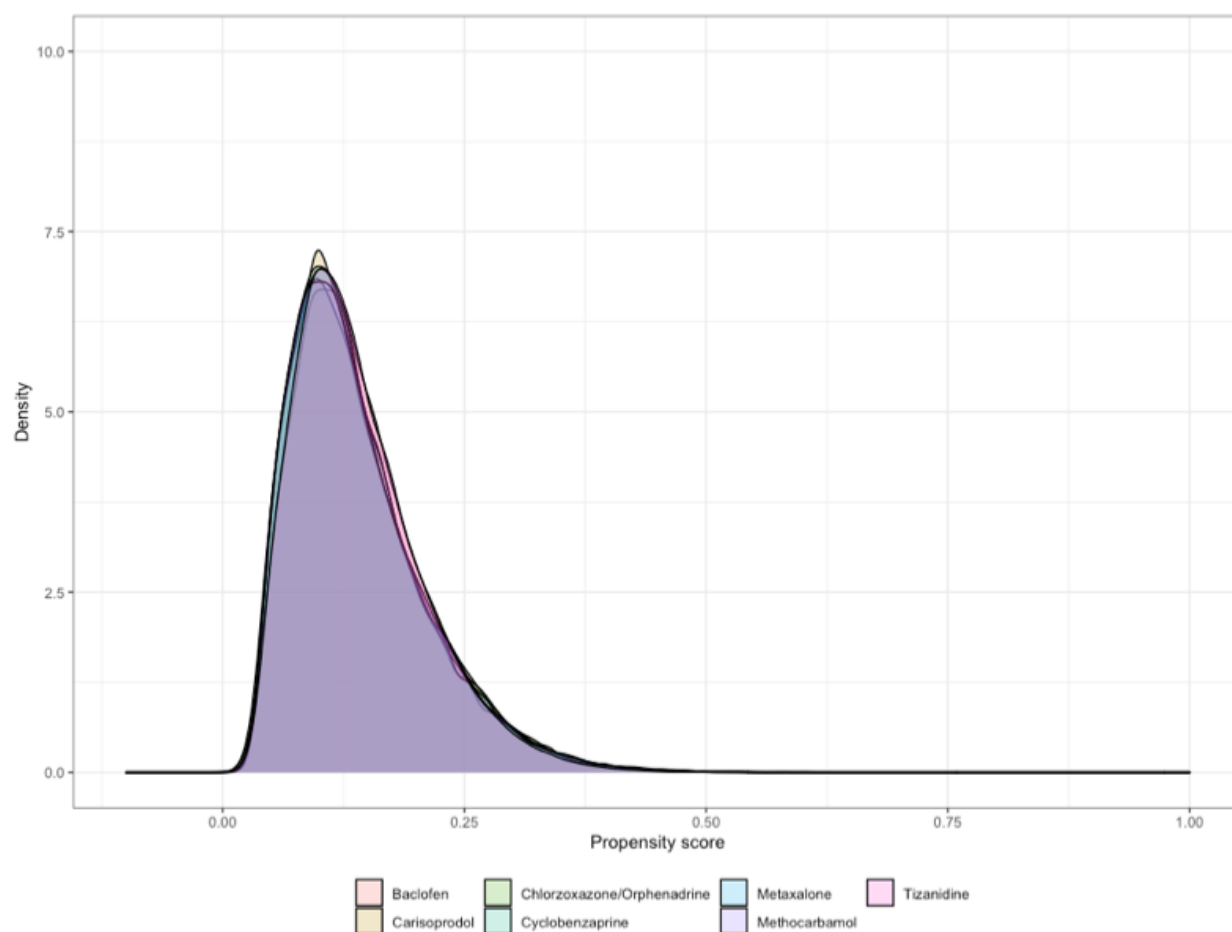
\*Plotted curves show the probability of receiving treatment with metaxalone for each treatment group.

**eFigure 9E. Propensity score distributions for treatment with methocarbamol after matching weights in IBM® MarketScan® Research Database**



\*Plotted curves show the probability of receiving treatment with methocarbamol for each treatment group.

**eFigure 9F. Propensity score distributions for treatment with tizanidine after matching weights in IBM® MarketScan® Research Database**



\*Plotted curves show the probability of receiving treatment with tizanidine for each treatment group.

**eTable 1. ICD-9-CM and ICD-10-CM code definitions for opioid overdose in claims data**

| ICD-9-CM definition |                                                             | ICD-10-CM definition (ending in A, D, or S)  |                                        |
|---------------------|-------------------------------------------------------------|----------------------------------------------|----------------------------------------|
| 965.00              | Poisoning by opium (alkaloids) unspecified                  | T40.0X1x<br>T40.0X2x<br>T40.0X3x<br>T40.0X4x | Poisoning by opium                     |
| 965.02              | Poisoning by methadone                                      | T40.2X1x<br>T40.2X2x<br>T40.2X3x<br>T40.2X4x | Poisoning by other opioids             |
| 965.09              | Poisoning by other opiates and related narcotics            | T40.3X1x<br>T40.3X2x<br>T40.3X3x<br>T40.3X4x | Poisoning by methadone                 |
| E850.1              | Accidental poisoning by methadone                           | T40.4X1x<br>T40.4X2x<br>T40.4X3x<br>T40.4X4x | Poisoning by other synthetic narcotics |
| E850.2              | Accidental poisoning by other opiates and related narcotics | T40.601x<br>T40.602x<br>T40.603x<br>T40.604x | Poisoning by unspecified narcotics     |
|                     |                                                             | T40.691x<br>T40.692x<br>T40.693x<br>T40.694x | Poisoning by other narcotics           |

**eTable 2. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy, pooled (pre-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 136650        | 117633        | 32152                          | 552649          | 67435         | 124662        | 214838        |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 59.34 (14.98) | 51.76 (13.78) | 52.10 (14.68)                  | 54.14 (14.31)   | 52.59 (14.10) | 54.70 (14.66) | 57.83 (14.54) | 0.239 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.042 |
| Unknown                                | 73 (0.1)      | 31 (0.0)      | 16 (0.0)                       | 174 (0.0)       | 16 (0.0)      | 35 (0.0)      | 35 (0.0)      |       |
| Male                                   | 52401 (38.3)  | 47041 (40.0)  | 11695 (36.4)                   | 205548 (37.2)   | 23989 (35.6)  | 48784 (39.1)  | 79394 (37.0)  |       |
| Female                                 | 84176 (61.6)  | 70561 (60.0)  | 20441 (63.6)                   | 346927 (62.8)   | 43430 (64.4)  | 75843 (60.8)  | 135409 (63.0) |       |
| Race                                   |               |               |                                |                 |               |               |               | 0.174 |
| Unknown                                | 71978 (52.7)  | 84503 (71.8)  | 21025 (65.4)                   | 381487 (69.0)   | 50299 (74.6)  | 86204 (69.2)  | 144688 (67.3) |       |
| Asian                                  | 926 (0.7)     | 414 (0.4)     | 132 (0.4)                      | 2479 (0.4)      | 192 (0.3)     | 522 (0.4)     | 612 (0.3)     |       |
| Black                                  | 9407 (6.9)    | 5050 (4.3)    | 1472 (4.6)                     | 26035 (4.7)     | 2220 (3.3)    | 5398 (4.3)    | 8957 (4.2)    |       |
| White                                  | 49325 (36.1)  | 25886 (22.0)  | 8994 (28.0)                    | 134294 (24.3)   | 13812 (20.5)  | 30846 (24.7)  | 58144 (27.1)  |       |
| Other                                  | 5014 (3.7)    | 1780 (1.5)    | 529 (1.6)                      | 8354 (1.5)      | 912 (1.4)     | 1692 (1.4)    | 2437 (1.1)    |       |
| Ethnicity                              |               |               |                                |                 |               |               |               | 0.167 |
| Unknown                                | 73388 (53.7)  | 85399 (72.6)  | 21277 (66.2)                   | 384991 (69.7)   | 50829 (75.4)  | 86857 (69.7)  | 145738 (67.8) |       |
| Hispanic                               | 2740 (2.0)    | 704 (0.6)     | 235 (0.7)                      | 4146 (0.8)      | 341 (0.5)     | 876 (0.7)     | 1108 (0.5)    |       |
| Non-Hispanic                           | 60522 (44.3)  | 31530 (26.8)  | 10640 (33.1)                   | 163512 (29.6)   | 16265 (24.1)  | 36929 (29.6)  | 67992 (31.6)  |       |
| State                                  |               |               |                                |                 |               |               |               | 0.523 |
| AK                                     | 131 (0.1)     | 189 (0.2)     | 28 (0.1)                       | 812 (0.1)       | 56 (0.1)      | 134 (0.1)     | 419 (0.2)     |       |
| AL                                     | 3264 (2.4)    | 2589 (2.2)    | 771 (2.4)                      | 13283 (2.4)     | 1410 (2.1)    | 6915 (5.5)    | 9163 (4.3)    |       |
| AR                                     | 1239 (0.9)    | 1611 (1.4)    | 260 (0.8)                      | 5883 (1.1)      | 578 (0.9)     | 1128 (0.9)    | 3477 (1.6)    |       |
| AZ                                     | 3012 (2.2)    | 3648 (3.1)    | 414 (1.3)                      | 9324 (1.7)      | 1003 (1.5)    | 2622 (2.1)    | 4044 (1.9)    |       |
| CA                                     | 27527 (20.1)  | 16908 (14.4)  | 624 (1.9)                      | 31745 (5.7)     | 2496 (3.7)    | 8624 (6.9)    | 7386 (3.4)    |       |
| CO                                     | 1645 (1.2)    | 1441 (1.2)    | 387 (1.2)                      | 8226 (1.5)      | 985 (1.5)     | 1851 (1.5)    | 3163 (1.5)    |       |
| CT                                     | 1062 (0.8)    | 1393 (1.2)    | 241 (0.7)                      | 6574 (1.2)      | 1006 (1.5)    | 2159 (1.7)    | 1192 (0.6)    |       |
| DC                                     | 80 (0.1)      | 47 (0.0)      | 38 (0.1)                       | 582 (0.1)       | 41 (0.1)      | 53 (0.0)      | 89 (0.0)      |       |
| DE                                     | 247 (0.2)     | 487 (0.4)     | 78 (0.2)                       | 1970 (0.4)      | 439 (0.7)     | 132 (0.1)     | 911 (0.4)     |       |
| FL                                     | 10278 (7.5)   | 9062 (7.7)    | 1750 (5.4)                     | 33019 (6.0)     | 4736 (7.0)    | 9074 (7.3)    | 15934 (7.4)   |       |
| GA                                     | 5218 (3.8)    | 7849 (6.7)    | 1168 (3.6)                     | 25666 (4.6)     | 3249 (4.8)    | 5881 (4.7)    | 14514 (6.8)   |       |
| HI                                     | 142 (0.1)     | 248 (0.2)     | 36 (0.1)                       | 442 (0.1)       | 27 (0.0)      | 81 (0.1)      | 157 (0.1)     |       |
| IA                                     | 919 (0.7)     | 262 (0.2)     | 197 (0.6)                      | 4548 (0.8)      | 555 (0.8)     | 573 (0.5)     | 1207 (0.6)    |       |
| ID                                     | 735 (0.5)     | 836 (0.7)     | 171 (0.5)                      | 3542 (0.6)      | 247 (0.4)     | 1074 (0.9)    | 1124 (0.5)    |       |
| IL                                     | 3859 (2.8)    | 2280 (1.9)    | 2921 (9.1)                     | 26522 (4.8)     | 1856 (2.8)    | 3350 (2.7)    | 4841 (2.3)    |       |
| IN                                     | 4083 (3.0)    | 2302 (2.0)    | 2066 (6.4)                     | 24766 (4.5)     | 2884 (4.3)    | 3607 (2.9)    | 8183 (3.8)    |       |
| KS                                     | 886 (0.6)     | 642 (0.5)     | 378 (1.2)                      | 5040 (0.9)      | 529 (0.8)     | 692 (0.6)     | 1361 (0.6)    |       |
| KY                                     | 3146 (2.3)    | 1012 (0.9)    | 654 (2.0)                      | 11411 (2.1)     | 1596 (2.4)    | 3135 (2.5)    | 6497 (3.0)    |       |
| LA                                     | 2139 (1.6)    | 4513 (3.8)    | 1246 (3.9)                     | 13115 (2.4)     | 1510 (2.2)    | 3996 (3.2)    | 5546 (2.6)    |       |
| MA                                     | 1127 (0.8)    | 430 (0.4)     | 161 (0.5)                      | 3580 (0.6)      | 274 (0.4)     | 480 (0.4)     | 1353 (0.6)    |       |
| MD                                     | 1216 (0.9)    | 1621 (1.4)    | 298 (0.9)                      | 7975 (1.4)      | 1793 (2.7)    | 989 (0.8)     | 1985 (0.9)    |       |
| ME                                     | 769 (0.6)     | 208 (0.2)     | 126 (0.4)                      | 4852 (0.9)      | 190 (0.3)     | 578 (0.5)     | 689 (0.3)     |       |
| MI                                     | 4560 (3.3)    | 3961 (3.4)    | 1722 (5.4)                     | 22606 (4.1)     | 3955 (5.9)    | 4532 (3.6)    | 4881 (2.3)    |       |
| MN                                     | 630 (0.5)     | 415 (0.4)     | 283 (0.9)                      | 5469 (1.0)      | 275 (0.4)     | 1150 (0.9)    | 1314 (0.6)    |       |
| MO                                     | 4608 (3.4)    | 4508 (3.8)    | 1938 (6.0)                     | 23758 (4.3)     | 3048 (4.5)    | 3845 (3.1)    | 7907 (3.7)    |       |
| MS                                     | 1226 (0.9)    | 1753 (1.5)    | 358 (1.1)                      | 6008 (1.1)      | 893 (1.3)     | 1786 (1.4)    | 3923 (1.8)    |       |
| MT                                     | 306 (0.2)     | 184 (0.2)     | 92 (0.3)                       | 1714 (0.3)      | 232 (0.3)     | 609 (0.5)     | 428 (0.2)     |       |
| NC                                     | 5269 (3.9)    | 4862 (4.1)    | 1655 (5.1)                     | 26122 (4.7)     | 4216 (6.3)    | 4966 (4.0)    | 10755 (5.0)   |       |
| ND                                     | 108 (0.1)     | 53 (0.0)      | 48 (0.1)                       | 705 (0.1)       | 45 (0.1)      | 67 (0.1)      | 163 (0.1)     |       |
| NE                                     | 309 (0.2)     | 170 (0.1)     | 82 (0.3)                       | 2358 (0.4)      | 312 (0.5)     | 126 (0.1)     | 641 (0.3)     |       |

|                              | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|------------------------------|--------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| NH                           | 360 (0.3)    | 257 (0.2)    | 102 (0.3)                      | 2305 (0.4)      | 233 (0.3)   | 266 (0.2)     | 687 (0.3)    |       |
| NJ                           | 1277 (0.9)   | 1127 (1.0)   | 336 (1.0)                      | 6790 (1.2)      | 1378 (2.0)  | 522 (0.4)     | 2646 (1.2)   |       |
| NM                           | 1391 (1.0)   | 674 (0.6)    | 248 (0.8)                      | 3062 (0.6)      | 199 (0.3)   | 946 (0.8)     | 1251 (0.6)   |       |
| NV                           | 1112 (0.8)   | 2512 (2.1)   | 98 (0.3)                       | 3473 (0.6)      | 356 (0.5)   | 1072 (0.9)    | 2148 (1.0)   |       |
| NY                           | 5010 (3.7)   | 3312 (2.8)   | 911 (2.8)                      | 20685 (3.7)     | 3044 (4.5)  | 3801 (3.0)    | 6337 (2.9)   |       |
| OH                           | 3933 (2.9)   | 2631 (2.2)   | 2072 (6.4)                     | 25645 (4.6)     | 3172 (4.7)  | 6334 (5.1)    | 12507 (5.8)  |       |
| OK                           | 2446 (1.8)   | 2946 (2.5)   | 843 (2.6)                      | 11011 (2.0)     | 942 (1.4)   | 1656 (1.3)    | 5185 (2.4)   |       |
| OR                           | 1373 (1.0)   | 578 (0.5)    | 101 (0.3)                      | 5781 (1.0)      | 437 (0.6)   | 1220 (1.0)    | 2103 (1.0)   |       |
| PA                           | 2881 (2.1)   | 3027 (2.6)   | 788 (2.5)                      | 15434 (2.8)     | 2495 (3.7)  | 2685 (2.2)    | 3087 (1.4)   |       |
| RI                           | 416 (0.3)    | 468 (0.4)    | 85 (0.3)                       | 2340 (0.4)      | 283 (0.4)   | 369 (0.3)     | 415 (0.2)    |       |
| SC                           | 2720 (2.0)   | 3219 (2.7)   | 768 (2.4)                      | 15709 (2.8)     | 1996 (3.0)  | 1826 (1.5)    | 6783 (3.2)   |       |
| SD                           | 244 (0.2)    | 95 (0.1)     | 58 (0.2)                       | 1079 (0.2)      | 90 (0.1)    | 117 (0.1)     | 172 (0.1)    |       |
| TN                           | 4772 (3.5)   | 5524 (4.7)   | 1441 (4.5)                     | 20511 (3.7)     | 2120 (3.1)  | 7371 (5.9)    | 8538 (4.0)   |       |
| TX                           | 9408 (6.9)   | 9876 (8.4)   | 1852 (5.8)                     | 38923 (7.0)     | 5063 (7.5)  | 10557 (8.5)   | 21800 (10.1) |       |
| UT                           | 816 (0.6)    | 1089 (0.9)   | 140 (0.4)                      | 3572 (0.6)      | 332 (0.5)   | 1036 (0.8)    | 1858 (0.9)   |       |
| VA                           | 2365 (1.7)   | 1520 (1.3)   | 978 (3.0)                      | 11649 (2.1)     | 1766 (2.6)  | 2316 (1.9)    | 3895 (1.8)   |       |
| VT                           | 289 (0.2)    | 108 (0.1)    | 71 (0.2)                       | 2012 (0.4)      | 101 (0.1)   | 544 (0.4)     | 358 (0.2)    |       |
| WA                           | 2306 (1.7)   | 1128 (1.0)   | 95 (0.3)                       | 8478 (1.5)      | 419 (0.6)   | 4291 (3.4)    | 3446 (1.6)   |       |
| WI                           | 2052 (1.5)   | 858 (0.7)    | 422 (1.3)                      | 10493 (1.9)     | 1005 (1.5)  | 809 (0.6)     | 4629 (2.2)   |       |
| WV                           | 1586 (1.2)   | 1083 (0.9)   | 476 (1.5)                      | 10950 (2.0)     | 1472 (2.2)  | 2628 (2.1)    | 3555 (1.7)   |       |
| WY                           | 153 (0.1)    | 117 (0.1)    | 76 (0.2)                       | 1130 (0.2)      | 96 (0.1)    | 87 (0.1)      | 191 (0.1)    |       |
| Year                         |              |              |                                |                 |             |               |              | 0.556 |
| 2000                         | 439 (0.3)    | 1125 (1.0)   | 366 (1.1)                      | 1936 (0.4)      | 432 (0.6)   | 422 (0.3)     | 353 (0.2)    |       |
| 2001                         | 1000 (0.7)   | 2255 (1.9)   | 628 (2.0)                      | 3996 (0.7)      | 1238 (1.8)  | 853 (0.7)     | 1364 (0.6)   |       |
| 2002                         | 1043 (0.8)   | 2005 (1.7)   | 540 (1.7)                      | 3911 (0.7)      | 1528 (2.3)  | 799 (0.6)     | 1644 (0.8)   |       |
| 2003                         | 2101 (1.5)   | 4770 (4.1)   | 1032 (3.2)                     | 9942 (1.8)      | 3142 (4.7)  | 2126 (1.7)    | 2766 (1.3)   |       |
| 2004                         | 3417 (2.5)   | 7829 (6.7)   | 2059 (6.4)                     | 22234 (4.0)     | 4962 (7.4)  | 5399 (4.3)    | 4962 (2.3)   |       |
| 2005                         | 3123 (2.3)   | 6842 (5.8)   | 1683 (5.2)                     | 19634 (3.6)     | 5071 (7.5)  | 3744 (3.0)    | 4365 (2.0)   |       |
| 2006                         | 3411 (2.5)   | 7416 (6.3)   | 1700 (5.3)                     | 21672 (3.9)     | 5572 (8.3)  | 4186 (3.4)    | 4872 (2.3)   |       |
| 2007                         | 3907 (2.9)   | 7588 (6.5)   | 1826 (5.7)                     | 23991 (4.3)     | 5821 (8.6)  | 4897 (3.9)    | 5575 (2.6)   |       |
| 2008                         | 4560 (3.3)   | 9009 (7.7)   | 1922 (6.0)                     | 30676 (5.6)     | 5953 (8.8)  | 5802 (4.7)    | 6474 (3.0)   |       |
| 2009                         | 5772 (4.2)   | 10547 (9.0)  | 2280 (7.1)                     | 38764 (7.0)     | 5347 (7.9)  | 7411 (5.9)    | 8107 (3.8)   |       |
| 2010                         | 6258 (4.6)   | 10325 (8.8)  | 2345 (7.3)                     | 41245 (7.5)     | 4668 (6.9)  | 8544 (6.9)    | 8511 (4.0)   |       |
| 2011                         | 7201 (5.3)   | 9958 (8.5)   | 2537 (7.9)                     | 47899 (8.7)     | 4644 (6.9)  | 10781 (8.6)   | 10593 (4.9)  |       |
| 2012                         | 11196 (8.2)  | 10057 (8.5)  | 3379 (10.5)                    | 60404 (10.9)    | 5126 (7.6)  | 14825 (11.9)  | 16864 (7.8)  |       |
| 2013                         | 13917 (10.2) | 9651 (8.2)   | 2570 (8.0)                     | 58507 (10.6)    | 4505 (6.7)  | 14560 (11.7)  | 19504 (9.1)  |       |
| 2014                         | 16087 (11.8) | 6704 (5.7)   | 2083 (6.5)                     | 41892 (7.6)     | 3400 (5.0)  | 11502 (9.2)   | 23002 (10.7) |       |
| 2015                         | 14728 (10.8) | 3949 (3.4)   | 1595 (5.0)                     | 31020 (5.6)     | 2258 (3.3)  | 8454 (6.8)    | 23253 (10.8) |       |
| 2016                         | 14244 (10.4) | 3281 (2.8)   | 1284 (4.0)                     | 25932 (4.7)     | 1756 (2.6)  | 8122 (6.5)    | 25929 (12.1) |       |
| 2017                         | 13165 (9.6)  | 2905 (2.5)   | 1132 (3.5)                     | 37098 (6.7)     | 1180 (1.7)  | 6699 (5.4)    | 23729 (11.0) |       |
| 2018                         | 6638 (4.9)   | 967 (0.8)    | 863 (2.7)                      | 20113 (3.6)     | 651 (1.0)   | 3845 (3.1)    | 13410 (6.2)  |       |
| 2019                         | 4443 (3.3)   | 450 (0.4)    | 328 (1.0)                      | 11783 (2.1)     | 181 (0.3)   | 1691 (1.4)    | 9561 (4.5)   |       |
| <b>Comorbidities (n (%))</b> |              |              |                                |                 |             |               |              |       |
| Opioid dependence            | 7592 (5.6)   | 3355 (2.9)   | 1028 (3.2)                     | 17964 (3.3)     | 1470 (2.2)  | 6151 (4.9)    | 12784 (6.0)  | 0.090 |
| Opioid abuse                 | 612 (0.4)    | 429 (0.4)    | 117 (0.4)                      | 1736 (0.3)      | 164 (0.2)   | 610 (0.5)     | 768 (0.4)    | 0.016 |
| Alcohol abuse                | 3354 (2.5)   | 2053 (1.7)   | 622 (1.9)                      | 11084 (2.0)     | 1089 (1.6)  | 3107 (2.5)    | 3698 (1.7)   | 0.029 |
| Tobacco use                  | 23612 (17.3) | 13564 (11.5) | 4141 (12.9)                    | 82410 (14.9)    | 6162 (9.1)  | 19404 (15.6)  | 37488 (17.4) | 0.109 |
| Other drug abuse             | 5550 (4.1)   | 4243 (3.6)   | 1212 (3.8)                     | 17444 (3.2)     | 1982 (2.9)  | 5511 (4.4)    | 7607 (3.5)   | 0.033 |
| Anxiety                      | 30194 (22.1) | 20232 (17.2) | 5910 (18.4)                    | 102594 (18.6)   | 9738 (14.4) | 24517 (19.7)  | 48513 (22.6) | 0.087 |
| Bipolar disorder             | 6027 (4.4)   | 4058 (3.4)   | 1308 (4.1)                     | 20840 (3.8)     | 2264 (3.4)  | 4908 (3.9)    | 8715 (4.1)   | 0.023 |
| Bone fracture                | 10919 (8.0)  | 6496 (5.5)   | 1960 (6.1)                     | 36104 (6.5)     | 3984 (5.9)  | 9163 (7.4)    | 14805 (6.9)  | 0.042 |
| Cancer                       | 11773 (8.6)  | 5888 (5.0)   | 1679 (5.2)                     | 35598 (6.4)     | 3753 (5.6)  | 7692 (6.2)    | 13894 (6.5)  | 0.055 |

|                                         | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone   | Methocarbamol | Tizanidine    | SMD   |
|-----------------------------------------|--------------|--------------|--------------------------------|-----------------|--------------|---------------|---------------|-------|
| Chronic renal insufficiency             | 14502 (10.6) | 4167 (3.5)   | 1415 (4.4)                     | 33575 (6.1)     | 2408 (3.6)   | 7515 (6.0)    | 19915 (9.3)   | 0.132 |
| Congestive heart failure                | 16311 (11.9) | 5783 (4.9)   | 1767 (5.5)                     | 37251 (6.7)     | 3118 (4.6)   | 8806 (7.1)    | 20175 (9.4)   | 0.117 |
| COPD/asthma/oxygen                      | 35864 (26.2) | 21000 (17.9) | 5750 (17.9)                    | 109745 (19.9)   | 10808 (16.0) | 24832 (19.9)  | 51027 (23.8)  | 0.105 |
| Dementia                                | 8085 (5.9)   | 1582 (1.3)   | 579 (1.8)                      | 12856 (2.3)     | 1133 (1.7)   | 3315 (2.7)    | 7343 (3.4)    | 0.099 |
| Depression                              | 34093 (24.9) | 22257 (18.9) | 6634 (20.6)                    | 115284 (20.9)   | 13372 (19.8) | 27319 (21.9)  | 48408 (22.5)  | 0.057 |
| Diabetes                                | 45831 (33.5) | 22026 (18.7) | 6698 (20.8)                    | 137137 (24.8)   | 12344 (18.3) | 30301 (24.3)  | 66475 (30.9)  | 0.164 |
| Epilepsy                                | 4873 (3.6)   | 2931 (2.5)   | 854 (2.7)                      | 12499 (2.3)     | 1562 (2.3)   | 3035 (2.4)    | 5295 (2.5)    | 0.027 |
| HIV                                     | 1212 (0.9)   | 837 (0.7)    | 188 (0.6)                      | 4106 (0.7)      | 405 (0.6)    | 821 (0.7)     | 1048 (0.5)    | 0.019 |
| Intentional self-harm                   | 120 (0.1)    | 82 (0.1)     | 21 (0.1)                       | 451 (0.1)       | 46 (0.1)     | 117 (0.1)     | 154 (0.1)     | 0.005 |
| Liver disease                           | 10622 (7.8)  | 6216 (5.3)   | 1604 (5.0)                     | 32024 (5.8)     | 3114 (4.6)   | 7017 (5.6)    | 12665 (5.9)   | 0.047 |
| Musculoskeletal injury                  | 11164 (8.2)  | 11185 (9.5)  | 3330 (10.4)                    | 56022 (10.1)    | 6609 (9.8)   | 12332 (9.9)   | 18028 (8.4)   | 0.034 |
| Multiple sclerosis                      | 3786 (2.8)   | 574 (0.5)    | 140 (0.4)                      | 2859 (0.5)      | 402 (0.6)    | 569 (0.5)     | 2016 (0.9)    | 0.067 |
| Obesity                                 | 18974 (13.9) | 8184 (7.0)   | 2545 (7.9)                     | 60043 (10.9)    | 4390 (6.5)   | 13878 (11.1)  | 30595 (14.2)  | 0.127 |
| Pneumonia                               | 6469 (4.7)   | 4038 (3.4)   | 1045 (3.3)                     | 19077 (3.5)     | 2225 (3.3)   | 4336 (3.5)    | 6875 (3.2)    | 0.026 |
| Psychosis                               | 4433 (3.2)   | 1811 (1.5)   | 624 (1.9)                      | 10243 (1.9)     | 1051 (1.6)   | 2569 (2.1)    | 4017 (1.9)    | 0.040 |
| Renal dysfunction                       | 18770 (13.7) | 7109 (6.0)   | 2268 (7.1)                     | 48279 (8.7)     | 4152 (6.2)   | 11048 (8.9)   | 25054 (11.7)  | 0.118 |
| Spasticity                              | 37565 (27.5) | 15937 (13.5) | 4642 (14.4)                    | 83754 (15.2)    | 9578 (14.2)  | 21184 (17.0)  | 42753 (19.9)  | 0.136 |
| Urinary calculus                        | 4790 (3.5)   | 3210 (2.7)   | 1055 (3.3)                     | 17784 (3.2)     | 1889 (2.8)   | 4049 (3.2)    | 7178 (3.3)    | 0.019 |
| Urinary tract infection                 | 21369 (15.6) | 11491 (9.8)  | 3699 (11.5)                    | 62169 (11.2)    | 6885 (10.2)  | 14165 (11.4)  | 25760 (12.0)  | 0.062 |
| <b>Pain conditions (n (%))</b>          |              |              |                                |                 |              |               |               |       |
| Abdominal pain                          | 27425 (20.1) | 19667 (16.7) | 6165 (19.2)                    | 102599 (18.6)   | 11826 (17.5) | 22797 (18.3)  | 38421 (17.9)  | 0.034 |
| Back and neck pain                      | 98716 (72.2) | 78661 (66.9) | 22297 (69.3)                   | 380207 (68.8)   | 46364 (68.8) | 91637 (73.5)  | 167491 (78.0) | 0.099 |
| Back pain without radiculopathy         | 89945 (65.8) | 73241 (62.3) | 20735 (64.5)                   | 350811 (63.5)   | 42641 (63.2) | 84927 (68.1)  | 151449 (70.5) | 0.074 |
| Back pain with radiculopathy            | 34078 (24.9) | 23430 (19.9) | 6332 (19.7)                    | 117106 (21.2)   | 13515 (20.0) | 32471 (26.0)  | 64857 (30.2)  | 0.109 |
| Dental pain                             | 1892 (1.4)   | 1998 (1.7)   | 680 (2.1)                      | 9137 (1.7)      | 966 (1.4)    | 1926 (1.5)    | 2173 (1.0)    | 0.032 |
| Diabetic neuropathy                     | 12999 (9.5)  | 3942 (3.4)   | 1313 (4.1)                     | 30499 (5.5)     | 2111 (3.1)   | 6733 (5.4)    | 19129 (8.9)   | 0.128 |
| Fibromyalgia                            | 18718 (13.7) | 14869 (12.6) | 4506 (14.0)                    | 69851 (12.6)    | 9825 (14.6)  | 15924 (12.8)  | 34142 (15.9)  | 0.041 |
| Headache                                | 21281 (15.6) | 18706 (15.9) | 5817 (18.1)                    | 86915 (15.7)    | 10689 (15.9) | 19203 (15.4)  | 36408 (16.9)  | 0.028 |
| Osteoarthritis                          | 42659 (31.2) | 25130 (21.4) | 7359 (22.9)                    | 143604 (26.0)   | 14893 (22.1) | 33039 (26.5)  | 66600 (31.0)  | 0.111 |
| Rheumatoid arthritis                    | 7506 (5.5)   | 4967 (4.2)   | 1523 (4.7)                     | 28914 (5.2)     | 3368 (5.0)   | 6025 (4.8)    | 12362 (5.8)   | 0.028 |
| Postherpetic neuralgia                  | 574 (0.4)    | 222 (0.2)    | 77 (0.2)                       | 1357 (0.2)      | 162 (0.2)    | 388 (0.3)     | 789 (0.4)     | 0.018 |
| Other arthritis                         | 85174 (62.3) | 59181 (50.3) | 17314 (53.9)                   | 310262 (56.1)   | 35357 (52.4) | 71317 (57.2)  | 128994 (60.0) | 0.105 |
| Other neuropathy                        | 56956 (41.7) | 38348 (32.6) | 10368 (32.2)                   | 189744 (34.3)   | 22406 (33.2) | 49870 (40.0)  | 98985 (46.1)  | 0.131 |
| Other unspecified pain                  | 69679 (51.0) | 32219 (27.4) | 10746 (33.4)                   | 209325 (37.9)   | 17455 (25.9) | 52230 (41.9)  | 118797 (55.3) | 0.288 |
| <b>Other prescription fills (n (%))</b> |              |              |                                |                 |              |               |               |       |
| Antibiotics                             | 82929 (60.7) | 70213 (59.7) | 19850 (61.7)                   | 332345 (60.1)   | 41070 (60.9) | 74509 (59.8)  | 125567 (58.4) | 0.026 |
| Anticonvulsants                         | 16721 (12.2) | 10910 (9.3)  | 3425 (10.7)                    | 50511 (9.1)     | 7362 (10.9)  | 11868 (9.5)   | 24078 (11.2)  | 0.045 |
| Antidepressants, SSRIs                  | 39515 (28.9) | 31296 (26.6) | 9158 (28.5)                    | 152541 (27.6)   | 19592 (29.1) | 34667 (27.8)  | 59653 (27.8)  | 0.023 |
| Antidepressants, SNRIs                  | 24202 (17.7) | 16022 (13.6) | 4928 (15.3)                    | 83279 (15.1)    | 11300 (16.8) | 19361 (15.5)  | 39822 (18.5)  | 0.056 |
| Antidepressants, TCAs                   | 14644 (10.7) | 11511 (9.8)  | 3487 (10.8)                    | 52242 (9.5)     | 6935 (10.3)  | 11815 (9.5)   | 21748 (10.1)  | 0.023 |
| Antidepressants, other                  | 27190 (19.9) | 18164 (15.4) | 5416 (16.8)                    | 91106 (16.5)    | 11576 (17.2) | 21813 (17.5)  | 40308 (18.8)  | 0.046 |
| Antidiabetics                           | 34847 (25.5) | 17763 (15.1) | 5538 (17.2)                    | 111402 (20.2)   | 10427 (15.5) | 24326 (19.5)  | 52005 (24.2)  | 0.124 |
| Antipsychotics, atypical                | 12166 (8.9)  | 7651 (6.5)   | 2496 (7.8)                     | 37357 (6.8)     | 4661 (6.9)   | 9005 (7.2)    | 15097 (7.0)   | 0.034 |
| Antipsychotics, typical                 | 4607 (3.4)   | 2967 (2.5)   | 895 (2.8)                      | 13362 (2.4)     | 1652 (2.4)   | 2810 (2.3)    | 4009 (1.9)    | 0.034 |
| Barbiturates                            | 831 (0.6)    | 867 (0.7)    | 211 (0.7)                      | 2429 (0.4)      | 513 (0.8)    | 668 (0.5)     | 675 (0.3)     | 0.027 |
| Benzodiazepines                         | 54969 (40.2) | 57955 (49.3) | 14245 (44.3)                   | 220416 (39.9)   | 29037 (43.1) | 50875 (40.8)  | 87060 (40.5)  | 0.075 |
| CNS stimulants                          | 3931 (2.9)   | 4165 (3.5)   | 1144 (3.6)                     | 16938 (3.1)     | 2279 (3.4)   | 4179 (3.4)    | 7055 (3.3)    | 0.017 |
| Dementia agents                         | 4097 (3.0)   | 1040 (0.9)   | 416 (1.3)                      | 7350 (1.3)      | 743 (1.1)    | 1958 (1.6)    | 4430 (2.1)    | 0.062 |
| Gabapentinoids                          | 53655 (39.3) | 26212 (22.3) | 8104 (25.2)                    | 152164 (27.5)   | 16852 (25.0) | 38348 (30.8)  | 82192 (38.3)  | 0.173 |
| Lithium                                 | 706 (0.5)    | 722 (0.6)    | 198 (0.6)                      | 2817 (0.5)      | 402 (0.6)    | 662 (0.5)     | 983 (0.5)     | 0.010 |
| Multiple sclerosis agents               | 1599 (1.2)   | 197 (0.2)    | 51 (0.2)                       | 1065 (0.2)      | 162 (0.2)    | 200 (0.2)     | 826 (0.4)     | 0.046 |
| NSAIDs                                  | 51715 (37.8) | 45633 (38.8) | 15557 (48.4)                   | 239559 (43.3)   | 31229 (46.3) | 54752 (43.9)  | 84637 (39.4)  | 0.099 |

|                                                                                       | Baclofen             | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine      | Metaxalone           | Methocarbamol        | Tizanidine           | SMD   |
|---------------------------------------------------------------------------------------|----------------------|----------------------|--------------------------------|----------------------|----------------------|----------------------|----------------------|-------|
| Other sedative hypnotics                                                              | 21533 (15.8)         | 22867 (19.4)         | 5417 (16.8)                    | 94724 (17.1)         | 13642 (20.2)         | 20903 (16.8)         | 34460 (16.0)         | 0.051 |
| Smoking cessation                                                                     | 11220 (8.2)          | 9684 (8.2)           | 2884 (9.0)                     | 48617 (8.8)          | 6453 (9.6)           | 10650 (8.5)          | 17901 (8.3)          | 0.020 |
| Triptans                                                                              | 5206 (3.8)           | 5900 (5.0)           | 1784 (5.5)                     | 25887 (4.7)          | 4090 (6.1)           | 5503 (4.4)           | 10357 (4.8)          | 0.041 |
| Other CNS depressants                                                                 | 701 (0.5)            | 497 (0.4)            | 130 (0.4)                      | 2161 (0.4)           | 346 (0.5)            | 421 (0.3)            | 1183 (0.6)           | 0.014 |
| <b>Prescription opioid utilization (n (%))</b>                                        |                      |                      |                                |                      |                      |                      |                      |       |
| Prescription opioid on index date                                                     |                      |                      |                                |                      |                      |                      |                      |       |
| Buprenorphine                                                                         | 752 (0.6)            | 453 (0.4)            | 168 (0.5)                      | 1984 (0.4)           | 263 (0.4)            | 912 (0.7)            | 1374 (0.6)           | 0.024 |
| Butorphanol                                                                           | 226 (0.2)            | 519 (0.4)            | 166 (0.5)                      | 1792 (0.3)           | 297 (0.4)            | 302 (0.2)            | 630 (0.3)            | 0.026 |
| Codeine                                                                               | 6391 (4.7)           | 6230 (5.3)           | 1818 (5.7)                     | 26163 (4.7)          | 3165 (4.7)           | 5798 (4.7)           | 6942 (3.2)           | 0.040 |
| Dihydrocodeine                                                                        | 47 (0.0)             | 155 (0.1)            | 54 (0.2)                       | 525 (0.1)            | 145 (0.2)            | 136 (0.1)            | 131 (0.1)            | 0.022 |
| Fentanyl                                                                              | 11406 (8.3)          | 7213 (6.1)           | 1860 (5.8)                     | 31230 (5.7)          | 5003 (7.4)           | 7367 (5.9)           | 14880 (6.9)          | 0.047 |
| Hydrocodone                                                                           | 67543 (49.4)         | 74535 (63.4)         | 19093 (59.4)                   | 320486 (58.0)        | 37539 (55.7)         | 72855 (58.4)         | 109578 (51.0)        | 0.118 |
| Hydromorphone                                                                         | 4218 (3.1)           | 2738 (2.3)           | 582 (1.8)                      | 10983 (2.0)          | 1234 (1.8)           | 3155 (2.5)           | 5159 (2.4)           | 0.036 |
| Levorphanol                                                                           | 36 (0.0)             | 8 (0.0)              | 6 (0.0)                        | 61 (0.0)             | 12 (0.0)             | 20 (0.0)             | 65 (0.0)             | 0.007 |
| Meperidine                                                                            | 210 (0.2)            | 576 (0.5)            | 103 (0.3)                      | 1474 (0.3)           | 220 (0.3)            | 401 (0.3)            | 390 (0.2)            | 0.024 |
| Methadone                                                                             | 6106 (4.5)           | 4200 (3.6)           | 885 (2.8)                      | 14515 (2.6)          | 1932 (2.9)           | 3475 (2.8)           | 7540 (3.5)           | 0.041 |
| Morphine                                                                              | 12739 (9.3)          | 7712 (6.6)           | 1788 (5.6)                     | 32579 (5.9)          | 4084 (6.1)           | 8370 (6.7)           | 18140 (8.4)          | 0.063 |
| Opium                                                                                 | 35 (0.0)             | 32 (0.0)             | 8 (0.0)                        | 209 (0.0)            | 26 (0.0)             | 47 (0.0)             | 47 (0.0)             | 0.005 |
| Oxycodone                                                                             | 45046 (33.0)         | 40200 (34.2)         | 9126 (28.4)                    | 174285 (31.5)        | 20398 (30.2)         | 42027 (33.7)         | 75236 (35.0)         | 0.061 |
| Oxymorphone                                                                           | 1626 (1.2)           | 1171 (1.0)           | 303 (0.9)                      | 4511 (0.8)           | 659 (1.0)            | 1189 (1.0)           | 3234 (1.5)           | 0.023 |
| Pentazocine                                                                           | 130 (0.1)            | 385 (0.3)            | 130 (0.4)                      | 1020 (0.2)           | 233 (0.3)            | 267 (0.2)            | 309 (0.1)            | 0.029 |
| Propoxyphene                                                                          | 561 (0.4)            | 2150 (1.8)           | 753 (2.3)                      | 8202 (1.5)           | 1621 (2.4)           | 1682 (1.3)           | 1270 (0.6)           | 0.082 |
| Tapentadol                                                                            | 948 (0.7)            | 530 (0.5)            | 224 (0.7)                      | 2998 (0.5)           | 405 (0.6)            | 957 (0.8)            | 2050 (1.0)           | 0.024 |
| Tramadol                                                                              | 26493 (19.4)         | 17100 (14.5)         | 7442 (23.1)                    | 120158 (21.7)        | 15977 (23.7)         | 26378 (21.2)         | 40159 (18.7)         | 0.093 |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 174.41 (16.22)       | 173.85 (16.96)       | 173.88 (16.78)                 | 173.81 (16.91)       | 173.40 (17.27)       | 173.65 (17.05)       | 175.16 (15.20)       | 0.040 |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                      |                      |                                |                      |                      |                      |                      |       |
| (Index - 180) to (index - 151)                                                        | 2041.52<br>(3269.98) | 2191.49<br>(3602.14) | 1723.45<br>(2923.87)           | 1660.02<br>(2773.02) | 1792.28<br>(3022.63) | 1689.71<br>(2790.32) | 1982.64<br>(3051.50) | 0.078 |
| (Index - 150) to (index - 121)                                                        | 2095.37<br>(3267.09) | 2257.69<br>(3592.06) | 1789.24<br>(2947.06)           | 1715.72<br>(2800.69) | 1862.07<br>(3054.63) | 1750.04<br>(2833.02) | 2031.11<br>(3076.34) | 0.078 |
| (Index - 120) to (index - 91)                                                         | 2280.98<br>(3401.67) | 2473.03<br>(3750.09) | 1927.07<br>(3069.97)           | 1855.53<br>(2855.79) | 2024.12<br>(3147.32) | 1889.60<br>(2879.86) | 2181.86<br>(3154.96) | 0.085 |
| (Index - 90) to (index - 61)                                                          | 2282.92<br>(3359.19) | 2489.72<br>(3762.64) | 1930.23<br>(3144.79)           | 1868.05<br>(2872.89) | 2050.27<br>(3169.38) | 1905.50<br>(2883.68) | 2179.47<br>(3155.05) | 0.084 |
| (Index - 60) to (index - 31)                                                          | 2283.46<br>(3402.36) | 2498.78<br>(3764.78) | 1941.61<br>(3146.19)           | 1876.66<br>(2880.58) | 2048.47<br>(3166.99) | 1925.09<br>(2915.54) | 2165.75<br>(3136.06) | 0.082 |
| (Index - 30) to index                                                                 | 2774.32<br>(4173.59) | 3205.55<br>(4834.63) | 2265.17<br>(3612.70)           | 2217.93<br>(3420.26) | 2448.39<br>(3789.77) | 2296.46<br>(3416.64) | 2706.55<br>(3977.95) | 0.104 |
| <b>Healthcare utilization (mean (SD))</b>                                             |                      |                      |                                |                      |                      |                      |                      |       |
| Number of physician visits                                                            | 10.12 (8.82)         | 8.19 (7.06)          | 8.64 (7.41)                    | 8.65 (7.39)          | 8.61 (7.21)          | 9.07 (7.51)          | 9.51 (7.27)          | 0.100 |
| Number of distinct prescribed medications                                             | 13.56 (6.35)         | 11.84 (6.19)         | 12.65 (6.43)                   | 12.38 (6.24)         | 12.58 (6.41)         | 12.53 (6.21)         | 12.86 (6.17)         | 0.095 |
| Number of hospitalizations                                                            | 0.33 (1.93)          | 0.23 (0.69)          | 0.21 (0.68)                    | 0.25 (1.03)          | 0.22 (0.72)          | 0.32 (1.12)          | 0.23 (1.10)          | 0.047 |
| Number of hospitalization days                                                        | 1.69 (35.76)         | 1.14 (4.47)          | 1.08 (4.01)                    | 1.24 (5.48)          | 1.17 (4.35)          | 1.61 (6.22)          | 1.17 (4.98)          | 0.032 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 3. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy, pooled (post-matching weights)**

|                                        | Baclofen       | Carisoprodol   | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone     | Methocarbamol  | Tizanidine     | SMD   |
|----------------------------------------|----------------|----------------|--------------------------------|-----------------|----------------|----------------|----------------|-------|
| n                                      | 24330.44       | 24693.74       | 24825.01                       | 24799.6         | 24765.06       | 24758.49       | 24646.45       |       |
| <b>Demographic information (n (%))</b> |                |                |                                |                 |                |                |                |       |
| Age (mean (SD))                        | 52.65 (14.58)  | 53.05 (13.96)  | 53.12 (14.52)                  | 53.12 (14.14)   | 52.88 (14.31)  | 53.12 (14.43)  | 52.43 (14.20)  | 0.022 |
| Sex                                    |                |                |                                |                 |                |                |                | 0.005 |
| Unknown                                | 5.0 (0.0)      | 5.6 (0.0)      | 4.1 (0.0)                      | 6.0 (0.0)       | 4.5 (0.0)      | 6.6 (0.0)      | 6.4 (0.0)      |       |
| Male                                   | 9243.9 (38.0)  | 9297.4 (37.7)  | 9409.5 (37.9)                  | 9424.0 (38.0)   | 9316.9 (37.6)  | 9387.6 (37.9)  | 9344.7 (37.9)  |       |
| Female                                 | 15081.5 (62.0) | 15390.7 (62.3) | 15411.4 (62.1)                 | 15369.6 (62.0)  | 15443.6 (62.4) | 15364.3 (62.1) | 15295.3 (62.1) |       |
| Race                                   |                |                |                                |                 |                |                |                | 0.015 |
| Unknown                                | 17475.1 (71.8) | 17592.6 (71.2) | 17735.2 (71.4)                 | 17702.2 (71.4)  | 17656.5 (71.3) | 17669.4 (71.4) | 17636.8 (71.6) |       |
| Asian                                  | 68.4 (0.3)     | 84.4 (0.3)     | 83.3 (0.3)                     | 77.7 (0.3)      | 83.2 (0.3)     | 77.8 (0.3)     | 76.1 (0.3)     |       |
| Black                                  | 770.7 (3.2)    | 857.8 (3.5)    | 887.6 (3.6)                    | 905.3 (3.7)     | 852.8 (3.4)    | 889.2 (3.6)    | 862.7 (3.5)    |       |
| White                                  | 5722.6 (23.5)  | 5805.1 (23.5)  | 5771.3 (23.2)                  | 5782.7 (23.3)   | 5830.3 (23.5)  | 5795.3 (23.4)  | 5759.2 (23.4)  |       |
| Other                                  | 293.6 (1.2)    | 353.8 (1.4)    | 347.6 (1.4)                    | 331.7 (1.3)     | 342.3 (1.4)    | 326.7 (1.3)    | 311.7 (1.3)    |       |
| Ethnicity                              |                |                |                                |                 |                |                |                | 0.009 |
| Unknown                                | 17637.5 (72.5) | 17783.9 (72.0) | 17909.6 (72.1)                 | 17876.8 (72.1)  | 17834.2 (72.0) | 17832.7 (72.0) | 17802.1 (72.2) |       |
| Hispanic                               | 112.6 (0.5)    | 141.1 (0.6)    | 151.0 (0.6)                    | 133.9 (0.5)     | 141.4 (0.6)    | 138.8 (0.6)    | 124.1 (0.5)    |       |
| Non-Hispanic                           | 6580.4 (27.0)  | 6768.7 (27.4)  | 6764.3 (27.2)                  | 6788.9 (27.4)   | 6789.5 (27.4)  | 6786.9 (27.4)  | 6720.3 (27.3)  |       |
| State                                  |                |                |                                |                 |                |                |                | 0.048 |
| AK                                     | 23.5 (0.1)     | 28.3 (0.1)     | 26.5 (0.1)                     | 26.4 (0.1)      | 27.8 (0.1)     | 25.6 (0.1)     | 27.3 (0.1)     |       |
| AL                                     | 582.5 (2.4)    | 611.1 (2.5)    | 664.5 (2.7)                    | 650.8 (2.6)     | 637.4 (2.6)    | 659.6 (2.7)    | 617.9 (2.5)    |       |
| AR                                     | 213.0 (0.9)    | 223.6 (0.9)    | 214.1 (0.9)                    | 216.9 (0.9)     | 211.6 (0.9)    | 228.2 (0.9)    | 235.8 (1.0)    |       |
| AZ                                     | 410.0 (1.7)    | 395.1 (1.6)    | 391.3 (1.6)                    | 399.5 (1.6)     | 409.8 (1.7)    | 413.0 (1.7)    | 349.3 (1.4)    |       |
| CA                                     | 611.0 (2.5)    | 638.0 (2.6)    | 620.1 (2.5)                    | 625.6 (2.5)     | 628.3 (2.5)    | 663.1 (2.7)    | 553.5 (2.2)    |       |
| CO                                     | 339.3 (1.4)    | 365.9 (1.5)    | 347.4 (1.4)                    | 352.5 (1.4)     | 363.5 (1.5)    | 334.1 (1.3)    | 371.8 (1.5)    |       |
| CT                                     | 204.1 (0.8)    | 280.4 (1.1)    | 224.8 (0.9)                    | 231.5 (0.9)     | 256.9 (1.0)    | 223.8 (0.9)    | 228.4 (0.9)    |       |
| DC                                     | 13.8 (0.1)     | 13.2 (0.1)     | 13.1 (0.1)                     | 13.7 (0.1)      | 15.9 (0.1)     | 13.6 (0.1)     | 11.7 (0.0)     |       |
| DE                                     | 67.4 (0.3)     | 71.1 (0.3)     | 71.9 (0.3)                     | 73.2 (0.3)      | 74.9 (0.3)     | 73.3 (0.3)     | 77.3 (0.3)     |       |
| FL                                     | 1642.6 (6.8)   | 1617.5 (6.6)   | 1661.6 (6.7)                   | 1658.3 (6.7)    | 1590.9 (6.4)   | 1660.7 (6.7)   | 1700.0 (6.9)   |       |
| GA                                     | 1002.2 (4.1)   | 1011.0 (4.1)   | 1023.4 (4.1)                   | 1023.2 (4.1)    | 993.3 (4.0)    | 1036.1 (4.2)   | 1049.2 (4.3)   |       |
| HI                                     | 20.2 (0.1)     | 21.5 (0.1)     | 23.8 (0.1)                     | 22.3 (0.1)      | 21.9 (0.1)     | 22.0 (0.1)     | 20.9 (0.1)     |       |
| IA                                     | 164.9 (0.7)    | 176.5 (0.7)    | 170.5 (0.7)                    | 166.4 (0.7)     | 170.8 (0.7)    | 165.3 (0.7)    | 164.8 (0.7)    |       |
| ID                                     | 146.4 (0.6)    | 150.5 (0.6)    | 150.6 (0.6)                    | 145.7 (0.6)     | 143.6 (0.6)    | 143.4 (0.6)    | 155.5 (0.6)    |       |
| IL                                     | 928.8 (3.8)    | 1018.7 (4.1)   | 967.2 (3.9)                    | 965.3 (3.9)     | 967.1 (3.9)    | 985.7 (4.0)    | 917.5 (3.7)    |       |
| IN                                     | 1371.3 (5.6)   | 1309.8 (5.3)   | 1356.5 (5.5)                   | 1339.9 (5.4)    | 1326.5 (5.4)   | 1358.5 (5.5)   | 1376.1 (5.6)   |       |
| KS                                     | 254.0 (1.0)    | 237.1 (1.0)    | 240.8 (1.0)                    | 242.1 (1.0)     | 242.2 (1.0)    | 227.7 (0.9)    | 246.2 (1.0)    |       |
| KY                                     | 650.8 (2.7)    | 574.6 (2.3)    | 589.3 (2.4)                    | 580.3 (2.3)     | 580.3 (2.3)    | 586.0 (2.4)    | 610.0 (2.5)    |       |
| LA                                     | 843.6 (3.5)    | 787.6 (3.2)    | 802.0 (3.2)                    | 819.2 (3.3)     | 761.4 (3.1)    | 785.8 (3.2)    | 837.0 (3.4)    |       |
| MA                                     | 142.0 (0.6)    | 158.6 (0.6)    | 148.4 (0.6)                    | 144.9 (0.6)     | 143.3 (0.6)    | 144.2 (0.6)    | 146.1 (0.6)    |       |
| MD                                     | 270.5 (1.1)    | 285.5 (1.2)    | 279.0 (1.1)                    | 279.9 (1.1)     | 290.1 (1.2)    | 274.5 (1.1)    | 297.9 (1.2)    |       |
| ME                                     | 94.7 (0.4)     | 103.9 (0.4)    | 101.1 (0.4)                    | 93.6 (0.4)      | 92.6 (0.4)     | 86.6 (0.3)     | 84.6 (0.3)     |       |
| MI                                     | 1354.8 (5.6)   | 1338.5 (5.4)   | 1434.9 (5.8)                   | 1441.7 (5.8)    | 1406.5 (5.7)   | 1360.3 (5.5)   | 1387.4 (5.6)   |       |
| MN                                     | 183.4 (0.8)    | 199.9 (0.8)    | 186.3 (0.8)                    | 182.2 (0.7)     | 205.0 (0.8)    | 187.0 (0.8)    | 187.7 (0.8)    |       |
| MO                                     | 1311.2 (5.4)   | 1339.9 (5.4)   | 1409.1 (5.7)                   | 1419.1 (5.7)    | 1553.1 (6.3)   | 1441.3 (5.8)   | 1420.2 (5.8)   |       |
| MS                                     | 275.7 (1.1)    | 288.9 (1.2)    | 300.4 (1.2)                    | 298.2 (1.2)     | 296.3 (1.2)    | 287.9 (1.2)    | 316.0 (1.3)    |       |
| MT                                     | 82.0 (0.3)     | 80.1 (0.3)     | 78.3 (0.3)                     | 82.6 (0.3)      | 86.3 (0.3)     | 76.2 (0.3)     | 81.8 (0.3)     |       |
| NC                                     | 1295.0 (5.3)   | 1382.2 (5.6)   | 1345.3 (5.4)                   | 1353.0 (5.5)    | 1329.5 (5.4)   | 1340.7 (5.4)   | 1280.9 (5.2)   |       |
| ND                                     | 16.3 (0.1)     | 25.2 (0.1)     | 19.3 (0.1)                     | 19.4 (0.1)      | 20.9 (0.1)     | 15.6 (0.1)     | 18.2 (0.1)     |       |

|                              | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| NE                           | 64.3 (0.3)    | 67.0 (0.3)    | 65.4 (0.3)                     | 65.5 (0.3)      | 66.4 (0.3)    | 69.0 (0.3)    | 69.4 (0.3)    |       |
| NH                           | 88.0 (0.4)    | 100.2 (0.4)   | 88.2 (0.4)                     | 88.4 (0.4)      | 85.6 (0.3)    | 88.4 (0.4)    | 91.2 (0.4)    |       |
| NJ                           | 277.3 (1.1)   | 317.3 (1.3)   | 290.1 (1.2)                    | 290.0 (1.2)     | 298.2 (1.2)   | 299.5 (1.2)   | 291.8 (1.2)   |       |
| NM                           | 178.8 (0.7)   | 176.1 (0.7)   | 183.7 (0.7)                    | 181.3 (0.7)     | 179.2 (0.7)   | 174.4 (0.7)   | 156.4 (0.6)   |       |
| NV                           | 90.8 (0.4)    | 92.8 (0.4)    | 96.5 (0.4)                     | 98.1 (0.4)      | 90.3 (0.4)    | 91.4 (0.4)    | 88.7 (0.4)    |       |
| NY                           | 889.7 (3.7)   | 908.7 (3.7)   | 876.9 (3.5)                    | 874.2 (3.5)     | 885.3 (3.6)   | 892.4 (3.6)   | 845.4 (3.4)   |       |
| OH                           | 1358.4 (5.6)  | 1365.9 (5.5)  | 1388.5 (5.6)                   | 1390.7 (5.6)    | 1366.5 (5.5)  | 1407.8 (5.7)  | 1425.5 (5.8)  |       |
| OK                           | 609.8 (2.5)   | 593.9 (2.4)   | 600.7 (2.4)                    | 607.7 (2.5)     | 617.9 (2.5)   | 615.5 (2.5)   | 603.5 (2.4)   |       |
| OR                           | 97.3 (0.4)    | 107.5 (0.4)   | 100.0 (0.4)                    | 100.8 (0.4)     | 106.0 (0.4)   | 101.3 (0.4)   | 99.6 (0.4)    |       |
| PA                           | 692.6 (2.8)   | 741.7 (3.0)   | 709.8 (2.9)                    | 715.3 (2.9)     | 723.0 (2.9)   | 689.9 (2.8)   | 716.0 (2.9)   |       |
| RI                           | 61.9 (0.3)    | 81.2 (0.3)    | 79.0 (0.3)                     | 76.9 (0.3)      | 76.4 (0.3)    | 81.6 (0.3)    | 69.9 (0.3)    |       |
| SC                           | 669.9 (2.8)   | 700.0 (2.8)   | 685.4 (2.8)                    | 676.0 (2.7)     | 653.9 (2.6)   | 675.8 (2.7)   | 697.5 (2.8)   |       |
| SD                           | 39.1 (0.2)    | 51.1 (0.2)    | 41.4 (0.2)                     | 41.6 (0.2)      | 43.2 (0.2)    | 35.2 (0.1)    | 36.0 (0.1)    |       |
| TN                           | 1232.6 (5.1)  | 1176.5 (4.8)  | 1224.2 (4.9)                   | 1202.3 (4.8)    | 1196.6 (4.8)  | 1237.3 (5.0)  | 1215.8 (4.9)  |       |
| TX                           | 1675.6 (6.9)  | 1692.2 (6.9)  | 1706.9 (6.9)                   | 1717.3 (6.9)    | 1742.1 (7.0)  | 1699.4 (6.9)  | 1702.3 (6.9)  |       |
| UT                           | 128.2 (0.5)   | 132.6 (0.5)   | 126.8 (0.5)                    | 126.1 (0.5)     | 135.6 (0.5)   | 130.1 (0.5)   | 134.7 (0.5)   |       |
| VA                           | 690.8 (2.8)   | 721.2 (2.9)   | 702.5 (2.8)                    | 707.4 (2.9)     | 707.0 (2.9)   | 687.2 (2.8)   | 689.0 (2.8)   |       |
| VT                           | 42.1 (0.2)    | 53.8 (0.2)    | 54.7 (0.2)                     | 53.4 (0.2)      | 47.6 (0.2)    | 52.8 (0.2)    | 53.7 (0.2)    |       |
| WA                           | 90.9 (0.4)    | 99.2 (0.4)    | 93.9 (0.4)                     | 94.2 (0.4)      | 100.0 (0.4)   | 97.3 (0.4)    | 84.4 (0.3)    |       |
| WI                           | 351.0 (1.4)   | 365.2 (1.5)   | 366.0 (1.5)                    | 364.8 (1.5)     | 355.9 (1.4)   | 350.0 (1.4)   | 335.7 (1.4)   |       |
| WV                           | 447.2 (1.8)   | 377.6 (1.5)   | 439.5 (1.8)                    | 418.4 (1.7)     | 401.0 (1.6)   | 417.4 (1.7)   | 425.6 (1.7)   |       |
| WY                           | 39.4 (0.2)    | 38.1 (0.2)    | 43.3 (0.2)                     | 41.7 (0.2)      | 39.7 (0.2)    | 45.0 (0.2)    | 43.9 (0.2)    |       |
| Year                         |               |               |                                |                 |               |               |               | 0.033 |
| 2000                         | 191.3 (0.8)   | 183.3 (0.7)   | 174.0 (0.7)                    | 166.3 (0.7)     | 172.7 (0.7)   | 169.6 (0.7)   | 152.2 (0.6)   |       |
| 2001                         | 352.9 (1.5)   | 382.8 (1.6)   | 359.9 (1.4)                    | 341.3 (1.4)     | 389.4 (1.6)   | 324.1 (1.3)   | 328.5 (1.3)   |       |
| 2002                         | 317.1 (1.3)   | 361.2 (1.5)   | 330.5 (1.3)                    | 314.9 (1.3)     | 377.0 (1.5)   | 313.0 (1.3)   | 318.1 (1.3)   |       |
| 2003                         | 682.5 (2.8)   | 758.7 (3.1)   | 738.5 (3.0)                    | 737.6 (3.0)     | 803.0 (3.2)   | 730.7 (3.0)   | 737.0 (3.0)   |       |
| 2004                         | 1355.6 (5.6)  | 1444.3 (5.8)  | 1441.8 (5.8)                   | 1424.1 (5.7)    | 1355.6 (5.5)  | 1427.9 (5.8)  | 1436.2 (5.8)  |       |
| 2005                         | 1130.6 (4.6)  | 1255.3 (5.1)  | 1247.2 (5.0)                   | 1242.5 (5.0)    | 1243.5 (5.0)  | 1215.3 (4.9)  | 1237.1 (5.0)  |       |
| 2006                         | 1171.3 (4.8)  | 1308.6 (5.3)  | 1287.9 (5.2)                   | 1273.2 (5.1)    | 1254.6 (5.1)  | 1239.3 (5.0)  | 1291.6 (5.2)  |       |
| 2007                         | 1301.7 (5.4)  | 1395.2 (5.7)  | 1385.3 (5.6)                   | 1374.1 (5.5)    | 1353.1 (5.5)  | 1357.4 (5.5)  | 1373.5 (5.6)  |       |
| 2008                         | 1439.1 (5.9)  | 1553.0 (6.3)  | 1517.7 (6.1)                   | 1520.6 (6.1)    | 1485.9 (6.0)  | 1492.1 (6.0)  | 1501.8 (6.1)  |       |
| 2009                         | 1821.7 (7.5)  | 1845.1 (7.5)  | 1790.5 (7.2)                   | 1812.0 (7.3)    | 1788.8 (7.2)  | 1794.1 (7.2)  | 1804.4 (7.3)  |       |
| 2010                         | 1832.1 (7.5)  | 1847.6 (7.5)  | 1817.6 (7.3)                   | 1843.1 (7.4)    | 1858.8 (7.5)  | 1835.2 (7.4)  | 1795.4 (7.3)  |       |
| 2011                         | 2023.9 (8.3)  | 1959.1 (7.9)  | 2004.7 (8.1)                   | 2015.1 (8.1)    | 2013.6 (8.1)  | 2057.9 (8.3)  | 2017.6 (8.2)  |       |
| 2012                         | 2666.2 (11.0) | 2618.5 (10.6) | 2666.3 (10.7)                  | 2689.9 (10.8)   | 2697.0 (10.9) | 2737.8 (11.1) | 2655.5 (10.8) |       |
| 2013                         | 2265.4 (9.3)  | 2221.5 (9.0)  | 2291.6 (9.2)                   | 2302.0 (9.3)    | 2295.4 (9.3)  | 2317.7 (9.4)  | 2270.4 (9.2)  |       |
| 2014                         | 1820.7 (7.5)  | 1773.4 (7.2)  | 1823.4 (7.3)                   | 1827.4 (7.4)    | 1820.8 (7.4)  | 1832.1 (7.4)  | 1792.6 (7.3)  |       |
| 2015                         | 1353.9 (5.6)  | 1342.8 (5.4)  | 1343.4 (5.4)                   | 1356.4 (5.5)    | 1331.4 (5.4)  | 1353.4 (5.5)  | 1343.3 (5.5)  |       |
| 2016                         | 1098.6 (4.5)  | 1015.7 (4.1)  | 1097.4 (4.4)                   | 1096.8 (4.4)    | 1065.0 (4.3)  | 1072.8 (4.3)  | 1085.8 (4.4)  |       |
| 2017                         | 863.7 (3.5)   | 806.2 (3.3)   | 851.6 (3.4)                    | 831.4 (3.4)     | 835.3 (3.4)   | 842.4 (3.4)   | 867.3 (3.5)   |       |
| 2018                         | 474.3 (1.9)   | 452.3 (1.8)   | 480.4 (1.9)                    | 464.2 (1.9)     | 460.0 (1.9)   | 476.3 (1.9)   | 470.1 (1.9)   |       |
| 2019                         | 168.1 (0.7)   | 169.1 (0.7)   | 175.6 (0.7)                    | 166.6 (0.7)     | 164.1 (0.7)   | 169.4 (0.7)   | 168.0 (0.7)   |       |
| <b>Comorbidities (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Opioid dependence            | 792.8 (3.3)   | 788.3 (3.2)   | 768.6 (3.1)                    | 754.5 (3.0)     | 767.8 (3.1)   | 786.0 (3.2)   | 781.3 (3.2)   | 0.005 |
| Opioid abuse                 | 79.6 (0.3)    | 74.0 (0.3)    | 76.7 (0.3)                     | 76.0 (0.3)      | 69.0 (0.3)    | 67.8 (0.3)    | 75.3 (0.3)    | 0.004 |
| Alcohol abuse                | 441.0 (1.8)   | 451.8 (1.8)   | 443.9 (1.8)                    | 447.4 (1.8)     | 435.2 (1.8)   | 433.0 (1.7)   | 428.2 (1.7)   | 0.003 |
| Tobacco use                  | 3004.9 (12.4) | 2987.1 (12.1) | 2979.7 (12.0)                  | 2998.3 (12.1)   | 2955.8 (11.9) | 3026.9 (12.2) | 3019.4 (12.3) | 0.005 |
| Other drug abuse             | 928.8 (3.8)   | 891.7 (3.6)   | 871.1 (3.5)                    | 873.6 (3.5)     | 875.3 (3.5)   | 900.1 (3.6)   | 882.2 (3.6)   | 0.006 |
| Anxiety                      | 4380.5 (18.0) | 4304.3 (17.4) | 4317.0 (17.4)                  | 4336.2 (17.5)   | 4352.7 (17.6) | 4376.4 (17.7) | 4391.4 (17.8) | 0.007 |
| Bipolar disorder             | 919.9 (3.8)   | 931.6 (3.8)   | 918.8 (3.7)                    | 915.6 (3.7)     | 926.1 (3.7)   | 950.0 (3.8)   | 932.6 (3.8)   | 0.003 |

|                                         | Baclofen       | Carisoprodol   | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone     | Methocarbamol  | Tizanidine     | SMD   |
|-----------------------------------------|----------------|----------------|--------------------------------|-----------------|----------------|----------------|----------------|-------|
| Bone fracture                           | 1475.0 (6.1)   | 1468.3 (5.9)   | 1457.9 (5.9)                   | 1464.8 (5.9)    | 1456.0 (5.9)   | 1456.2 (5.9)   | 1470.1 (6.0)   | 0.003 |
| Cancer                                  | 1395.1 (5.7)   | 1400.6 (5.7)   | 1364.2 (5.5)                   | 1386.7 (5.6)    | 1379.3 (5.6)   | 1389.4 (5.6)   | 1351.9 (5.5)   | 0.005 |
| Chronic renal<br>insufficiency          | 1078.9 (4.4)   | 1097.4 (4.4)   | 1130.3 (4.6)                   | 1116.6 (4.5)    | 1096.9 (4.4)   | 1151.9 (4.7)   | 1056.9 (4.3)   | 0.006 |
| Congestive heart failure                | 1332.5 (5.5)   | 1326.1 (5.4)   | 1383.5 (5.6)                   | 1376.7 (5.6)    | 1372.9 (5.5)   | 1436.4 (5.8)   | 1307.9 (5.3)   | 0.008 |
| COPD/asthma/oxygen                      | 4290.4 (17.6)  | 4335.4 (17.6)  | 4396.2 (17.7)                  | 4356.2 (17.6)   | 4296.5 (17.3)  | 4449.0 (18.0)  | 4281.4 (17.4)  | 0.007 |
| Dementia                                | 471.3 (1.9)    | 451.8 (1.8)    | 459.6 (1.9)                    | 468.4 (1.9)     | 479.4 (1.9)    | 471.3 (1.9)    | 456.0 (1.9)    | 0.004 |
| Depression                              | 5152.5 (21.2)  | 5113.0 (20.7)  | 5084.8 (20.5)                  | 5055.7 (20.4)   | 5145.7 (20.8)  | 5028.8 (20.3)  | 5117.2 (20.8)  | 0.009 |
| Diabetes                                | 4965.3 (20.4)  | 5152.3 (20.9)  | 5211.6 (21.0)                  | 5209.7 (21.0)   | 5110.2 (20.6)  | 5258.1 (21.2)  | 5022.1 (20.4)  | 0.010 |
| Epilepsy                                | 630.8 (2.6)    | 620.5 (2.5)    | 625.7 (2.5)                    | 624.4 (2.5)     | 625.5 (2.5)    | 620.9 (2.5)    | 644.2 (2.6)    | 0.003 |
| HIV                                     | 140.9 (0.6)    | 142.4 (0.6)    | 145.7 (0.6)                    | 145.1 (0.6)     | 144.0 (0.6)    | 142.3 (0.6)    | 134.9 (0.5)    | 0.002 |
| Intentional self-harm                   | 15.1 (0.1)     | 14.4 (0.1)     | 14.2 (0.1)                     | 15.4 (0.1)      | 13.0 (0.1)     | 14.8 (0.1)     | 16.8 (0.1)     | 0.002 |
| Liver disease                           | 1212.7 (5.0)   | 1222.0 (4.9)   | 1244.6 (5.0)                   | 1230.9 (5.0)    | 1215.8 (4.9)   | 1253.2 (5.1)   | 1213.9 (4.9)   | 0.003 |
| Musculoskeletal injury                  | 2304.8 (9.5)   | 2337.8 (9.5)   | 2348.7 (9.5)                   | 2331.7 (9.4)    | 2302.9 (9.3)   | 2370.1 (9.6)   | 2323.9 (9.4)   | 0.003 |
| Multiple sclerosis                      | 135.7 (0.6)    | 115.1 (0.5)    | 123.6 (0.5)                    | 123.7 (0.5)     | 129.6 (0.5)    | 106.6 (0.4)    | 133.3 (0.5)    | 0.008 |
| Obesity                                 | 1948.4 (8.0)   | 1924.8 (7.8)   | 1967.3 (7.9)                   | 1955.9 (7.9)    | 1950.4 (7.9)   | 1990.5 (8.0)   | 1920.6 (7.8)   | 0.004 |
| Pneumonia                               | 824.2 (3.4)    | 819.8 (3.3)    | 825.5 (3.3)                    | 817.3 (3.3)     | 822.3 (3.3)    | 849.5 (3.4)    | 811.5 (3.3)    | 0.003 |
| Psychosis                               | 430.6 (1.8)    | 431.5 (1.7)    | 421.4 (1.7)                    | 430.9 (1.7)     | 433.5 (1.8)    | 443.0 (1.8)    | 424.3 (1.7)    | 0.003 |
| Renal dysfunction                       | 1740.3 (7.2)   | 1762.9 (7.1)   | 1796.2 (7.2)                   | 1792.7 (7.2)    | 1771.9 (7.2)   | 1837.2 (7.4)   | 1710.2 (6.9)   | 0.006 |
| Spasticity                              | 3974.7 (16.3)  | 3865.3 (15.7)  | 3822.2 (15.4)                  | 3856.6 (15.6)   | 3912.7 (15.8)  | 3785.8 (15.3)  | 3913.9 (15.9)  | 0.011 |
| Urinary calculus                        | 761.8 (3.1)    | 757.9 (3.1)    | 752.4 (3.0)                    | 768.0 (3.1)     | 765.2 (3.1)    | 797.0 (3.2)    | 764.8 (3.1)    | 0.004 |
| Urinary tract infection                 | 2673.3 (11.0)  | 2768.4 (11.2)  | 2739.8 (11.0)                  | 2752.0 (11.1)   | 2759.4 (11.1)  | 2791.1 (11.3)  | 2723.7 (11.1)  | 0.004 |
| <b>Pain conditions (n (%))</b>          |                |                |                                |                 |                |                |                |       |
| Abdominal pain                          | 4442.0 (18.3)  | 4468.3 (18.1)  | 4482.3 (18.1)                  | 4497.0 (18.1)   | 4473.7 (18.1)  | 4561.6 (18.4)  | 4482.5 (18.2)  | 0.004 |
| Back and neck pain                      | 17426.3 (71.6) | 17129.0 (69.4) | 17231.7 (69.4)                 | 17220.6 (69.4)  | 17184.6 (69.4) | 17268.6 (69.7) | 17275.7 (70.1) | 0.018 |
| Back pain without<br>radiculopathy      | 15939.0 (65.5) | 15790.2 (63.9) | 15884.6 (64.0)                 | 15876.0 (64.0)  | 15768.1 (63.7) | 15902.4 (64.2) | 15851.6 (64.3) | 0.013 |
| Back pain with<br>radiculopathy         | 5476.3 (22.5)  | 5115.1 (20.7)  | 5159.1 (20.8)                  | 5157.8 (20.8)   | 5124.9 (20.7)  | 5117.5 (20.7)  | 5321.2 (21.6)  | 0.017 |
| Dental pain                             | 363.2 (1.5)    | 399.2 (1.6)    | 395.6 (1.6)                    | 389.8 (1.6)     | 386.6 (1.6)    | 400.5 (1.6)    | 383.3 (1.6)    | 0.004 |
| Diabetic neuropathy                     | 1019.6 (4.2)   | 1006.2 (4.1)   | 1024.7 (4.1)                   | 1006.6 (4.1)    | 982.6 (4.0)    | 1039.6 (4.2)   | 976.1 (4.0)    | 0.006 |
| Fibromyalgia                            | 3833.4 (15.8)  | 3670.5 (14.9)  | 3623.9 (14.6)                  | 3554.8 (14.3)   | 3671.1 (14.8)  | 3585.4 (14.5)  | 3794.4 (15.4)  | 0.017 |
| Headache                                | 4240.2 (17.4)  | 4176.1 (16.9)  | 4130.3 (16.6)                  | 4111.1 (16.6)   | 4170.3 (16.8)  | 4136.5 (16.7)  | 4319.1 (17.5)  | 0.012 |
| Osteoarthritis                          | 5555.4 (22.8)  | 5702.8 (23.1)  | 5752.1 (23.2)                  | 5735.9 (23.1)   | 5637.9 (22.8)  | 5745.4 (23.2)  | 5582.8 (22.7)  | 0.006 |
| Rheumatoid arthritis                    | 1155.4 (4.7)   | 1202.1 (4.9)   | 1194.3 (4.8)                   | 1192.5 (4.8)    | 1190.7 (4.8)   | 1182.2 (4.8)   | 1172.2 (4.8)   | 0.002 |
| Postherpetic neuralgia                  | 68.5 (0.3)     | 57.4 (0.2)     | 58.9 (0.2)                     | 63.7 (0.3)      | 68.6 (0.3)     | 63.1 (0.3)     | 63.9 (0.3)     | 0.004 |
| Other arthritis                         | 13185.8 (54.2) | 13324.0 (54.0) | 13334.3 (53.7)                 | 13359.9 (53.9)  | 13318.9 (53.8) | 13344.9 (53.9) | 13319.7 (54.0) | 0.004 |
| Other neuropathy                        | 8939.8 (36.7)  | 8448.7 (34.2)  | 8440.4 (34.0)                  | 8446.7 (34.1)   | 8452.4 (34.1)  | 8388.4 (33.9)  | 8729.4 (35.4)  | 0.023 |
| Other unspecified pain                  | 8693.7 (35.7)  | 8464.2 (34.3)  | 8491.8 (34.2)                  | 8496.0 (34.3)   | 8442.5 (34.1)  | 8574.7 (34.6)  | 8572.0 (34.8)  | 0.013 |
| <b>Other prescription fills (n (%))</b> |                |                |                                |                 |                |                |                |       |
| Antibiotics                             | 14597.9 (60.0) | 14926.3 (60.4) | 14968.7 (60.3)                 | 14952.1 (60.3)  | 14961.7 (60.4) | 14968.9 (60.5) | 14866.3 (60.3) | 0.004 |
| Anticonvulsants                         | 2773.4 (11.4)  | 2716.8 (11.0)  | 2625.2 (10.6)                  | 2620.2 (10.6)   | 2691.0 (10.9)  | 2612.4 (10.6)  | 2780.6 (11.3)  | 0.013 |
| Antidepressants, SSRIs                  | 6825.7 (28.1)  | 6948.4 (28.1)  | 6947.3 (28.0)                  | 6941.4 (28.0)   | 6941.9 (28.0)  | 6904.9 (27.9)  | 6951.6 (28.2)  | 0.003 |
| Antidepressants, SNRIs                  | 3982.8 (16.4)  | 3980.9 (16.1)  | 3920.4 (15.8)                  | 3915.8 (15.8)   | 3995.0 (16.1)  | 3931.7 (15.9)  | 4056.9 (16.5)  | 0.009 |
| Antidepressants, TCAs                   | 2710.1 (11.1)  | 2696.7 (10.9)  | 2614.4 (10.5)                  | 2595.3 (10.5)   | 2623.9 (10.6)  | 2562.4 (10.3)  | 2659.9 (10.8)  | 0.011 |
| Antidepressants, other                  | 4148.8 (17.1)  | 4261.8 (17.3)  | 4153.9 (16.7)                  | 4132.3 (16.7)   | 4195.6 (16.9)  | 4116.9 (16.6)  | 4194.7 (17.0)  | 0.008 |
| Antidiabetics                           | 4059.2 (16.7)  | 4237.7 (17.2)  | 4262.9 (17.2)                  | 4260.1 (17.2)   | 4162.5 (16.8)  | 4288.0 (17.3)  | 4109.1 (16.7)  | 0.008 |
| Antipsychotics, atypical                | 1791.0 (7.4)   | 1772.4 (7.2)   | 1779.6 (7.2)                   | 1764.2 (7.1)    | 1805.2 (7.3)   | 1805.6 (7.3)   | 1804.1 (7.3)   | 0.004 |
| Antipsychotics, typical                 | 647.9 (2.7)    | 660.7 (2.7)    | 636.6 (2.6)                    | 630.9 (2.5)     | 647.2 (2.6)    | 623.8 (2.5)    | 647.7 (2.6)    | 0.005 |
| Barbiturates                            | 157.2 (0.6)    | 165.7 (0.7)    | 151.1 (0.6)                    | 151.6 (0.6)     | 154.6 (0.6)    | 143.6 (0.6)    | 155.4 (0.6)    | 0.004 |
| Benzodiazepines                         | 10854.6 (44.6) | 10841.7 (43.9) | 10768.4 (43.4)                 | 10761.2 (43.4)  | 10817.8 (43.7) | 10763.6 (43.5) | 10893.9 (44.2) | 0.011 |
| CNS stimulants                          | 903.1 (3.7)    | 923.2 (3.7)    | 899.9 (3.6)                    | 892.5 (3.6)     | 908.2 (3.7)    | 883.0 (3.6)    | 940.3 (3.8)    | 0.006 |

|                                                                                            | Baclofen          | Carisoprodol      | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone        | Methocarbamol     | Tizanidine        | SMD   |
|--------------------------------------------------------------------------------------------|-------------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|-------------------|-------|
| Dementia agents                                                                            | 330.3 (1.4)       | 315.0 (1.3)       | 324.1 (1.3)                    | 322.6 (1.3)       | 326.3 (1.3)       | 328.4 (1.3)       | 306.5 (1.2)       | 0.004 |
| Gabapentinoids                                                                             | 6862.0 (28.2)     | 6684.5 (27.1)     | 6570.0 (26.5)                  | 6588.4 (26.6)     | 6629.8 (26.8)     | 6530.9 (26.4)     | 6749.9 (27.4)     | 0.017 |
| Lithium                                                                                    | 137.6 (0.6)       | 144.0 (0.6)       | 142.2 (0.6)                    | 141.3 (0.6)       | 145.6 (0.6)       | 151.9 (0.6)       | 140.2 (0.6)       | 0.002 |
| Multiple sclerosis<br>agents                                                               | 58.1 (0.2)        | 42.7 (0.2)        | 45.2 (0.2)                     | 44.2 (0.2)        | 46.8 (0.2)        | 38.4 (0.2)        | 47.0 (0.2)        | 0.006 |
| NSAIDs                                                                                     | 10796.2 (44.4)    | 11197.4 (45.3)    | 11109.9 (44.8)                 | 11101.2 (44.8)    | 11098.8 (44.8)    | 11134.3 (45.0)    | 11047.8 (44.8)    | 0.007 |
| Other sedative<br>hypnotics                                                                | 4454.5 (18.3)     | 4473.6 (18.1)     | 4392.4 (17.7)                  | 4391.1 (17.7)     | 4418.4 (17.8)     | 4411.9 (17.8)     | 4451.3 (18.1)     | 0.007 |
| Smoking cessation                                                                          | 2183.7 (9.0)      | 2196.3 (8.9)      | 2164.5 (8.7)                   | 2162.4 (8.7)      | 2195.0 (8.9)      | 2151.4 (8.7)      | 2200.3 (8.9)      | 0.005 |
| Triptans                                                                                   | 1346.7 (5.5)      | 1324.3 (5.4)      | 1288.8 (5.2)                   | 1286.3 (5.2)      | 1307.0 (5.3)      | 1261.5 (5.1)      | 1384.8 (5.6)      | 0.010 |
| Other CNS depressants                                                                      | 112.4 (0.5)       | 105.8 (0.4)       | 107.2 (0.4)                    | 103.4 (0.4)       | 106.8 (0.4)       | 104.7 (0.4)       | 109.6 (0.4)       | 0.003 |
| <b>Prescription opioid utilization (n (%))</b>                                             |                   |                   |                                |                   |                   |                   |                   |       |
| Prescription opioid on<br>index date                                                       |                   |                   |                                |                   |                   |                   |                   |       |
| Buprenorphine                                                                              | 146.0 (0.6)       | 146.0 (0.6)       | 134.0 (0.5)                    | 132.3 (0.5)       | 136.5 (0.6)       | 134.6 (0.5)       | 146.8 (0.6)       | 0.005 |
| Butorphanol                                                                                | 108.3 (0.4)       | 107.3 (0.4)       | 99.0 (0.4)                     | 100.7 (0.4)       | 102.9 (0.4)       | 104.0 (0.4)       | 105.6 (0.4)       | 0.003 |
| Codeine                                                                                    | 1077.6 (4.4)      | 1219.3 (4.9)      | 1171.3 (4.7)                   | 1173.2 (4.7)      | 1171.8 (4.7)      | 1179.4 (4.8)      | 1122.4 (4.6)      | 0.009 |
| Dihydrocodeine                                                                             | 31.6 (0.1)        | 30.8 (0.1)        | 34.4 (0.1)                     | 31.2 (0.1)        | 31.7 (0.1)        | 31.9 (0.1)        | 32.6 (0.1)        | 0.001 |
| Fentanyl                                                                                   | 1707.1 (7.0)      | 1632.0 (6.6)      | 1560.5 (6.3)                   | 1568.5 (6.3)      | 1637.1 (6.6)      | 1546.4 (6.2)      | 1623.8 (6.6)      | 0.012 |
| Hydrocodone                                                                                | 13771.2 (56.6)    | 13981.5 (56.6)    | 14275.8 (57.5)                 | 14287.4 (57.6)    | 14187.5 (57.3)    | 14253.0 (57.6)    | 14025.3 (56.9)    | 0.011 |
| Hydromorphone                                                                              | 548.0 (2.3)       | 508.2 (2.1)       | 479.6 (1.9)                    | 479.5 (1.9)       | 489.1 (2.0)       | 472.7 (1.9)       | 506.9 (2.1)       | 0.009 |
| Levorphanol                                                                                | 3.7 (0.0)         | 2.8 (0.0)         | 3.1 (0.0)                      | 2.2 (0.0)         | 2.2 (0.0)         | 2.6 (0.0)         | 3.7 (0.0)         | 0.003 |
| Meperidine                                                                                 | 73.6 (0.3)        | 79.4 (0.3)        | 80.3 (0.3)                     | 75.8 (0.3)        | 71.9 (0.3)        | 75.4 (0.3)        | 75.1 (0.3)        | 0.002 |
| Methadone                                                                                  | 850.1 (3.5)       | 765.7 (3.1)       | 750.7 (3.0)                    | 736.8 (3.0)       | 759.2 (3.1)       | 757.9 (3.1)       | 787.2 (3.2)       | 0.011 |
| Morphine                                                                                   | 1692.9 (7.0)      | 1579.2 (6.4)      | 1513.0 (6.1)                   | 1516.1 (6.1)      | 1567.1 (6.3)      | 1508.3 (6.1)      | 1611.4 (6.5)      | 0.015 |
| Opium                                                                                      | 8.3 (0.0)         | 8.4 (0.0)         | 6.7 (0.0)                      | 6.3 (0.0)         | 5.9 (0.0)         | 6.5 (0.0)         | 6.8 (0.0)         | 0.003 |
| Oxycodone                                                                                  | 7846.3 (32.2)     | 7702.6 (31.2)     | 7556.2 (30.4)                  | 7571.9 (30.5)     | 7609.8 (30.7)     | 7511.2 (30.3)     | 7737.9 (31.4)     | 0.017 |
| Oxymorphone                                                                                | 304.2 (1.3)       | 289.5 (1.2)       | 272.0 (1.1)                    | 272.9 (1.1)       | 274.1 (1.1)       | 279.1 (1.1)       | 294.3 (1.2)       | 0.006 |
| Pentazocine                                                                                | 76.3 (0.3)        | 79.7 (0.3)        | 76.9 (0.3)                     | 72.6 (0.3)        | 75.1 (0.3)        | 77.2 (0.3)        | 71.9 (0.3)        | 0.002 |
| Propoxyphene                                                                               | 385.8 (1.6)       | 406.4 (1.6)       | 396.1 (1.6)                    | 384.6 (1.6)       | 385.1 (1.6)       | 397.6 (1.6)       | 373.3 (1.5)       | 0.004 |
| Tapentadol                                                                                 | 196.4 (0.8)       | 188.8 (0.8)       | 183.8 (0.7)                    | 185.7 (0.7)       | 195.5 (0.8)       | 178.1 (0.7)       | 199.3 (0.8)       | 0.005 |
| Tramadol                                                                                   | 4942.8 (20.3)     | 5323.2 (21.6)     | 5346.7 (21.5)                  | 5341.5 (21.5)     | 5276.7 (21.3)     | 5324.1 (21.5)     | 5264.1 (21.4)     | 0.010 |
| Number of days<br>covered by prescription<br>opioids in 180 days pre-<br>index (mean (SD)) | 174.23 (16.32)    | 174.10 (16.56)    | 174.00 (16.68)                 | 173.98 (16.61)    | 174.00 (16.57)    | 173.98 (16.59)    | 174.06 (16.60)    | 0.006 |
| Total dispensed MMEs<br>per interval (days)<br>(mean (SD))                                 |                   |                   |                                |                   |                   |                   |                   |       |
| (Index - 180) to<br>(index - 151)                                                          | 1959.86 (3195.34) | 1902.29 (3036.60) | 1810.27 (2974.34)              | 1813.23 (3103.42) | 1840.48 (3088.81) | 1826.03 (3125.36) | 1893.27 (3064.74) | 0.021 |
| (Index - 150) to<br>(index - 121)                                                          | 2024.76 (3203.60) | 1971.67 (3054.14) | 1878.02 (3021.94)              | 1877.00 (3143.77) | 1909.88 (3133.64) | 1896.89 (3182.06) | 1961.03 (3124.42) | 0.021 |
| (Index - 120) to<br>(index - 91)                                                           | 2194.19 (3288.79) | 2123.62 (3102.39) | 2020.50 (3085.97)              | 2024.16 (3200.77) | 2057.54 (3229.48) | 2043.34 (3283.71) | 2115.51 (3153.22) | 0.024 |
| (Index - 90) to<br>(index - 61)                                                            | 2183.92 (3208.45) | 2123.40 (3096.32) | 2023.00 (3101.10)              | 2027.45 (3187.39) | 2061.22 (3192.00) | 2037.90 (3217.93) | 2115.54 (3152.78) | 0.023 |
| (Index - 60) to<br>(index - 31)                                                            | 2209.64 (3313.17) | 2132.25 (3096.40) | 2040.21 (3129.95)              | 2041.79 (3215.06) | 2076.80 (3218.49) | 2054.64 (3256.91) | 2128.21 (3175.75) | 0.023 |
| (Index - 30) to<br>index                                                                   | 2631.41 (3778.28) | 2537.68 (3538.30) | 2415.82 (3721.36)              | 2416.39 (3801.31) | 2449.88 (3767.53) | 2425.86 (3794.14) | 2532.62 (3612.86) | 0.026 |
| <b>Healthcare utilization (mean (SD))</b>                                                  |                   |                   |                                |                   |                   |                   |                   |       |

|                                           | <b>Baclofen</b> | <b>Carisoprodol</b> | <b>Chlorzoxazone/<br/>orphenadrine</b> | <b>Cyclobenzaprine</b> | <b>Metaxalone</b> | <b>Methocarbamol</b> | <b>Tizanidine</b> | <b>SMD</b> |
|-------------------------------------------|-----------------|---------------------|----------------------------------------|------------------------|-------------------|----------------------|-------------------|------------|
| Number of physician visits                | 8.80 (7.16)     | 8.65 (7.37)         | 8.61 (7.25)                            | 8.60 (7.24)            | 8.64 (7.18)       | 8.65 (7.15)          | 8.71 (7.10)       | 0.011      |
| Number of distinct prescribed medications | 12.47 (6.25)    | 12.53 (6.45)        | 12.42 (6.29)                           | 12.40 (6.28)           | 12.46 (6.31)      | 12.46 (6.24)         | 12.44 (6.32)      | 0.008      |
| Number of hospitalizations                | 0.21 (0.64)     | 0.21 (0.62)         | 0.21 (0.68)                            | 0.21 (0.62)            | 0.22 (0.64)       | 0.22 (0.60)          | 0.21 (0.65)       | 0.005      |
| Number of hospitalization days            | 1.16 (5.33)     | 1.11 (4.81)         | 1.10 (4.05)                            | 1.11 (4.30)            | 1.13 (4.03)       | 1.15 (4.28)          | 1.12 (4.69)       | 0.006      |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 4A. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in Medicaid Analytic eXtract (MAX), 2000-2014 (pre-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 24487         | 21726         | 8017                           | 93997           | 12686         | 19118         | 18440         |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 46.18 (10.49) | 43.57 (10.36) | 43.02 (10.79)                  | 44.08 (10.74)   | 44.14 (10.52) | 44.19 (10.90) | 43.67 (10.37) | 0.101 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.060 |
| Unknown                                | 71 (0.3)      | 26 (0.1)      | 13 (0.2)                       | 163 (0.2)       | 13 (0.1)      | 32 (0.2)      | 32 (0.2)      |       |
| Male                                   | 9038 (36.9)   | 7062 (32.5)   | 2479 (30.9)                    | 29994 (31.9)    | 3794 (29.9)   | 6462 (33.8)   | 6106 (33.1)   |       |
| Female                                 | 15378 (62.8)  | 14638 (67.4)  | 5525 (68.9)                    | 63840 (67.9)    | 8879 (70.0)   | 12624 (66.0)  | 12302 (66.7)  |       |
| Race                                   |               |               |                                |                 |               |               |               | 0.119 |
| Asian                                  | 464 (1.9)     | 325 (1.5)     | 112 (1.4)                      | 1739 (1.9)      | 175 (1.4)     | 333 (1.7)     | 247 (1.3)     |       |
| Black                                  | 3741 (15.3)   | 3092 (14.2)   | 1142 (14.2)                    | 15358 (16.3)    | 1857 (14.6)   | 3126 (16.4)   | 2027 (11.0)   |       |
| White                                  | 17434 (71.2)  | 16942 (78.0)  | 6315 (78.8)                    | 70930 (75.5)    | 9838 (77.6)   | 14509 (75.9)  | 15228 (82.6)  |       |
| Other                                  | 2848 (11.6)   | 1367 (6.3)    | 448 (5.6)                      | 5970 (6.4)      | 816 (6.4)     | 1150 (6.0)    | 938 (5.1)     |       |
| Ethnicity                              |               |               |                                |                 |               |               |               | 0.098 |
| Unknown                                | 840 (3.4)     | 771 (3.5)     | 222 (2.8)                      | 2654 (2.8)      | 484 (3.8)     | 474 (2.5)     | 532 (2.9)     |       |
| Hispanic                               | 1628 (6.6)    | 487 (2.2)     | 194 (2.4)                      | 2987 (3.2)      | 303 (2.4)     | 610 (3.2)     | 360 (2.0)     |       |
| Non-Hispanic                           | 22019 (89.9)  | 20468 (94.2)  | 7601 (94.8)                    | 88356 (94.0)    | 11899 (93.8)  | 18034 (94.3)  | 17548 (95.2)  |       |
| State                                  |               |               |                                |                 |               |               |               | 0.942 |
| AK                                     | 51 (0.2)      | 134 (0.6)     | 17 (0.2)                       | 450 (0.5)       | 35 (0.3)      | 80 (0.4)      | 184 (1.0)     |       |
| AL                                     | 231 (0.9)     | 126 (0.6)     | 109 (1.4)                      | 1899 (2.0)      | 84 (0.7)      | 835 (4.4)     | 610 (3.3)     |       |
| AR                                     | 53 (0.2)      | 352 (1.6)     | 36 (0.4)                       | 424 (0.5)       | 147 (1.2)     | 116 (0.6)     | 145 (0.8)     |       |
| AZ                                     | 1 (0.0)       | 1 (0.0)       | 0 (0.0)                        | 5 (0.0)         | 1 (0.0)       | 2 (0.0)       | 2 (0.0)       |       |
| CA                                     | 13546 (55.3)  | 1220 (5.6)    | 31 (0.4)                       | 910 (1.0)       | 82 (0.6)      | 319 (1.7)     | 176 (1.0)     |       |
| CO                                     | 4 (0.0)       | 0 (0.0)       | 0 (0.0)                        | 10 (0.0)        | 2 (0.0)       | 1 (0.0)       | 5 (0.0)       |       |
| CT                                     | 266 (1.1)     | 572 (2.6)     | 113 (1.4)                      | 2677 (2.8)      | 307 (2.4)     | 772 (4.0)     | 240 (1.3)     |       |
| DC                                     | 21 (0.1)      | 26 (0.1)      | 24 (0.3)                       | 230 (0.2)       | 17 (0.1)      | 19 (0.1)      | 5 (0.0)       |       |
| DE                                     | 1 (0.0)       | 0 (0.0)       | 0 (0.0)                        | 1 (0.0)         | 3 (0.0)       | 0 (0.0)       | 3 (0.0)       |       |
| FL                                     | 463 (1.9)     | 1108 (5.1)    | 148 (1.8)                      | 3028 (3.2)      | 669 (5.3)     | 743 (3.9)     | 478 (2.6)     |       |
| GA                                     | 234 (1.0)     | 1511 (7.0)    | 281 (3.5)                      | 2411 (2.6)      | 911 (7.2)     | 468 (2.4)     | 770 (4.2)     |       |
| HI                                     | 44 (0.2)      | 157 (0.7)     | 23 (0.3)                       | 197 (0.2)       | 14 (0.1)      | 37 (0.2)      | 23 (0.1)      |       |
| IA                                     | 2 (0.0)       | 2 (0.0)       | 1 (0.0)                        | 10 (0.0)        | 3 (0.0)       | 2 (0.0)       | 1 (0.0)       |       |
| ID                                     | 69 (0.3)      | 141 (0.6)     | 55 (0.7)                       | 761 (0.8)       | 76 (0.6)      | 224 (1.2)     | 120 (0.7)     |       |
| IL                                     | 1003 (4.1)    | 759 (3.5)     | 1511 (18.8)                    | 12010 (12.8)    | 140 (1.1)     | 1666 (8.7)    | 1168 (6.3)    |       |
| IN                                     | 875 (3.6)     | 505 (2.3)     | 648 (8.1)                      | 6419 (6.8)      | 447 (3.5)     | 1208 (6.3)    | 1622 (8.8)    |       |
| KS                                     | 115 (0.5)     | 106 (0.5)     | 82 (1.0)                       | 912 (1.0)       | 85 (0.7)      | 35 (0.2)      | 94 (0.5)      |       |
| KY                                     | 8 (0.0)       | 2 (0.0)       | 4 (0.0)                        | 18 (0.0)        | 17 (0.1)      | 16 (0.1)      | 20 (0.1)      |       |
| LA                                     | 308 (1.3)     | 2324 (10.7)   | 409 (5.1)                      | 4023 (4.3)      | 603 (4.8)     | 920 (4.8)     | 762 (4.1)     |       |
| MA                                     | 42 (0.2)      | 9 (0.0)       | 11 (0.1)                       | 113 (0.1)       | 10 (0.1)      | 11 (0.1)      | 33 (0.2)      |       |
| MD                                     | 80 (0.3)      | 36 (0.2)      | 2 (0.0)                        | 213 (0.2)       | 24 (0.2)      | 22 (0.1)      | 20 (0.1)      |       |
| ME                                     | 371 (1.5)     | 93 (0.4)      | 91 (1.1)                       | 2781 (3.0)      | 70 (0.6)      | 362 (1.9)     | 301 (1.6)     |       |
| MI                                     | 0 (0.0)       | 0 (0.0)       | 1 (0.0)                        | 0 (0.0)         | 0 (0.0)       | 0 (0.0)       | 0 (0.0)       |       |
| MN                                     | 202 (0.8)     | 189 (0.9)     | 127 (1.6)                      | 1769 (1.9)      | 102 (0.8)     | 303 (1.6)     | 276 (1.5)     |       |
| MO                                     | 1474 (6.0)    | 2420 (11.1)   | 1142 (14.2)                    | 10601 (11.3)    | 1698 (13.4)   | 1817 (9.5)    | 2251 (12.2)   |       |
| MS                                     | 66 (0.3)      | 473 (2.2)     | 71 (0.9)                       | 666 (0.7)       | 250 (2.0)     | 138 (0.7)     | 282 (1.5)     |       |
| MT                                     | 81 (0.3)      | 82 (0.4)      | 35 (0.4)                       | 643 (0.7)       | 91 (0.7)      | 198 (1.0)     | 127 (0.7)     |       |
| NC                                     | 617 (2.5)     | 2005 (9.2)    | 651 (8.1)                      | 6421 (6.8)      | 1884 (14.9)   | 900 (4.7)     | 1608 (8.7)    |       |
| ND                                     | 23 (0.1)      | 34 (0.2)      | 35 (0.4)                       | 359 (0.4)       | 32 (0.3)      | 37 (0.2)      | 61 (0.3)      |       |
| NE                                     | 8 (0.0)       | 1 (0.0)       | 4 (0.0)                        | 41 (0.0)        | 7 (0.1)       | 4 (0.0)       | 13 (0.1)      |       |
| NH                                     | 102 (0.4)     | 131 (0.6)     | 46 (0.6)                       | 938 (1.0)       | 83 (0.7)      | 122 (0.6)     | 229 (1.2)     |       |

|                                                                | Baclofen              | Carisoprodol          | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine       | Metaxalone            | Methocarbamol         | Tizanidine            | SMD   |
|----------------------------------------------------------------|-----------------------|-----------------------|--------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-------|
| NJ                                                             | 86 (0.4)              | 201 (0.9)             | 69 (0.9)                       | 732 (0.8)             | 236 (1.9)             | 54 (0.3)              | 149 (0.8)             |       |
| NM                                                             | 32 (0.1)              | 28 (0.1)              | 16 (0.2)                       | 197 (0.2)             | 3 (0.0)               | 53 (0.3)              | 6 (0.0)               |       |
| NV                                                             | 16 (0.1)              | 212 (1.0)             | 6 (0.1)                        | 105 (0.1)             | 40 (0.3)              | 28 (0.1)              | 48 (0.3)              |       |
| NY                                                             | 860 (3.5)             | 1029 (4.7)            | 301 (3.8)                      | 6044 (6.4)            | 957 (7.5)             | 1213 (6.3)            | 908 (4.9)             |       |
| OH                                                             | 94 (0.4)              | 6 (0.0)               | 13 (0.2)                       | 510 (0.5)             | 6 (0.0)               | 125 (0.7)             | 185 (1.0)             |       |
| OK                                                             | 44 (0.2)              | 132 (0.6)             | 25 (0.3)                       | 265 (0.3)             | 11 (0.1)              | 54 (0.3)              | 74 (0.4)              |       |
| OR                                                             | 11 (0.0)              | 12 (0.1)              | 2 (0.0)                        | 93 (0.1)              | 4 (0.0)               | 22 (0.1)              | 4 (0.0)               |       |
| PA                                                             | 221 (0.9)             | 519 (2.4)             | 188 (2.3)                      | 1665 (1.8)            | 588 (4.6)             | 218 (1.1)             | 346 (1.9)             |       |
| RI                                                             | 31 (0.1)              | 129 (0.6)             | 24 (0.3)                       | 561 (0.6)             | 89 (0.7)              | 110 (0.6)             | 54 (0.3)              |       |
| SC                                                             | 140 (0.6)             | 769 (3.5)             | 115 (1.4)                      | 1174 (1.2)            | 499 (3.9)             | 115 (0.6)             | 437 (2.4)             |       |
| SD                                                             | 77 (0.3)              | 60 (0.3)              | 25 (0.3)                       | 572 (0.6)             | 58 (0.5)              | 65 (0.3)              | 74 (0.4)              |       |
| TN                                                             | 716 (2.9)             | 2331 (10.7)           | 574 (7.2)                      | 6848 (7.3)            | 491 (3.9)             | 2675 (14.0)           | 1312 (7.1)            |       |
| TX                                                             | 0 (0.0)               | 0 (0.0)               | 0 (0.0)                        | 0 (0.0)               | 0 (0.0)               | 0 (0.0)               | 0 (0.0)               |       |
| UT                                                             | 7 (0.0)               | 63 (0.3)              | 6 (0.1)                        | 105 (0.1)             | 18 (0.1)              | 28 (0.1)              | 20 (0.1)              |       |
| VA                                                             | 354 (1.4)             | 539 (2.5)             | 389 (4.9)                      | 2194 (2.3)            | 481 (3.8)             | 538 (2.8)             | 590 (3.2)             |       |
| VT                                                             | 178 (0.7)             | 87 (0.4)              | 66 (0.8)                       | 1705 (1.8)            | 94 (0.7)              | 426 (2.2)             | 236 (1.3)             |       |
| WA                                                             | 38 (0.2)              | 97 (0.4)              | 4 (0.0)                        | 144 (0.2)             | 19 (0.1)              | 87 (0.5)              | 37 (0.2)              |       |
| WI                                                             | 245 (1.0)             | 284 (1.3)             | 152 (1.9)                      | 2535 (2.7)            | 280 (2.2)             | 206 (1.1)             | 361 (2.0)             |       |
| WV                                                             | 909 (3.7)             | 665 (3.1)             | 307 (3.8)                      | 7052 (7.5)            | 888 (7.0)             | 1706 (8.9)            | 1899 (10.3)           |       |
| WY                                                             | 67 (0.3)              | 44 (0.2)              | 27 (0.3)                       | 556 (0.6)             | 30 (0.2)              | 18 (0.1)              | 71 (0.4)              |       |
| Socioeconomic status (% (SD))                                  |                       |                       |                                |                       |                       |                       |                       |       |
| Households with 1-1.5 occupants per room                       | 3.51 (3.48)           | 2.02 (1.95)           | 1.71 (1.66)                    | 1.82 (1.84)           | 1.79 (1.70)           | 1.89 (1.98)           | 1.72 (1.72)           | 0.229 |
| Households with > 1.5 occupants per room                       | 1.66 (2.31)           | 0.81 (1.17)           | 0.69 (1.02)                    | 0.76 (1.14)           | 0.74 (1.08)           | 0.81 (1.25)           | 0.71 (1.07)           | 0.181 |
| Median value of homes (mean (SD))                              | 253154.82 (185900.90) | 164116.27 (108322.75) | 144957.31 (87661.69)           | 159431.31 (110057.87) | 158055.49 (106977.26) | 165191.14 (115144.52) | 155660.51 (105892.48) | 0.239 |
| Median value of homes ranked 1-100 (mean (SD))                 | 63.02 (26.59)         | 44.92 (24.78)         | 39.48 (23.46)                  | 43.12 (25.07)         | 43.09 (23.92)         | 44.53 (25.23)         | 41.92 (24.47)         | 0.294 |
| Median household income (mean (SD))                            | 50005.57 (17498.11)   | 46068.81 (15077.63)   | 45830.75 (14194.14)            | 47038.59 (15479.48)   | 45642.35 (14865.88)   | 46209.53 (15309.22)   | 46746.07 (15333.51)   | 0.097 |
| Median value of income ranked 1-100 (mean (SD))                | 41.49 (25.69)         | 35.28 (24.62)         | 35.30 (23.82)                  | 37.16 (24.99)         | 34.44 (23.98)         | 35.65 (24.91)         | 36.50 (24.85)         | 0.100 |
| Individuals below the poverty line                             | 19.44 (8.60)          | 19.41 (8.50)          | 18.91 (8.72)                   | 18.82 (9.06)          | 19.33 (8.55)          | 19.27 (9.08)          | 18.64 (8.65)          | 0.044 |
| Individuals > 16 years who are unemployed                      | 8.76 (3.93)           | 7.99 (3.72)           | 7.75 (3.97)                    | 7.86 (4.09)           | 7.87 (3.73)           | 7.97 (4.18)           | 7.62 (3.77)           | 0.098 |
| Individuals > 25 years with < 12 <sup>th</sup> grade education | 29.04 (8.65)          | 34.14 (8.24)          | 34.76 (7.86)                   | 34.29 (8.36)          | 34.56 (8.17)          | 34.58 (8.42)          | 34.82 (8.32)          | 0.214 |
| Individuals > 25 years with 4-year college education           | 14.40 (7.58)          | 13.12 (6.54)          | 13.03 (6.46)                   | 13.64 (6.73)          | 13.13 (6.42)          | 13.24 (6.73)          | 13.23 (6.71)          | 0.072 |
| Households with > 1 persons per room                           | 5.17 (5.27)           | 2.83 (2.77)           | 2.40 (2.34)                    | 2.58 (2.63)           | 2.54 (2.43)           | 2.70 (2.92)           | 2.43 (2.44)           | 0.234 |
| Socioeconomic status index score (mean (SD))                   | 54.84 (6.29)          | 52.25 (6.11)          | 51.84 (5.82)                   | 52.44 (6.17)          | 52.01 (5.91)          | 52.25 (6.15)          | 52.22 (6.15)          | 0.154 |
| Rural-urban continuum codes                                    |                       |                       |                                |                       |                       |                       |                       | 0.107 |
| Unknown                                                        | 86 (0.4)              | 168 (0.8)             | 38 (0.5)                       | 637 (0.7)             | 92 (0.7)              | 104 (0.5)             | 96 (0.5)              |       |
| Metropolitan                                                   | 20027 (81.8)          | 15333 (70.6)          | 5546 (69.2)                    | 67115 (71.4)          | 8840 (69.7)           | 13554 (70.9)          | 12803 (69.4)          |       |
| Rural                                                          | 792 (3.2)             | 1365 (6.3)            | 599 (7.5)                      | 5770 (6.1)            | 851 (6.7)             | 1254 (6.6)            | 1233 (6.7)            |       |
| Urban                                                          | 3582 (14.6)           | 4860 (22.4)           | 1834 (22.9)                    | 20475 (21.8)          | 2903 (22.9)           | 4206 (22.0)           | 4308 (23.4)           |       |
| Year                                                           |                       |                       |                                |                       |                       |                       |                       | 0.499 |
| 2000                                                           | 439 (1.8)             | 1125 (5.2)            | 366 (4.6)                      | 1936 (2.1)            | 432 (3.4)             | 422 (2.2)             | 353 (1.9)             |       |
| 2001                                                           | 1000 (4.1)            | 2255 (10.4)           | 628 (7.8)                      | 3996 (4.3)            | 1238 (9.8)            | 853 (4.5)             | 1364 (7.4)            |       |
| 2002                                                           | 1043 (4.3)            | 2005 (9.2)            | 540 (6.7)                      | 3911 (4.2)            | 1528 (12.0)           | 799 (4.2)             | 1644 (8.9)            |       |
| 2003                                                           | 1699 (6.9)            | 3203 (14.7)           | 697 (8.7)                      | 6770 (7.2)            | 1995 (15.7)           | 1397 (7.3)            | 1798 (9.8)            |       |
| 2004                                                           | 2284 (9.3)            | 3786 (17.4)           | 1179 (14.7)                    | 13032 (13.9)          | 1924 (15.2)           | 3384 (17.7)           | 2433 (13.2)           |       |

|                                 | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|---------------------------------|--------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| 2005                            | 1453 (5.9)   | 1848 (8.5)   | 538 (6.7)                      | 6133 (6.5)      | 1227 (9.7)  | 982 (5.1)     | 985 (5.3)    |       |
| 2006                            | 1623 (6.6)   | 1744 (8.0)   | 517 (6.4)                      | 6106 (6.5)      | 1143 (9.0)  | 1009 (5.3)    | 988 (5.4)    |       |
| 2007                            | 1821 (7.4)   | 1203 (5.5)   | 485 (6.0)                      | 5806 (6.2)      | 926 (7.3)   | 982 (5.1)     | 976 (5.3)    |       |
| 2008                            | 2063 (8.4)   | 1147 (5.3)   | 465 (5.8)                      | 6847 (7.3)      | 742 (5.8)   | 1103 (5.8)    | 931 (5.0)    |       |
| 2009                            | 2388 (9.8)   | 1384 (6.4)   | 588 (7.3)                      | 8229 (8.8)      | 502 (4.0)   | 1398 (7.3)    | 1238 (6.7)   |       |
| 2010                            | 2389 (9.8)   | 891 (4.1)    | 578 (7.2)                      | 7827 (8.3)      | 279 (2.2)   | 1404 (7.3)    | 1135 (6.2)   |       |
| 2011                            | 2522 (10.3)  | 535 (2.5)    | 616 (7.7)                      | 9369 (10.0)     | 275 (2.2)   | 1927 (10.1)   | 1587 (8.6)   |       |
| 2012                            | 1967 (8.0)   | 379 (1.7)    | 565 (7.0)                      | 8599 (9.1)      | 235 (1.9)   | 2074 (10.8)   | 1733 (9.4)   |       |
| 2013                            | 1157 (4.7)   | 192 (0.9)    | 161 (2.0)                      | 3822 (4.1)      | 164 (1.3)   | 970 (5.1)     | 813 (4.4)    |       |
| 2014                            | 639 (2.6)    | 29 (0.1)     | 94 (1.2)                       | 1614 (1.7)      | 76 (0.6)    | 414 (2.2)     | 462 (2.5)    |       |
| <b>Comorbidities (n (%))</b>    |              |              |                                |                 |             |               |              |       |
| Opioid dependence               | 886 (3.6)    | 767 (3.5)    | 217 (2.7)                      | 2994 (3.2)      | 351 (2.8)   | 893 (4.7)     | 564 (3.1)    | 0.042 |
| Opioid abuse                    | 136 (0.6)    | 127 (0.6)    | 54 (0.7)                       | 531 (0.6)       | 67 (0.5)    | 160 (0.8)     | 97 (0.5)     | 0.015 |
| Alcohol abuse                   | 992 (4.1)    | 806 (3.7)    | 316 (3.9)                      | 4205 (4.5)      | 491 (3.9)   | 914 (4.8)     | 626 (3.4)    | 0.028 |
| Tobacco use                     | 2386 (9.7)   | 2114 (9.7)   | 1063 (13.3)                    | 12632 (13.4)    | 1245 (9.8)  | 2750 (14.4)   | 2127 (11.5)  | 0.073 |
| Other drug abuse                | 1589 (6.5)   | 1560 (7.2)   | 539 (6.7)                      | 6187 (6.6)      | 787 (6.2)   | 1629 (8.5)    | 1234 (6.7)   | 0.031 |
| Anxiety                         | 4237 (17.3)  | 4469 (20.6)  | 1703 (21.2)                    | 18301 (19.5)    | 2384 (18.8) | 3968 (20.8)   | 3975 (21.6)  | 0.045 |
| Bipolar disorder                | 1753 (7.2)   | 1352 (6.2)   | 557 (6.9)                      | 6930 (7.4)      | 817 (6.4)   | 1478 (7.7)    | 1347 (7.3)   | 0.025 |
| Bone fracture                   | 1765 (7.2)   | 1479 (6.8)   | 548 (6.8)                      | 6261 (6.7)      | 797 (6.3)   | 1338 (7.0)    | 1106 (6.0)   | 0.020 |
| Cancer                          | 1414 (5.8)   | 893 (4.1)    | 338 (4.2)                      | 4826 (5.1)      | 535 (4.2)   | 863 (4.5)     | 731 (4.0)    | 0.035 |
| Chronic renal insufficiency     | 622 (2.5)    | 299 (1.4)    | 130 (1.6)                      | 2059 (2.2)      | 212 (1.7)   | 347 (1.8)     | 303 (1.6)    | 0.033 |
| Congestive heart failure        | 1183 (4.8)   | 849 (3.9)    | 284 (3.5)                      | 3867 (4.1)      | 539 (4.2)   | 734 (3.8)     | 589 (3.2)    | 0.032 |
| COPD/asthma/oxygen              | 5705 (23.3)  | 4840 (22.3)  | 1763 (22.0)                    | 21467 (22.8)    | 2915 (23.0) | 4667 (24.4)   | 4032 (21.9)  | 0.025 |
| Dementia                        | 357 (1.5)    | 127 (0.6)    | 64 (0.8)                       | 728 (0.8)       | 89 (0.7)    | 142 (0.7)     | 172 (0.9)    | 0.031 |
| Depression                      | 6259 (25.6)  | 5020 (23.1)  | 2079 (25.9)                    | 23856 (25.4)    | 3285 (25.9) | 4977 (26.0)   | 5003 (27.1)  | 0.030 |
| Diabetes                        | 4738 (19.3)  | 3443 (15.8)  | 1382 (17.2)                    | 18006 (19.2)    | 2393 (18.9) | 3559 (18.6)   | 3156 (17.1)  | 0.040 |
| Epilepsy                        | 1464 (6.0)   | 1091 (5.0)   | 386 (4.8)                      | 3978 (4.2)      | 605 (4.8)   | 874 (4.6)     | 943 (5.1)    | 0.029 |
| HIV                             | 760 (3.1)    | 520 (2.4)    | 129 (1.6)                      | 2474 (2.6)      | 267 (2.1)   | 511 (2.7)     | 343 (1.9)    | 0.042 |
| Intentional self-harm           | 25 (0.1)     | 33 (0.2)     | 11 (0.1)                       | 156 (0.2)       | 24 (0.2)    | 48 (0.3)      | 29 (0.2)     | 0.013 |
| Liver disease                   | 2704 (11.0)  | 1723 (7.9)   | 544 (6.8)                      | 7084 (7.5)      | 861 (6.8)   | 1491 (7.8)    | 1291 (7.0)   | 0.054 |
| Musculoskeletal injury          | 2291 (9.4)   | 2445 (11.3)  | 1001 (12.5)                    | 11092 (11.8)    | 1492 (11.8) | 2280 (11.9)   | 1729 (9.4)   | 0.046 |
| Multiple sclerosis              | 620 (2.5)    | 107 (0.5)    | 35 (0.4)                       | 504 (0.5)       | 72 (0.6)    | 79 (0.4)      | 237 (1.3)    | 0.070 |
| Obesity                         | 1598 (6.5)   | 1041 (4.8)   | 477 (5.9)                      | 6014 (6.4)      | 680 (5.4)   | 1184 (6.2)    | 1033 (5.6)   | 0.032 |
| Pneumonia                       | 1464 (6.0)   | 1023 (4.7)   | 334 (4.2)                      | 4258 (4.5)      | 567 (4.5)   | 835 (4.4)     | 734 (4.0)    | 0.032 |
| Psychosis                       | 1258 (5.1)   | 715 (3.3)    | 308 (3.8)                      | 3556 (3.8)      | 479 (3.8)   | 841 (4.4)     | 566 (3.1)    | 0.041 |
| Renal dysfunction               | 1280 (5.2)   | 777 (3.6)    | 323 (4.0)                      | 4446 (4.7)      | 480 (3.8)   | 832 (4.4)     | 742 (4.0)    | 0.034 |
| Spasticity                      | 5060 (20.7)  | 2387 (11.0)  | 893 (11.1)                     | 10282 (10.9)    | 1491 (11.8) | 2156 (11.3)   | 2644 (14.3)  | 0.098 |
| Urinary calculus                | 630 (2.6)    | 596 (2.7)    | 268 (3.3)                      | 2753 (2.9)      | 336 (2.6)   | 591 (3.1)     | 474 (2.6)    | 0.021 |
| Urinary tract infection         | 3364 (13.7)  | 2489 (11.5)  | 1098 (13.7)                    | 11084 (11.8)    | 1502 (11.8) | 2202 (11.5)   | 2077 (11.3)  | 0.035 |
| <b>Pain conditions (n (%))</b>  |              |              |                                |                 |             |               |              |       |
| Abdominal pain                  | 5589 (22.8)  | 5021 (23.1)  | 2001 (25.0)                    | 22572 (24.0)    | 2999 (23.6) | 4581 (24.0)   | 4038 (21.9)  | 0.028 |
| Back and neck pain              | 16158 (66.0) | 14089 (64.8) | 5492 (68.5)                    | 61455 (65.4)    | 8599 (67.8) | 12896 (67.5)  | 12906 (70.0) | 0.048 |
| Back pain without radiculopathy | 15167 (61.9) | 13549 (62.4) | 5290 (66.0)                    | 58618 (62.4)    | 8241 (65.0) | 12249 (64.1)  | 11968 (64.9) | 0.039 |
| Back pain with radiculopathy    | 3182 (13.0)  | 2484 (11.4)  | 1054 (13.1)                    | 11596 (12.3)    | 1633 (12.9) | 2677 (14.0)   | 3114 (16.9)  | 0.055 |
| Dental pain                     | 1064 (4.3)   | 1205 (5.5)   | 489 (6.1)                      | 5678 (6.0)      | 662 (5.2)   | 1189 (6.2)    | 900 (4.9)    | 0.038 |
| Diabetic neuropathy             | 650 (2.7)    | 399 (1.8)    | 197 (2.5)                      | 2603 (2.8)      | 333 (2.6)   | 529 (2.8)     | 495 (2.7)    | 0.022 |
| Fibromyalgia                    | 2716 (11.1)  | 2259 (10.4)  | 944 (11.8)                     | 9830 (10.5)     | 1579 (12.4) | 1974 (10.3)   | 2940 (15.9)  | 0.064 |
| Headache                        | 4273 (17.5)  | 4500 (20.7)  | 1756 (21.9)                    | 17895 (19.0)    | 2612 (20.6) | 3719 (19.5)   | 3907 (21.2)  | 0.045 |
| Osteoarthritis                  | 4252 (17.4)  | 3639 (16.7)  | 1325 (16.5)                    | 15834 (16.8)    | 2239 (17.6) | 3333 (17.4)   | 3060 (16.6)  | 0.014 |
| Rheumatoid arthritis            | 808 (3.3)    | 748 (3.4)    | 247 (3.1)                      | 3036 (3.2)      | 386 (3.0)   | 589 (3.1)     | 605 (3.3)    | 0.010 |
| Postherpetic neuralgia          | 37 (0.2)     | 19 (0.1)     | 7 (0.1)                        | 100 (0.1)       | 11 (0.1)    | 16 (0.1)      | 28 (0.2)     | 0.010 |
| Other arthritis                 | 13054 (53.3) | 10743 (49.4) | 4147 (51.7)                    | 48945 (52.1)    | 6609 (52.1) | 10069 (52.7)  | 9520 (51.6)  | 0.027 |

|                                                                                       | Baclofen             | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone           | Methocarbamol        | Tizanidine           | SMD   |
|---------------------------------------------------------------------------------------|----------------------|----------------------|--------------------------------|-------------------|----------------------|----------------------|----------------------|-------|
| Other neuropathy                                                                      | 6411 (26.2)          | 4870 (22.4)          | 1914 (23.9)                    | 22151 (23.6)      | 3146 (24.8)          | 4836 (25.3)          | 5823 (31.6)          | 0.074 |
| Other unspecified pain                                                                | 5371 (21.9)          | 2636 (12.1)          | 1456 (18.2)                    | 18375 (19.5)      | 1662 (13.1)          | 3765 (19.7)          | 4065 (22.0)          | 0.124 |
| <b>Other prescription fills (n (%))</b>                                               |                      |                      |                                |                   |                      |                      |                      |       |
| Antibiotics                                                                           | 15959 (65.2)         | 15052 (69.3)         | 5710 (71.2)                    | 64865 (69.0)      | 8874 (70.0)          | 13223 (69.2)         | 12244 (66.4)         | 0.052 |
| Anticonvulsants                                                                       | 4245 (17.3)          | 2874 (13.2)          | 1152 (14.4)                    | 12731 (13.5)      | 1935 (15.3)          | 2747 (14.4)          | 3462 (18.8)          | 0.066 |
| Antidepressants, SSRIs                                                                | 8129 (33.2)          | 7389 (34.0)          | 2838 (35.4)                    | 32164 (34.2)      | 4672 (36.8)          | 6630 (34.7)          | 6760 (36.7)          | 0.035 |
| Antidepressants, SNRIs                                                                | 3644 (14.9)          | 2533 (11.7)          | 1092 (13.6)                    | 12801 (13.6)      | 1699 (13.4)          | 2612 (13.7)          | 3023 (16.4)          | 0.047 |
| Antidepressants, TCAs                                                                 | 4058 (16.6)          | 3285 (15.1)          | 1218 (15.2)                    | 13373 (14.2)      | 2011 (15.9)          | 2656 (13.9)          | 3152 (17.1)          | 0.040 |
| Antidepressants, other                                                                | 5706 (23.3)          | 4416 (20.3)          | 1681 (21.0)                    | 19456 (20.7)      | 2875 (22.7)          | 4146 (21.7)          | 4187 (22.7)          | 0.034 |
| Antidiabetics                                                                         | 4085 (16.7)          | 2967 (13.7)          | 1257 (15.7)                    | 16366 (17.4)      | 2126 (16.8)          | 3176 (16.6)          | 2818 (15.3)          | 0.040 |
| Antipsychotics, atypical                                                              | 3925 (16.0)          | 2739 (12.6)          | 1174 (14.6)                    | 13321 (14.2)      | 1761 (13.9)          | 2969 (15.5)          | 2674 (14.5)          | 0.038 |
| Antipsychotics, typical                                                               | 1405 (5.7)           | 993 (4.6)            | 378 (4.7)                      | 4004 (4.3)        | 518 (4.1)            | 777 (4.1)            | 736 (4.0)            | 0.032 |
| Barbiturates                                                                          | 462 (1.9)            | 201 (0.9)            | 59 (0.7)                       | 498 (0.5)         | 110 (0.9)            | 113 (0.6)            | 97 (0.5)             | 0.048 |
| Benzodiazepines                                                                       | 11190 (45.7)         | 13701 (63.1)         | 4470 (55.8)                    | 47419 (50.4)      | 6742 (53.1)          | 9979 (52.2)          | 10399 (56.4)         | 0.130 |
| CNS stimulants                                                                        | 422 (1.7)            | 353 (1.6)            | 187 (2.3)                      | 2005 (2.1)        | 182 (1.4)            | 354 (1.9)            | 458 (2.5)            | 0.034 |
| Dementia agents                                                                       | 124 (0.5)            | 60 (0.3)             | 23 (0.3)                       | 311 (0.3)         | 44 (0.3)             | 75 (0.4)             | 81 (0.4)             | 0.016 |
| Gabapentinoids                                                                        | 7805 (31.9)          | 4061 (18.7)          | 1712 (21.4)                    | 22256 (23.7)      | 2778 (21.9)          | 4885 (25.6)          | 5884 (31.9)          | 0.142 |
| Lithium                                                                               | 314 (1.3)            | 273 (1.3)            | 95 (1.2)                       | 1090 (1.2)        | 166 (1.3)            | 238 (1.2)            | 232 (1.3)            | 0.006 |
| Multiple sclerosis agents                                                             | 242 (1.0)            | 42 (0.2)             | 12 (0.1)                       | 192 (0.2)         | 28 (0.2)             | 26 (0.1)             | 106 (0.6)            | 0.048 |
| NSAIDs                                                                                | 12063 (49.3)         | 10373 (47.7)         | 4683 (58.4)                    | 50772 (54.0)      | 6961 (54.9)          | 10680 (55.9)         | 9207 (49.9)          | 0.096 |
| Other sedative hypnotics                                                              | 4836 (19.7)          | 4045 (18.6)          | 1269 (15.8)                    | 15950 (17.0)      | 2362 (18.6)          | 3248 (17.0)          | 3525 (19.1)          | 0.044 |
| Smoking cessation                                                                     | 2837 (11.6)          | 2359 (10.9)          | 950 (11.8)                     | 12253 (13.0)      | 1551 (12.2)          | 2364 (12.4)          | 2278 (12.4)          | 0.025 |
| Triptans                                                                              | 1202 (4.9)           | 1182 (5.4)           | 474 (5.9)                      | 4921 (5.2)        | 777 (6.1)            | 971 (5.1)            | 1220 (6.6)           | 0.032 |
| Other CNS depressants                                                                 | 125 (0.5)            | 84 (0.4)             | 26 (0.3)                       | 330 (0.4)         | 53 (0.4)             | 62 (0.3)             | 98 (0.5)             | 0.016 |
| <b>Prescription opioid utilization (n (%))</b>                                        |                      |                      |                                |                   |                      |                      |                      |       |
| Prescription opioid on index date                                                     |                      |                      |                                |                   |                      |                      |                      |       |
| Buprenorphine                                                                         | 35 (0.1)             | 22 (0.1)             | 9 (0.1)                        | 119 (0.1)         | 8 (0.1)              | 62 (0.3)             | 39 (0.2)             | 0.024 |
| Butorphanol                                                                           | 44 (0.2)             | 155 (0.7)            | 42 (0.5)                       | 322 (0.3)         | 80 (0.6)             | 53 (0.3)             | 94 (0.5)             | 0.036 |
| Codeine                                                                               | 2577 (10.5)          | 1711 (7.9)           | 615 (7.7)                      | 6689 (7.1)        | 812 (6.4)            | 1514 (7.9)           | 810 (4.4)            | 0.082 |
| Dihydrocodeine                                                                        | 22 (0.1)             | 90 (0.4)             | 30 (0.4)                       | 290 (0.3)         | 84 (0.7)             | 91 (0.5)             | 52 (0.3)             | 0.036 |
| Fentanyl                                                                              | 1956 (8.0)           | 1264 (5.8)           | 416 (5.2)                      | 4844 (5.2)        | 817 (6.4)            | 886 (4.6)            | 1460 (7.9)           | 0.066 |
| Hydrocodone                                                                           | 12597 (51.4)         | 14298 (65.8)         | 5256 (65.6)                    | 58218 (61.9)      | 7444 (58.7)          | 11919 (62.3)         | 10554 (57.2)         | 0.124 |
| Hydromorphone                                                                         | 904 (3.7)            | 369 (1.7)            | 138 (1.7)                      | 1585 (1.7)        | 173 (1.4)            | 384 (2.0)            | 375 (2.0)            | 0.050 |
| Levorphanol                                                                           | 3 (0.0)              | 1 (0.0)              | 0 (0.0)                        | 5 (0.0)           | 2 (0.0)              | 1 (0.0)              | 0 (0.0)              | 0.009 |
| Meperidine                                                                            | 72 (0.3)             | 150 (0.7)            | 37 (0.5)                       | 428 (0.5)         | 50 (0.4)             | 116 (0.6)            | 82 (0.4)             | 0.022 |
| Methadone                                                                             | 1907 (7.8)           | 1080 (5.0)           | 291 (3.6)                      | 3679 (3.9)        | 517 (4.1)            | 703 (3.7)            | 1201 (6.5)           | 0.081 |
| Morphine                                                                              | 2462 (10.1)          | 1340 (6.2)           | 393 (4.9)                      | 5334 (5.7)        | 727 (5.7)            | 1105 (5.8)           | 1573 (8.5)           | 0.079 |
| Opium                                                                                 | 1 (0.0)              | 9 (0.0)              | 0 (0.0)                        | 24 (0.0)          | 1 (0.0)              | 4 (0.0)              | 3 (0.0)              | 0.014 |
| Oxycodone                                                                             | 7100 (29.0)          | 7208 (33.2)          | 2158 (26.9)                    | 28745 (30.6)      | 4029 (31.8)          | 5603 (29.3)          | 6177 (33.5)          | 0.063 |
| Oxymorphone                                                                           | 71 (0.3)             | 44 (0.2)             | 10 (0.1)                       | 242 (0.3)         | 22 (0.2)             | 46 (0.2)             | 87 (0.5)             | 0.024 |
| Pentazocine                                                                           | 42 (0.2)             | 156 (0.7)            | 49 (0.6)                       | 340 (0.4)         | 91 (0.7)             | 89 (0.5)             | 82 (0.4)             | 0.035 |
| Propoxyphene                                                                          | 234 (1.0)            | 830 (3.8)            | 350 (4.4)                      | 3451 (3.7)        | 515 (4.1)            | 763 (4.0)            | 487 (2.6)            | 0.078 |
| Tapentadol                                                                            | 24 (0.1)             | 29 (0.1)             | 6 (0.1)                        | 82 (0.1)          | 4 (0.0)              | 27 (0.1)             | 31 (0.2)             | 0.018 |
| Tramadol                                                                              | 5031 (20.5)          | 2929 (13.5)          | 1756 (21.9)                    | 19445 (20.7)      | 2571 (20.3)          | 4005 (20.9)          | 3153 (17.1)          | 0.083 |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 172.32 (18.41)       | 172.24 (18.62)       | 172.38 (18.47)                 | 172.09 (18.81)    | 172.60 (18.10)       | 171.73 (19.23)       | 173.26 (17.50)       | 0.030 |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                      |                      |                                |                   |                      |                      |                      |       |
| (Index - 180) to (index - 151)                                                        | 2200.60<br>(3763.49) | 2037.70<br>(3473.13) | 1616.44<br>(2988.81)           | 1596.53 (2807.31) | 1757.09<br>(2932.59) | 1552.67<br>(2812.34) | 2111.27<br>(3406.40) | 0.101 |
| (Index - 150) to (index - 121)                                                        | 2303.54<br>(3744.13) | 2142.84<br>(3524.32) | 1713.26<br>(2998.30)           | 1685.83 (2908.33) | 1861.94<br>(3012.09) | 1613.74<br>(2831.85) | 2227.91<br>(3510.86) | 0.105 |

|                                           | Baclofen             | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone           | Methocarbamol        | Tizanidine           | SMD   |
|-------------------------------------------|----------------------|----------------------|--------------------------------|-------------------|----------------------|----------------------|----------------------|-------|
| (Index - 120) to (index - 91)             | 2569.50<br>(3920.81) | 2412.62<br>(3775.42) | 1874.99<br>(3332.14)           | 1855.49 (3008.39) | 2044.15<br>(3110.12) | 1763.90<br>(2897.49) | 2442.92<br>(3716.05) | 0.115 |
| (Index - 90) to (index - 61)              | 2592.82<br>(3927.06) | 2432.76<br>(3760.30) | 1916.86<br>(3662.00)           | 1878.81 (2994.07) | 2072.92<br>(3066.03) | 1796.96<br>(2923.94) | 2483.15<br>(3641.49) | 0.113 |
| (Index - 60) to (index - 31)              | 2608.33<br>(3968.67) | 2432.00<br>(3686.72) | 1907.65<br>(3512.93)           | 1903.96 (3020.82) | 2074.47<br>(3056.29) | 1815.17<br>(2956.83) | 2474.72<br>(3645.12) | 0.112 |
| (Index - 30) to index                     | 3243.69<br>(5043.90) | 3076.98<br>(4748.32) | 2206.97<br>(3905.20)           | 2223.54 (3558.47) | 2477.96<br>(3794.34) | 2108.04<br>(3499.88) | 3196.52<br>(4731.23) | 0.140 |
| <b>Healthcare utilization (mean (SD))</b> |                      |                      |                                |                   |                      |                      |                      |       |
| Number of physician visits                | 8.35 (10.11)         | 8.88 (8.13)          | 9.35 (8.67)                    | 9.10 (8.81)       | 9.30 (8.18)          | 9.23 (8.71)          | 9.30 (8.14)          | 0.043 |
| Number of distinct prescribed medications | 14.38 (7.18)         | 14.22 (7.33)         | 14.62 (7.45)                   | 14.41 (7.39)      | 14.88 (7.54)         | 14.74 (7.45)         | 14.48 (7.35)         | 0.037 |
| Number of hospitalizations                | 0.36 (0.98)          | 0.31 (0.82)          | 0.30 (0.82)                    | 0.33 (0.88)       | 0.31 (0.82)          | 0.37 (1.13)          | 0.28 (0.76)          | 0.044 |
| Number of hospitalization days            | 2.16 (8.34)          | 1.60 (6.92)          | 1.51 (5.17)                    | 1.51 (9.65)       | 1.65 (6.19)          | 1.65 (11.28)         | 1.35 (9.95)          | 0.033 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 4B. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in Medicaid Analytic eXtract (MAX), 2000-2014 (post-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 4317.17       | 4502.02       | 4516.39                        | 4528.80         | 4540.96       | 4507.05       | 4457.50       |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 43.90 (10.52) | 43.75 (10.34) | 43.78 (10.63)                  | 43.86 (10.59)   | 43.85 (10.51) | 43.73 (10.71) | 43.77 (10.43) | 0.007 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.014 |
| Unknown                                | 4.0 (0.1)     | 4.5 (0.1)     | 3.2 (0.1)                      | 4.9 (0.1)       | 3.8 (0.1)     | 5.3 (0.1)     | 5.1 (0.1)     |       |
| Male                                   | 1409.9 (32.7) | 1481.9 (32.9) | 1500.7 (33.2)                  | 1530.2 (33.8)   | 1534.3 (33.8) | 1515.2 (33.6) | 1497.6 (33.6) |       |
| Female                                 | 2903.3 (67.2) | 3015.7 (67.0) | 3012.5 (66.7)                  | 2993.7 (66.1)   | 3002.8 (66.1) | 2986.6 (66.3) | 2954.8 (66.3) |       |
| Race                                   |               |               |                                |                 |               |               |               | 0.038 |
| Asian                                  | 54.8 (1.3)    | 71.3 (1.6)    | 67.1 (1.5)                     | 65.8 (1.5)      | 72.8 (1.6)    | 65.2 (1.4)    | 64.3 (1.4)    |       |
| Black                                  | 519.1 (12.0)  | 629.2 (14.0)  | 633.2 (14.0)                   | 641.7 (14.2)    | 580.1 (12.8)  | 621.7 (13.8)  | 611.2 (13.7)  |       |
| White                                  | 3510.4 (81.3) | 3512.0 (78.0) | 3529.7 (78.2)                  | 3552.4 (78.4)   | 3612.4 (79.6) | 3554.8 (78.9) | 3529.7 (79.2) |       |
| Other                                  | 232.9 (5.4)   | 289.5 (6.4)   | 286.3 (6.3)                    | 268.9 (5.9)     | 275.7 (6.1)   | 265.3 (5.9)   | 252.2 (5.7)   |       |
| Ethnicity                              |               |               |                                |                 |               |               |               | 0.025 |
| Unknown                                | 138.4 (3.2)   | 160.3 (3.6)   | 150.2 (3.3)                    | 150.1 (3.3)     | 151.4 (3.3)   | 139.8 (3.1)   | 141.1 (3.2)   |       |
| Hispanic                               | 82.9 (1.9)    | 113.8 (2.5)   | 121.8 (2.7)                    | 103.6 (2.3)     | 109.3 (2.4)   | 110.5 (2.5)   | 95.9 (2.2)    |       |
| Non-Hispanic                           | 4095.8 (94.9) | 4227.9 (93.9) | 4244.4 (94.0)                  | 4275.1 (94.4)   | 4280.2 (94.3) | 4256.8 (94.4) | 4220.6 (94.7) |       |
| State                                  |               |               |                                |                 |               |               |               | 0.098 |
| AK                                     | 13.8 (0.3)    | 16.1 (0.4)    | 15.7 (0.3)                     | 15.9 (0.4)      | 17.3 (0.4)    | 15.6 (0.3)    | 15.3 (0.3)    |       |
| AL                                     | 65.8 (1.5)    | 53.9 (1.2)    | 67.8 (1.5)                     | 65.3 (1.4)      | 61.7 (1.4)    | 62.1 (1.4)    | 66.1 (1.5)    |       |
| AR                                     | 27.2 (0.6)    | 30.3 (0.7)    | 30.8 (0.7)                     | 30.3 (0.7)      | 31.1 (0.7)    | 30.6 (0.7)    | 32.1 (0.7)    |       |
| AZ                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| CA                                     | 31.6 (0.7)    | 33.7 (0.7)    | 30.4 (0.7)                     | 33.8 (0.7)      | 31.6 (0.7)    | 34.7 (0.8)    | 22.2 (0.5)    |       |
| CO                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| CT                                     | 91.5 (2.1)    | 146.8 (3.3)   | 98.4 (2.2)                     | 104.2 (2.3)     | 118.2 (2.6)   | 102.3 (2.3)   | 102.3 (2.3)   |       |
| DC                                     | 3.3 (0.1)     | 4.7 (0.1)     | 4.4 (0.1)                      | 5.0 (0.1)       | 6.2 (0.1)     | 5.0 (0.1)     | 5.0 (0.1)     |       |
| DE                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| FL                                     | 124.4 (2.9)   | 127.0 (2.8)   | 141.4 (3.1)                    | 139.3 (3.1)     | 116.3 (2.6)   | 147.7 (3.3)   | 134.3 (3.0)   |       |
| GA                                     | 175.3 (4.1)   | 184.7 (4.1)   | 185.5 (4.1)                    | 184.9 (4.1)     | 178.5 (3.9)   | 185.9 (4.1)   | 183.9 (4.1)   |       |
| HI                                     | 14.4 (0.3)    | 12.9 (0.3)    | 13.9 (0.3)                     | 13.3 (0.3)      | 13.6 (0.3)    | 12.5 (0.3)    | 14.1 (0.3)    |       |
| IA                                     | 0.4 (0.0)     | 0.6 (0.0)     | 0.7 (0.0)                      | 0.6 (0.0)       | 0.6 (0.0)     | 0.6 (0.0)     | 0.6 (0.0)     |       |
| ID                                     | 35.3 (0.8)    | 40.5 (0.9)    | 43.4 (1.0)                     | 39.8 (0.9)      | 38.3 (0.8)    | 38.3 (0.8)    | 42.7 (1.0)    |       |
| IL                                     | 124.3 (2.9)   | 166.8 (3.7)   | 128.2 (2.8)                    | 134.7 (3.0)     | 139.2 (3.1)   | 142.0 (3.1)   | 139.0 (3.1)   |       |
| IN                                     | 298.9 (6.9)   | 296.1 (6.6)   | 314.8 (7.0)                    | 317.6 (7.0)     | 302.5 (6.7)   | 320.2 (7.1)   | 324.4 (7.3)   |       |
| KS                                     | 38.0 (0.9)    | 31.7 (0.7)    | 34.9 (0.8)                     | 33.9 (0.7)      | 29.5 (0.7)    | 34.9 (0.8)    | 28.8 (0.6)    |       |
| KY                                     | 2.9 (0.1)     | 2.0 (0.0)     | 2.2 (0.0)                      | 1.8 (0.0)       | 1.7 (0.0)     | 2.1 (0.0)     | 2.0 (0.0)     |       |
| LA                                     | 206.5 (4.8)   | 236.3 (5.2)   | 215.0 (4.8)                    | 225.4 (5.0)     | 180.7 (4.0)   | 213.5 (4.7)   | 218.6 (4.9)   |       |
| MA                                     | 5.0 (0.1)     | 5.8 (0.1)     | 6.0 (0.1)                      | 6.8 (0.2)       | 5.7 (0.1)     | 7.6 (0.2)     | 6.5 (0.1)     |       |
| MD                                     | 1.8 (0.0)     | 2.8 (0.1)     | 2.0 (0.0)                      | 1.9 (0.0)       | 2.3 (0.1)     | 2.1 (0.0)     | 2.1 (0.0)     |       |
| ME                                     | 60.4 (1.4)    | 65.4 (1.5)    | 67.0 (1.5)                     | 59.4 (1.3)      | 55.9 (1.2)    | 53.2 (1.2)    | 51.9 (1.2)    |       |
| MI                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| MN                                     | 72.2 (1.7)    | 82.9 (1.8)    | 75.5 (1.7)                     | 72.7 (1.6)      | 82.2 (1.8)    | 75.8 (1.7)    | 69.8 (1.6)    |       |
| MO                                     | 684.0 (15.8)  | 642.8 (14.3)  | 716.4 (15.9)                   | 740.0 (16.3)    | 859.5 (18.9)  | 735.9 (16.3)  | 753.4 (16.9)  |       |
| MS                                     | 39.5 (0.9)    | 52.2 (1.2)    | 49.4 (1.1)                     | 49.6 (1.1)      | 48.2 (1.1)    | 49.3 (1.1)    | 51.7 (1.2)    |       |
| MT                                     | 28.5 (0.7)    | 27.6 (0.6)    | 29.4 (0.7)                     | 31.4 (0.7)      | 35.0 (0.8)    | 28.9 (0.6)    | 30.0 (0.7)    |       |
| NC                                     | 438.9 (10.2)  | 468.7 (10.4)  | 440.2 (9.7)                    | 447.5 (9.9)     | 455.3 (10.0)  | 457.3 (10.1)  | 439.1 (9.9)   |       |
| ND                                     | 9.8 (0.2)     | 18.2 (0.4)    | 13.9 (0.3)                     | 13.9 (0.3)      | 15.0 (0.3)    | 11.1 (0.2)    | 12.5 (0.3)    |       |
| NE                                     | 0.7 (0.0)     | 0.9 (0.0)     | 0.9 (0.0)                      | 0.6 (0.0)       | 0.9 (0.0)     | 0.8 (0.0)     | 1.4 (0.0)     |       |
| NH                                     | 38.1 (0.9)    | 44.1 (1.0)    | 37.1 (0.8)                     | 39.1 (0.9)      | 32.4 (0.7)    | 38.1 (0.8)    | 38.2 (0.9)    |       |

|                                                                | Baclofen              | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine       | Metaxalone            | Methocarbamol         | Tizanidine            | SMD   |
|----------------------------------------------------------------|-----------------------|----------------------|--------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-------|
| NJ                                                             | 33.7 (0.8)            | 50.4 (1.1)           | 42.7 (0.9)                     | 44.6 (1.0)            | 47.4 (1.0)            | 45.2 (1.0)            | 38.0 (0.9)            |       |
| NM                                                             | 3.7 (0.1)             | 2.9 (0.1)            | 3.6 (0.1)                      | 2.8 (0.1)             | 3.0 (0.1)             | 2.3 (0.1)             | 2.1 (0.0)             |       |
| NV                                                             | 4.3 (0.1)             | 6.3 (0.1)            | 5.9 (0.1)                      | 5.9 (0.1)             | 5.3 (0.1)             | 6.0 (0.1)             | 5.1 (0.1)             |       |
| NY                                                             | 269.6 (6.2)           | 308.2 (6.8)          | 283.1 (6.3)                    | 283.7 (6.3)           | 283.7 (6.2)           | 282.5 (6.3)           | 267.9 (6.0)           |       |
| OH                                                             | 5.0 (0.1)             | 4.7 (0.1)            | 4.8 (0.1)                      | 4.8 (0.1)             | 4.8 (0.1)             | 5.1 (0.1)             | 5.1 (0.1)             |       |
| OK                                                             | 9.1 (0.2)             | 10.0 (0.2)           | 11.8 (0.3)                     | 11.9 (0.3)            | 8.3 (0.2)             | 10.6 (0.2)            | 9.0 (0.2)             |       |
| OR                                                             | 1.7 (0.0)             | 2.0 (0.0)            | 2.0 (0.0)                      | 1.9 (0.0)             | 2.0 (0.0)             | 2.1 (0.0)             | 1.9 (0.0)             |       |
| PA                                                             | 107.7 (2.5)           | 133.9 (3.0)          | 135.2 (3.0)                    | 135.4 (3.0)           | 134.2 (3.0)           | 131.1 (2.9)           | 128.7 (2.9)           |       |
| RI                                                             | 14.5 (0.3)            | 21.0 (0.5)           | 20.2 (0.4)                     | 19.5 (0.4)            | 19.4 (0.4)            | 20.0 (0.4)            | 18.3 (0.4)            |       |
| SC                                                             | 81.7 (1.9)            | 92.4 (2.1)           | 88.6 (2.0)                     | 88.6 (2.0)            | 88.2 (1.9)            | 86.1 (1.9)            | 87.9 (2.0)            |       |
| SD                                                             | 19.8 (0.5)            | 29.6 (0.7)           | 22.0 (0.5)                     | 22.0 (0.5)            | 23.3 (0.5)            | 16.1 (0.4)            | 19.7 (0.4)            |       |
| TN                                                             | 449.3 (10.4)          | 415.3 (9.2)          | 428.3 (9.5)                    | 421.9 (9.3)           | 421.4 (9.3)           | 432.7 (9.6)           | 428.7 (9.6)           |       |
| TX                                                             | 0 (0.0)               | 0 (0.0)              | 0 (0.0)                        | 0 (0.0)               | 0 (0.0)               | 0 (0.0)               | 0 (0.0)               |       |
| UT                                                             | 3.6 (0.1)             | 5.0 (0.1)            | 5.4 (0.1)                      | 4.8 (0.1)             | 4.8 (0.1)             | 4.7 (0.1)             | 5.2 (0.1)             |       |
| VA                                                             | 222.1 (5.1)           | 220.7 (4.9)          | 222.5 (4.9)                    | 224.4 (5.0)           | 215.8 (4.8)           | 212.3 (4.7)           | 208.0 (4.7)           |       |
| VT                                                             | 39.6 (0.9)            | 51.0 (1.1)           | 51.6 (1.1)                     | 50.6 (1.1)            | 44.4 (1.0)            | 50.1 (1.1)            | 50.4 (1.1)            |       |
| WA                                                             | 3.2 (0.1)             | 4.0 (0.1)            | 4.0 (0.1)                      | 4.0 (0.1)             | 4.2 (0.1)             | 3.9 (0.1)             | 4.4 (0.1)             |       |
| WI                                                             | 107.8 (2.5)           | 120.0 (2.7)          | 117.8 (2.6)                    | 116.6 (2.6)           | 110.2 (2.4)           | 110.7 (2.5)           | 109.3 (2.5)           |       |
| WV                                                             | 298.5 (6.9)           | 218.6 (4.9)          | 287.6 (6.4)                    | 264.3 (5.8)           | 250.1 (5.5)           | 262.2 (5.8)           | 268.9 (6.0)           |       |
| WY                                                             | 9.9 (0.2)             | 10.7 (0.2)           | 13.9 (0.3)                     | 12.2 (0.3)            | 11.0 (0.2)            | 15.3 (0.3)            | 11.1 (0.2)            |       |
| Socioeconomic status (% (SD)) <sup>1</sup>                     |                       |                      |                                |                       |                       |                       |                       |       |
| Households with 1-1.5 occupants per room                       | 1.77 (1.74)           | 1.76 (1.69)          | 1.79 (1.78)                    | 1.78 (1.75)           | 1.73 (1.66)           | 1.82 (1.84)           | 1.77 (1.73)           | 0.019 |
| Households with > 1.5 occupants per room                       | 0.74 (1.14)           | 0.70 (0.99)          | 0.74 (1.14)                    | 0.73 (1.09)           | 0.71 (1.05)           | 0.77 (1.17)           | 0.73 (1.08)           | 0.024 |
| Median value of homes (mean (SD))                              | 159647.09 (111879.69) | 152896.00 (94394.19) | 151858.17 (97241.17)           | 156251.59 (107157.18) | 154103.86 (102074.17) | 160015.68 (110306.71) | 156734.06 (107454.08) | 0.037 |
| Median value of homes ranked 1-100 (mean (SD))                 | 43.16 (24.09)         | 42.14 (23.92)        | 41.67 (23.36)                  | 42.35 (24.13)         | 42.13 (23.60)         | 43.18 (24.53)         | 42.16 (24.35)         | 0.027 |
| Median household income (mean (SD))                            | 46221.63 (14726.74)   | 45862.59 (14779.76)  | 45115.69 (13976.20)            | 45991.64 (14875.90)   | 45902.88 (14864.01)   | 45881.42 (14705.87)   | 46169.11 (15203.33)   | 0.026 |
| Median value of income ranked 1-100 (mean (SD))                | 35.59 (23.94)         | 35.05 (24.27)        | 33.95 (23.40)                  | 35.25 (24.22)         | 34.99 (24.06)         | 35.15 (24.22)         | 35.45 (24.63)         | 0.024 |
| Individuals below the poverty line                             | 18.73 (8.53)          | 19.11 (8.68)         | 19.21 (8.69)                   | 19.01 (8.79)          | 19.07 (8.61)          | 19.02 (8.80)          | 18.97 (8.71)          | 0.020 |
| Individuals > 16 years who are unemployed                      | 7.54 (3.76)           | 7.79 (3.82)          | 7.62 (3.80)                    | 7.69 (3.82)           | 7.66 (3.74)           | 7.70 (3.83)           | 7.60 (3.72)           | 0.026 |
| Individuals > 25 years with < 12 <sup>th</sup> grade education | 34.65 (8.54)          | 34.71 (8.14)         | 35.13 (7.88)                   | 34.73 (8.23)          | 34.84 (8.17)          | 34.70 (8.19)          | 34.78 (8.20)          | 0.021 |
| Individuals > 25 years with 4-year college education           | 13.36 (6.77)          | 13.12 (6.51)         | 12.92 (6.25)                   | 13.25 (6.52)          | 13.15 (6.49)          | 13.10 (6.48)          | 13.20 (6.60)          | 0.025 |
| Households with > 1 persons per room                           | 2.50 (2.57)           | 2.46 (2.34)          | 2.53 (2.59)                    | 2.51 (2.50)           | 2.44 (2.36)           | 2.59 (2.71)           | 2.49 (2.47)           | 0.023 |
| Socioeconomic status index score (mean (SD))                   | 52.24 (5.95)          | 52.01 (5.99)         | 51.79 (5.74)                   | 52.08 (5.99)          | 52.01 (5.92)          | 52.11 (5.97)          | 52.09 (6.09)          | 0.026 |
| Rural-urban continuum codes <sup>1</sup>                       |                       |                      |                                |                       |                       |                       |                       | 0.029 |
| Unknown                                                        | 29.1 (0.7)            | 29.7 (0.7)           | 28.4 (0.6)                     | 29.9 (0.7)            | 24.8 (0.5)            | 24.3 (0.5)            | 25.3 (0.6)            |       |
| Metropolitan                                                   | 2994.5 (69.4)         | 3011.0 (66.9)        | 3084.7 (68.3)                  | 3137.1 (69.3)         | 3092.8 (68.1)         | 3062.4 (68.0)         | 3063.0 (68.7)         |       |
| Rural                                                          | 324.0 (7.5)           | 355.5 (7.9)          | 352.3 (7.8)                    | 339.3 (7.5)           | 341.3 (7.5)           | 370.5 (8.2)           | 336.3 (7.5)           |       |
| Urban                                                          | 969.3 (22.5)          | 1105.6 (24.6)        | 1050.7 (23.3)                  | 1022.2 (22.6)         | 1081.8 (23.8)         | 1049.6 (23.3)         | 1032.6 (23.2)         |       |
| Year                                                           |                       |                      |                                |                       |                       |                       |                       | 0.092 |
| 2000                                                           | 191.3 (4.4)           | 183.3 (4.1)          | 174.0 (3.9)                    | 166.3 (3.7)           | 172.7 (3.8)           | 169.6 (3.8)           | 152.2 (3.4)           |       |
| 2001                                                           | 352.9 (8.2)           | 382.9 (8.5)          | 359.9 (8.0)                    | 341.3 (7.5)           | 389.4 (8.6)           | 324.1 (7.2)           | 328.5 (7.4)           |       |
| 2002                                                           | 317.1 (7.3)           | 361.3 (8.0)          | 330.5 (7.3)                    | 314.9 (7.0)           | 377.1 (8.3)           | 313.1 (6.9)           | 318.1 (7.1)           |       |

|                                 | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|---------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| 2003                            | 450.5 (10.4)  | 520.3 (11.6)  | 495.5 (11.0)                   | 505.4 (11.2)    | 566.7 (12.5)  | 500.4 (11.1)  | 498.7 (11.2)  |       |
| 2004                            | 738.2 (17.1)  | 773.8 (17.2)  | 799.0 (17.7)                   | 784.4 (17.3)    | 693.1 (15.3)  | 788.3 (17.5)  | 784.1 (17.6)  |       |
| 2005                            | 288.2 (6.7)   | 340.9 (7.6)   | 351.4 (7.8)                    | 344.8 (7.6)     | 322.0 (7.1)   | 336.8 (7.5)   | 337.9 (7.6)   |       |
| 2006                            | 282.0 (6.5)   | 332.0 (7.4)   | 352.1 (7.8)                    | 340.6 (7.5)     | 311.0 (6.8)   | 322.5 (7.2)   | 332.5 (7.5)   |       |
| 2007                            | 272.0 (6.3)   | 295.9 (6.6)   | 307.7 (6.8)                    | 309.2 (6.8)     | 278.5 (6.1)   | 305.8 (6.8)   | 297.3 (6.7)   |       |
| 2008                            | 249.8 (5.8)   | 298.9 (6.6)   | 304.0 (6.7)                    | 299.4 (6.6)     | 262.4 (5.8)   | 288.8 (6.4)   | 294.7 (6.6)   |       |
| 2009                            | 320.4 (7.4)   | 340.4 (7.6)   | 301.5 (6.7)                    | 317.8 (7.0)     | 317.2 (7.0)   | 324.2 (7.2)   | 314.6 (7.1)   |       |
| 2010                            | 254.1 (5.9)   | 234.2 (5.2)   | 209.5 (4.6)                    | 235.6 (5.2)     | 251.9 (5.5)   | 240.9 (5.3)   | 230.5 (5.2)   |       |
| 2011                            | 246.3 (5.7)   | 190.1 (4.2)   | 217.4 (4.8)                    | 234.4 (5.2)     | 243.7 (5.4)   | 240.1 (5.3)   | 239.4 (5.4)   |       |
| 2012                            | 203.6 (4.7)   | 156.1 (3.5)   | 177.5 (3.9)                    | 196.4 (4.3)     | 205.2 (4.5)   | 206.6 (4.6)   | 201.9 (4.5)   |       |
| 2013                            | 118.1 (2.7)   | 72.8 (1.6)    | 106.8 (2.4)                    | 111.5 (2.5)     | 116.9 (2.6)   | 117.6 (2.6)   | 102.1 (2.3)   |       |
| 2014                            | 32.5 (0.8)    | 19.2 (0.4)    | 29.6 (0.7)                     | 26.6 (0.6)      | 33.1 (0.7)    | 28.2 (0.6)    | 25.1 (0.6)    |       |
| <b>Comorbidities (n (%))</b>    |               |               |                                |                 |               |               |               |       |
| Opioid dependence               | 121.4 (2.8)   | 125.7 (2.8)   | 136.7 (3.0)                    | 130.5 (2.9)     | 133.5 (2.9)   | 138.1 (3.1)   | 120.8 (2.7)   | 0.009 |
| Opioid abuse                    | 23.8 (0.6)    | 24.0 (0.5)    | 25.7 (0.6)                     | 25.9 (0.6)      | 25.9 (0.6)    | 20.0 (0.4)    | 24.9 (0.6)    | 0.006 |
| Alcohol abuse                   | 170.8 (4.0)   | 190.2 (4.2)   | 185.8 (4.1)                    | 188.5 (4.2)     | 184.6 (4.1)   | 178.4 (4.0)   | 180.0 (4.0)   | 0.006 |
| Tobacco use                     | 485.5 (11.2)  | 526.4 (11.7)  | 500.5 (11.1)                   | 516.5 (11.4)    | 513.0 (11.3)  | 506.8 (11.2)  | 525.1 (11.8)  | 0.009 |
| Other drug abuse                | 283.9 (6.6)   | 304.2 (6.8)   | 304.6 (6.7)                    | 300.0 (6.6)     | 297.1 (6.5)   | 304.1 (6.7)   | 287.8 (6.5)   | 0.006 |
| Anxiety                         | 867.5 (20.1)  | 879.0 (19.5)  | 865.6 (19.2)                   | 890.1 (19.7)    | 912.8 (20.1)  | 879.5 (19.5)  | 885.7 (19.9)  | 0.010 |
| Bipolar disorder                | 288.3 (6.7)   | 297.4 (6.6)   | 312.3 (6.9)                    | 309.2 (6.8)     | 323.2 (7.1)   | 310.6 (6.9)   | 307.1 (6.9)   | 0.008 |
| Bone fracture                   | 293.1 (6.8)   | 297.8 (6.6)   | 290.8 (6.4)                    | 296.5 (6.5)     | 304.4 (6.7)   | 289.5 (6.4)   | 301.8 (6.8)   | 0.007 |
| Cancer                          | 205.3 (4.8)   | 198.7 (4.4)   | 202.0 (4.5)                    | 206.3 (4.6)     | 209.9 (4.6)   | 210.1 (4.7)   | 208.8 (4.7)   | 0.007 |
| Chronic renal insufficiency     | 77.9 (1.8)    | 75.5 (1.7)    | 77.3 (1.7)                     | 77.3 (1.7)      | 78.3 (1.7)    | 74.1 (1.6)    | 76.8 (1.7)    | 0.004 |
| Congestive heart failure        | 161.1 (3.7)   | 166.5 (3.7)   | 178.9 (4.0)                    | 175.8 (3.9)     | 176.5 (3.9)   | 173.2 (3.8)   | 164.0 (3.7)   | 0.007 |
| COPD/asthma/oxygen              | 998.2 (23.1)  | 1019.7 (22.7) | 1021.7 (22.6)                  | 1018.2 (22.5)   | 1005.3 (22.1) | 1012.0 (22.5) | 997.1 (22.4)  | 0.008 |
| Dementia                        | 38.6 (0.9)    | 39.6 (0.9)    | 34.2 (0.8)                     | 35.7 (0.8)      | 42.1 (0.9)    | 36.9 (0.8)    | 34.6 (0.8)    | 0.009 |
| Depression                      | 1155.8 (26.8) | 1168.8 (26.0) | 1201.3 (26.6)                  | 1181.1 (26.1)   | 1223.2 (26.9) | 1152.3 (25.6) | 1166.7 (26.2) | 0.014 |
| Diabetes                        | 723.3 (16.8)  | 809.1 (18.0)  | 795.0 (17.6)                   | 810.7 (17.9)    | 796.1 (17.5)  | 787.1 (17.5)  | 791.1 (17.7)  | 0.012 |
| Epilepsy                        | 213.3 (4.9)   | 227.6 (5.1)   | 231.9 (5.1)                    | 229.1 (5.1)     | 227.7 (5.0)   | 216.3 (4.8)   | 235.4 (5.3)   | 0.008 |
| HIV                             | 83.1 (1.9)    | 88.4 (2.0)    | 94.1 (2.1)                     | 93.1 (2.1)      | 86.7 (1.9)    | 88.0 (2.0)    | 86.0 (1.9)    | 0.006 |
| Intentional self-harm           | 6.5 (0.2)     | 7.9 (0.2)     | 6.3 (0.1)                      | 7.1 (0.2)       | 6.1 (0.1)     | 6.4 (0.1)     | 8.0 (0.2)     | 0.005 |
| Liver disease                   | 308.9 (7.2)   | 325.2 (7.2)   | 335.1 (7.4)                    | 328.4 (7.3)     | 335.4 (7.4)   | 332.8 (7.4)   | 321.8 (7.2)   | 0.005 |
| Musculoskeletal injury          | 455.9 (10.6)  | 508.0 (11.3)  | 490.2 (10.9)                   | 484.5 (10.7)    | 492.2 (10.8)  | 493.3 (10.9)  | 475.9 (10.7)  | 0.009 |
| Multiple sclerosis              | 26.4 (0.6)    | 21.6 (0.5)    | 25.0 (0.6)                     | 25.5 (0.6)      | 25.4 (0.6)    | 21.3 (0.5)    | 22.7 (0.5)    | 0.008 |
| Obesity                         | 235.8 (5.5)   | 241.3 (5.4)   | 240.5 (5.3)                    | 243.4 (5.4)     | 230.0 (5.1)   | 237.5 (5.3)   | 234.4 (5.3)   | 0.006 |
| Pneumonia                       | 191.0 (4.4)   | 204.4 (4.5)   | 209.2 (4.6)                    | 207.2 (4.6)     | 207.1 (4.6)   | 205.0 (4.5)   | 210.8 (4.7)   | 0.005 |
| Psychosis                       | 174.1 (4.0)   | 163.9 (3.6)   | 162.1 (3.6)                    | 171.5 (3.8)     | 176.0 (3.9)   | 170.0 (3.8)   | 169.6 (3.8)   | 0.009 |
| Renal dysfunction               | 177.6 (4.1)   | 178.6 (4.0)   | 178.9 (4.0)                    | 184.3 (4.1)     | 183.9 (4.0)   | 172.2 (3.8)   | 182.9 (4.1)   | 0.006 |
| Spasticity                      | 568.0 (13.2)  | 595.0 (13.2)  | 566.4 (12.5)                   | 598.0 (13.2)    | 612.3 (13.5)  | 571.1 (12.7)  | 594.7 (13.3)  | 0.012 |
| Urinary calculus                | 117.4 (2.7)   | 130.8 (2.9)   | 118.8 (2.6)                    | 131.0 (2.9)     | 128.6 (2.8)   | 133.9 (3.0)   | 133.9 (3.0)   | 0.010 |
| Urinary tract infection         | 511.7 (11.9)  | 576.9 (12.8)  | 568.9 (12.6)                   | 579.6 (12.8)    | 585.6 (12.9)  | 580.0 (12.9)  | 563.1 (12.6)  | 0.011 |
| <b>Pain conditions (n (%))</b>  |               |               |                                |                 |               |               |               |       |
| Abdominal pain                  | 1007.3 (23.3) | 1066.1 (23.7) | 1060.2 (23.5)                  | 1067.2 (23.6)   | 1055.4 (23.2) | 1064.2 (23.6) | 1047.4 (23.5) | 0.004 |
| Back and neck pain              | 3024.5 (70.1) | 3044.5 (67.6) | 3029.0 (67.1)                  | 3025.6 (66.8)   | 3055.1 (67.3) | 3030.5 (67.2) | 2982.3 (66.9) | 0.023 |
| Back pain without radiculopathy | 2841.4 (65.8) | 2907.4 (64.6) | 2889.1 (64.0)                  | 2876.6 (63.5)   | 2894.1 (63.7) | 2873.0 (63.7) | 2825.6 (63.4) | 0.019 |
| Back pain with radiculopathy    | 660.5 (15.3)  | 581.3 (12.9)  | 580.4 (12.9)                   | 588.9 (13.0)    | 609.5 (13.4)  | 575.0 (12.8)  | 599.0 (13.4)  | 0.026 |
| Dental pain                     | 214.7 (5.0)   | 252.2 (5.6)   | 245.2 (5.4)                    | 240.7 (5.3)     | 238.6 (5.3)   | 242.7 (5.4)   | 236.0 (5.3)   | 0.010 |
| Diabetic neuropathy             | 122.8 (2.8)   | 111.6 (2.5)   | 115.3 (2.6)                    | 120.2 (2.7)     | 120.2 (2.6)   | 117.6 (2.6)   | 118.8 (2.7)   | 0.008 |
| Fibromyalgia                    | 609.7 (14.1)  | 540.1 (12.0)  | 561.5 (12.4)                   | 536.0 (11.8)    | 568.2 (12.5)  | 516.1 (11.5)  | 556.4 (12.5)  | 0.028 |
| Headache                        | 858.5 (19.9)  | 896.6 (19.9)  | 897.2 (19.9)                   | 889.1 (19.6)    | 901.9 (19.9)  | 875.7 (19.4)  | 887.9 (19.9)  | 0.005 |
| Osteoarthritis                  | 717.7 (16.6)  | 741.4 (16.5)  | 750.1 (16.6)                   | 747.4 (16.5)    | 741.5 (16.3)  | 736.4 (16.3)  | 728.1 (16.3)  | 0.004 |
| Rheumatoid arthritis            | 137.6 (3.2)   | 135.7 (3.0)   | 139.5 (3.1)                    | 137.8 (3.0)     | 138.6 (3.1)   | 134.9 (3.0)   | 138.1 (3.1)   | 0.004 |

|                                                                                             | Baclofen       | Carisoprodol   | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone     | Methocarbamol  | Tizanidine     | SMD    |
|---------------------------------------------------------------------------------------------|----------------|----------------|--------------------------------|-----------------|----------------|----------------|----------------|--------|
| Postherpetic neuralgia                                                                      | 6.7 (0.2)      | 3.9 (0.1)      | 2.3 (0.1)                      | 4.1 (0.1)       | 6.6 (0.1)      | 3.2 (0.1)      | 5.6 (0.1)      | 0.015  |
| Other arthritis                                                                             | 2239.3 (51.9)  | 2342.8 (52.0)  | 2293.1 (50.8)                  | 2339.4 (51.7)   | 2359.4 (52.0)  | 2299.8 (51.0)  | 2308.4 (51.8)  | 0.011  |
| Other neuropathy                                                                            | 1247.4 (28.9)  | 1131.5 (25.1)  | 1114.7 (24.7)                  | 1129.5 (24.9)   | 1150.9 (25.3)  | 1110.7 (24.6)  | 1147.6 (25.7)  | 0.033  |
| Other unspecified pain                                                                      | 759.5 (17.6)   | 741.7 (16.5)   | 740.5 (16.4)                   | 774.5 (17.1)    | 786.6 (17.3)   | 777.2 (17.2)   | 756.8 (17.0)   | 0.014  |
| <b>Other prescription fills (n (%))</b>                                                     |                |                |                                |                 |                |                |                |        |
| Antibiotics                                                                                 | 2949.4 (68.3)  | 3132.5 (69.6)  | 3136.4 (69.4)                  | 3144.0 (69.4)   | 3131.9 (69.0)  | 3119.2 (69.2)  | 3096.1 (69.5)  | 0.010  |
| Anticonvulsants                                                                             | 737.6 (17.1)   | 712.5 (15.8)   | 701.7 (15.5)                   | 705.2 (15.6)    | 725.4 (16.0)   | 684.4 (15.2)   | 714.4 (16.0)   | 0.018  |
| Antidepressants, SSRIs                                                                      | 1553.0 (36.0)  | 1614.7 (35.9)  | 1621.7 (35.9)                  | 1618.7 (35.7)   | 1643.5 (36.2)  | 1594.8 (35.4)  | 1614.6 (36.2)  | 0.007  |
| Antidepressants, SNRIs                                                                      | 658.8 (15.3)   | 619.9 (13.8)   | 611.0 (13.5)                   | 631.5 (13.9)    | 640.5 (14.1)   | 634.4 (14.1)   | 636.1 (14.3)   | 0.017  |
| Antidepressants, TCAs                                                                       | 721.7 (16.7)   | 732.9 (16.3)   | 724.9 (16.1)                   | 723.6 (16.0)    | 731.7 (16.1)   | 705.8 (15.7)   | 722.9 (16.2)   | 0.010  |
| Antidepressants, other                                                                      | 1010.4 (23.4)  | 1010.1 (22.4)  | 1009.7 (22.4)                  | 999.2 (22.1)    | 1019.5 (22.5)  | 989.9 (22.0)   | 1003.3 (22.5)  | 0.012  |
| Antidiabetics                                                                               | 660.0 (15.3)   | 724.2 (16.1)   | 705.9 (15.6)                   | 723.5 (16.0)    | 713.4 (15.7)   | 709.0 (15.7)   | 707.6 (15.9)   | 0.009  |
| Antipsychotics, atypical                                                                    | 645.0 (14.9)   | 661.6 (14.7)   | 666.3 (14.8)                   | 661.2 (14.6)    | 681.9 (15.0)   | 663.7 (14.7)   | 667.8 (15.0)   | 0.005  |
| Antipsychotics, typical                                                                     | 209.7 (4.9)    | 209.7 (4.7)    | 202.9 (4.5)                    | 206.6 (4.6)     | 209.9 (4.6)    | 190.7 (4.2)    | 204.3 (4.6)    | 0.010  |
| Barbiturates                                                                                | 35.4 (0.8)     | 32.7 (0.7)     | 32.0 (0.7)                     | 32.0 (0.7)      | 32.9 (0.7)     | 29.3 (0.6)     | 29.4 (0.7)     | 0.007  |
| Benzodiazepines                                                                             | 2501.5 (57.9)  | 2441.8 (54.2)  | 2475.7 (54.8)                  | 2482.7 (54.8)   | 2512.4 (55.3)  | 2457.8 (54.5)  | 2466.8 (55.3)  | 0.025  |
| CNS stimulants                                                                              | 72.6 (1.7)     | 90.5 (2.0)     | 91.9 (2.0)                     | 82.4 (1.8)      | 83.2 (1.8)     | 85.0 (1.9)     | 81.7 (1.8)     | 0.010  |
| Dementia agents                                                                             | 14.0 (0.3)     | 14.3 (0.3)     | 17.4 (0.4)                     | 15.1 (0.3)      | 16.6 (0.4)     | 15.0 (0.3)     | 18.0 (0.4)     | 0.007  |
| Gabapentinoids                                                                              | 1150.1 (26.6)  | 1071.7 (23.8)  | 1045.1 (23.1)                  | 1074.0 (23.7)   | 1114.1 (24.5)  | 1064.5 (23.6)  | 1088.1 (24.4)  | 0.029  |
| Lithium                                                                                     | 48.9 (1.1)     | 54.7 (1.2)     | 56.7 (1.3)                     | 57.6 (1.3)      | 62.9 (1.4)     | 58.2 (1.3)     | 55.3 (1.2)     | 0.008  |
| Multiple sclerosis agents                                                                   | 9.4 (0.2)      | 6.9 (0.2)      | 8.1 (0.2)                      | 8.6 (0.2)       | 9.3 (0.2)      | 8.0 (0.2)      | 7.3 (0.2)      | 0.006  |
| NSAIDs                                                                                      | 2225.7 (51.6)  | 2448.7 (54.4)  | 2416.1 (53.5)                  | 2411.7 (53.3)   | 2439.1 (53.7)  | 2401.8 (53.3)  | 2387.3 (53.6)  | 0.019  |
| Other sedative hypnotics                                                                    | 810.2 (18.8)   | 839.0 (18.6)   | 800.0 (17.7)                   | 812.8 (17.9)    | 813.3 (17.9)   | 815.0 (18.1)   | 799.3 (17.9)   | 0.012  |
| Smoking cessation                                                                           | 536.6 (12.4)   | 529.8 (11.8)   | 532.3 (11.8)                   | 534.7 (11.8)    | 540.6 (11.9)   | 519.1 (11.5)   | 534.9 (12.0)   | 0.010  |
| Triptans                                                                                    | 252.2 (5.8)    | 243.0 (5.4)    | 248.1 (5.5)                    | 240.9 (5.3)     | 234.3 (5.2)    | 229.2 (5.1)    | 248.5 (5.6)    | 0.014  |
| Other CNS depressants                                                                       | 23.9 (0.6)     | 18.9 (0.4)     | 19.6 (0.4)                     | 17.7 (0.4)      | 17.6 (0.4)     | 18.1 (0.4)     | 18.0 (0.4)     | 0.008  |
| <b>Prescription opioid utilization (n (%))</b>                                              |                |                |                                |                 |                |                |                |        |
| Prescription opioid on index date                                                           |                |                |                                |                 |                |                |                |        |
| Buprenorphine                                                                               | 5.2 (0.1)      | 4.3 (0.1)      | 6.1 (0.1)                      | 4.5 (0.1)       | 5.8 (0.1)      | 5.6 (0.1)      | 4.1 (0.1)      | 0.006  |
| Butorphanol                                                                                 | 19.3 (0.4)     | 24.0 (0.5)     | 21.6 (0.5)                     | 20.8 (0.5)      | 22.7 (0.5)     | 22.0 (0.5)     | 20.2 (0.5)     | 0.005  |
| Codeine                                                                                     | 231.1 (5.4)    | 310.3 (6.9)    | 302.0 (6.7)                    | 300.9 (6.6)     | 300.5 (6.6)    | 291.5 (6.5)    | 280.2 (6.3)    | 0.022  |
| Dihydrocodeine                                                                              | 17.2 (0.4)     | 16.6 (0.4)     | 19.7 (0.4)                     | 16.8 (0.4)      | 16.6 (0.4)     | 16.2 (0.4)     | 17.6 (0.4)     | 0.005  |
| Fentanyl                                                                                    | 301.1 (7.0)    | 283.5 (6.3)    | 277.7 (6.1)                    | 275.7 (6.1)     | 300.5 (6.6)    | 275.9 (6.1)    | 281.0 (6.3)    | 0.015  |
| Hydrocodone                                                                                 | 2580.3 (59.8)  | 2629.4 (58.4)  | 2710.0 (60.0)                  | 2719.2 (60.0)   | 2710.6 (59.7)  | 2753.3 (61.1)  | 2694.7 (60.5)  | 0.019  |
| Hydromorphone                                                                               | 97.4 (2.3)     | 71.8 (1.6)     | 75.6 (1.7)                     | 81.5 (1.8)      | 78.1 (1.7)     | 80.9 (1.8)     | 77.3 (1.7)     | 0.016  |
| Levorphanol                                                                                 | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)      | <0.001 |
| Meperidine                                                                                  | 21.9 (0.5)     | 23.0 (0.5)     | 25.2 (0.6)                     | 22.4 (0.5)      | 20.4 (0.4)     | 21.1 (0.5)     | 19.8 (0.4)     | 0.007  |
| Methadone                                                                                   | 247.1 (5.7)    | 201.2 (4.5)    | 210.1 (4.7)                    | 204.8 (4.5)     | 210.6 (4.6)    | 215.7 (4.8)    | 209.3 (4.7)    | 0.019  |
| Morphine                                                                                    | 299.6 (6.9)    | 270.1 (6.0)    | 262.1 (5.8)                    | 276.4 (6.1)     | 288.8 (6.4)    | 258.8 (5.7)    | 277.7 (6.2)    | 0.019  |
| Opium                                                                                       | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)      | <0.001 |
| Oxycodone                                                                                   | 1449.4 (33.6)  | 1484.0 (33.0)  | 1446.9 (32.0)                  | 1460.6 (32.3)   | 1480.7 (32.6)  | 1445.3 (32.1)  | 1448.3 (32.5)  | 0.014  |
| Oxymorphone                                                                                 | 10.2 (0.2)     | 10.2 (0.2)     | 7.6 (0.2)                      | 9.4 (0.2)       | 7.9 (0.2)      | 9.7 (0.2)      | 8.1 (0.2)      | 0.007  |
| Pentazocine                                                                                 | 26.6 (0.6)     | 26.5 (0.6)     | 26.6 (0.6)                     | 24.2 (0.5)      | 26.8 (0.6)     | 25.6 (0.6)     | 22.5 (0.5)     | 0.006  |
| Propoxyphene                                                                                | 150.6 (3.5)    | 165.0 (3.7)    | 154.0 (3.4)                    | 149.1 (3.3)     | 152.9 (3.4)    | 159.1 (3.5)    | 143.6 (3.2)    | 0.010  |
| Tapentadol                                                                                  | 5.8 (0.1)      | 4.0 (0.1)      | 3.3 (0.1)                      | 3.6 (0.1)       | 4.0 (0.1)      | 3.5 (0.1)      | 3.4 (0.1)      | 0.007  |
| Tramadol                                                                                    | 753.3 (17.4)   | 906.8 (20.1)   | 849.3 (18.8)                   | 855.2 (18.9)    | 836.6 (18.4)   | 862.5 (19.1)   | 843.9 (18.9)   | 0.023  |
| Number of days covered by prescription<br>opioids in 180 days pre-index date (mean<br>(SD)) | 173.04 (17.70) | 172.59 (18.23) | 172.43 (18.54)                 | 172.42 (18.39)  | 172.64 (18.29) | 172.32 (18.67) | 172.41 (18.41) | 0.015  |
| Total dispensed MMEs per interval (days)<br>(mean (SD))                                     |                |                |                                |                 |                |                |                |        |

|                                           | Baclofen             | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone           | Methocarbamol     | Tizanidine           | SMD   |
|-------------------------------------------|----------------------|----------------------|--------------------------------|-------------------|----------------------|-------------------|----------------------|-------|
| (Index - 180) to (index - 151)            | 1989.14<br>(3313.74) | 1833.80<br>(2981.59) | 1756.21 (2942.26)              | 1779.36 (3184.13) | 1848.46<br>(3079.27) | 1795.70 (3155.31) | 1848.11<br>(3089.26) | 0.027 |
| (Index - 150) to (index - 121)            | 2077.54<br>(3373.55) | 1950.92<br>(3097.75) | 1875.11 (3152.17)              | 1885.55 (3359.48) | 1949.92<br>(3120.17) | 1909.17 (3297.04) | 1939.44<br>(3121.38) | 0.023 |
| (Index - 120) to (index - 91)             | 2313.86<br>(3511.30) | 2126.45<br>(3105.87) | 2027.04 (3260.13)              | 2064.66 (3425.53) | 2128.42<br>(3301.52) | 2068.62 (3334.24) | 2147.90<br>(3280.50) | 0.031 |
| (Index - 90) to (index - 61)              | 2329.87<br>(3499.06) | 2173.36<br>(3231.73) | 2053.37 (3320.07)              | 2096.10 (3404.63) | 2155.71<br>(3192.60) | 2101.13 (3298.22) | 2165.01<br>(3259.10) | 0.030 |
| (Index - 60) to (index - 31)              | 2366.77<br>(3549.59) | 2175.93<br>(3172.30) | 2079.46 (3289.29)              | 2106.26 (3375.00) | 2187.63<br>(3251.14) | 2106.00 (3322.62) | 2185.37<br>(3303.35) | 0.031 |
| (Index - 30) to index                     | 2836.96<br>(4124.38) | 2576.85<br>(3627.39) | 2481.93 (4000.78)              | 2500.28 (4038.57) | 2571.80<br>(3882.30) | 2506.44 (4096.36) | 2608.75<br>(3684.21) | 0.032 |
| <b>Healthcare utilization (mean (SD))</b> |                      |                      |                                |                   |                      |                   |                      |       |
| Number of physician visits                | 9.56 (8.64)          | 9.34 (8.42)          | 9.39 (8.55)                    | 9.35 (8.46)       | 9.42 (8.55)          | 9.29 (8.30)       | 9.44 (8.50)          | 0.012 |
| Number of distinct prescribed medications | 14.84 (7.40)         | 14.78 (7.61)         | 14.73 (7.50)                   | 14.71 (7.47)      | 14.83 (7.58)         | 14.64 (7.37)      | 14.77 (7.48)         | 0.011 |
| Number of hospitalizations                | 0.31 (0.81)          | 0.31 (0.84)          | 0.30 (0.80)                    | 0.32 (0.82)       | 0.31 (0.82)          | 0.30 (0.78)       | 0.31 (0.81)          | 0.008 |
| Number of hospitalization days            | 1.61 (9.52)          | 1.61 (8.16)          | 1.63 (5.42)                    | 1.67 (6.65)       | 1.68 (5.77)          | 1.66 (6.95)       | 1.75 (7.79)          | 0.008 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

<sup>1</sup>Socioeconomic status measures and rural-urban continuum codes were not included in the propensity score model

**eTable 5A. Characteristics of patients with non-missing values for socioeconomic status measures and rural-urban continuum codes who initiated skeletal muscle relaxants while on long-term opioid therapy in Medicaid Analytic eXtract (MAX), 2000-2014 (pre-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 23828         | 20802         | 7717                           | 90258           | 12054         | 18360         | 17612         |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 46.20 (10.50) | 43.55 (10.37) | 42.98 (10.81)                  | 44.04 (10.75)   | 44.08 (10.52) | 44.18 (10.93) | 43.62 (10.38) | 0.102 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.060 |
| Unknown                                | 70 (0.3)      | 25 (0.1)      | 13 (0.2)                       | 159 (0.2)       | 12 (0.1)      | 31 (0.2)      | 32 (0.2)      |       |
| Male                                   | 8766 (36.8)   | 6740 (32.4)   | 2379 (30.8)                    | 28657 (31.8)    | 3590 (29.8)   | 6188 (33.7)   | 5781 (32.8)   |       |
| Female                                 | 14992 (62.9)  | 14037 (67.5)  | 5325 (69.0)                    | 61442 (68.1)    | 8452 (70.1)   | 12141 (66.1)  | 11799 (67.0)  |       |
| Race                                   |               |               |                                |                 |               |               |               | 0.120 |
| Asian                                  | 448 (1.9)     | 311 (1.5)     | 107 (1.4)                      | 1616 (1.8)      | 172 (1.4)     | 315 (1.7)     | 231 (1.3)     |       |
| Black                                  | 3679 (15.4)   | 2961 (14.2)   | 1089 (14.1)                    | 14867 (16.5)    | 1771 (14.7)   | 3011 (16.4)   | 1956 (11.1)   |       |
| White                                  | 16909 (71.0)  | 16223 (78.0)  | 6089 (78.9)                    | 67991 (75.3)    | 9333 (77.4)   | 13921 (75.8)  | 14524 (82.5)  |       |
| Other                                  | 2792 (11.7)   | 1307 (6.3)    | 432 (5.6)                      | 5784 (6.4)      | 778 (6.5)     | 1113 (6.1)    | 901 (5.1)     |       |
| Ethnicity                              |               |               |                                |                 |               |               |               | 0.099 |
| Unknown                                | 809 (3.4)     | 732 (3.5)     | 213 (2.8)                      | 2547 (2.8)      | 461 (3.8)     | 453 (2.5)     | 510 (2.9)     |       |
| Hispanic                               | 1608 (6.7)    | 469 (2.3)     | 189 (2.4)                      | 2911 (3.2)      | 290 (2.4)     | 595 (3.2)     | 346 (2.0)     |       |
| Non-Hispanic                           | 21411 (89.9)  | 19601 (94.2)  | 7315 (94.8)                    | 84800 (94.0)    | 11303 (93.8)  | 17312 (94.3)  | 16756 (95.1)  |       |
| State                                  |               |               |                                |                 |               |               |               | 0.948 |
| AK                                     | 48 (0.2)      | 126 (0.6)     | 17 (0.2)                       | 431 (0.5)       | 35 (0.3)      | 74 (0.4)      | 181 (1.0)     |       |
| AL                                     | 219 (0.9)     | 121 (0.6)     | 102 (1.3)                      | 1806 (2.0)      | 78 (0.6)      | 804 (4.4)     | 581 (3.3)     |       |
| AR                                     | 45 (0.2)      | 325 (1.6)     | 32 (0.4)                       | 387 (0.4)       | 132 (1.1)     | 108 (0.6)     | 139 (0.8)     |       |
| AZ                                     | 1 (0.0)       | 1 (0.0)       | 0 (0.0)                        | 5 (0.0)         | 1 (0.0)       | 2 (0.0)       | 2 (0.0)       |       |
| CA                                     | 13325 (55.9)  | 1187 (5.7)    | 31 (0.4)                       | 895 (1.0)       | 80 (0.7)      | 311 (1.7)     | 169 (1.0)     |       |
| CO                                     | 4 (0.0)       | 0 (0.0)       | 0 (0.0)                        | 10 (0.0)        | 2 (0.0)       | 1 (0.0)       | 5 (0.0)       |       |
| CT                                     | 256 (1.1)     | 555 (2.7)     | 107 (1.4)                      | 2584 (2.9)      | 294 (2.4)     | 757 (4.1)     | 230 (1.3)     |       |
| DC                                     | 21 (0.1)      | 26 (0.1)      | 24 (0.3)                       | 230 (0.3)       | 17 (0.1)      | 19 (0.1)      | 5 (0.0)       |       |
| DE                                     | 1 (0.0)       | 0 (0.0)       | 0 (0.0)                        | 1 (0.0)         | 3 (0.0)       | 0 (0.0)       | 2 (0.0)       |       |
| FL                                     | 451 (1.9)     | 1048 (5.0)    | 141 (1.8)                      | 2904 (3.2)      | 637 (5.3)     | 705 (3.8)     | 457 (2.6)     |       |
| GA                                     | 221 (0.9)     | 1466 (7.0)    | 273 (3.5)                      | 2348 (2.6)      | 877 (7.3)     | 452 (2.5)     | 758 (4.3)     |       |
| HI                                     | 43 (0.2)      | 151 (0.7)     | 23 (0.3)                       | 193 (0.2)       | 14 (0.1)      | 37 (0.2)      | 23 (0.1)      |       |
| IA                                     | 1 (0.0)       | 2 (0.0)       | 1 (0.0)                        | 10 (0.0)        | 3 (0.0)       | 2 (0.0)       | 1 (0.0)       |       |
| ID                                     | 69 (0.3)      | 138 (0.7)     | 55 (0.7)                       | 756 (0.8)       | 75 (0.6)      | 219 (1.2)     | 120 (0.7)     |       |
| IL                                     | 992 (4.2)     | 750 (3.6)     | 1485 (19.2)                    | 11852 (13.1)    | 138 (1.1)     | 1642 (8.9)    | 1154 (6.6)    |       |
| IN                                     | 868 (3.6)     | 496 (2.4)     | 643 (8.3)                      | 6328 (7.0)      | 439 (3.6)     | 1185 (6.5)    | 1589 (9.0)    |       |
| KS                                     | 114 (0.5)     | 104 (0.5)     | 76 (1.0)                       | 895 (1.0)       | 84 (0.7)      | 35 (0.2)      | 93 (0.5)      |       |
| KY                                     | 8 (0.0)       | 2 (0.0)       | 4 (0.1)                        | 16 (0.0)        | 15 (0.1)      | 16 (0.1)      | 20 (0.1)      |       |
| LA                                     | 294 (1.2)     | 2194 (10.5)   | 378 (4.9)                      | 3792 (4.2)      | 557 (4.6)     | 883 (4.8)     | 721 (4.1)     |       |
| MA                                     | 42 (0.2)      | 8 (0.0)       | 10 (0.1)                       | 106 (0.1)       | 9 (0.1)       | 11 (0.1)      | 32 (0.2)      |       |
| MD                                     | 78 (0.3)      | 36 (0.2)      | 2 (0.0)                        | 212 (0.2)       | 24 (0.2)      | 21 (0.1)      | 20 (0.1)      |       |
| ME                                     | 366 (1.5)     | 93 (0.4)      | 89 (1.2)                       | 2705 (3.0)      | 69 (0.6)      | 359 (2.0)     | 292 (1.7)     |       |
| MI                                     | 0 (0.0)       | 0 (0.0)       | 1 (0.0)                        | 0 (0.0)         | 0 (0.0)       | 0 (0.0)       | 0 (0.0)       |       |
| MN                                     | 198 (0.8)     | 185 (0.9)     | 125 (1.6)                      | 1733 (1.9)      | 101 (0.8)     | 297 (1.6)     | 270 (1.5)     |       |
| MO                                     | 1447 (6.1)    | 2365 (11.4)   | 1113 (14.4)                    | 10371 (11.5)    | 1648 (13.7)   | 1781 (9.7)    | 2204 (12.5)   |       |
| MS                                     | 59 (0.2)      | 445 (2.1)     | 69 (0.9)                       | 633 (0.7)       | 234 (1.9)     | 130 (0.7)     | 273 (1.6)     |       |
| MT                                     | 72 (0.3)      | 81 (0.4)      | 33 (0.4)                       | 622 (0.7)       | 88 (0.7)      | 190 (1.0)     | 118 (0.7)     |       |
| NC                                     | 590 (2.5)     | 1927 (9.3)    | 619 (8.0)                      | 6143 (6.8)      | 1808 (15.0)   | 871 (4.7)     | 1538 (8.7)    |       |
| ND                                     | 22 (0.1)      | 34 (0.2)      | 33 (0.4)                       | 335 (0.4)       | 32 (0.3)      | 37 (0.2)      | 57 (0.3)      |       |
| NE                                     | 8 (0.0)       | 1 (0.0)       | 4 (0.1)                        | 39 (0.0)        | 6 (0.0)       | 4 (0.0)       | 12 (0.1)      |       |

|                                                                | Baclofen              | Carisoprodol          | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine       | Metaxalone            | Methocarbamol         | Tizanidine            | SMD   |
|----------------------------------------------------------------|-----------------------|-----------------------|--------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-------|
| NH                                                             | 97 (0.4)              | 126 (0.6)             | 42 (0.5)                       | 895 (1.0)             | 80 (0.7)              | 117 (0.6)             | 221 (1.3)             |       |
| NJ                                                             | 79 (0.3)              | 194 (0.9)             | 60 (0.8)                       | 681 (0.8)             | 218 (1.8)             | 53 (0.3)              | 133 (0.8)             |       |
| NM                                                             | 29 (0.1)              | 27 (0.1)              | 15 (0.2)                       | 182 (0.2)             | 3 (0.0)               | 48 (0.3)              | 5 (0.0)               |       |
| NV                                                             | 16 (0.1)              | 201 (1.0)             | 6 (0.1)                        | 98 (0.1)              | 38 (0.3)              | 25 (0.1)              | 47 (0.3)              |       |
| NY                                                             | 848 (3.6)             | 1014 (4.9)            | 298 (3.9)                      | 5958 (6.6)            | 934 (7.7)             | 1194 (6.5)            | 892 (5.1)             |       |
| OH                                                             | 93 (0.4)              | 6 (0.0)               | 13 (0.2)                       | 503 (0.6)             | 6 (0.0)               | 125 (0.7)             | 183 (1.0)             |       |
| OK                                                             | 42 (0.2)              | 127 (0.6)             | 24 (0.3)                       | 259 (0.3)             | 11 (0.1)              | 48 (0.3)              | 71 (0.4)              |       |
| OR                                                             | 10 (0.0)              | 12 (0.1)              | 2 (0.0)                        | 92 (0.1)              | 4 (0.0)               | 22 (0.1)              | 4 (0.0)               |       |
| PA                                                             | 214 (0.9)             | 509 (2.4)             | 185 (2.4)                      | 1629 (1.8)            | 577 (4.8)             | 212 (1.2)             | 342 (1.9)             |       |
| RI                                                             | 18 (0.1)              | 77 (0.4)              | 12 (0.2)                       | 344 (0.4)             | 54 (0.4)              | 74 (0.4)              | 31 (0.2)              |       |
| SC                                                             | 134 (0.6)             | 735 (3.5)             | 111 (1.4)                      | 1127 (1.2)            | 473 (3.9)             | 109 (0.6)             | 414 (2.4)             |       |
| SD                                                             | 70 (0.3)              | 54 (0.3)              | 23 (0.3)                       | 511 (0.6)             | 57 (0.5)              | 57 (0.3)              | 71 (0.4)              |       |
| TN                                                             | 697 (2.9)             | 2261 (10.9)           | 565 (7.3)                      | 6636 (7.4)            | 473 (3.9)             | 2623 (14.3)           | 1277 (7.3)            |       |
| TX                                                             | 0 (0.0)               | 0 (0.0)               | 0 (0.0)                        | 0 (0.0)               | 0 (0.0)               | 0 (0.0)               | 0 (0.0)               |       |
| UT                                                             | 7 (0.0)               | 61 (0.3)              | 5 (0.1)                        | 101 (0.1)             | 17 (0.1)              | 22 (0.1)              | 19 (0.1)              |       |
| VA                                                             | 330 (1.4)             | 479 (2.3)             | 358 (4.6)                      | 2061 (2.3)            | 439 (3.6)             | 497 (2.7)             | 542 (3.1)             |       |
| VT                                                             | 171 (0.7)             | 80 (0.4)              | 62 (0.8)                       | 1593 (1.8)            | 88 (0.7)              | 402 (2.2)             | 222 (1.3)             |       |
| WA                                                             | 37 (0.2)              | 92 (0.4)              | 4 (0.1)                        | 143 (0.2)             | 19 (0.2)              | 85 (0.5)              | 35 (0.2)              |       |
| WI                                                             | 241 (1.0)             | 284 (1.4)             | 151 (2.0)                      | 2495 (2.8)            | 278 (2.3)             | 203 (1.1)             | 357 (2.0)             |       |
| WV                                                             | 765 (3.2)             | 556 (2.7)             | 265 (3.4)                      | 6076 (6.7)            | 756 (6.3)             | 1476 (8.0)            | 1617 (9.2)            |       |
| WY                                                             | 67 (0.3)              | 40 (0.2)              | 26 (0.3)                       | 532 (0.6)             | 29 (0.2)              | 15 (0.1)              | 63 (0.4)              |       |
| Socioeconomic status (% (SD))                                  |                       |                       |                                |                       |                       |                       |                       |       |
| Households with 1-1.5 occupants per room                       | 3.51 (3.48)           | 2.02 (1.95)           | 1.71 (1.65)                    | 1.82 (1.84)           | 1.79 (1.70)           | 1.89 (1.98)           | 1.72 (1.72)           | 0.229 |
| Households with > 1.5 occupants per room                       | 1.66 (2.31)           | 0.81 (1.17)           | 0.69 (0.98)                    | 0.76 (1.13)           | 0.74 (1.08)           | 0.81 (1.24)           | 0.71 (1.07)           | 0.182 |
| Median value of homes (mean (SD))                              | 253154.82 (185900.90) | 164114.43 (108323.36) | 144961.84 (87666.47)           | 159440.18 (110061.23) | 158063.59 (106978.00) | 165201.42 (115146.57) | 155663.36 (105894.81) | 0.239 |
| Median value of homes ranked 1-100 (mean (SD))                 | 63.02 (26.59)         | 44.92 (24.78)         | 39.48 (23.47)                  | 43.12 (25.07)         | 43.09 (23.92)         | 44.54 (25.23)         | 41.92 (24.47)         | 0.294 |
| Median household income (mean (SD))                            | 50005.57 (17498.11)   | 46067.03 (15075.28)   | 45833.56 (14192.89)            | 47040.30 (15479.39)   | 45642.31 (14866.49)   | 46211.46 (15308.89)   | 46747.18 (15333.24)   | 0.097 |
| Median value of income ranked 1-100 (mean (SD))                | 41.49 (25.69)         | 35.28 (24.62)         | 35.30 (23.82)                  | 37.16 (24.99)         | 34.44 (23.99)         | 35.65 (24.91)         | 36.51 (24.85)         | 0.100 |
| Individuals below the poverty line                             | 19.44 (8.60)          | 19.41 (8.50)          | 18.90 (8.70)                   | 18.81 (9.06)          | 19.33 (8.55)          | 19.26 (9.07)          | 18.64 (8.65)          | 0.044 |
| Individuals > 16 years who are unemployed                      | 8.76 (3.93)           | 7.99 (3.72)           | 7.75 (3.96)                    | 7.85 (4.09)           | 7.87 (3.73)           | 7.97 (4.18)           | 7.62 (3.77)           | 0.099 |
| Individuals > 25 years with < 12 <sup>th</sup> grade education | 29.04 (8.65)          | 34.13 (8.23)          | 34.76 (7.86)                   | 34.29 (8.35)          | 34.56 (8.17)          | 34.58 (8.42)          | 34.81 (8.32)          | 0.214 |
| Individuals > 25 years with 4-year college education           | 14.40 (7.58)          | 13.12 (6.54)          | 13.03 (6.46)                   | 13.64 (6.73)          | 13.13 (6.41)          | 13.24 (6.73)          | 13.23 (6.71)          | 0.072 |
| Households with > 1 persons per room                           | 5.17 (5.27)           | 2.84 (2.77)           | 2.39 (2.29)                    | 2.58 (2.62)           | 2.54 (2.43)           | 2.70 (2.91)           | 2.43 (2.44)           | 0.235 |
| Socioeconomic status index score ranked 1-100 (mean (SD))      | 54.84 (6.29)          | 52.25 (6.11)          | 51.84 (5.81)                   | 52.44 (6.17)          | 52.01 (5.91)          | 52.25 (6.15)          | 52.22 (6.15)          | 0.154 |
| Rural-urban continuum codes                                    |                       |                       |                                |                       |                       |                       |                       | 0.103 |
| Metropolitan                                                   | 19673 (82.6)          | 14850 (71.4)          | 5376 (69.7)                    | 65182 (72.2)          | 8515 (70.6)           | 13174 (71.8)          | 12356 (70.2)          |       |
| Rural                                                          | 756 (3.2)             | 1286 (6.2)            | 564 (7.3)                      | 5493 (6.1)            | 794 (6.6)             | 1195 (6.5)            | 1166 (6.6)            |       |
| Urban                                                          | 3399 (14.3)           | 4666 (22.4)           | 1777 (23.0)                    | 19583 (21.7)          | 2745 (22.8)           | 3991 (21.7)           | 4090 (23.2)           |       |
| Year                                                           |                       |                       |                                |                       |                       |                       |                       | 0.500 |
| 2000                                                           | 420 (1.8)             | 1055 (5.1)            | 357 (4.6)                      | 1847 (2.0)            | 407 (3.4)             | 389 (2.1)             | 341 (1.9)             |       |
| 2001                                                           | 950 (4.0)             | 2137 (10.3)           | 597 (7.7)                      | 3816 (4.2)            | 1164 (9.7)            | 816 (4.4)             | 1299 (7.4)            |       |
| 2002                                                           | 1008 (4.2)            | 1902 (9.1)            | 505 (6.5)                      | 3723 (4.1)            | 1446 (12.0)           | 746 (4.1)             | 1570 (8.9)            |       |

|                                 | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|---------------------------------|--------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| 2003                            | 1643 (6.9)   | 3069 (14.8)  | 667 (8.6)                      | 6451 (7.1)      | 1895 (15.7) | 1335 (7.3)    | 1718 (9.8)   |       |
| 2004                            | 2187 (9.2)   | 3628 (17.4)  | 1143 (14.8)                    | 12490 (13.8)    | 1841 (15.3) | 3285 (17.9)   | 2345 (13.3)  |       |
| 2005                            | 1408 (5.9)   | 1764 (8.5)   | 517 (6.7)                      | 5839 (6.5)      | 1158 (9.6)  | 939 (5.1)     | 944 (5.4)    |       |
| 2006                            | 1588 (6.7)   | 1673 (8.0)   | 494 (6.4)                      | 5813 (6.4)      | 1093 (9.1)  | 961 (5.2)     | 943 (5.4)    |       |
| 2007                            | 1779 (7.5)   | 1156 (5.6)   | 462 (6.0)                      | 5579 (6.2)      | 866 (7.2)   | 950 (5.2)     | 932 (5.3)    |       |
| 2008                            | 2021 (8.5)   | 1112 (5.3)   | 444 (5.8)                      | 6579 (7.3)      | 700 (5.8)   | 1054 (5.7)    | 884 (5.0)    |       |
| 2009                            | 2340 (9.8)   | 1338 (6.4)   | 568 (7.4)                      | 7972 (8.8)      | 487 (4.0)   | 1343 (7.3)    | 1190 (6.8)   |       |
| 2010                            | 2352 (9.9)   | 862 (4.1)    | 572 (7.4)                      | 7562 (8.4)      | 270 (2.2)   | 1356 (7.4)    | 1080 (6.1)   |       |
| 2011                            | 2463 (10.3)  | 516 (2.5)    | 598 (7.7)                      | 9063 (10.0)     | 267 (2.2)   | 1857 (10.1)   | 1508 (8.6)   |       |
| 2012                            | 1918 (8.0)   | 372 (1.8)    | 547 (7.1)                      | 8326 (9.2)      | 227 (1.9)   | 2003 (10.9)   | 1657 (9.4)   |       |
| 2013                            | 1130 (4.7)   | 191 (0.9)    | 153 (2.0)                      | 3671 (4.1)      | 159 (1.3)   | 937 (5.1)     | 770 (4.4)    |       |
| 2014                            | 621 (2.6)    | 27 (0.1)     | 93 (1.2)                       | 1527 (1.7)      | 74 (0.6)    | 389 (2.1)     | 431 (2.4)    |       |
| <b>Comorbidities (n (%))</b>    |              |              |                                |                 |             |               |              |       |
| Opioid dependence               | 869 (3.6)    | 738 (3.5)    | 210 (2.7)                      | 2892 (3.2)      | 338 (2.8)   | 873 (4.8)     | 538 (3.1)    | 0.043 |
| Opioid abuse                    | 131 (0.5)    | 121 (0.6)    | 51 (0.7)                       | 506 (0.6)       | 62 (0.5)    | 157 (0.9)     | 93 (0.5)     | 0.016 |
| Alcohol abuse                   | 965 (4.0)    | 765 (3.7)    | 303 (3.9)                      | 4040 (4.5)      | 468 (3.9)   | 886 (4.8)     | 601 (3.4)    | 0.029 |
| Tobacco use                     | 2319 (9.7)   | 2051 (9.9)   | 1027 (13.3)                    | 12223 (13.5)    | 1201 (10.0) | 2664 (14.5)   | 2050 (11.6)  | 0.074 |
| Other drug abuse                | 1542 (6.5)   | 1504 (7.2)   | 518 (6.7)                      | 5950 (6.6)      | 748 (6.2)   | 1575 (8.6)    | 1178 (6.7)   | 0.032 |
| Anxiety                         | 4104 (17.2)  | 4306 (20.7)  | 1658 (21.5)                    | 17539 (19.4)    | 2285 (19.0) | 3794 (20.7)   | 3769 (21.4)  | 0.045 |
| Bipolar disorder                | 1708 (7.2)   | 1314 (6.3)   | 543 (7.0)                      | 6686 (7.4)      | 783 (6.5)   | 1420 (7.7)    | 1286 (7.3)   | 0.024 |
| Bone fracture                   | 1717 (7.2)   | 1406 (6.8)   | 520 (6.7)                      | 5952 (6.6)      | 758 (6.3)   | 1286 (7.0)    | 1048 (6.0)   | 0.021 |
| Cancer                          | 1376 (5.8)   | 859 (4.1)    | 320 (4.1)                      | 4633 (5.1)      | 507 (4.2)   | 834 (4.5)     | 698 (4.0)    | 0.035 |
| Chronic renal insufficiency     | 611 (2.6)    | 288 (1.4)    | 121 (1.6)                      | 1978 (2.2)      | 205 (1.7)   | 326 (1.8)     | 294 (1.7)    | 0.034 |
| Congestive heart failure        | 1153 (4.8)   | 811 (3.9)    | 270 (3.5)                      | 3708 (4.1)      | 515 (4.3)   | 708 (3.9)     | 566 (3.2)    | 0.033 |
| COPD/asthma/oxygen              | 5534 (23.2)  | 4615 (22.2)  | 1689 (21.9)                    | 20557 (22.8)    | 2739 (22.7) | 4466 (24.3)   | 3837 (21.8)  | 0.025 |
| Dementia                        | 342 (1.4)    | 122 (0.6)    | 63 (0.8)                       | 691 (0.8)       | 89 (0.7)    | 137 (0.7)     | 167 (0.9)    | 0.030 |
| Depression                      | 6089 (25.6)  | 4812 (23.1)  | 1994 (25.8)                    | 22886 (25.4)    | 3122 (25.9) | 4770 (26.0)   | 4777 (27.1)  | 0.030 |
| Diabetes                        | 4619 (19.4)  | 3286 (15.8)  | 1323 (17.1)                    | 17217 (19.1)    | 2254 (18.7) | 3393 (18.5)   | 3008 (17.1)  | 0.041 |
| Epilepsy                        | 1425 (6.0)   | 1041 (5.0)   | 367 (4.8)                      | 3845 (4.3)      | 582 (4.8)   | 839 (4.6)     | 898 (5.1)    | 0.028 |
| HIV                             | 748 (3.1)    | 503 (2.4)    | 128 (1.7)                      | 2407 (2.7)      | 256 (2.1)   | 499 (2.7)     | 334 (1.9)    | 0.042 |
| Intentional self-harm           | 24 (0.1)     | 33 (0.2)     | 10 (0.1)                       | 148 (0.2)       | 24 (0.2)    | 45 (0.2)      | 28 (0.2)     | 0.013 |
| Liver disease                   | 2649 (11.1)  | 1663 (8.0)   | 523 (6.8)                      | 6829 (7.6)      | 810 (6.7)   | 1429 (7.8)    | 1235 (7.0)   | 0.056 |
| Musculoskeletal injury          | 2217 (9.3)   | 2337 (11.2)  | 959 (12.4)                     | 10608 (11.8)    | 1406 (11.7) | 2179 (11.9)   | 1636 (9.3)   | 0.046 |
| Multiple sclerosis              | 608 (2.6)    | 104 (0.5)    | 35 (0.5)                       | 490 (0.5)       | 70 (0.6)    | 76 (0.4)      | 226 (1.3)    | 0.070 |
| Obesity                         | 1560 (6.5)   | 998 (4.8)    | 461 (6.0)                      | 5817 (6.4)      | 646 (5.4)   | 1133 (6.2)    | 995 (5.6)    | 0.033 |
| Pneumonia                       | 1418 (6.0)   | 979 (4.7)    | 318 (4.1)                      | 4094 (4.5)      | 532 (4.4)   | 806 (4.4)     | 698 (4.0)    | 0.032 |
| Psychosis                       | 1228 (5.2)   | 687 (3.3)    | 296 (3.8)                      | 3422 (3.8)      | 457 (3.8)   | 816 (4.4)     | 540 (3.1)    | 0.042 |
| Renal dysfunction               | 1251 (5.3)   | 754 (3.6)    | 304 (3.9)                      | 4277 (4.7)      | 464 (3.8)   | 797 (4.3)     | 710 (4.0)    | 0.033 |
| Spasticity                      | 4929 (20.7)  | 2282 (11.0)  | 859 (11.1)                     | 9891 (11.0)     | 1423 (11.8) | 2078 (11.3)   | 2516 (14.3)  | 0.098 |
| Urinary calculus                | 615 (2.6)    | 572 (2.7)    | 256 (3.3)                      | 2621 (2.9)      | 319 (2.6)   | 572 (3.1)     | 451 (2.6)    | 0.020 |
| Urinary tract infection         | 3283 (13.8)  | 2395 (11.5)  | 1052 (13.6)                    | 10675 (11.8)    | 1423 (11.8) | 2122 (11.6)   | 1993 (11.3)  | 0.034 |
| <b>Pain conditions (n (%))</b>  |              |              |                                |                 |             |               |              |       |
| Abdominal pain                  | 5438 (22.8)  | 4838 (23.3)  | 1929 (25.0)                    | 21636 (24.0)    | 2857 (23.7) | 4392 (23.9)   | 3848 (21.8)  | 0.028 |
| Back and neck pain              | 15727 (66.0) | 13492 (64.9) | 5288 (68.5)                    | 58981 (65.3)    | 8168 (67.8) | 12378 (67.4)  | 12310 (69.9) | 0.047 |
| Back pain without radiculopathy | 14757 (61.9) | 12954 (62.3) | 5093 (66.0)                    | 56237 (62.3)    | 7821 (64.9) | 11740 (63.9)  | 11415 (64.8) | 0.040 |
| Back pain with radiculopathy    | 3097 (13.0)  | 2403 (11.6)  | 1018 (13.2)                    | 11219 (12.4)    | 1575 (13.1) | 2584 (14.1)   | 2990 (17.0)  | 0.054 |
| Dental pain                     | 1031 (4.3)   | 1138 (5.5)   | 469 (6.1)                      | 5378 (6.0)      | 629 (5.2)   | 1133 (6.2)    | 859 (4.9)    | 0.037 |
| Diabetic neuropathy             | 631 (2.6)    | 383 (1.8)    | 192 (2.5)                      | 2492 (2.8)      | 319 (2.6)   | 505 (2.8)     | 477 (2.7)    | 0.021 |
| Fibromyalgia                    | 2639 (11.1)  | 2183 (10.5)  | 917 (11.9)                     | 9464 (10.5)     | 1503 (12.5) | 1910 (10.4)   | 2829 (16.1)  | 0.064 |
| Headache                        | 4162 (17.5)  | 4302 (20.7)  | 1704 (22.1)                    | 17227 (19.1)    | 2491 (20.7) | 3576 (19.5)   | 3752 (21.3)  | 0.047 |
| Osteoarthritis                  | 4147 (17.4)  | 3478 (16.7)  | 1286 (16.7)                    | 15167 (16.8)    | 2117 (17.6) | 3195 (17.4)   | 2901 (16.5)  | 0.014 |
| Rheumatoid arthritis            | 794 (3.3)    | 712 (3.4)    | 236 (3.1)                      | 2926 (3.2)      | 363 (3.0)   | 568 (3.1)     | 576 (3.3)    | 0.011 |

|                                                                                              | Baclofen          | Carisoprodol      | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone        | Methocarbamol     | Tizanidine        | SMD   |
|----------------------------------------------------------------------------------------------|-------------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|-------------------|-------|
| Postherpetic neuralgia                                                                       | 36 (0.2)          | 18 (0.1)          | 7 (0.1)                        | 96 (0.1)          | 11 (0.1)          | 16 (0.1)          | 25 (0.1)          | 0.009 |
| Other arthritis                                                                              | 12710 (53.3)      | 10291 (49.5)      | 3993 (51.7)                    | 47000 (52.1)      | 6258 (51.9)       | 9664 (52.6)       | 9079 (51.6)       | 0.027 |
| Other neuropathy                                                                             | 6228 (26.1)       | 4680 (22.5)       | 1851 (24.0)                    | 21333 (23.6)      | 3019 (25.0)       | 4636 (25.3)       | 5577 (31.7)       | 0.073 |
| Other unspecified pain                                                                       | 5228 (21.9)       | 2547 (12.2)       | 1413 (18.3)                    | 17717 (19.6)      | 1577 (13.1)       | 3628 (19.8)       | 3880 (22.0)       | 0.123 |
| <b>Other prescription fills (n (%))</b>                                                      |                   |                   |                                |                   |                   |                   |                   |       |
| Antibiotics                                                                                  | 15515 (65.1)      | 14440 (69.4)      | 5478 (71.0)                    | 62284 (69.0)      | 8429 (69.9)       | 12708 (69.2)      | 11706 (66.5)      | 0.051 |
| Anticonvulsants                                                                              | 4130 (17.3)       | 2748 (13.2)       | 1107 (14.3)                    | 12253 (13.6)      | 1849 (15.3)       | 2645 (14.4)       | 3309 (18.8)       | 0.066 |
| Antidepressants, SSRIs                                                                       | 7914 (33.2)       | 7104 (34.2)       | 2726 (35.3)                    | 30954 (34.3)      | 4441 (36.8)       | 6377 (34.7)       | 6467 (36.7)       | 0.034 |
| Antidepressants, SNRIs                                                                       | 3563 (15.0)       | 2451 (11.8)       | 1056 (13.7)                    | 12293 (13.6)      | 1623 (13.5)       | 2522 (13.7)       | 2914 (16.5)       | 0.048 |
| Antidepressants, TCAs                                                                        | 3931 (16.5)       | 3156 (15.2)       | 1167 (15.1)                    | 12831 (14.2)      | 1896 (15.7)       | 2543 (13.9)       | 3023 (17.2)       | 0.04  |
| Antidepressants, other                                                                       | 5545 (23.3)       | 4260 (20.5)       | 1619 (21.0)                    | 18691 (20.7)      | 2729 (22.6)       | 3991 (21.7)       | 4022 (22.8)       | 0.033 |
| Antidiabetics                                                                                | 3978 (16.7)       | 2833 (13.6)       | 1200 (15.6)                    | 15657 (17.3)      | 2002 (16.6)       | 3037 (16.5)       | 2690 (15.3)       | 0.04  |
| Antipsychotics, atypical                                                                     | 3825 (16.1)       | 2642 (12.7)       | 1136 (14.7)                    | 12827 (14.2)      | 1688 (14.0)       | 2870 (15.6)       | 2567 (14.6)       | 0.037 |
| Antipsychotics, typical                                                                      | 1362 (5.7)        | 963 (4.6)         | 365 (4.7)                      | 3858 (4.3)        | 490 (4.1)         | 757 (4.1)         | 701 (4.0)         | 0.032 |
| Barbiturates                                                                                 | 454 (1.9)         | 195 (0.9)         | 52 (0.7)                       | 483 (0.5)         | 104 (0.9)         | 108 (0.6)         | 93 (0.5)          | 0.049 |
| Benzodiazepines                                                                              | 10842 (45.5)      | 13108 (63.0)      | 4311 (55.9)                    | 45379 (50.3)      | 6398 (53.1)       | 9564 (52.1)       | 9900 (56.2)       | 0.131 |
| CNS stimulants                                                                               | 413 (1.7)         | 339 (1.6)         | 181 (2.3)                      | 1934 (2.1)        | 174 (1.4)         | 340 (1.9)         | 438 (2.5)         | 0.034 |
| Dementia agents                                                                              | 122 (0.5)         | 57 (0.3)          | 23 (0.3)                       | 299 (0.3)         | 42 (0.3)          | 74 (0.4)          | 75 (0.4)          | 0.016 |
| Gabapentinoids                                                                               | 7581 (31.8)       | 3908 (18.8)       | 1651 (21.4)                    | 21373 (23.7)      | 2638 (21.9)       | 4671 (25.4)       | 5606 (31.8)       | 0.140 |
| Lithium                                                                                      | 306 (1.3)         | 263 (1.3)         | 92 (1.2)                       | 1053 (1.2)        | 158 (1.3)         | 231 (1.3)         | 220 (1.2)         | 0.005 |
| Multiple sclerosis agents                                                                    | 237 (1.0)         | 41 (0.2)          | 12 (0.2)                       | 186 (0.2)         | 28 (0.2)          | 24 (0.1)          | 100 (0.6)         | 0.048 |
| NSAIDs                                                                                       | 11736 (49.3)      | 9924 (47.7)       | 4512 (58.5)                    | 48772 (54.0)      | 6602 (54.8)       | 10252 (55.8)      | 8780 (49.9)       | 0.096 |
| Other sedative hypnotics                                                                     | 4716 (19.8)       | 3893 (18.7)       | 1226 (15.9)                    | 15337 (17.0)      | 2252 (18.7)       | 3133 (17.1)       | 3377 (19.2)       | 0.044 |
| Smoking cessation                                                                            | 2761 (11.6)       | 2279 (11.0)       | 924 (12.0)                     | 11841 (13.1)      | 1482 (12.3)       | 2290 (12.5)       | 2195 (12.5)       | 0.026 |
| Triptans                                                                                     | 1174 (4.9)        | 1133 (5.4)        | 454 (5.9)                      | 4743 (5.3)        | 746 (6.2)         | 936 (5.1)         | 1167 (6.6)        | 0.032 |
| Other CNS depressants                                                                        | 124 (0.5)         | 83 (0.4)          | 26 (0.3)                       | 324 (0.4)         | 50 (0.4)          | 61 (0.3)          | 95 (0.5)          | 0.015 |
| <b>Prescription opioid utilization (n (%))</b>                                               |                   |                   |                                |                   |                   |                   |                   |       |
| Prescription opioid on index date                                                            |                   |                   |                                |                   |                   |                   |                   |       |
| Buprenorphine                                                                                | 32 (0.1)          | 21 (0.1)          | 9 (0.1)                        | 119 (0.1)         | 8 (0.1)           | 61 (0.3)          | 39 (0.2)          | 0.024 |
| Butorphanol                                                                                  | 44 (0.2)          | 147 (0.7)         | 42 (0.5)                       | 310 (0.3)         | 74 (0.6)          | 52 (0.3)          | 91 (0.5)          | 0.035 |
| Codeine                                                                                      | 2518 (10.6)       | 1634 (7.9)        | 593 (7.7)                      | 6459 (7.2)        | 769 (6.4)         | 1455 (7.9)        | 776 (4.4)         | 0.082 |
| Dihydrocodeine                                                                               | 21 (0.1)          | 87 (0.4)          | 28 (0.4)                       | 276 (0.3)         | 79 (0.7)          | 89 (0.5)          | 50 (0.3)          | 0.036 |
| Fentanyl                                                                                     | 1913 (8.0)        | 1231 (5.9)        | 403 (5.2)                      | 4698 (5.2)        | 783 (6.5)         | 854 (4.7)         | 1419 (8.1)        | 0.067 |
| Hydrocodone                                                                                  | 12248 (51.4)      | 13653 (65.6)      | 5046 (65.4)                    | 55792 (61.8)      | 7057 (58.5)       | 11394 (62.1)      | 10045 (57.0)      | 0.123 |
| Hydromorphone                                                                                | 894 (3.8)         | 356 (1.7)         | 130 (1.7)                      | 1541 (1.7)        | 167 (1.4)         | 374 (2.0)         | 365 (2.1)         | 0.051 |
| Levorphanol                                                                                  | 3 (0.0)           | 1 (0.0)           | 0 (0.0)                        | 5 (0.0)           | 2 (0.0)           | 1 (0.0)           | 0 (0.0)           | 0.009 |
| Meperidine                                                                                   | 70 (0.3)          | 145 (0.7)         | 36 (0.5)                       | 408 (0.5)         | 48 (0.4)          | 113 (0.6)         | 77 (0.4)          | 0.023 |
| Methadone                                                                                    | 1875 (7.9)        | 1040 (5.0)        | 284 (3.7)                      | 3558 (3.9)        | 510 (4.2)         | 685 (3.7)         | 1169 (6.6)        | 0.082 |
| Morphine                                                                                     | 2408 (10.1)       | 1304 (6.3)        | 382 (5.0)                      | 5162 (5.7)        | 700 (5.8)         | 1078 (5.9)        | 1513 (8.6)        | 0.079 |
| Opium                                                                                        | 1 (0.0)           | 9 (0.0)           | 0 (0.0)                        | 22 (0.0)          | 1 (0.0)           | 4 (0.0)           | 3 (0.0)           | 0.014 |
| Oxycodone                                                                                    | 6872 (28.8)       | 6913 (33.2)       | 2074 (26.9)                    | 27631 (30.6)      | 3839 (31.8)       | 5423 (29.5)       | 5916 (33.6)       | 0.065 |
| Oxymorphone                                                                                  | 70 (0.3)          | 44 (0.2)          | 10 (0.1)                       | 231 (0.3)         | 20 (0.2)          | 44 (0.2)          | 79 (0.4)          | 0.023 |
| Pentazocine                                                                                  | 37 (0.2)          | 146 (0.7)         | 48 (0.6)                       | 323 (0.4)         | 84 (0.7)          | 85 (0.5)          | 78 (0.4)          | 0.036 |
| Propoxyphene                                                                                 | 222 (0.9)         | 797 (3.8)         | 339 (4.4)                      | 3325 (3.7)        | 490 (4.1)         | 734 (4.0)         | 471 (2.7)         | 0.079 |
| Tapentadol                                                                                   | 22 (0.1)          | 29 (0.1)          | 5 (0.1)                        | 81 (0.1)          | 4 (0.0)           | 27 (0.1)          | 31 (0.2)          | 0.019 |
| Tramadol                                                                                     | 4911 (20.6)       | 2830 (13.6)       | 1701 (22.0)                    | 18809 (20.8)      | 2454 (20.4)       | 3859 (21.0)       | 3052 (17.3)       | 0.082 |
| Number of days covered by<br>prescription opioids in 180 days pre-<br>index date (mean (SD)) | 172.31 (18.40)    | 172.19 (18.66)    | 172.33 (18.53)                 | 172.06 (18.86)    | 172.57 (18.15)    | 171.67 (19.30)    | 173.25 (17.50)    | 0.031 |
| Total dispensed MMEs per interval<br>(days) (mean (SD))                                      |                   |                   |                                |                   |                   |                   |                   |       |
| (Index - 180) to (index - 151)                                                               | 2203.65 (3772.46) | 2055.24 (3504.84) | 1619.28 (2977.02)              | 1602.97 (2818.42) | 1780.75 (2974.76) | 1561.60 (2830.24) | 2134.50 (3444.66) | 0.101 |

|                                           | Baclofen          | Carisoprodol      | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone        | Methocarbamol     | Tizanidine        | SMD   |
|-------------------------------------------|-------------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|-------------------|-------|
| (Index - 150) to (index - 121)            | 2308.26 (3751.56) | 2154.86 (3546.12) | 1715.85 (2988.45)              | 1691.94 (2916.01) | 1885.30 (3053.31) | 1623.60 (2845.14) | 2250.49 (3546.10) | 0.105 |
| (Index - 120) to (index - 91)             | 2569.73 (3919.24) | 2427.58 (3798.97) | 1882.89 (3341.79)              | 1862.42 (3016.10) | 2065.59 (3143.58) | 1776.60 (2918.09) | 2465.03 (3760.28) | 0.114 |
| (Index - 90) to (index - 61)              | 2599.37 (3937.64) | 2448.39 (3769.75) | 1928.91 (3695.72)              | 1885.37 (3001.02) | 2099.96 (3100.83) | 1810.62 (2945.37) | 2507.91 (3676.87) | 0.113 |
| (Index - 60) to (index - 31)              | 2614.06 (3976.16) | 2446.06 (3705.39) | 1909.78 (3510.51)              | 1910.74 (3025.44) | 2097.50 (3084.55) | 1825.91 (2974.22) | 2500.46 (3688.73) | 0.112 |
| (Index - 30) to index                     | 3246.04 (5058.94) | 3094.14 (4772.05) | 2212.74 (3922.79)              | 2231.40 (3572.96) | 2504.75 (3830.11) | 2120.49 (3514.84) | 3226.72 (4769.98) | 0.140 |
| <b>Healthcare utilization (mean (SD))</b> |                   |                   |                                |                   |                   |                   |                   |       |
| Number of physician visits                | 8.35 (10.11)      | 8.90 (8.16)       | 9.34 (8.62)                    | 9.10 (8.83)       | 9.30 (8.21)       | 9.24 (8.74)       | 9.32 (8.15)       | 0.043 |
| Number of distinct prescribed medications | 14.38 (7.17)      | 14.24 (7.34)      | 14.60 (7.44)                   | 14.41 (7.40)      | 14.86 (7.53)      | 14.75 (7.47)      | 14.49 (7.35)      | 0.036 |
| Number of hospitalizations                | 0.37 (0.98)       | 0.31 (0.82)       | 0.30 (0.81)                    | 0.33 (0.89)       | 0.31 (0.83)       | 0.37 (1.14)       | 0.28 (0.76)       | 0.046 |
| Number of hospitalization days            | 2.15 (8.37)       | 1.61 (6.99)       | 1.49 (5.02)                    | 1.52 (9.51)       | 1.65 (6.25)       | 1.66 (11.48)      | 1.35 (10.14)      | 0.033 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 5B. Characteristics of patients with non-missing values for socioeconomic status measures and rural-urban continuum codes who initiated skeletal muscle relaxants while on long-term opioid therapy in Medicaid Analytic eXtract (MAX), 2000-2014 (post-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 4105.7        | 4273.52       | 4298.19                        | 4303.69         | 4316.56       | 4283.74       | 4232.67       |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 43.88 (10.55) | 43.73 (10.35) | 43.72 (10.68)                  | 43.82 (10.60)   | 43.84 (10.51) | 43.71 (10.74) | 43.74 (10.45) | 0.008 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.014 |
| Unknown                                | 4.0 (0.1)     | 4.5 (0.1)     | 3.1 (0.1)                      | 4.7 (0.1)       | 3.5 (0.1)     | 5.0 (0.1)     | 4.9 (0.1)     |       |
| Male                                   | 1336.2 (32.5) | 1396.7 (32.7) | 1419.4 (33.0)                  | 1446.0 (33.6)   | 1449.5 (33.6) | 1433.0 (33.5) | 1419.8 (33.5) |       |
| Female                                 | 2765.5 (67.4) | 2872.3 (67.2) | 2875.7 (66.9)                  | 2853.0 (66.3)   | 2863.5 (66.3) | 2845.7 (66.4) | 2808.0 (66.3) |       |
| Race                                   |               |               |                                |                 |               |               |               | 0.036 |
| Asian                                  | 53.4 (1.3)    | 66.3 (1.6)    | 63.9 (1.5)                     | 62.3 (1.4)      | 68.9 (1.6)    | 62.0 (1.4)    | 62.8 (1.5)    |       |
| Black                                  | 498.3 (12.1)  | 585.1 (13.7)  | 599.7 (14.0)                   | 607.9 (14.1)    | 547.9 (12.7)  | 588.3 (13.7)  | 579.1 (13.7)  |       |
| White                                  | 3331.9 (81.2) | 3345.6 (78.3) | 3361.1 (78.2)                  | 3378.3 (78.5)   | 3438.7 (79.7) | 3377.6 (78.8) | 3351.5 (79.2) |       |
| Other                                  | 222.1 (5.4)   | 276.5 (6.5)   | 273.5 (6.4)                    | 255.2 (5.9)     | 261.0 (6.0)   | 255.9 (6.0)   | 239.2 (5.7)   |       |
| Ethnicity                              |               |               |                                |                 |               |               |               | 0.024 |
| Unknown                                | 131.3 (3.2)   | 151.9 (3.6)   | 144.7 (3.4)                    | 141.4 (3.3)     | 142.9 (3.3)   | 134.4 (3.1)   | 133.2 (3.1)   |       |
| Hispanic                               | 79.2 (1.9)    | 110.2 (2.6)   | 116.1 (2.7)                    | 99.7 (2.3)      | 103.8 (2.4)   | 106.6 (2.5)   | 91.8 (2.2)    |       |
| Non-Hispanic                           | 3895.2 (94.9) | 4011.5 (93.9) | 4037.3 (93.9)                  | 4062.6 (94.4)   | 4069.8 (94.3) | 4042.7 (94.4) | 4007.7 (94.7) |       |
| State                                  |               |               |                                |                 |               |               |               | 0.099 |
| AK                                     | 13.3 (0.3)    | 16.0 (0.4)    | 16.0 (0.4)                     | 15.9 (0.4)      | 16.7 (0.4)    | 15.8 (0.4)    | 15.3 (0.4)    |       |
| AL                                     | 61.9 (1.5)    | 50.6 (1.2)    | 62.9 (1.5)                     | 61.1 (1.4)      | 57.5 (1.3)    | 58.2 (1.4)    | 63.0 (1.5)    |       |
| AR                                     | 24.0 (0.6)    | 26.2 (0.6)    | 26.5 (0.6)                     | 26.3 (0.6)      | 27.3 (0.6)    | 26.6 (0.6)    | 27.8 (0.7)    |       |
| AZ                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| CA                                     | 31.5 (0.8)    | 33.8 (0.8)    | 30.1 (0.7)                     | 33.2 (0.8)      | 32.1 (0.7)    | 33.8 (0.8)    | 21.7 (0.5)    |       |
| CO                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| CT                                     | 85.8 (2.1)    | 135.8 (3.2)   | 92.3 (2.1)                     | 97.4 (2.3)      | 111.7 (2.6)   | 96.7 (2.3)    | 95.8 (2.3)    |       |
| DC                                     | 2.9 (0.1)     | 4.7 (0.1)     | 4.9 (0.1)                      | 4.9 (0.1)       | 6.3 (0.1)     | 4.5 (0.1)     | 4.8 (0.1)     |       |
| DE                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| FL                                     | 119.2 (2.9)   | 121.5 (2.8)   | 134.8 (3.1)                    | 132.8 (3.1)     | 110.2 (2.6)   | 141.1 (3.3)   | 127.3 (3.0)   |       |
| GA                                     | 166.3 (4.1)   | 174.6 (4.1)   | 176.3 (4.1)                    | 176.0 (4.1)     | 168.8 (3.9)   | 176.1 (4.1)   | 172.8 (4.1)   |       |
| HI                                     | 14.6 (0.4)    | 12.8 (0.3)    | 14.0 (0.3)                     | 13.1 (0.3)      | 13.0 (0.3)    | 13.4 (0.3)    | 13.9 (0.3)    |       |
| IA                                     | 0.3 (0.0)     | 0.5 (0.0)     | 0.7 (0.0)                      | 0.6 (0.0)       | 0.6 (0.0)     | 0.6 (0.0)     | 0.5 (0.0)     |       |
| ID                                     | 35.1 (0.9)    | 40.1 (0.9)    | 43.5 (1.0)                     | 39.5 (0.9)      | 37.7 (0.9)    | 37.8 (0.9)    | 42.4 (1.0)    |       |
| IL                                     | 121.5 (3.0)   | 163.8 (3.8)   | 127.0 (3.0)                    | 132.7 (3.1)     | 137.3 (3.2)   | 137.3 (3.2)   | 136.3 (3.2)   |       |
| IN                                     | 295.0 (7.2)   | 292.8 (6.9)   | 308.0 (7.2)                    | 312.0 (7.3)     | 296.5 (6.9)   | 315.8 (7.4)   | 317.2 (7.5)   |       |
| KS                                     | 37.5 (0.9)    | 31.8 (0.7)    | 35.0 (0.8)                     | 34.0 (0.8)      | 29.2 (0.7)    | 34.8 (0.8)    | 28.0 (0.7)    |       |
| KY                                     | 2.9 (0.1)     | 2.0 (0.0)     | 2.2 (0.1)                      | 1.8 (0.0)       | 1.7 (0.0)     | 2.2 (0.1)     | 2.0 (0.0)     |       |
| LA                                     | 196.9 (4.8)   | 222.9 (5.2)   | 205.3 (4.8)                    | 212.8 (4.9)     | 171.1 (4.0)   | 201.8 (4.7)   | 207.6 (4.9)   |       |
| MA                                     | 4.7 (0.1)     | 5.5 (0.1)     | 4.9 (0.1)                      | 6.1 (0.1)       | 5.3 (0.1)     | 6.5 (0.2)     | 5.7 (0.1)     |       |
| MD                                     | 1.9 (0.0)     | 2.8 (0.1)     | 2.0 (0.0)                      | 2.0 (0.0)       | 2.4 (0.1)     | 1.9 (0.0)     | 2.2 (0.1)     |       |
| ME                                     | 58.6 (1.4)    | 63.3 (1.5)    | 65.6 (1.5)                     | 58.2 (1.4)      | 54.5 (1.3)    | 52.7 (1.2)    | 50.2 (1.2)    |       |
| MI                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| MN                                     | 71.0 (1.7)    | 81.4 (1.9)    | 74.0 (1.7)                     | 70.5 (1.6)      | 80.2 (1.9)    | 74.6 (1.7)    | 67.7 (1.6)    |       |
| MO                                     | 663.3 (16.2)  | 620.6 (14.5)  | 693.8 (16.1)                   | 718.4 (16.7)    | 832.1 (19.3)  | 711.1 (16.6)  | 731.6 (17.3)  |       |
| MS                                     | 34.6 (0.8)    | 47.9 (1.1)    | 45.1 (1.0)                     | 45.4 (1.1)      | 43.3 (1.0)    | 45.2 (1.1)    | 47.1 (1.1)    |       |
| MT                                     | 26.1 (0.6)    | 26.0 (0.6)    | 27.0 (0.6)                     | 28.9 (0.7)      | 33.2 (0.8)    | 26.8 (0.6)    | 28.4 (0.7)    |       |
| NC                                     | 418.6 (10.2)  | 444.5 (10.4)  | 416.6 (9.7)                    | 425.5 (9.9)     | 435.0 (10.1)  | 434.0 (10.1)  | 416.2 (9.8)   |       |
| ND                                     | 9.7 (0.2)     | 17.6 (0.4)    | 13.6 (0.3)                     | 13.2 (0.3)      | 14.5 (0.3)    | 10.0 (0.2)    | 12.4 (0.3)    |       |

|                                                                | Baclofen              | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine      | Metaxalone           | Methocarbamol        | Tizanidine           | SMD   |
|----------------------------------------------------------------|-----------------------|----------------------|--------------------------------|----------------------|----------------------|----------------------|----------------------|-------|
| NE                                                             | 0.8 (0.0)             | 0.7 (0.0)            | 0.9 (0.0)                      | 0.6 (0.0)            | 0.8 (0.0)            | 0.7 (0.0)            | 1.0 (0.0)            |       |
| NH                                                             | 35.5 (0.9)            | 41.6 (1.0)           | 34.2 (0.8)                     | 36.2 (0.8)           | 29.2 (0.7)           | 35.3 (0.8)           | 35.0 (0.8)           |       |
| NJ                                                             | 30.9 (0.8)            | 45.6 (1.1)           | 40.5 (0.9)                     | 41.0 (1.0)           | 43.8 (1.0)           | 42.1 (1.0)           | 35.3 (0.8)           |       |
| NM                                                             | 3.2 (0.1)             | 2.7 (0.1)            | 3.4 (0.1)                      | 2.6 (0.1)            | 3.0 (0.1)            | 2.3 (0.1)            | 2.3 (0.1)            |       |
| NV                                                             | 4.6 (0.1)             | 6.4 (0.1)            | 5.9 (0.1)                      | 5.8 (0.1)            | 5.4 (0.1)            | 5.7 (0.1)            | 5.1 (0.1)            |       |
| NY                                                             | 261.4 (6.4)           | 297.9 (7.0)          | 277.1 (6.4)                    | 275.6 (6.4)          | 273.5 (6.3)          | 267.7 (6.3)          | 259.1 (6.1)          |       |
| OH                                                             | 4.9 (0.1)             | 4.7 (0.1)            | 4.9 (0.1)                      | 4.8 (0.1)            | 4.8 (0.1)            | 5.0 (0.1)            | 5.1 (0.1)            |       |
| OK                                                             | 9.1 (0.2)             | 9.9 (0.2)            | 11.7 (0.3)                     | 11.5 (0.3)           | 7.9 (0.2)            | 10.7 (0.3)           | 8.6 (0.2)            |       |
| OR                                                             | 2.0 (0.0)             | 2.1 (0.0)            | 2.0 (0.0)                      | 1.9 (0.0)            | 2.1 (0.0)            | 2.0 (0.0)            | 1.9 (0.0)            |       |
| PA                                                             | 103.8 (2.5)           | 129.5 (3.0)          | 130.7 (3.0)                    | 130.2 (3.0)          | 129.6 (3.0)          | 128.4 (3.0)          | 123.8 (2.9)          |       |
| RI                                                             | 7.5 (0.2)             | 10.7 (0.2)           | 10.1 (0.2)                     | 10.4 (0.2)           | 10.4 (0.2)           | 10.5 (0.2)           | 9.4 (0.2)            |       |
| SC                                                             | 76.2 (1.9)            | 88.0 (2.1)           | 84.3 (2.0)                     | 84.4 (2.0)           | 83.6 (1.9)           | 82.0 (1.9)           | 83.8 (2.0)           |       |
| SD                                                             | 18.1 (0.4)            | 26.0 (0.6)           | 19.9 (0.5)                     | 20.2 (0.5)           | 21.3 (0.5)           | 13.9 (0.3)           | 18.6 (0.4)           |       |
| TN                                                             | 433.8 (10.6)          | 399.8 (9.4)          | 417.3 (9.7)                    | 407.4 (9.5)          | 407.9 (9.4)          | 417.8 (9.8)          | 414.7 (9.8)          |       |
| TX                                                             | 0 (0.0)               | 0 (0.0)              | 0 (0.0)                        | 0 (0.0)              | 0 (0.0)              | 0 (0.0)              | 0 (0.0)              |       |
| UT                                                             | 2.9 (0.1)             | 4.4 (0.1)            | 4.7 (0.1)                      | 4.3 (0.1)            | 4.4 (0.1)            | 4.2 (0.1)            | 4.7 (0.1)            |       |
| VA                                                             | 201.3 (4.9)           | 201.3 (4.7)          | 202.3 (4.7)                    | 203.6 (4.7)          | 197.1 (4.6)          | 199.3 (4.7)          | 188.6 (4.5)          |       |
| VT                                                             | 36.9 (0.9)            | 45.2 (1.1)           | 49.1 (1.1)                     | 46.8 (1.1)           | 40.7 (0.9)           | 46.1 (1.1)           | 45.8 (1.1)           |       |
| WA                                                             | 3.1 (0.1)             | 4.0 (0.1)            | 4.0 (0.1)                      | 4.0 (0.1)            | 4.2 (0.1)            | 4.0 (0.1)            | 4.5 (0.1)            |       |
| WI                                                             | 106.3 (2.6)           | 117.6 (2.8)          | 116.9 (2.7)                    | 114.6 (2.7)          | 108.4 (2.5)          | 110.0 (2.6)          | 107.4 (2.5)          |       |
| WV                                                             | 257.2 (6.3)           | 186.5 (4.4)          | 244.9 (5.7)                    | 224.8 (5.2)          | 211.1 (4.9)          | 223.4 (5.2)          | 229.7 (5.4)          |       |
| WY                                                             | 9.0 (0.2)             | 9.5 (0.2)            | 11.2 (0.3)                     | 10.7 (0.2)           | 9.4 (0.2)            | 13.2 (0.3)           | 10.2 (0.2)           |       |
| Socioeconomic status (% (SD)) <sup>1</sup>                     |                       |                      |                                |                      |                      |                      |                      |       |
| Households with 1-1.5 occupants per room                       | 1.72 (1.66)           | 1.76 (1.69)          | 1.81 (1.78)                    | 1.76 (1.70)          | 1.76 (1.69)          | 1.75 (1.72)          | 1.75 (1.70)          | 0.016 |
| Households with > 1.5 occupants per room                       | 0.70 (1.07)           | 0.72 (1.03)          | 0.74 (1.09)                    | 0.72 (1.06)          | 0.73 (1.08)          | 0.72 (1.08)          | 0.71 (1.05)          | 0.013 |
| Median value of homes (mean (SD))                              | 155009.54 (104452.64) | 153255.97 (93591.99) | 154148.71 (99278.21)           | 153260.63 (97684.35) | 152804.99 (98881.20) | 153505.71 (97348.65) | 152564.59 (94601.97) | 0.010 |
| Median value of homes ranked 1-100 (mean (SD))                 | 42.10 (23.77)         | 42.39 (23.76)        | 42.42 (23.51)                  | 42.04 (23.74)        | 41.87 (23.39)        | 41.90 (24.02)        | 41.79 (23.76)        | 0.013 |
| Median household income (mean (SD))                            | 45818.31 (14078.05)   | 45789.24 (14304.05)  | 45458.11 (14372.28)            | 45450.35 (14136.20)  | 45530.47 (14081.87)  | 45563.32 (14173.26)  | 45570.96 (14266.60)  | 0.012 |
| Median value of income ranked 1-100 (mean (SD))                | 35.13 (23.59)         | 35.03 (23.95)        | 34.45 (23.74)                  | 34.45 (23.68)        | 34.56 (23.58)        | 34.68 (23.83)        | 34.62 (23.94)        | 0.013 |
| Individuals below the poverty line                             | 18.85 (8.56)          | 18.98 (8.55)         | 19.14 (8.68)                   | 19.12 (8.71)         | 19.09 (8.51)         | 19.00 (8.69)         | 19.04 (8.58)         | 0.014 |
| Individuals > 16 years who are unemployed                      | 7.53 (3.76)           | 7.68 (3.71)          | 7.65 (3.83)                    | 7.68 (3.77)          | 7.63 (3.67)          | 7.67 (3.77)          | 7.62 (3.68)          | 0.015 |
| Individuals > 25 years with < 12 <sup>th</sup> grade education | 34.97 (8.41)          | 34.78 (8.16)         | 34.90 (7.92)                   | 34.86 (8.11)         | 34.91 (8.10)         | 34.89 (8.11)         | 34.96 (8.07)         | 0.009 |
| Individuals > 25 years with 4-year college education           | 13.13 (6.58)          | 13.15 (6.45)         | 13.07 (6.37)                   | 13.10 (6.35)         | 13.11 (6.40)         | 13.08 (6.40)         | 13.09 (6.40)         | 0.005 |
| Households with > 1 persons per room                           | 2.42 (2.41)           | 2.47 (2.37)          | 2.54 (2.53)                    | 2.48 (2.43)          | 2.49 (2.42)          | 2.47 (2.49)          | 2.46 (2.40)          | 0.017 |
| Socioeconomic status index score (mean (SD))                   | 52.04 (5.86)          | 52.05 (5.89)         | 51.95 (5.82)                   | 51.93 (5.83)         | 51.93 (5.80)         | 51.95 (5.89)         | 51.93 (5.90)         | 0.010 |
| Rural-urban continuum codes <sup>1</sup>                       |                       |                      |                                |                      |                      |                      |                      | 0.012 |
| Metropolitan                                                   | 2858.2 (69.6)         | 2977.0 (69.7)        | 2964.6 (69.0)                  | 2989.8 (69.5)        | 2989.2 (69.2)        | 2957.4 (69.0)        | 2919.7 (69.0)        |       |
| Rural                                                          | 306.4 (7.5)           | 324.9 (7.6)          | 318.7 (7.4)                    | 316.8 (7.4)          | 334.3 (7.7)          | 328.7 (7.7)          | 320.3 (7.6)          |       |
| Urban                                                          | 941.2 (22.9)          | 971.7 (22.7)         | 1014.9 (23.6)                  | 997.1 (23.2)         | 993.0 (23.0)         | 997.6 (23.3)         | 992.7 (23.5)         |       |
| Year                                                           |                       |                      |                                |                      |                      |                      |                      | 0.094 |
| 2000                                                           | 178.8 (4.4)           | 172.9 (4.0)          | 165.0 (3.8)                    | 156.2 (3.6)          | 162.3 (3.8)          | 160.6 (3.7)          | 141.8 (3.4)          |       |
| 2001                                                           | 333.0 (8.1)           | 359.8 (8.4)          | 337.6 (7.9)                    | 317.8 (7.4)          | 365.4 (8.5)          | 302.1 (7.1)          | 307.4 (7.3)          |       |

|                                 | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|---------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| 2002                            | 293.3 (7.1)   | 337.4 (7.9)   | 311.7 (7.3)                    | 294.8 (6.8)     | 356.8 (8.3)   | 292.5 (6.8)   | 297.7 (7.0)   |       |
| 2003                            | 431.4 (10.5)  | 494.0 (11.6)  | 473.2 (11.0)                   | 480.9 (11.2)    | 544.8 (12.6)  | 472.5 (11.0)  | 474.4 (11.2)  |       |
| 2004                            | 703.5 (17.1)  | 732.8 (17.1)  | 762.1 (17.7)                   | 746.8 (17.4)    | 655.7 (15.2)  | 756.2 (17.7)  | 748.3 (17.7)  |       |
| 2005                            | 271.7 (6.6)   | 324.5 (7.6)   | 333.4 (7.8)                    | 326.9 (7.6)     | 303.9 (7.0)   | 318.5 (7.4)   | 317.3 (7.5)   |       |
| 2006                            | 265.8 (6.5)   | 317.6 (7.4)   | 334.7 (7.8)                    | 324.5 (7.5)     | 292.5 (6.8)   | 308.0 (7.2)   | 312.1 (7.4)   |       |
| 2007                            | 259.6 (6.3)   | 280.8 (6.6)   | 288.9 (6.7)                    | 292.7 (6.8)     | 263.2 (6.1)   | 289.0 (6.7)   | 283.5 (6.7)   |       |
| 2008                            | 236.3 (5.8)   | 282.6 (6.6)   | 286.9 (6.7)                    | 284.9 (6.6)     | 248.4 (5.8)   | 274.2 (6.4)   | 279.3 (6.6)   |       |
| 2009                            | 308.8 (7.5)   | 323.7 (7.6)   | 290.0 (6.7)                    | 305.3 (7.1)     | 305.5 (7.1)   | 311.0 (7.3)   | 301.5 (7.1)   |       |
| 2010                            | 244.7 (6.0)   | 226.8 (5.3)   | 203.6 (4.7)                    | 227.2 (5.3)     | 244.8 (5.7)   | 232.9 (5.4)   | 223.4 (5.3)   |       |
| 2011                            | 238.2 (5.8)   | 183.7 (4.3)   | 211.7 (4.9)                    | 225.2 (5.2)     | 233.8 (5.4)   | 229.5 (5.4)   | 230.3 (5.4)   |       |
| 2012                            | 197.4 (4.8)   | 149.6 (3.5)   | 171.8 (4.0)                    | 188.9 (4.4)     | 196.3 (4.5)   | 198.2 (4.6)   | 194.1 (4.6)   |       |
| 2013                            | 113.4 (2.8)   | 69.8 (1.6)    | 100.2 (2.3)                    | 106.7 (2.5)     | 112.9 (2.6)   | 112.5 (2.6)   | 98.1 (2.3)    |       |
| 2014                            | 29.8 (0.7)    | 17.4 (0.4)    | 27.2 (0.6)                     | 24.9 (0.6)      | 30.3 (0.7)    | 26.3 (0.6)    | 23.2 (0.5)    |       |
| <b>Comorbidities (n (%))</b>    |               |               |                                |                 |               |               |               |       |
| Opioid dependence               | 118.5 (2.9)   | 118.7 (2.8)   | 129.6 (3.0)                    | 124.8 (2.9)     | 126.4 (2.9)   | 135.0 (3.2)   | 113.8 (2.7)   | 0.011 |
| Opioid abuse                    | 22.2 (0.5)    | 22.0 (0.5)    | 23.2 (0.5)                     | 23.9 (0.6)      | 24.6 (0.6)    | 18.8 (0.4)    | 23.2 (0.5)    | 0.006 |
| Alcohol abuse                   | 163.2 (4.0)   | 180.1 (4.2)   | 174.7 (4.1)                    | 178.8 (4.2)     | 175.0 (4.1)   | 169.3 (4.0)   | 170.3 (4.0)   | 0.006 |
| Tobacco use                     | 469.7 (11.4)  | 504.2 (11.8)  | 481.9 (11.2)                   | 494.8 (11.5)    | 493.5 (11.4)  | 486.8 (11.4)  | 503.3 (11.9)  | 0.009 |
| Other drug abuse                | 271.5 (6.6)   | 286.5 (6.7)   | 287.9 (6.7)                    | 284.3 (6.6)     | 281.7 (6.5)   | 288.7 (6.7)   | 272.6 (6.4)   | 0.005 |
| Anxiety                         | 827.6 (20.2)  | 836.8 (19.6)  | 827.6 (19.3)                   | 847.8 (19.7)    | 868.5 (20.1)  | 838.2 (19.6)  | 844.6 (20.0)  | 0.010 |
| Bipolar disorder                | 279.7 (6.8)   | 286.2 (6.7)   | 302.1 (7.0)                    | 296.5 (6.9)     | 310.9 (7.2)   | 298.2 (7.0)   | 291.9 (6.9)   | 0.008 |
| Bone fracture                   | 274.8 (6.7)   | 279.6 (6.5)   | 274.1 (6.4)                    | 280.3 (6.5)     | 288.6 (6.7)   | 271.0 (6.3)   | 284.0 (6.7)   | 0.008 |
| Cancer                          | 196.4 (4.8)   | 188.7 (4.4)   | 189.3 (4.4)                    | 194.3 (4.5)     | 198.8 (4.6)   | 198.0 (4.6)   | 196.7 (4.6)   | 0.008 |
| Chronic renal insufficiency     | 72.7 (1.8)    | 70.7 (1.7)    | 72.8 (1.7)                     | 72.8 (1.7)      | 73.9 (1.7)    | 69.8 (1.6)    | 72.6 (1.7)    | 0.004 |
| Congestive heart failure        | 153.4 (3.7)   | 157.4 (3.7)   | 169.7 (3.9)                    | 166.8 (3.9)     | 167.4 (3.9)   | 164.8 (3.8)   | 156.5 (3.7)   | 0.006 |
| COPD/asthma/oxygen              | 948.9 (23.1)  | 963.4 (22.5)  | 968.2 (22.5)                   | 960.9 (22.3)    | 956.2 (22.2)  | 963.0 (22.5)  | 945.5 (22.3)  | 0.008 |
| Dementia                        | 35.8 (0.9)    | 38.8 (0.9)    | 33.5 (0.8)                     | 34.7 (0.8)      | 40.4 (0.9)    | 36.7 (0.9)    | 33.4 (0.8)    | 0.008 |
| Depression                      | 1088.9 (26.5) | 1109.6 (26.0) | 1140.2 (26.5)                  | 1118.5 (26.0)   | 1160.6 (26.9) | 1091.1 (25.5) | 1104.2 (26.1) | 0.013 |
| Diabetes                        | 680.1 (16.6)  | 760.3 (17.8)  | 754.3 (17.5)                   | 766.3 (17.8)    | 755.8 (17.5)  | 746.6 (17.4)  | 752.4 (17.8)  | 0.012 |
| Epilepsy                        | 200.5 (4.9)   | 216.0 (5.1)   | 219.6 (5.1)                    | 216.8 (5.0)     | 215.9 (5.0)   | 206.7 (4.8)   | 222.8 (5.3)   | 0.008 |
| HIV                             | 80.6 (2.0)    | 85.0 (2.0)    | 91.5 (2.1)                     | 90.2 (2.1)      | 83.8 (1.9)    | 86.4 (2.0)    | 84.0 (2.0)    | 0.006 |
| Intentional self-harm           | 6.4 (0.2)     | 7.0 (0.2)     | 6.0 (0.1)                      | 6.6 (0.2)       | 5.6 (0.1)     | 5.6 (0.1)     | 7.4 (0.2)     | 0.005 |
| Liver disease                   | 295.5 (7.2)   | 306.9 (7.2)   | 318.0 (7.4)                    | 310.1 (7.2)     | 319.4 (7.4)   | 315.1 (7.4)   | 306.2 (7.2)   | 0.004 |
| Musculoskeletal injury          | 434.3 (10.6)  | 479.2 (11.2)  | 462.6 (10.8)                   | 458.0 (10.6)    | 466.5 (10.8)  | 467.0 (10.9)  | 449.6 (10.6)  | 0.008 |
| Multiple sclerosis              | 26.0 (0.6)    | 20.4 (0.5)    | 24.3 (0.6)                     | 24.7 (0.6)      | 25.5 (0.6)    | 20.7 (0.5)    | 22.2 (0.5)    | 0.009 |
| Obesity                         | 225.4 (5.5)   | 228.0 (5.3)   | 229.4 (5.3)                    | 231.1 (5.4)     | 219.1 (5.1)   | 226.2 (5.3)   | 224.6 (5.3)   | 0.006 |
| Pneumonia                       | 180.2 (4.4)   | 194.8 (4.6)   | 199.7 (4.6)                    | 195.3 (4.5)     | 197.8 (4.6)   | 194.6 (4.5)   | 199.4 (4.7)   | 0.006 |
| Psychosis                       | 163.6 (4.0)   | 153.1 (3.6)   | 153.6 (3.6)                    | 162.7 (3.8)     | 167.3 (3.9)   | 162.1 (3.8)   | 159.6 (3.8)   | 0.009 |
| Renal dysfunction               | 169.5 (4.1)   | 169.6 (4.0)   | 169.9 (4.0)                    | 174.5 (4.1)     | 173.9 (4.0)   | 162.1 (3.8)   | 174.4 (4.1)   | 0.007 |
| Spasticity                      | 536.0 (13.1)  | 564.4 (13.2)  | 539.9 (12.6)                   | 568.2 (13.2)    | 586.3 (13.6)  | 543.1 (12.7)  | 563.2 (13.3)  | 0.013 |
| Urinary calculus                | 110.0 (2.7)   | 120.8 (2.8)   | 112.1 (2.6)                    | 124.3 (2.9)     | 121.8 (2.8)   | 127.3 (3.0)   | 128.5 (3.0)   | 0.011 |
| Urinary tract infection         | 481.4 (11.7)  | 546.2 (12.8)  | 536.3 (12.5)                   | 549.7 (12.8)    | 559.2 (13.0)  | 548.8 (12.8)  | 536.0 (12.7)  | 0.013 |
| <b>Pain conditions (n (%))</b>  |               |               |                                |                 |               |               |               |       |
| Abdominal pain                  | 957.3 (23.3)  | 1009.6 (23.6) | 1014.1 (23.6)                  | 1013.3 (23.5)   | 1003.3 (23.2) | 1009.1 (23.6) | 996.9 (23.6)  | 0.004 |
| Back and neck pain              | 2876.5 (70.1) | 2894.7 (67.7) | 2882.5 (67.1)                  | 2877.1 (66.9)   | 2917.7 (67.6) | 2885.4 (67.4) | 2831.1 (66.9) | 0.024 |
| Back pain without radiculopathy | 2704.0 (65.9) | 2762.2 (64.6) | 2746.4 (63.9)                  | 2734.4 (63.5)   | 2759.9 (63.9) | 2736.0 (63.9) | 2679.7 (63.3) | 0.020 |
| Back pain with radiculopathy    | 631.9 (15.4)  | 554.3 (13.0)  | 555.7 (12.9)                   | 563.4 (13.1)    | 581.3 (13.5)  | 550.4 (12.8)  | 576.0 (13.6)  | 0.026 |
| Dental pain                     | 204.8 (5.0)   | 236.9 (5.5)   | 230.4 (5.4)                    | 227.7 (5.3)     | 228.5 (5.3)   | 227.0 (5.3)   | 224.2 (5.3)   | 0.008 |
| Diabetic neuropathy             | 117.1 (2.9)   | 105.3 (2.5)   | 111.5 (2.6)                    | 114.4 (2.7)     | 114.3 (2.6)   | 115.0 (2.7)   | 114.1 (2.7)   | 0.008 |
| Fibromyalgia                    | 582.3 (14.2)  | 514.3 (12.0)  | 534.6 (12.4)                   | 512.8 (11.9)    | 545.9 (12.6)  | 488.5 (11.4)  | 532.1 (12.6)  | 0.030 |
| Headache                        | 817.1 (19.9)  | 855.5 (20.0)  | 861.6 (20.0)                   | 847.7 (19.7)    | 861.2 (19.9)  | 836.2 (19.5)  | 845.5 (20.0)  | 0.005 |
| Osteoarthritis                  | 686.6 (16.7)  | 701.6 (16.4)  | 715.8 (16.7)                   | 712.0 (16.5)    | 709.7 (16.4)  | 706.7 (16.5)  | 692.7 (16.4)  | 0.004 |

|                                                                                       | Baclofen       | Carisoprodol   | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone     | Methocarbamol  | Tizanidine     | SMD    |
|---------------------------------------------------------------------------------------|----------------|----------------|--------------------------------|-----------------|----------------|----------------|----------------|--------|
| Rheumatoid arthritis                                                                  | 133.3 (3.2)    | 129.6 (3.0)    | 131.0 (3.0)                    | 130.6 (3.0)     | 131.3 (3.0)    | 126.1 (2.9)    | 129.4 (3.1)    | 0.005  |
| Postherpetic neuralgia                                                                | 6.4 (0.2)      | 3.9 (0.1)      | 2.2 (0.1)                      | 3.9 (0.1)       | 6.2 (0.1)      | 3.2 (0.1)      | 5.4 (0.1)      | 0.015  |
| Other arthritis                                                                       | 2128.5 (51.8)  | 2221.1 (52.0)  | 2174.1 (50.6)                  | 2222.2 (51.6)   | 2246.7 (52.0)  | 2184.0 (51.0)  | 2187.5 (51.7)  | 0.013  |
| Other neuropathy                                                                      | 1191.8 (29.0)  | 1082.6 (25.3)  | 1067.9 (24.8)                  | 1079.9 (25.1)   | 1098.5 (25.4)  | 1065.5 (24.9)  | 1096.9 (25.9)  | 0.032  |
| Other unspecified pain                                                                | 728.6 (17.7)   | 712.5 (16.7)   | 707.4 (16.5)                   | 740.2 (17.2)    | 754.3 (17.5)   | 738.2 (17.2)   | 722.5 (17.1)   | 0.014  |
| <b>Other prescription fills (n (%))</b>                                               |                |                |                                |                 |                |                |                |        |
| Antibiotics                                                                           | 2798.9 (68.2)  | 2971.1 (69.5)  | 2978.5 (69.3)                  | 2982.8 (69.3)   | 2972.8 (68.9)  | 2960.5 (69.1)  | 2939.7 (69.5)  | 0.011  |
| Anticonvulsants                                                                       | 702.3 (17.1)   | 678.9 (15.9)   | 668.2 (15.5)                   | 671.2 (15.6)    | 684.4 (15.9)   | 654.2 (15.3)   | 673.1 (15.9)   | 0.017  |
| Antidepressants, SSRIs                                                                | 1475.1 (35.9)  | 1532.5 (35.9)  | 1544.6 (35.9)                  | 1539.9 (35.8)   | 1568.2 (36.3)  | 1518.0 (35.4)  | 1530.2 (36.2)  | 0.007  |
| Antidepressants, SNRIs                                                                | 626.9 (15.3)   | 591.4 (13.8)   | 589.5 (13.7)                   | 604.5 (14.0)    | 611.5 (14.2)   | 605.5 (14.1)   | 604.6 (14.3)   | 0.015  |
| Antidepressants, TCAs                                                                 | 676.9 (16.5)   | 690.6 (16.2)   | 688.5 (16.0)                   | 683.7 (15.9)    | 691.2 (16.0)   | 664.3 (15.5)   | 682.5 (16.1)   | 0.009  |
| Antidepressants, other                                                                | 965.6 (23.5)   | 958.8 (22.4)   | 963.6 (22.4)                   | 950.1 (22.1)    | 972.5 (22.5)   | 941.4 (22.0)   | 949.8 (22.4)   | 0.013  |
| Antidiabetics                                                                         | 617.6 (15.0)   | 682.0 (16.0)   | 668.6 (15.6)                   | 682.9 (15.9)    | 674.8 (15.6)   | 672.6 (15.7)   | 673.2 (15.9)   | 0.010  |
| Antipsychotics, atypical                                                              | 614.7 (15.0)   | 631.8 (14.8)   | 639.6 (14.9)                   | 630.3 (14.6)    | 648.9 (15.0)   | 632.2 (14.8)   | 634.2 (15.0)   | 0.005  |
| Antipsychotics, typical                                                               | 194.9 (4.7)    | 197.7 (4.6)    | 192.3 (4.5)                    | 195.2 (4.5)     | 199.0 (4.6)    | 181.3 (4.2)    | 191.6 (4.5)    | 0.009  |
| Barbiturates                                                                          | 33.1 (0.8)     | 30.6 (0.7)     | 29.0 (0.7)                     | 29.2 (0.7)      | 30.2 (0.7)     | 27.6 (0.6)     | 26.8 (0.6)     | 0.008  |
| Benzodiazepines                                                                       | 2377.5 (57.9)  | 2316.7 (54.2)  | 2352.4 (54.7)                  | 2354.1 (54.7)   | 2382.6 (55.2)  | 2336.3 (54.5)  | 2339.3 (55.3)  | 0.025  |
| CNS stimulants                                                                        | 68.9 (1.7)     | 85.1 (2.0)     | 88.1 (2.1)                     | 79.2 (1.8)      | 80.1 (1.9)     | 82.8 (1.9)     | 77.4 (1.8)     | 0.011  |
| Dementia agents                                                                       | 14.3 (0.3)     | 14.3 (0.3)     | 17.7 (0.4)                     | 14.5 (0.3)      | 16.6 (0.4)     | 14.8 (0.3)     | 17.8 (0.4)     | 0.007  |
| Gabapentinoids                                                                        | 1088.1 (26.5)  | 1020.7 (23.9)  | 988.2 (23.0)                   | 1022.1 (23.7)   | 1060.6 (24.6)  | 1018.3 (23.8)  | 1035.0 (24.5)  | 0.028  |
| Lithium                                                                               | 47.3 (1.2)     | 53.2 (1.2)     | 54.5 (1.3)                     | 55.2 (1.3)      | 61.1 (1.4)     | 56.7 (1.3)     | 53.4 (1.3)     | 0.008  |
| Multiple sclerosis agents                                                             | 9.4 (0.2)      | 5.9 (0.1)      | 8.1 (0.2)                      | 8.4 (0.2)       | 9.4 (0.2)      | 7.9 (0.2)      | 7.1 (0.2)      | 0.008  |
| NSAIDs                                                                                | 2111.2 (51.4)  | 2321.6 (54.3)  | 2303.6 (53.6)                  | 2290.0 (53.2)   | 2310.7 (53.5)  | 2273.2 (53.1)  | 2266.2 (53.5)  | 0.019  |
| Other sedative hypnotics                                                              | 778.2 (19.0)   | 800.1 (18.7)   | 763.1 (17.8)                   | 774.2 (18.0)    | 775.5 (18.0)   | 776.6 (18.1)   | 761.4 (18.0)   | 0.013  |
| Smoking cessation                                                                     | 516.4 (12.6)   | 505.5 (11.8)   | 510.5 (11.9)                   | 511.1 (11.9)    | 518.1 (12.0)   | 499.6 (11.7)   | 509.7 (12.0)   | 0.010  |
| Triptans                                                                              | 238.3 (5.8)    | 234.1 (5.5)    | 238.9 (5.6)                    | 229.5 (5.3)     | 221.2 (5.1)    | 217.1 (5.1)    | 235.5 (5.6)    | 0.014  |
| Other CNS depressants                                                                 | 23.4 (0.6)     | 18.8 (0.4)     | 19.8 (0.5)                     | 17.6 (0.4)      | 17.7 (0.4)     | 17.9 (0.4)     | 18.0 (0.4)     | 0.008  |
| <b>Prescription opioid utilization (n (%))</b>                                        |                |                |                                |                 |                |                |                |        |
| Prescription opioid on index date                                                     |                |                |                                |                 |                |                |                |        |
| Buprenorphine                                                                         | 4.6 (0.1)      | 4.4 (0.1)      | 6.0 (0.1)                      | 4.4 (0.1)       | 5.6 (0.1)      | 5.7 (0.1)      | 4.0 (0.1)      | 0.006  |
| Butorphanol                                                                           | 18.8 (0.5)     | 23.6 (0.6)     | 21.3 (0.5)                     | 20.4 (0.5)      | 23.3 (0.5)     | 21.7 (0.5)     | 19.7 (0.5)     | 0.006  |
| Codeine                                                                               | 222.2 (5.4)    | 292.7 (6.8)    | 283.9 (6.6)                    | 284.5 (6.6)     | 284.5 (6.6)    | 272.8 (6.4)    | 266.0 (6.3)    | 0.021  |
| Dihydrocodeine                                                                        | 16.6 (0.4)     | 15.8 (0.4)     | 18.5 (0.4)                     | 16.1 (0.4)      | 16.2 (0.4)     | 15.4 (0.4)     | 16.4 (0.4)     | 0.004  |
| Fentanyl                                                                              | 287.3 (7.0)    | 272.9 (6.4)    | 266.8 (6.2)                    | 264.3 (6.1)     | 291.0 (6.7)    | 265.0 (6.2)    | 269.4 (6.4)    | 0.015  |
| Hydrocodone                                                                           | 2444.5 (59.5)  | 2492.6 (58.3)  | 2575.7 (59.9)                  | 2580.3 (60.0)   | 2574.1 (59.6)  | 2610.3 (60.9)  | 2555.5 (60.4)  | 0.019  |
| Hydromorphone                                                                         | 92.5 (2.3)     | 67.2 (1.6)     | 70.7 (1.6)                     | 77.0 (1.8)      | 71.3 (1.7)     | 77.0 (1.8)     | 72.0 (1.7)     | 0.017  |
| Levorphanol                                                                           | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)      | <0.001 |
| Meperidine                                                                            | 20.8 (0.5)     | 22.1 (0.5)     | 25.4 (0.6)                     | 21.3 (0.5)      | 20.1 (0.5)     | 20.7 (0.5)     | 18.8 (0.4)     | 0.008  |
| Methadone                                                                             | 240.5 (5.9)    | 195.7 (4.6)    | 202.0 (4.7)                    | 198.1 (4.6)     | 203.8 (4.7)    | 211.3 (4.9)    | 200.7 (4.7)    | 0.020  |
| Morphine                                                                              | 288.1 (7.0)    | 260.3 (6.1)    | 252.0 (5.9)                    | 265.6 (6.2)     | 278.1 (6.4)    | 251.3 (5.9)    | 265.6 (6.3)    | 0.019  |
| Opium                                                                                 | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)      | 0.0 (0.0)      | 0.0 (0.0)      | <0.001 |
| Oxycodone                                                                             | 1377.8 (33.6)  | 1407.1 (32.9)  | 1380.7 (32.1)                  | 1386.6 (32.2)   | 1407.4 (32.6)  | 1378.6 (32.2)  | 1374.8 (32.5)  | 0.013  |
| Oxymorphone                                                                           | 10.1 (0.2)     | 9.8 (0.2)      | 7.5 (0.2)                      | 9.2 (0.2)       | 8.1 (0.2)      | 8.8 (0.2)      | 7.7 (0.2)      | 0.007  |
| Pentazocine                                                                           | 23.7 (0.6)     | 23.7 (0.6)     | 23.8 (0.6)                     | 21.6 (0.5)      | 23.2 (0.5)     | 23.3 (0.5)     | 19.5 (0.5)     | 0.006  |
| Propoxyphene                                                                          | 141.8 (3.5)    | 155.0 (3.6)    | 149.7 (3.5)                    | 141.8 (3.3)     | 146.1 (3.4)    | 151.1 (3.5)    | 137.0 (3.2)    | 0.009  |
| Tapentadol                                                                            | 5.8 (0.1)      | 3.4 (0.1)      | 3.1 (0.1)                      | 3.3 (0.1)       | 4.0 (0.1)      | 3.3 (0.1)      | 3.0 (0.1)      | 0.008  |
| Tramadol                                                                              | 722.1 (17.6)   | 858.5 (20.1)   | 811.9 (18.9)                   | 817.9 (19.0)    | 799.2 (18.5)   | 823.5 (19.2)   | 804.7 (19.0)   | 0.022  |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 173.05 (17.72) | 172.61 (18.23) | 172.35 (18.64)                 | 172.39 (18.45)  | 172.58 (18.36) | 172.27 (18.77) | 172.34 (18.48) | 0.016  |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                |                |                                |                 |                |                |                |        |

|                                           | Baclofen             | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine      | Metaxalone           | Methocarbamol        | Tizanidine           | SMD   |
|-------------------------------------------|----------------------|----------------------|--------------------------------|----------------------|----------------------|----------------------|----------------------|-------|
| (Index - 180) to (index - 151)            | 2006.53<br>(3331.20) | 1848.10<br>(2991.47) | 1766.89<br>(2931.80)           | 1791.02<br>(3233.27) | 1859.45<br>(3092.03) | 1812.44<br>(3177.45) | 1851.81<br>(3096.80) | 0.027 |
| (Index - 150) to (index - 121)            | 2096.70<br>(3385.66) | 1965.09<br>(3113.53) | 1885.36<br>(3152.09)           | 1897.96<br>(3413.08) | 1959.22<br>(3129.37) | 1925.22<br>(3309.89) | 1947.02<br>(3127.96) | 0.023 |
| (Index - 120) to (index - 91)             | 2338.06<br>(3542.94) | 2138.81<br>(3113.30) | 2042.20<br>(3262.05)           | 2079.66<br>(3483.87) | 2135.43<br>(3290.90) | 2089.59<br>(3359.16) | 2153.23<br>(3299.45) | 0.031 |
| (Index - 90) to (index - 61)              | 2356.49<br>(3541.96) | 2195.03<br>(3243.55) | 2076.13<br>(3331.49)           | 2113.84<br>(3459.00) | 2172.25<br>(3203.87) | 2124.27<br>(3337.33) | 2181.65<br>(3295.53) | 0.030 |
| (Index - 60) to (index - 31)              | 2383.95<br>(3558.70) | 2188.61<br>(3180.65) | 2090.65<br>(3270.67)           | 2118.13<br>(3412.22) | 2196.71<br>(3238.82) | 2126.04<br>(3344.62) | 2194.56<br>(3329.88) | 0.031 |
| (Index - 30) to index                     | 2861.96<br>(4159.51) | 2599.11<br>(3652.94) | 2498.37<br>(4007.68)           | 2515.92<br>(4101.00) | 2584.76<br>(3887.68) | 2533.81<br>(4129.75) | 2619.35<br>(3695.72) | 0.032 |
| <b>Healthcare utilization (mean (SD))</b> |                      |                      |                                |                      |                      |                      |                      |       |
| Number of physician visits                | 9.58 (8.63)          | 9.33 (8.43)          | 9.40 (8.53)                    | 9.34 (8.46)          | 9.45 (8.59)          | 9.32 (8.34)          | 9.45 (8.51)          | 0.013 |
| Number of distinct prescribed medications | 14.82 (7.42)         | 14.78 (7.63)         | 14.74 (7.52)                   | 14.70 (7.47)         | 14.83 (7.60)         | 14.65 (7.39)         | 14.78 (7.49)         | 0.011 |
| Number of hospitalizations                | 0.31 (0.81)          | 0.31 (0.84)          | 0.30 (0.78)                    | 0.31 (0.82)          | 0.31 (0.83)          | 0.30 (0.78)          | 0.31 (0.81)          | 0.007 |
| Number of hospitalization days            | 1.62 (8.83)          | 1.59 (8.26)          | 1.63 (5.27)                    | 1.65 (6.88)          | 1.68 (5.90)          | 1.67 (7.29)          | 1.73 (8.12)          | 0.008 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

<sup>1</sup>Socioeconomic status measures and rural-urban continuum codes were not included in the propensity score model

**eTable 6. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in Medicare diabetes, heart failure, and/or stroke, 2012-2017 (pre-matching weights)**

|                                        | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone   | Methocarbamol | Tizanidine   | SMD   |
|----------------------------------------|--------------|--------------|--------------------------------|-----------------|--------------|---------------|--------------|-------|
| n                                      | 40185        | 11404        | 3110                           | 77165           | 4450         | 19340         | 51710        |       |
| <b>Demographic information (n (%))</b> |              |              |                                |                 |              |               |              |       |
| Age (mean (SD))                        | 72.97 (7.09) | 71.07 (6.19) | 72.99 (7.17)                   | 72.10 (7.00)    | 73.93 (7.49) | 72.65 (7.09)  | 72.22 (6.53) | 0.153 |
| Sex                                    |              |              |                                |                 |              |               |              |       |
| Male                                   | 13775 (34.3) | 4179 (36.6)  | 1008 (32.4)                    | 24612 (31.9)    | 1360 (30.6)  | 6462 (33.4)   | 17010 (32.9) | 0.049 |
| Female                                 | 26410 (65.7) | 7225 (63.4)  | 2102 (67.6)                    | 52553 (68.1)    | 3090 (69.4)  | 12878 (66.6)  | 34700 (67.1) |       |
| Race                                   |              |              |                                |                 |              |               |              | 0.141 |
| Asian                                  | 462 (1.1)    | 89 (0.8)     | 20 (0.6)                       | 740 (1.0)       | 17 (0.4)     | 189 (1.0)     | 365 (0.7)    |       |
| Black                                  | 5666 (14.1)  | 1958 (17.2)  | 330 (10.6)                     | 10677 (13.8)    | 363 (8.2)    | 2272 (11.7)   | 6930 (13.4)  |       |
| White                                  | 31891 (79.4) | 8944 (78.4)  | 2679 (86.1)                    | 63364 (82.1)    | 3974 (89.3)  | 16337 (84.5)  | 42916 (83.0) |       |
| Other                                  | 2166 (5.4)   | 413 (3.6)    | 81 (2.6)                       | 2384 (3.1)      | 96 (2.2)     | 542 (2.8)     | 1499 (2.9)   |       |
| Ethnicity                              |              |              |                                |                 |              |               |              | 0.056 |
| Unknown                                | 570 (1.4)    | 125 (1.1)    | 30 (1.0)                       | 850 (1.1)       | 46 (1.0)     | 179 (0.9)     | 518 (1.0)    |       |
| Hispanic                               | 1112 (2.8)   | 217 (1.9)    | 41 (1.3)                       | 1159 (1.5)      | 38 (0.9)     | 266 (1.4)     | 748 (1.4)    |       |
| Non-Hispanic                           | 38503 (95.8) | 11062 (97.0) | 3039 (97.7)                    | 75156 (97.4)    | 4366 (98.1)  | 18895 (97.7)  | 50444 (97.6) |       |
| State                                  |              |              |                                |                 |              |               |              | 0.541 |
| AK                                     | 51 (0.1)     | 10 (0.1)     | 3 (0.1)                        | 133 (0.2)       | 4 (0.1)      | 24 (0.1)      | 73 (0.1)     |       |
| AL                                     | 1104 (2.7)   | 308 (2.7)    | 98 (3.2)                       | 2271 (2.9)      | 97 (2.2)     | 1500 (7.8)    | 2650 (5.1)   |       |
| AR                                     | 488 (1.2)    | 298 (2.6)    | 41 (1.3)                       | 1142 (1.5)      | 45 (1.0)     | 276 (1.4)     | 1179 (2.3)   |       |
| AZ                                     | 558 (1.4)    | 253 (2.2)    | 50 (1.6)                       | 974 (1.3)       | 61 (1.4)     | 319 (1.6)     | 592 (1.1)    |       |
| CA                                     | 5946 (14.8)  | 2255 (19.8)  | 65 (2.1)                       | 4211 (5.5)      | 209 (4.7)    | 1057 (5.5)    | 1696 (3.3)   |       |
| CO                                     | 258 (0.6)    | 72 (0.6)     | 23 (0.7)                       | 692 (0.9)       | 47 (1.1)     | 143 (0.7)     | 385 (0.7)    |       |
| CT                                     | 260 (0.6)    | 88 (0.8)     | 22 (0.7)                       | 590 (0.8)       | 54 (1.2)     | 287 (1.5)     | 196 (0.4)    |       |
| DC                                     | 22 (0.1)     | 2 (0.0)      | 3 (0.1)                        | 108 (0.1)       | 2 (0.0)      | 8 (0.0)       | 26 (0.1)     |       |
| DE                                     | 91 (0.2)     | 45 (0.4)     | 14 (0.5)                       | 363 (0.5)       | 44 (1.0)     | 20 (0.1)      | 270 (0.5)    |       |
| FL                                     | 3100 (7.7)   | 792 (6.9)    | 236 (7.6)                      | 5074 (6.6)      | 374 (8.4)    | 1698 (8.8)    | 3670 (7.1)   |       |
| GA                                     | 1302 (3.2)   | 683 (6.0)    | 98 (3.2)                       | 2979 (3.9)      | 147 (3.3)    | 766 (4.0)     | 2799 (5.4)   |       |
| HI                                     | 25 (0.1)     | 16 (0.1)     | 3 (0.1)                        | 51 (0.1)        | 0 (0.0)      | 13 (0.1)      | 22 (0.0)     |       |
| IA                                     | 352 (0.9)    | 41 (0.4)     | 31 (1.0)                       | 898 (1.2)       | 40 (0.9)     | 92 (0.5)      | 381 (0.7)    |       |
| ID                                     | 156 (0.4)    | 65 (0.6)     | 14 (0.5)                       | 331 (0.4)       | 11 (0.2)     | 142 (0.7)     | 215 (0.4)    |       |
| IL                                     | 1151 (2.9)   | 172 (1.5)    | 180 (5.8)                      | 3188 (4.1)      | 137 (3.1)    | 391 (2.0)     | 1160 (2.2)   |       |
| IN                                     | 1038 (2.6)   | 143 (1.3)    | 145 (4.7)                      | 2809 (3.6)      | 173 (3.9)    | 383 (2.0)     | 1617 (3.1)   |       |
| KS                                     | 391 (1.0)    | 83 (0.7)     | 48 (1.5)                       | 1069 (1.4)      | 32 (0.7)     | 183 (0.9)     | 461 (0.9)    |       |
| KY                                     | 1380 (3.4)   | 153 (1.3)    | 124 (4.0)                      | 2381 (3.1)      | 148 (3.3)    | 646 (3.3)     | 2250 (4.4)   |       |
| LA                                     | 751 (1.9)    | 354 (3.1)    | 112 (3.6)                      | 1840 (2.4)      | 75 (1.7)     | 557 (2.9)     | 1551 (3.0)   |       |
| MA                                     | 565 (1.4)    | 80 (0.7)     | 23 (0.7)                       | 928 (1.2)       | 30 (0.7)     | 149 (0.8)     | 541 (1.0)    |       |
| MD                                     | 496 (1.2)    | 156 (1.4)    | 42 (1.4)                       | 1524 (2.0)      | 190 (4.3)    | 226 (1.2)     | 675 (1.3)    |       |
| ME                                     | 204 (0.5)    | 9 (0.1)      | 4 (0.1)                        | 395 (0.5)       | 5 (0.1)      | 59 (0.3)      | 126 (0.2)    |       |
| MI                                     | 2046 (5.1)   | 598 (5.2)    | 164 (5.3)                      | 3998 (5.2)      | 269 (6.0)    | 759 (3.9)     | 1781 (3.4)   |       |
| MN                                     | 131 (0.3)    | 12 (0.1)     | 10 (0.3)                       | 384 (0.5)       | 10 (0.2)     | 74 (0.4)      | 195 (0.4)    |       |
| MO                                     | 1013 (2.5)   | 206 (1.8)    | 86 (2.8)                       | 1932 (2.5)      | 103 (2.3)    | 344 (1.8)     | 1332 (2.6)   |       |
| MS                                     | 672 (1.7)    | 296 (2.6)    | 73 (2.3)                       | 1564 (2.0)      | 57 (1.3)     | 500 (2.6)     | 1672 (3.2)   |       |
| MT                                     | 116 (0.3)    | 14 (0.1)     | 5 (0.2)                        | 237 (0.3)       | 12 (0.3)     | 111 (0.6)     | 120 (0.2)    |       |
| NC                                     | 1723 (4.3)   | 459 (4.0)    | 166 (5.3)                      | 4015 (5.2)      | 198 (4.4)    | 838 (4.3)     | 2590 (5.0)   |       |
| ND                                     | 60 (0.1)     | 7 (0.1)      | 3 (0.1)                        | 146 (0.2)       | 0 (0.0)      | 13 (0.1)      | 57 (0.1)     |       |
| NE                                     | 130 (0.3)    | 26 (0.2)     | 16 (0.5)                       | 502 (0.7)       | 24 (0.5)     | 32 (0.2)      | 200 (0.4)    |       |
| NH                                     | 115 (0.3)    | 21 (0.2)     | 4 (0.1)                        | 365 (0.5)       | 16 (0.4)     | 41 (0.2)      | 132 (0.3)    |       |
| NJ                                     | 614 (1.5)    | 217 (1.9)    | 83 (2.7)                       | 2112 (2.7)      | 263 (5.9)    | 160 (0.8)     | 1019 (2.0)   |       |

|                              | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|------------------------------|--------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| NM                           | 299 (0.7)    | 54 (0.5)     | 23 (0.7)                       | 400 (0.5)       | 16 (0.4)    | 128 (0.7)     | 213 (0.4)    |       |
| NV                           | 359 (0.9)    | 215 (1.9)    | 10 (0.3)                       | 534 (0.7)       | 20 (0.4)    | 191 (1.0)     | 570 (1.1)    |       |
| NY                           | 1231 (3.1)   | 195 (1.7)    | 69 (2.2)                       | 2390 (3.1)      | 179 (4.0)   | 418 (2.2)     | 1299 (2.5)   |       |
| OH                           | 1171 (2.9)   | 166 (1.5)    | 189 (6.1)                      | 3154 (4.1)      | 185 (4.2)   | 792 (4.1)     | 2641 (5.1)   |       |
| OK                           | 964 (2.4)    | 361 (3.2)    | 152 (4.9)                      | 2118 (2.7)      | 69 (1.6)    | 366 (1.9)     | 1518 (2.9)   |       |
| OR                           | 464 (1.2)    | 68 (0.6)     | 11 (0.4)                       | 756 (1.0)       | 40 (0.9)    | 214 (1.1)     | 537 (1.0)    |       |
| PA                           | 1051 (2.6)   | 221 (1.9)    | 54 (1.7)                       | 2127 (2.8)      | 198 (4.4)   | 415 (2.1)     | 877 (1.7)    |       |
| RI                           | 100 (0.2)    | 12 (0.1)     | 6 (0.2)                        | 144 (0.2)       | 5 (0.1)     | 22 (0.1)      | 63 (0.1)     |       |
| SC                           | 661 (1.6)    | 259 (2.3)    | 83 (2.7)                       | 1890 (2.4)      | 124 (2.8)   | 260 (1.3)     | 1380 (2.7)   |       |
| SD                           | 110 (0.3)    | 4 (0.0)      | 11 (0.4)                       | 186 (0.2)       | 3 (0.1)     | 22 (0.1)      | 49 (0.1)     |       |
| TN                           | 1698 (4.2)   | 463 (4.1)    | 95 (3.1)                       | 2681 (3.5)      | 106 (2.4)   | 931 (4.8)     | 2345 (4.5)   |       |
| TX                           | 2972 (7.4)   | 1009 (8.8)   | 247 (7.9)                      | 5489 (7.1)      | 309 (6.9)   | 2022 (10.5)   | 4908 (9.5)   |       |
| UT                           | 210 (0.5)    | 85 (0.7)     | 6 (0.2)                        | 372 (0.5)       | 25 (0.6)    | 141 (0.7)     | 257 (0.5)    |       |
| VA                           | 877 (2.2)    | 113 (1.0)    | 87 (2.8)                       | 2074 (2.7)      | 144 (3.2)   | 361 (1.9)     | 1129 (2.2)   |       |
| VT                           | 59 (0.1)     | 5 (0.0)      | 2 (0.1)                        | 127 (0.2)       | 0 (0.0)     | 59 (0.3)      | 58 (0.1)     |       |
| WA                           | 750 (1.9)    | 116 (1.0)    | 14 (0.5)                       | 1224 (1.6)      | 29 (0.7)    | 771 (4.0)     | 833 (1.6)    |       |
| WI                           | 454 (1.1)    | 39 (0.3)     | 17 (0.5)                       | 983 (1.3)       | 36 (0.8)    | 102 (0.5)     | 647 (1.3)    |       |
| WV                           | 403 (1.0)    | 67 (0.6)     | 29 (0.9)                       | 1162 (1.5)      | 77 (1.7)    | 297 (1.5)     | 701 (1.4)    |       |
| WY                           | 43 (0.1)     | 18 (0.2)     | 16 (0.5)                       | 148 (0.2)       | 8 (0.2)     | 17 (0.1)      | 52 (0.1)     |       |
| Year                         |              |              |                                |                 |             |               |              | 0.365 |
| 2012                         | 3693 (9.2)   | 1643 (14.4)  | 623 (20.0)                     | 11840 (15.3)    | 862 (19.4)  | 2929 (15.1)   | 4496 (8.7)   |       |
| 2013                         | 7361 (18.3)  | 4097 (35.9)  | 848 (27.3)                     | 22454 (29.1)    | 1290 (29.0) | 5789 (29.9)   | 8817 (17.1)  |       |
| 2014                         | 8509 (21.2)  | 2876 (25.2)  | 689 (22.2)                     | 14571 (18.9)    | 1045 (23.5) | 4137 (21.4)   | 9954 (19.2)  |       |
| 2015                         | 8067 (20.1)  | 1338 (11.7)  | 474 (15.2)                     | 10852 (14.1)    | 669 (15.0)  | 2773 (14.3)   | 10016 (19.4) |       |
| 2016                         | 6588 (16.4)  | 826 (7.2)    | 236 (7.6)                      | 6244 (8.1)      | 314 (7.1)   | 1982 (10.2)   | 9528 (18.4)  |       |
| 2017                         | 5967 (14.8)  | 624 (5.5)    | 240 (7.7)                      | 11204 (14.5)    | 270 (6.1)   | 1730 (8.9)    | 8899 (17.2)  |       |
| <b>Comorbidities (n (%))</b> |              |              |                                |                 |             |               |              |       |
| Opioid dependence            | 2124 (5.3)   | 502 (4.4)    | 129 (4.1)                      | 3102 (4.0)      | 153 (3.4)   | 996 (5.1)     | 3456 (6.7)   | 0.059 |
| Opioid abuse                 | 178 (0.4)    | 64 (0.6)     | 8 (0.3)                        | 233 (0.3)       | 13 (0.3)    | 87 (0.4)      | 163 (0.3)    | 0.021 |
| Alcohol abuse                | 856 (2.1)    | 244 (2.1)    | 48 (1.5)                       | 1386 (1.8)      | 68 (1.5)    | 419 (2.2)     | 878 (1.7)    | 0.025 |
| Tobacco use                  | 10170 (25.3) | 2684 (23.5)  | 705 (22.7)                     | 18940 (24.5)    | 937 (21.1)  | 4898 (25.3)   | 13438 (26.0) | 0.049 |
| Other drug abuse             | 1522 (3.8)   | 506 (4.4)    | 99 (3.2)                       | 2444 (3.2)      | 139 (3.1)   | 752 (3.9)     | 1980 (3.8)   | 0.031 |
| Anxiety                      | 11019 (27.4) | 3045 (26.7)  | 799 (25.7)                     | 19717 (25.6)    | 1089 (24.5) | 5144 (26.6)   | 14430 (27.9) | 0.033 |
| Bipolar disorder             | 1428 (3.6)   | 318 (2.8)    | 100 (3.2)                      | 2472 (3.2)      | 133 (3.0)   | 642 (3.3)     | 1646 (3.2)   | 0.016 |
| Bone fracture                | 4286 (10.7)  | 954 (8.4)    | 341 (11.0)                     | 8147 (10.6)     | 531 (11.9)  | 2400 (12.4)   | 5238 (10.1)  | 0.050 |
| Cancer                       | 4707 (11.7)  | 1204 (10.6)  | 347 (11.2)                     | 8883 (11.5)     | 583 (13.1)  | 2256 (11.7)   | 5610 (10.8)  | 0.029 |
| Chronic renal insufficiency  | 8821 (22.0)  | 1765 (15.5)  | 605 (19.5)                     | 15581 (20.2)    | 868 (19.5)  | 3865 (20.0)   | 11015 (21.3) | 0.058 |
| Congestive heart failure     | 10964 (27.3) | 2521 (22.1)  | 756 (24.3)                     | 19032 (24.7)    | 1051 (23.6) | 4965 (25.7)   | 12791 (24.7) | 0.044 |
| COPD/asthma/oxygen           | 16289 (40.5) | 4686 (41.1)  | 1149 (36.9)                    | 30338 (39.3)    | 1574 (35.4) | 7532 (38.9)   | 20670 (40.0) | 0.050 |
| Dementia                     | 5512 (13.7)  | 736 (6.5)    | 273 (8.8)                      | 7195 (9.3)      | 474 (10.7)  | 1967 (10.2)   | 4527 (8.8)   | 0.087 |
| Depression                   | 12499 (31.1) | 3006 (26.4)  | 863 (27.7)                     | 22415 (29.0)    | 1365 (30.7) | 5756 (29.8)   | 14589 (28.2) | 0.045 |
| Diabetes                     | 25235 (62.8) | 6365 (55.8)  | 1836 (59.0)                    | 48156 (62.4)    | 2471 (55.5) | 11648 (60.2)  | 33036 (63.9) | 0.083 |
| Epilepsy                     | 1626 (4.0)   | 360 (3.2)    | 87 (2.8)                       | 2339 (3.0)      | 133 (3.0)   | 626 (3.2)     | 1536 (3.0)   | 0.024 |
| HIV                          | 134 (0.3)    | 46 (0.4)     | 8 (0.3)                        | 253 (0.3)       | 13 (0.3)    | 43 (0.2)      | 134 (0.3)    | 0.013 |
| Intentional self-harm        | 34 (0.1)     | 6 (0.1)      | 0 (0.0)                        | 61 (0.1)        | 3 (0.1)     | 14 (0.1)      | 34 (0.1)     | 0.014 |
| Liver disease                | 3424 (8.5)   | 893 (7.8)    | 218 (7.0)                      | 6069 (7.9)      | 312 (7.0)   | 1420 (7.3)    | 3896 (7.5)   | 0.024 |
| Musculoskeletal injury       | 3401 (8.5)   | 1053 (9.2)   | 307 (9.9)                      | 7318 (9.5)      | 427 (9.6)   | 1963 (10.1)   | 4533 (8.8)   | 0.025 |
| Multiple sclerosis           | 563 (1.4)    | 55 (0.5)     | 9 (0.3)                        | 294 (0.4)       | 23 (0.5)    | 72 (0.4)      | 269 (0.5)    | 0.042 |
| Obesity                      | 8420 (21.0)  | 1920 (16.8)  | 530 (17.0)                     | 16148 (20.9)    | 834 (18.7)  | 4065 (21.0)   | 11101 (21.5) | 0.058 |
| Pneumonia                    | 2893 (7.2)   | 845 (7.4)    | 222 (7.1)                      | 5302 (6.9)      | 330 (7.4)   | 1338 (6.9)    | 3029 (5.9)   | 0.023 |
| Psychosis                    | 1948 (4.8)   | 363 (3.2)    | 105 (3.4)                      | 2956 (3.8)      | 183 (4.1)   | 766 (4.0)     | 1665 (3.2)   | 0.036 |
| Renal dysfunction            | 10794 (26.9) | 2419 (21.2)  | 801 (25.8)                     | 19786 (25.6)    | 1133 (25.5) | 4962 (25.7)   | 13290 (25.7) | 0.039 |

|                                                | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|------------------------------------------------|--------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| Spasticity                                     | 15039 (37.4) | 3025 (26.5)  | 902 (29.0)                     | 22203 (28.8)    | 1502 (33.8) | 6075 (31.4)   | 15481 (29.9) | 0.093 |
| Urinary calculus                               | 1812 (4.5)   | 457 (4.0)    | 128 (4.1)                      | 3458 (4.5)      | 211 (4.7)   | 870 (4.5)     | 2336 (4.5)   | 0.014 |
| Urinary tract infection                        | 9982 (24.8)  | 2217 (19.4)  | 712 (22.9)                     | 17222 (22.3)    | 1112 (25.0) | 4432 (22.9)   | 10753 (20.8) | 0.058 |
| <b>Pain conditions (n (%))</b>                 |              |              |                                |                 |             |               |              |       |
| Abdominal pain                                 | 9346 (23.3)  | 2349 (20.6)  | 751 (24.1)                     | 17549 (22.7)    | 1026 (23.1) | 4399 (22.7)   | 11469 (22.2) | 0.030 |
| Back and neck pain                             | 30400 (75.7) | 8657 (75.9)  | 2403 (77.3)                    | 58009 (75.2)    | 3459 (77.7) | 15542 (80.4)  | 42527 (82.2) | 0.075 |
| Back pain without radiculopathy                | 28200 (70.2) | 8163 (71.6)  | 2250 (72.3)                    | 53901 (69.9)    | 3226 (72.5) | 14603 (75.5)  | 39563 (76.5) | 0.068 |
| Back pain with radiculopathy                   | 11115 (27.7) | 2990 (26.2)  | 819 (26.3)                     | 19986 (25.9)    | 1315 (29.6) | 6109 (31.6)   | 17137 (33.1) | 0.075 |
| Dental pain                                    | 286 (0.7)    | 70 (0.6)     | 15 (0.5)                       | 540 (0.7)       | 25 (0.6)    | 131 (0.7)     | 284 (0.5)    | 0.014 |
| Diabetic neuropathy                            | 7741 (19.3)  | 1584 (13.9)  | 499 (16.0)                     | 13228 (17.1)    | 656 (14.7)  | 3232 (16.7)   | 10228 (19.8) | 0.071 |
| Fibromyalgia                                   | 5565 (13.8)  | 1702 (14.9)  | 525 (16.9)                     | 10923 (14.2)    | 819 (18.4)  | 2909 (15.0)   | 8086 (15.6)  | 0.052 |
| Headache                                       | 5778 (14.4)  | 1595 (14.0)  | 455 (14.6)                     | 10780 (14.0)    | 651 (14.6)  | 2744 (14.2)   | 7779 (15.0)  | 0.013 |
| Osteoarthritis                                 | 20238 (50.4) | 5396 (47.3)  | 1554 (50.0)                    | 38531 (49.9)    | 2210 (49.7) | 9800 (50.7)   | 26368 (51.0) | 0.026 |
| Rheumatoid arthritis                           | 3208 (8.0)   | 913 (8.0)    | 289 (9.3)                      | 6568 (8.5)      | 414 (9.3)   | 1615 (8.4)    | 4274 (8.3)   | 0.023 |
| Postherpetic neuralgia                         | 241 (0.6)    | 52 (0.5)     | 18 (0.6)                       | 354 (0.5)       | 33 (0.7)    | 139 (0.7)     | 324 (0.6)    | 0.018 |
| Other arthritis                                | 30961 (77.0) | 7932 (69.6)  | 2257 (72.6)                    | 57117 (74.0)    | 3366 (75.6) | 14662 (75.8)  | 38444 (74.3) | 0.066 |
| Other neuropathy                               | 18585 (46.2) | 4811 (42.2)  | 1360 (43.7)                    | 32827 (42.5)    | 2028 (45.6) | 9315 (48.2)   | 26040 (50.4) | 0.073 |
| Other unspecified pain                         | 26559 (66.1) | 6702 (58.8)  | 1945 (62.5)                    | 48243 (62.5)    | 2712 (60.9) | 12983 (67.1)  | 36984 (71.5) | 0.109 |
| <b>Other prescription fills (n (%))</b>        |              |              |                                |                 |             |               |              |       |
| Antibiotics                                    | 26691 (66.4) | 7551 (66.2)  | 2081 (66.9)                    | 51586 (66.9)    | 3053 (68.6) | 13009 (67.3)  | 34145 (66.0) | 0.021 |
| Anticonvulsants                                | 3701 (9.2)   | 769 (6.7)    | 204 (6.6)                      | 5321 (6.9)      | 328 (7.4)   | 1332 (6.9)    | 3903 (7.5)   | 0.036 |
| Antidepressants, SSRIs                         | 12069 (30.0) | 3099 (27.2)  | 893 (28.7)                     | 22703 (29.4)    | 1334 (30.0) | 5711 (29.5)   | 15095 (29.2) | 0.024 |
| Antidepressants, SNRIs                         | 7026 (17.5)  | 1608 (14.1)  | 464 (14.9)                     | 12244 (15.9)    | 846 (19.0)  | 3203 (16.6)   | 9127 (17.7)  | 0.056 |
| Antidepressants, TCAs                          | 3232 (8.0)   | 1006 (8.8)   | 275 (8.8)                      | 6357 (8.2)      | 343 (7.7)   | 1647 (8.5)    | 4497 (8.7)   | 0.019 |
| Antidepressants, other                         | 7920 (19.7)  | 1812 (15.9)  | 493 (15.9)                     | 13339 (17.3)    | 832 (18.7)  | 3500 (18.1)   | 9726 (18.8)  | 0.047 |
| Antidiabetics                                  | 17941 (44.6) | 4519 (39.6)  | 1294 (41.6)                    | 35436 (45.9)    | 1734 (39.0) | 8426 (43.6)   | 24269 (46.9) | 0.076 |
| Antipsychotics, atypical                       | 3293 (8.2)   | 702 (6.2)    | 201 (6.5)                      | 5128 (6.6)      | 291 (6.5)   | 1283 (6.6)    | 3155 (6.1)   | 0.028 |
| Antipsychotics, typical                        | 1180 (2.9)   | 253 (2.2)    | 79 (2.5)                       | 1880 (2.4)      | 106 (2.4)   | 437 (2.3)     | 1009 (2.0)   | 0.023 |
| Barbiturates                                   | 60 (0.1)     | 18 (0.2)     | 3 (0.1)                        | 91 (0.1)        | 12 (0.3)    | 19 (0.1)      | 67 (0.1)     | 0.016 |
| Benzodiazepines                                | 14168 (35.3) | 4820 (42.3)  | 1023 (32.9)                    | 25480 (33.0)    | 1523 (34.2) | 6552 (33.9)   | 18587 (35.9) | 0.070 |
| CNS stimulants                                 | 427 (1.1)    | 150 (1.3)    | 22 (0.7)                       | 772 (1.0)       | 62 (1.4)    | 223 (1.2)     | 519 (1.0)    | 0.026 |
| Dementia agents                                | 2765 (6.9)   | 468 (4.1)    | 196 (6.3)                      | 4029 (5.2)      | 252 (5.7)   | 1119 (5.8)    | 2728 (5.3)   | 0.046 |
| Gabapentinoids                                 | 18157 (45.2) | 3955 (34.7)  | 1161 (37.3)                    | 30200 (39.1)    | 1675 (37.6) | 8245 (42.6)   | 23614 (45.7) | 0.104 |
| Lithium                                        | 66 (0.2)     | 20 (0.2)     | 4 (0.1)                        | 121 (0.2)       | 6 (0.1)     | 38 (0.2)      | 80 (0.2)     | 0.007 |
| Multiple sclerosis agents                      | 140 (0.3)    | 9 (0.1)      | 2 (0.1)                        | 69 (0.1)        | 3 (0.1)     | 13 (0.1)      | 45 (0.1)     | 0.020 |
| NSAIDs                                         | 13540 (33.7) | 3787 (33.2)  | 1119 (36.0)                    | 27356 (35.5)    | 1627 (36.6) | 6926 (35.8)   | 18082 (35.0) | 0.031 |
| Other sedative hypnotics                       | 5516 (13.7)  | 2118 (18.6)  | 516 (16.6)                     | 12636 (16.4)    | 761 (17.1)  | 3077 (15.9)   | 7371 (14.3)  | 0.054 |
| Smoking cessation                              | 2073 (5.2)   | 582 (5.1)    | 149 (4.8)                      | 4028 (5.2)      | 292 (6.6)   | 1008 (5.2)    | 2842 (5.5)   | 0.026 |
| Triptans                                       | 547 (1.4)    | 217 (1.9)    | 40 (1.3)                       | 1133 (1.5)      | 84 (1.9)    | 253 (1.3)     | 829 (1.6)    | 0.025 |
| Other CNS depressants                          | 125 (0.3)    | 21 (0.2)     | 9 (0.3)                        | 183 (0.2)       | 14 (0.3)    | 37 (0.2)      | 168 (0.3)    | 0.014 |
| <b>Prescription opioid utilization (n (%))</b> |              |              |                                |                 |             |               |              |       |
| Prescription opioid on index date              |              |              |                                |                 |             |               |              |       |
| Buprenorphine                                  | 143 (0.4)    | 35 (0.3)     | 11 (0.4)                       | 207 (0.3)       | 14 (0.3)    | 50 (0.3)      | 203 (0.4)    | 0.011 |
| Butorphanol                                    | 23 (0.1)     | 13 (0.1)     | 5 (0.2)                        | 55 (0.1)        | 2 (0.0)     | 6 (0.0)       | 31 (0.1)     | 0.018 |
| Codeine                                        | 1514 (3.8)   | 463 (4.1)    | 130 (4.2)                      | 2633 (3.4)      | 132 (3.0)   | 658 (3.4)     | 1523 (2.9)   | 0.032 |
| Dihydrocodeine                                 | 1 (0.0)      | 0 (0.0)      | 0 (0.0)                        | 6 (0.0)         | 0 (0.0)     | 0 (0.0)       | 2 (0.0)      | 0.006 |
| Fentanyl                                       | 3645 (9.1)   | 759 (6.7)    | 239 (7.7)                      | 6149 (8.0)      | 463 (10.4)  | 1552 (8.0)    | 3880 (7.5)   | 0.051 |
| Hydrocodone                                    | 20534 (51.1) | 7076 (62.0)  | 1669 (53.7)                    | 41566 (53.9)    | 2134 (48.0) | 10851 (56.1)  | 26946 (52.1) | 0.104 |
| Hydromorphone                                  | 915 (2.3)    | 295 (2.6)    | 61 (2.0)                       | 1570 (2.0)      | 121 (2.7)   | 475 (2.5)     | 1027 (2.0)   | 0.025 |
| Levorphanol                                    | 5 (0.0)      | 1 (0.0)      | 1 (0.0)                        | 7 (0.0)         | 1 (0.0)     | 1 (0.0)       | 3 (0.0)      | 0.009 |
| Meperidine                                     | 20 (0.0)     | 19 (0.2)     | 4 (0.1)                        | 63 (0.1)        | 3 (0.1)     | 14 (0.1)      | 25 (0.0)     | 0.016 |
| Methadone                                      | 1010 (2.5)   | 319 (2.8)    | 65 (2.1)                       | 1450 (1.9)      | 73 (1.6)    | 400 (2.1)     | 1186 (2.3)   | 0.032 |

|                                                                                       | Baclofen          | Carisoprodol      | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone        | Methocarbamol     | Tizanidine        | SMD    |
|---------------------------------------------------------------------------------------|-------------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|-------------------|--------|
| Morphine                                                                              | 3073 (7.6)        | 823 (7.2)         | 181 (5.8)                      | 4813 (6.2)        | 282 (6.3)         | 1382 (7.1)        | 3768 (7.3)        | 0.032  |
| Opium                                                                                 | 2 (0.0)           | 3 (0.0)           | 0 (0.0)                        | 15 (0.0)          | 3 (0.1)           | 3 (0.0)           | 8 (0.0)           | 0.016  |
| Oxycodone                                                                             | 11991 (29.8)      | 3540 (31.0)       | 868 (27.9)                     | 23720 (30.7)      | 1410 (31.7)       | 6204 (32.1)       | 16821 (32.5)      | 0.040  |
| Oxymorphone                                                                           | 295 (0.7)         | 98 (0.9)          | 23 (0.7)                       | 495 (0.6)         | 48 (1.1)          | 136 (0.7)         | 467 (0.9)         | 0.019  |
| Pentazocine                                                                           | 14 (0.0)          | 9 (0.1)           | 1 (0.0)                        | 42 (0.1)          | 1 (0.0)           | 11 (0.1)          | 20 (0.0)          | 0.010  |
| Propoxyphene                                                                          | 0.0 (0.0)         | 0.0 (0.0)         | 0.0 (0.0)                      | 0.0 (0.0)         | 0.0 (0.0)         | 0.0 (0.0)         | 0.0 (0.0)         | <0.001 |
| Tapentadol                                                                            | 135 (0.3)         | 38 (0.3)          | 15 (0.5)                       | 244 (0.3)         | 35 (0.8)          | 77 (0.4)          | 237 (0.5)         | 0.025  |
| Tramadol                                                                              | 8859 (22.0)       | 1651 (14.5)       | 780 (25.1)                     | 17456 (22.6)      | 1112 (25.0)       | 4345 (22.5)       | 10391 (20.1)      | 0.100  |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 174.81 (15.67)    | 176.71 (12.62)    | 174.73 (15.80)                 | 175.27 (14.89)    | 174.48 (15.71)    | 174.99 (15.14)    | 175.52 (14.50)    | 0.057  |
| Total dispensed MMEs per interval (days) mean (SD))                                   |                   |                   |                                |                   |                   |                   |                   |        |
| (Index - 180) to (index - 151)                                                        | 1632.29 (2394.85) | 2091.07 (2892.84) | 1557.73 (2364.28)              | 1571.69 (2277.30) | 1632.78 (2497.12) | 1572.46 (2322.66) | 1655.21 (2313.10) | 0.068  |
| (Index - 150) to (index - 121)                                                        | 1644.88 (2375.72) | 2084.73 (2838.20) | 1584.77 (2356.07)              | 1604.35 (2293.27) | 1669.78 (2453.16) | 1613.32 (2324.32) | 1690.45 (2346.41) | 0.065  |
| (Index - 120) to (index - 91)                                                         | 1782.45 (2480.28) | 2273.05 (2925.38) | 1679.47 (2300.87)              | 1716.81 (2313.21) | 1782.60 (2443.28) | 1730.71 (2338.10) | 1804.07 (2385.75) | 0.074  |
| (Index - 90) to (index - 61)                                                          | 1780.18 (2416.33) | 2197.00 (2906.52) | 1673.68 (2354.14)              | 1699.41 (2314.46) | 1791.62 (2560.85) | 1728.07 (2386.28) | 1780.64 (2356.25) | 0.066  |
| (Index - 60) to (index - 31)                                                          | 1766.85 (2408.14) | 2208.84 (2965.81) | 1657.64 (2253.55)              | 1715.80 (2336.62) | 1789.14 (2452.11) | 1735.64 (2394.50) | 1779.54 (2346.91) | 0.068  |
| (Index - 30) to index                                                                 | 2062.35 (2859.25) | 2803.66 (3702.76) | 1863.18 (2444.23)              | 1949.89 (2666.87) | 1997.61 (2779.37) | 1999.49 (2695.93) | 2132.25 (2873.75) | 0.100  |
| <b>Healthcare utilization (mean (SD))</b>                                             |                   |                   |                                |                   |                   |                   |                   |        |
| Number of physician visits                                                            | 13.50 (10.33)     | 11.75 (9.42)      | 12.33 (9.66)                   | 12.44 (9.68)      | 13.35 (10.01)     | 13.12 (9.95)      | 12.55 (9.13)      | 0.078  |
| Number of distinct prescribed medications                                             | 15.57 (5.92)      | 14.57 (5.80)      | 15.12 (5.82)                   | 15.24 (5.82)      | 15.40 (5.96)      | 15.34 (5.77)      | 15.29 (5.72)      | 0.060  |
| Number of hospitalizations                                                            | 0.35 (0.73)       | 0.32 (0.72)       | 0.32 (0.71)                    | 0.35 (0.73)       | 0.34 (0.73)       | 0.41 (0.76)       | 0.32 (0.70)       | 0.047  |
| Number of hospitalization days                                                        | 2.25 (5.93)       | 1.93 (5.40)       | 1.83 (5.20)                    | 2.07 (5.38)       | 2.24 (5.63)       | 2.57 (6.03)       | 1.93 (5.22)       | 0.054  |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 7. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in Medicare diabetes, heart failure, and/or stroke, 2012-2017 (post-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 2538.42       | 2599.43       | 2573.77                        | 2568.89         | 2567.9        | 2582.36       | 2552.51       |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 72.82 (7.04)  | 72.75 (6.90)  | 72.94 (7.06)                   | 72.97 (7.27)    | 73.04 (7.09)  | 72.88 (7.19)  | 72.74 (6.89)  | 0.019 |
| Sex                                    |               |               |                                |                 |               |               |               |       |
| Male                                   | 824.72 (32.5) | 834.33 (32.1) | 832.57 (32.3)                  | 837.19 (32.6)   | 802.8 (31.3)  | 842.76 (32.6) | 827.61 (32.4) | 0.011 |
| Female                                 | 1713.7 (67.5) | 1765.1 (67.9) | 1741.2 (67.7)                  | 1731.7 (67.4)   | 1765.1 (68.7) | 1739.6 (67.4) | 1724.9 (67.6) |       |
| Race                                   |               |               |                                |                 |               |               |               | 0.028 |
| Asian                                  | 13.6 (0.5)    | 13.1 (0.5)    | 16.1 (0.6)                     | 11.9 (0.5)      | 10.4 (0.4)    | 12.6 (0.5)    | 11.8 (0.5)    |       |
| Black                                  | 251.6 (9.9)   | 228.7 (8.8)   | 254.4 (9.9)                    | 263.6 (10.3)    | 272.7 (10.6)  | 267.5 (10.4)  | 251.5 (9.9)   |       |
| White                                  | 2212.4 (87.2) | 2293.3 (88.2) | 2242.0 (87.1)                  | 2230.5 (86.8)   | 2218.1 (86.4) | 2240.8 (86.8) | 2229.7 (87.4) |       |
| Other                                  | 60.8 (2.4)    | 64.4 (2.5)    | 61.2 (2.4)                     | 62.9 (2.4)      | 66.6 (2.6)    | 61.4 (2.4)    | 59.5 (2.3)    |       |
| Ethnicity                              |               |               |                                |                 |               |               |               | 0.013 |
| Unknown                                | 23.9 (0.9)    | 31.0 (1.2)    | 24.2 (0.9)                     | 24.5 (1.0)      | 26.2 (1.0)    | 23.5 (0.9)    | 24.2 (0.9)    |       |
| Hispanic                               | 29.6 (1.2)    | 27.4 (1.1)    | 29.3 (1.1)                     | 30.4 (1.2)      | 32.1 (1.2)    | 28.4 (1.1)    | 28.3 (1.1)    |       |
| Non-Hispanic                           | 2484.9 (97.9) | 2541.1 (97.8) | 2520.3 (97.9)                  | 2514.1 (97.9)   | 2509.6 (97.7) | 2530.4 (98.0) | 2500.0 (97.9) |       |
| State                                  |               |               |                                |                 |               |               |               | 0.052 |
| AK                                     | 2.6 (0.1)     | 3.9 (0.2)     | 2.9 (0.1)                      | 2.8 (0.1)       | 2.2 (0.1)     | 2.7 (0.1)     | 3.2 (0.1)     |       |
| AL                                     | 82.3 (3.2)    | 76.5 (2.9)    | 84.4 (3.3)                     | 82.9 (3.2)      | 85.1 (3.3)    | 83.6 (3.2)    | 84.9 (3.3)    |       |
| AR                                     | 36.9 (1.5)    | 36.7 (1.4)    | 36.7 (1.4)                     | 37.2 (1.4)      | 34.8 (1.4)    | 36.9 (1.4)    | 38.3 (1.5)    |       |
| AZ                                     | 47.9 (1.9)    | 52.7 (2.0)    | 46.4 (1.8)                     | 47.0 (1.8)      | 46.6 (1.8)    | 46.9 (1.8)    | 41.4 (1.6)    |       |
| CA                                     | 69.9 (2.8)    | 64.5 (2.5)    | 65.0 (2.5)                     | 65.0 (2.5)      | 63.7 (2.5)    | 64.7 (2.5)    | 62.3 (2.4)    |       |
| CO                                     | 23.9 (0.9)    | 26.9 (1.0)    | 22.1 (0.9)                     | 22.6 (0.9)      | 20.6 (0.8)    | 20.6 (0.8)    | 24.4 (1.0)    |       |
| CT                                     | 21.3 (0.8)    | 24.3 (0.9)    | 21.9 (0.8)                     | 21.6 (0.8)      | 23.9 (0.9)    | 21.0 (0.8)    | 20.9 (0.8)    |       |
| DC                                     | 1.3 (0.1)     | 2.0 (0.1)     | 1.8 (0.1)                      | 1.4 (0.1)       | 1.5 (0.1)     | 1.3 (0.1)     | 1.1 (0.0)     |       |
| DE                                     | 12.4 (0.5)    | 12.6 (0.5)    | 14.0 (0.5)                     | 13.6 (0.5)      | 13.4 (0.5)    | 13.5 (0.5)    | 13.4 (0.5)    |       |
| FL                                     | 233.2 (9.2)   | 238.4 (9.2)   | 228.5 (8.9)                    | 225.3 (8.8)     | 224.1 (8.7)   | 227.1 (8.8)   | 228.6 (9.0)   |       |
| GA                                     | 93.6 (3.7)    | 92.1 (3.5)    | 95.5 (3.7)                     | 96.4 (3.8)      | 98.1 (3.8)    | 95.8 (3.7)    | 96.5 (3.8)    |       |
| HI                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| IA                                     | 25.9 (1.0)    | 28.5 (1.1)    | 26.0 (1.0)                     | 25.0 (1.0)      | 28.4 (1.1)    | 26.3 (1.0)    | 24.6 (1.0)    |       |
| ID                                     | 10.1 (0.4)    | 10.6 (0.4)    | 10.4 (0.4)                     | 10.2 (0.4)      | 11.0 (0.4)    | 10.2 (0.4)    | 11.4 (0.4)    |       |
| IL                                     | 96.9 (3.8)    | 111.8 (4.3)   | 103.6 (4.0)                    | 104.3 (4.1)     | 101.8 (4.0)   | 101.4 (3.9)   | 93.0 (3.6)    |       |
| IN                                     | 101.6 (4.0)   | 107.6 (4.1)   | 103.4 (4.0)                    | 103.7 (4.0)     | 103.3 (4.0)   | 103.6 (4.0)   | 104.0 (4.1)   |       |
| KS                                     | 29.7 (1.2)    | 29.0 (1.1)    | 30.8 (1.2)                     | 29.6 (1.2)      | 30.9 (1.2)    | 29.6 (1.1)    | 29.0 (1.1)    |       |
| KY                                     | 100.7 (4.0)   | 103.1 (4.0)   | 102.1 (4.0)                    | 100.0 (3.9)     | 95.2 (3.7)    | 102.2 (4.0)   | 108.4 (4.2)   |       |
| LA                                     | 70.4 (2.8)    | 65.6 (2.5)    | 71.5 (2.8)                     | 71.1 (2.8)      | 71.8 (2.8)    | 72.5 (2.8)    | 72.3 (2.8)    |       |
| MA                                     | 22.8 (0.9)    | 22.1 (0.8)    | 21.7 (0.8)                     | 21.1 (0.8)      | 22.8 (0.9)    | 21.7 (0.8)    | 22.2 (0.9)    |       |
| MD                                     | 36.8 (1.5)    | 43.5 (1.7)    | 41.8 (1.6)                     | 41.7 (1.6)      | 43.1 (1.7)    | 42.9 (1.7)    | 41.7 (1.6)    |       |
| ME                                     | 3.4 (0.1)     | 4.0 (0.2)     | 4.0 (0.2)                      | 3.6 (0.1)       | 4.1 (0.2)     | 3.9 (0.1)     | 3.4 (0.1)     |       |
| MI                                     | 151.0 (5.9)   | 139.6 (5.4)   | 157.9 (6.1)                    | 161.2 (6.3)     | 156.6 (6.1)   | 157.4 (6.1)   | 149.5 (5.9)   |       |
| MN                                     | 6.8 (0.3)     | 7.2 (0.3)     | 6.0 (0.2)                      | 7.1 (0.3)       | 7.4 (0.3)     | 7.5 (0.3)     | 7.1 (0.3)     |       |
| MO                                     | 72.9 (2.9)    | 81.8 (3.1)    | 76.2 (3.0)                     | 78.0 (3.0)      | 78.7 (3.1)    | 79.2 (3.1)    | 77.1 (3.0)    |       |
| MS                                     | 54.0 (2.1)    | 51.2 (2.0)    | 57.0 (2.2)                     | 52.1 (2.0)      | 54.7 (2.1)    | 52.9 (2.0)    | 57.8 (2.3)    |       |
| MT                                     | 4.6 (0.2)     | 5.0 (0.2)     | 5.0 (0.2)                      | 4.8 (0.2)       | 5.2 (0.2)     | 4.8 (0.2)     | 5.3 (0.2)     |       |
| NC                                     | 144.2 (5.7)   | 156.0 (6.0)   | 154.4 (6.0)                    | 152.6 (5.9)     | 151.6 (5.9)   | 154.0 (6.0)   | 147.3 (5.8)   |       |
| ND                                     | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |       |
| NE                                     | 15.1 (0.6)    | 11.2 (0.4)    | 14.1 (0.5)                     | 13.7 (0.5)      | 14.8 (0.6)    | 14.6 (0.6)    | 14.2 (0.6)    |       |
| NH                                     | 4.3 (0.2)     | 5.4 (0.2)     | 4.0 (0.2)                      | 4.0 (0.2)       | 3.7 (0.1)     | 3.9 (0.2)     | 4.1 (0.2)     |       |
| NJ                                     | 79.3 (3.1)    | 91.6 (3.5)    | 81.4 (3.2)                     | 79.4 (3.1)      | 80.7 (3.1)    | 80.7 (3.1)    | 77.9 (3.1)    |       |

|                              | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD    |
|------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|--------|
| NM                           | 14.9 (0.6)    | 14.9 (0.6)    | 14.2 (0.6)                     | 15.2 (0.6)      | 14.9 (0.6)    | 14.8 (0.6)    | 15.5 (0.6)    |        |
| NV                           | 10.7 (0.4)    | 9.2 (0.4)     | 10.0 (0.4)                     | 9.9 (0.4)       | 9.8 (0.4)     | 9.3 (0.4)     | 10.0 (0.4)    |        |
| NY                           | 64.5 (2.5)    | 69.6 (2.7)    | 65.8 (2.6)                     | 66.6 (2.6)      | 70.4 (2.7)    | 66.9 (2.6)    | 64.0 (2.5)    |        |
| OH                           | 115.5 (4.6)   | 118.9 (4.6)   | 115.3 (4.5)                    | 119.8 (4.7)     | 116.4 (4.5)   | 122.5 (4.7)   | 121.0 (4.7)   |        |
| OK                           | 66.4 (2.6)    | 66.3 (2.6)    | 68.1 (2.6)                     | 67.3 (2.6)      | 68.4 (2.7)    | 71.7 (2.8)    | 66.1 (2.6)    |        |
| OR                           | 10.6 (0.4)    | 10.4 (0.4)    | 11.0 (0.4)                     | 11.1 (0.4)      | 11.5 (0.4)    | 11.3 (0.4)    | 11.0 (0.4)    |        |
| PA                           | 51.5 (2.0)    | 51.1 (2.0)    | 53.8 (2.1)                     | 54.0 (2.1)      | 54.1 (2.1)    | 53.7 (2.1)    | 51.3 (2.0)    |        |
| RI                           | 4.5 (0.2)     | 3.6 (0.1)     | 4.1 (0.2)                      | 4.3 (0.2)       | 4.3 (0.2)     | 4.3 (0.2)     | 4.1 (0.2)     |        |
| SC                           | 82.8 (3.3)    | 88.4 (3.4)    | 81.3 (3.2)                     | 80.1 (3.1)      | 77.9 (3.0)    | 81.5 (3.2)    | 82.1 (3.2)    |        |
| SD                           | 2.2 (0.1)     | 3.3 (0.1)     | 2.1 (0.1)                      | 2.5 (0.1)       | 2.4 (0.1)     | 2.0 (0.1)     | 2.4 (0.1)     |        |
| TN                           | 89.1 (3.5)    | 81.5 (3.1)    | 87.8 (3.4)                     | 86.4 (3.4)      | 86.3 (3.4)    | 89.2 (3.5)    | 88.3 (3.5)    |        |
| TX                           | 228.2 (9.0)   | 223.1 (8.6)   | 229.1 (8.9)                    | 230.0 (9.0)     | 226.8 (8.8)   | 226.3 (8.8)   | 229.9 (9.0)   |        |
| UT                           | 5.9 (0.2)     | 6.2 (0.2)     | 6.0 (0.2)                      | 6.0 (0.2)       | 6.2 (0.2)     | 6.1 (0.2)     | 6.1 (0.2)     |        |
| VA                           | 69.5 (2.7)    | 78.6 (3.0)    | 70.9 (2.8)                     | 71.3 (2.8)      | 72.5 (2.8)    | 72.8 (2.8)    | 71.5 (2.8)    |        |
| VT                           | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     |        |
| WA                           | 13.4 (0.5)    | 16.4 (0.6)    | 13.8 (0.5)                     | 13.9 (0.5)      | 16.2 (0.6)    | 13.9 (0.5)    | 13.2 (0.5)    |        |
| WI                           | 15.9 (0.6)    | 17.7 (0.7)    | 15.7 (0.6)                     | 16.4 (0.6)      | 16.6 (0.6)    | 17.1 (0.7)    | 15.0 (0.6)    |        |
| WV                           | 28.8 (1.1)    | 28.8 (1.1)    | 27.2 (1.1)                     | 27.8 (1.1)      | 26.5 (1.0)    | 27.9 (1.1)    | 28.9 (1.1)    |        |
| WY                           | 8.4 (0.3)     | 6.0 (0.2)     | 7.1 (0.3)                      | 7.3 (0.3)       | 7.1 (0.3)     | 7.4 (0.3)     | 6.7 (0.3)     |        |
| Year                         |               |               |                                |                 |               |               |               | 0.025  |
| 2012                         | 474.8 (18.7)  | 517.5 (19.9)  | 489.5 (19.0)                   | 492.8 (19.2)    | 493.6 (19.2)  | 502.9 (19.5)  | 480.3 (18.8)  |        |
| 2013                         | 722.3 (28.5)  | 721.4 (27.8)  | 736.9 (28.6)                   | 736.1 (28.7)    | 731.7 (28.5)  | 745.3 (28.9)  | 729.4 (28.6)  |        |
| 2014                         | 587.7 (23.2)  | 595.4 (22.9)  | 588.9 (22.9)                   | 594.0 (23.1)    | 597.6 (23.3)  | 595.1 (23.0)  | 586.2 (23.0)  |        |
| 2015                         | 380.4 (15.0)  | 403.4 (15.5)  | 381.0 (14.8)                   | 380.5 (14.8)    | 376.6 (14.7)  | 378.6 (14.7)  | 378.5 (14.8)  |        |
| 2016                         | 196.4 (7.7)   | 173.5 (6.7)   | 196.0 (7.6)                    | 192.1 (7.5)     | 190.5 (7.4)   | 184.5 (7.1)   | 196.1 (7.7)   |        |
| 2017                         | 176.8 (7.0)   | 188.2 (7.2)   | 181.3 (7.0)                    | 173.4 (6.7)     | 178.0 (6.9)   | 175.8 (6.8)   | 182.0 (7.1)   |        |
| <b>Comorbidities (n (%))</b> |               |               |                                |                 |               |               |               |        |
| Opioid dependence            | 101.6 (4.0)   | 114.8 (4.4)   | 98.5 (3.8)                     | 95.8 (3.7)      | 96.6 (3.8)    | 103.6 (4.0)   | 103.0 (4.0)   | 0.014  |
| Opioid abuse                 | 7.1 (0.3)     | 7.8 (0.3)     | 7.0 (0.3)                      | 6.6 (0.3)       | 7.1 (0.3)     | 7.5 (0.3)     | 6.9 (0.3)     | 0.003  |
| Alcohol abuse                | 42.0 (1.7)    | 41.4 (1.6)    | 39.6 (1.5)                     | 39.8 (1.6)      | 44.8 (1.7)    | 40.3 (1.6)    | 37.8 (1.5)    | 0.008  |
| Tobacco use                  | 583.0 (23.0)  | 584.6 (22.5)  | 574.4 (22.3)                   | 571.8 (22.3)    | 582.0 (22.7)  | 586.4 (22.7)  | 572.4 (22.4)  | 0.007  |
| Other drug abuse             | 87.9 (3.5)    | 83.6 (3.2)    | 79.8 (3.1)                     | 82.3 (3.2)      | 79.5 (3.1)    | 86.5 (3.4)    | 85.1 (3.3)    | 0.009  |
| Anxiety                      | 652.6 (25.7)  | 666.2 (25.6)  | 656.4 (25.5)                   | 656.6 (25.6)    | 654.1 (25.5)  | 656.0 (25.4)  | 655.8 (25.7)  | 0.003  |
| Bipolar disorder             | 78.0 (3.1)    | 78.3 (3.0)    | 77.4 (3.0)                     | 79.0 (3.1)      | 84.0 (3.3)    | 81.8 (3.2)    | 78.6 (3.1)    | 0.006  |
| Bone fracture                | 277.0 (10.9)  | 284.0 (10.9)  | 269.3 (10.5)                   | 273.4 (10.6)    | 268.3 (10.5)  | 273.5 (10.6)  | 272.6 (10.7)  | 0.007  |
| Cancer                       | 294.2 (11.6)  | 302.3 (11.6)  | 294.1 (11.4)                   | 293.3 (11.4)    | 291.6 (11.4)  | 290.5 (11.3)  | 285.1 (11.2)  | 0.006  |
| Chronic renal insufficiency  | 481.5 (19.0)  | 482.8 (18.6)  | 484.9 (18.8)                   | 481.5 (18.7)    | 481.2 (18.7)  | 498.8 (19.3)  | 474.7 (18.6)  | 0.007  |
| Congestive heart failure     | 595.2 (23.4)  | 593.2 (22.8)  | 601.1 (23.4)                   | 606.1 (23.6)    | 614.4 (23.9)  | 618.5 (24.0)  | 599.1 (23.5)  | 0.011  |
| COPD/asthma/oxygen           | 947.5 (37.3)  | 934.3 (35.9)  | 944.3 (36.7)                   | 949.0 (36.9)    | 942.8 (36.7)  | 964.3 (37.3)  | 946.9 (37.1)  | 0.012  |
| Dementia                     | 222.1 (8.7)   | 201.6 (7.8)   | 220.9 (8.6)                    | 224.6 (8.7)     | 233.6 (9.1)   | 220.7 (8.5)   | 220.0 (8.6)   | 0.016  |
| Depression                   | 720.2 (28.4)  | 729.9 (28.1)  | 711.5 (27.6)                   | 719.5 (28.0)    | 739.2 (28.8)  | 719.0 (27.8)  | 721.8 (28.3)  | 0.010  |
| Diabetes                     | 1467.4 (57.8) | 1510.7 (58.1) | 1491.3 (57.9)                  | 1491.5 (58.1)   | 1504.3 (58.6) | 1496.4 (57.9) | 1484.8 (58.2) | 0.006  |
| Epilepsy                     | 72.5 (2.9)    | 71.3 (2.7)    | 71.5 (2.8)                     | 73.4 (2.9)      | 75.6 (2.9)    | 73.0 (2.8)    | 71.9 (2.8)    | 0.005  |
| Intentional self-harm        | 6.9 (0.3)     | 6.7 (0.3)     | 8.0 (0.3)                      | 7.3 (0.3)       | 8.3 (0.3)     | 7.3 (0.3)     | 6.3 (0.2)     | 0.006  |
| Liver disease                | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     | <0.001 |
| Musculoskeletal injury       | 182.8 (7.2)   | 182.7 (7.0)   | 182.2 (7.1)                    | 178.0 (6.9)     | 178.2 (6.9)   | 179.8 (7.0)   | 179.6 (7.0)   | 0.004  |
| Multiple sclerosis           | 249.2 (9.8)   | 265.9 (10.2)  | 247.5 (9.6)                    | 247.9 (9.7)     | 241.9 (9.4)   | 243.4 (9.4)   | 241.9 (9.5)   | 0.011  |
| Obesity                      | 8.6 (0.3)     | 7.6 (0.3)     | 8.5 (0.3)                      | 8.6 (0.3)       | 9.0 (0.3)     | 7.6 (0.3)     | 8.6 (0.3)     | 0.004  |
| Pneumonia                    | 447.5 (17.6)  | 473.2 (18.2)  | 452.9 (17.6)                   | 449.7 (17.5)    | 465.2 (18.1)  | 448.6 (17.4)  | 454.0 (17.8)  | 0.010  |
| Psychosis                    | 183.1 (7.2)   | 187.9 (7.2)   | 183.8 (7.1)                    | 182.6 (7.1)     | 188.4 (7.3)   | 189.8 (7.4)   | 183.5 (7.2)   | 0.004  |
| Renal dysfunction            | 87.0 (3.4)    | 83.8 (3.2)    | 84.4 (3.3)                     | 89.1 (3.5)      | 88.4 (3.4)    | 88.5 (3.4)    | 87.2 (3.4)    | 0.006  |
| Urinary calculus             | 640.2 (25.2)  | 643.1 (24.7)  | 637.8 (24.8)                   | 638.8 (24.9)    | 635.3 (24.7)  | 653.5 (25.3)  | 631.9 (24.8)  | 0.006  |

|                                                | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD    |
|------------------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|--------|
| Urinary tract infection                        | 768.1 (30.3)  | 760.5 (29.3)  | 750.3 (29.2)                   | 760.4 (29.6)    | 780.2 (30.4)  | 756.3 (29.3)  | 752.8 (29.5)  | 0.013  |
| <b>Pain conditions (n (%))</b>                 |               |               |                                |                 |               |               |               |        |
| Abdominal pain                                 | 599.0 (23.6)  | 609.1 (23.4)  | 601.1 (23.4)                   | 594.4 (23.1)    | 607.1 (23.6)  | 601.7 (23.3)  | 592.2 (23.2)  | 0.005  |
| Back and neck pain                             | 1983.4 (78.1) | 2019.1 (77.7) | 1977.0 (76.8)                  | 1980.8 (77.1)   | 1988.6 (77.4) | 1998.2 (77.4) | 1981.6 (77.6) | 0.012  |
| Back pain without radiculopathy                | 1861.1 (73.3) | 1888.6 (72.7) | 1847.6 (71.8)                  | 1853.6 (72.2)   | 1853.8 (72.2) | 1863.9 (72.2) | 1853.8 (72.6) | 0.013  |
| Back pain with radiculopathy                   | 706.1 (27.8)  | 738.3 (28.4)  | 692.4 (26.9)                   | 694.3 (27.0)    | 693.5 (27.0)  | 696.9 (27.0)  | 704.6 (27.6)  | 0.014  |
| Dental pain                                    | 13.2 (0.5)    | 12.5 (0.5)    | 12.6 (0.5)                     | 12.8 (0.5)      | 11.9 (0.5)    | 13.7 (0.5)    | 13.2 (0.5)    | 0.004  |
| Diabetic neuropathy                            | 399.4 (15.7)  | 410.4 (15.8)  | 398.4 (15.5)                   | 394.4 (15.4)    | 397.2 (15.5)  | 404.6 (15.7)  | 395.6 (15.5)  | 0.005  |
| Fibromyalgia                                   | 452.5 (17.8)  | 474.5 (18.3)  | 441.2 (17.1)                   | 432.9 (16.9)    | 448.9 (17.5)  | 440.7 (17.1)  | 449.8 (17.6)  | 0.016  |
| Headache                                       | 383.7 (15.1)  | 377.7 (14.5)  | 363.8 (14.1)                   | 369.8 (14.4)    | 384.0 (15.0)  | 377.2 (14.6)  | 371.6 (14.6)  | 0.011  |
| Osteoarthritis                                 | 1250.4 (49.3) | 1303.0 (50.1) | 1263.0 (49.1)                  | 1269.3 (49.4)   | 1278.6 (49.8) | 1277.0 (49.4) | 1257.5 (49.3) | 0.008  |
| Rheumatoid arthritis                           | 232.4 (9.2)   | 250.3 (9.6)   | 232.7 (9.0)                    | 234.6 (9.1)     | 240.1 (9.3)   | 233.8 (9.1)   | 230.0 (9.0)   | 0.008  |
| Postherpetic neuralgia                         | 14.1 (0.6)    | 13.7 (0.5)    | 14.8 (0.6)                     | 14.9 (0.6)      | 15.8 (0.6)    | 15.9 (0.6)    | 14.9 (0.6)    | 0.005  |
| Other arthritis                                | 1855.6 (73.1) | 1911.7 (73.5) | 1863.8 (72.4)                  | 1872.1 (72.9)   | 1883.0 (73.3) | 1882.7 (72.9) | 1858.4 (72.8) | 0.010  |
| Other neuropathy                               | 1139.0 (44.9) | 1191.1 (45.8) | 1121.3 (43.6)                  | 1126.1 (43.8)   | 1137.6 (44.3) | 1129.8 (43.8) | 1136.8 (44.5) | 0.019  |
| Other unspecified pain                         | 1596.8 (62.9) | 1648.2 (63.4) | 1599.6 (62.1)                  | 1593.1 (62.0)   | 1590.8 (61.9) | 1604.3 (62.1) | 1599.5 (62.7) | 0.013  |
| <b>Other prescription fills (n (%))</b>        |               |               |                                |                 |               |               |               |        |
| Antibiotics                                    | 1703.8 (67.1) | 1741.1 (67.0) | 1736.3 (67.5)                  | 1727.5 (67.2)   | 1740.6 (67.8) | 1740.2 (67.4) | 1722.8 (67.5) | 0.007  |
| Anticonvulsants                                | 177.2 (7.0)   | 180.7 (7.0)   | 171.2 (6.7)                    | 172.9 (6.7)     | 176.0 (6.9)   | 169.1 (6.5)   | 173.6 (6.8)   | 0.008  |
| Antidepressants, SSRIs                         | 750.9 (29.6)  | 765.4 (29.4)  | 738.4 (28.7)                   | 743.2 (28.9)    | 748.4 (29.1)  | 744.0 (28.8)  | 751.7 (29.5)  | 0.009  |
| Antidepressants, SNRIs                         | 408.4 (16.1)  | 422.0 (16.2)  | 405.0 (15.7)                   | 399.5 (15.6)    | 419.2 (16.3)  | 398.3 (15.4)  | 406.8 (15.9)  | 0.012  |
| Antidepressants, TCAs                          | 224.1 (8.8)   | 231.5 (8.9)   | 215.1 (8.4)                    | 219.7 (8.6)     | 227.7 (8.9)   | 218.0 (8.4)   | 222.7 (8.7)   | 0.009  |
| Antidepressants, other                         | 422.9 (16.7)  | 444.7 (17.1)  | 421.5 (16.4)                   | 420.1 (16.4)    | 420.8 (16.4)  | 422.5 (16.4)  | 422.1 (16.5)  | 0.008  |
| Antidiabetics                                  | 1040.5 (41.0) | 1086.6 (41.8) | 1058.8 (41.1)                  | 1057.3 (41.2)   | 1052.1 (41.0) | 1061.7 (41.1) | 1051.2 (41.2) | 0.006  |
| Antipsychotics, atypical                       | 167.0 (6.6)   | 154.2 (5.9)   | 164.2 (6.4)                    | 164.0 (6.4)     | 176.3 (6.9)   | 166.4 (6.4)   | 161.4 (6.3)   | 0.013  |
| Antipsychotics, typical                        | 61.5 (2.4)    | 61.7 (2.4)    | 62.2 (2.4)                     | 60.5 (2.4)      | 63.6 (2.5)    | 62.3 (2.4)    | 61.2 (2.4)    | 0.003  |
| Barbiturates                                   | 3.1 (0.1)     | 2.2 (0.1)     | 3.0 (0.1)                      | 2.8 (0.1)       | 2.5 (0.1)     | 2.3 (0.1)     | 3.1 (0.1)     | 0.006  |
| Benzodiazepines                                | 891.1 (35.1)  | 896.0 (34.5)  | 883.4 (34.3)                   | 880.1 (34.3)    | 878.0 (34.2)  | 895.3 (34.7)  | 890.0 (34.9)  | 0.009  |
| CNS stimulants                                 | 20.9 (0.8)    | 29.8 (1.1)    | 20.9 (0.8)                     | 20.7 (0.8)      | 23.5 (0.9)    | 20.6 (0.8)    | 21.5 (0.8)    | 0.013  |
| Dementia agents                                | 150.3 (5.9)   | 141.7 (5.4)   | 145.1 (5.6)                    | 147.8 (5.8)     | 159.1 (6.2)   | 149.3 (5.8)   | 143.6 (5.6)   | 0.012  |
| Gabapentinoids                                 | 961.2 (37.9)  | 989.2 (38.1)  | 947.7 (36.8)                   | 952.8 (37.1)    | 962.4 (37.5)  | 943.2 (36.5)  | 960.8 (37.6)  | 0.014  |
| Lithium                                        | 3.5 (0.1)     | 3.1 (0.1)     | 3.9 (0.1)                      | 3.4 (0.1)       | 4.2 (0.2)     | 3.3 (0.1)     | 3.0 (0.1)     | 0.005  |
| Multiple sclerosis agents                      | 1.9 (0.1)     | 1.9 (0.1)     | 1.5 (0.1)                      | 1.5 (0.1)       | 2.2 (0.1)     | 1.3 (0.0)     | 1.9 (0.1)     | 0.006  |
| NSAIDs                                         | 914.1 (36.0)  | 945.4 (36.4)  | 913.5 (35.5)                   | 919.1 (35.8)    | 918.3 (35.8)  | 931.4 (36.1)  | 916.4 (35.9)  | 0.007  |
| Other sedative hypnotics                       | 449.6 (17.7)  | 460.4 (17.7)  | 441.0 (17.1)                   | 434.9 (16.9)    | 442.1 (17.2)  | 434.9 (16.8)  | 432.7 (17.0)  | 0.011  |
| Smoking cessation                              | 133.6 (5.3)   | 135.8 (5.2)   | 130.1 (5.1)                    | 130.2 (5.1)     | 132.6 (5.2)   | 128.0 (5.0)   | 132.5 (5.2)   | 0.006  |
| Triptans                                       | 39.3 (1.5)    | 38.3 (1.5)    | 34.9 (1.4)                     | 36.4 (1.4)      | 37.6 (1.5)    | 35.0 (1.4)    | 37.7 (1.5)    | 0.007  |
| Other CNS depressants                          | 7.6 (0.3)     | 5.7 (0.2)     | 7.9 (0.3)                      | 6.3 (0.2)       | 7.0 (0.3)     | 8.4 (0.3)     | 6.4 (0.3)     | 0.009  |
| <b>Prescription opioid utilization (n (%))</b> |               |               |                                |                 |               |               |               |        |
| Prescription opioid on index date              |               |               |                                |                 |               |               |               |        |
| Buprenorphine                                  | 8.1 (0.3)     | 10.7 (0.4)    | 9.5 (0.4)                      | 8.1 (0.3)       | 8.2 (0.3)     | 8.0 (0.3)     | 8.6 (0.3)     | 0.007  |
| Butorphanol                                    | 1.7 (0.1)     | 1.1 (0.0)     | 1.5 (0.1)                      | 1.8 (0.1)       | 1.8 (0.1)     | 2.3 (0.1)     | 2.5 (0.1)     | 0.008  |
| Codeine                                        | 87.4 (3.4)    | 100.0 (3.8)   | 90.7 (3.5)                     | 95.1 (3.7)      | 96.3 (3.7)    | 95.7 (3.7)    | 90.1 (3.5)    | 0.009  |
| Dihydrocodeine                                 | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     | <0.001 |
| Fentanyl                                       | 205.5 (8.1)   | 211.9 (8.2)   | 198.7 (7.7)                    | 199.5 (7.8)     | 208.8 (8.1)   | 195.5 (7.6)   | 201.4 (7.9)   | 0.010  |
| Hydrocodone                                    | 1352.3 (53.3) | 1345.5 (51.8) | 1395.7 (54.2)                  | 1389.8 (54.1)   | 1371.3 (53.4) | 1390.1 (53.8) | 1377.1 (53.9) | 0.018  |
| Hydromorphone                                  | 57.7 (2.3)    | 62.7 (2.4)    | 54.6 (2.1)                     | 54.2 (2.1)      | 52.5 (2.0)    | 52.5 (2.0)    | 54.5 (2.1)    | 0.010  |
| Levorphanol                                    | 0.9 (0.0)     | 1.0 (0.0)     | 0.7 (0.0)                      | 0.3 (0.0)       | 0.4 (0.0)     | 0.7 (0.0)     | 0.5 (0.0)     | 0.008  |
| Meperidine                                     | 3.4 (0.1)     | 2.3 (0.1)     | 2.3 (0.1)                      | 2.4 (0.1)       | 2.9 (0.1)     | 2.3 (0.1)     | 2.3 (0.1)     | 0.005  |
| Methadone                                      | 52.9 (2.1)    | 54.6 (2.1)    | 50.1 (1.9)                     | 49.5 (1.9)      | 49.8 (1.9)    | 50.1 (1.9)    | 52.9 (2.1)    | 0.006  |
| Morphine                                       | 159.7 (6.3)   | 171.5 (6.6)   | 154.2 (6.0)                    | 153.7 (6.0)     | 152.6 (5.9)   | 153.4 (5.9)   | 156.1 (6.1)   | 0.011  |
| Opium                                          | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)                      | 0.0 (0.0)       | 0.0 (0.0)     | 0.0 (0.0)     | 0.0 (0.0)     | <0.001 |

|                                                                                       | Baclofen          | Carisoprodol      | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone        | Methocarbamol     | Tizanidine        | SMD    |
|---------------------------------------------------------------------------------------|-------------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|-------------------|--------|
| Oxycodone                                                                             | 763.8 (30.1)      | 808.0 (31.1)      | 738.8 (28.7)                   | 745.5 (29.0)      | 757.3 (29.5)      | 746.0 (28.9)      | 743.7 (29.1)      | 0.021  |
| Oxymorphone                                                                           | 23.7 (0.9)        | 23.6 (0.9)        | 20.0 (0.8)                     | 20.7 (0.8)        | 23.6 (0.9)        | 22.5 (0.9)        | 20.2 (0.8)        | 0.009  |
| Pentazocine                                                                           | 0.9 (0.0)         | 0.9 (0.0)         | 0.8 (0.0)                      | 0.8 (0.0)         | 0.4 (0.0)         | 0.7 (0.0)         | 0.8 (0.0)         | 0.004  |
| Propoxyphene                                                                          | 0.0 (0.0)         | 0.0 (0.0)         | 0.0 (0.0)                      | 0.0 (0.0)         | 0.0 (0.0)         | 0.0 (0.0)         | 0.0 (0.0)         | <0.001 |
| Tapentadol                                                                            | 16.8 (0.7)        | 12.0 (0.5)        | 12.9 (0.5)                     | 12.5 (0.5)        | 14.5 (0.6)        | 12.1 (0.5)        | 12.3 (0.5)        | 0.011  |
| Tramadol                                                                              | 576.6 (22.7)      | 613.7 (23.6)      | 608.7 (23.6)                   | 604.0 (23.5)      | 597.6 (23.3)      | 616.1 (23.9)      | 596.3 (23.4)      | 0.01   |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 175.21 (14.94)    | 174.76 (15.57)    | 174.94 (15.54)                 | 174.99 (15.26)    | 174.93 (14.92)    | 175.13 (14.96)    | 175.18 (14.89)    | 0.013  |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                   |                   |                                |                   |                   |                   |                   |        |
| (Index - 180) to (index - 151)                                                        | 1662.45 (2474.48) | 1696.52 (2365.88) | 1576.63 (2366.16)              | 1578.27 (2333.24) | 1584.90 (2427.51) | 1572.02 (2385.67) | 1618.26 (2339.93) | 0.023  |
| (Index - 150) to (index - 121)                                                        | 1682.18 (2496.57) | 1712.24 (2327.72) | 1610.23 (2357.06)              | 1605.47 (2328.23) | 1627.42 (2390.11) | 1608.27 (2379.19) | 1643.42 (2366.54) | 0.02   |
| (Index - 120) to (index - 91)                                                         | 1797.57 (2546.57) | 1853.62 (2354.72) | 1720.49 (2353.66)              | 1705.03 (2312.94) | 1742.70 (2379.90) | 1701.98 (2365.69) | 1741.34 (2354.94) | 0.026  |
| (Index - 90) to (index - 61)                                                          | 1788.81 (2463.79) | 1811.02 (2346.74) | 1714.34 (2396.49)              | 1699.11 (2351.65) | 1712.35 (2406.90) | 1677.08 (2359.81) | 1736.91 (2391.05) | 0.024  |
| (Index - 60) to (index - 31)                                                          | 1772.63 (2442.43) | 1808.53 (2348.76) | 1696.25 (2316.62)              | 1688.16 (2302.95) | 1701.71 (2302.55) | 1693.59 (2424.70) | 1718.87 (2315.70) | 0.022  |
| (Index - 30) to index                                                                 | 2007.65 (2676.68) | 2064.04 (2509.21) | 1924.16 (2519.22)              | 1908.42 (2597.79) | 1929.68 (2674.92) | 1921.61 (2694.98) | 1946.79 (2541.16) | 0.024  |
| <b>Healthcare utilization (mean (SD))</b>                                             |                   |                   |                                |                   |                   |                   |                   |        |
| Number of physician visits                                                            | 12.57 (9.45)      | 12.58 (10.19)     | 12.35 (9.71)                   | 12.35 (9.57)      | 12.49 (9.17)      | 12.46 (9.56)      | 12.38 (9.46)      | 0.012  |
| Number of distinct prescribed medications                                             | 15.18 (5.79)      | 15.19 (5.94)      | 15.07 (5.81)                   | 15.10 (5.77)      | 15.19 (5.87)      | 15.18 (5.80)      | 15.12 (5.78)      | 0.01   |
| Number of hospitalizations                                                            | 0.32 (0.70)       | 0.32 (0.69)       | 0.32 (0.72)                    | 0.32 (0.69)       | 0.33 (0.70)       | 0.32 (0.66)       | 0.32 (0.71)       | 0.006  |
| Number of hospitalization days                                                        | 1.91 (5.10)       | 1.89 (5.11)       | 1.91 (5.45)                    | 1.87 (4.98)       | 1.96 (4.97)       | 1.91 (4.78)       | 1.89 (5.10)       | 0.006  |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 8. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in Optum© Clinformatics® Data Mart, 2004-2019 (pre-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 36765         | 29202         | 6270                           | 140732          | 12786         | 29549         | 73286         |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 59.43 (13.20) | 52.53 (13.10) | 52.87 (13.28)                  | 55.22 (13.08)   | 52.27 (12.99) | 54.42 (13.37) | 58.02 (12.95) | 0.253 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.045 |
| Unknown                                | 2 (0.0)       | 5 (0.0)       | 3 (0.0)                        | 11 (0.0)        | 3 (0.0)       | 3 (0.0)       | 3 (0.0)       |       |
| Male                                   | 14767 (40.2)  | 12451 (42.6)  | 2501 (39.9)                    | 55313 (39.3)    | 4803 (37.6)   | 12051 (40.8)  | 28100 (38.3)  |       |
| Female                                 | 21996 (59.8)  | 16746 (57.3)  | 3766 (60.1)                    | 85408 (60.7)    | 7980 (62.4)   | 17495 (59.2)  | 45183 (61.7)  |       |
| State                                  |               |               |                                |                 |               |               |               | 0.481 |
| AK                                     | 3 (0.0)       | 5 (0.0)       | 1 (0.0)                        | 32 (0.0)        | 3 (0.0)       | 5 (0.0)       | 27 (0.0)      |       |
| AL                                     | 1170 (3.2)    | 849 (2.9)     | 226 (3.6)                      | 3615 (2.6)      | 286 (2.2)     | 1336 (4.5)    | 3490 (4.8)    |       |
| AR                                     | 490 (1.3)     | 346 (1.2)     | 82 (1.3)                       | 2411 (1.7)      | 116 (0.9)     | 302 (1.0)     | 1520 (2.1)    |       |
| AZ                                     | 1781 (4.8)    | 1905 (6.5)    | 198 (3.2)                      | 5081 (3.6)      | 452 (3.5)     | 1314 (4.4)    | 2496 (3.4)    |       |
| CA                                     | 4118 (11.2)   | 4350 (14.9)   | 156 (2.5)                      | 9161 (6.5)      | 515 (4.0)     | 2247 (7.6)    | 2685 (3.7)    |       |
| CO                                     | 1069 (2.9)    | 773 (2.6)     | 206 (3.3)                      | 4728 (3.4)      | 534 (4.2)     | 1070 (3.6)    | 2062 (2.8)    |       |
| CT                                     | 244 (0.7)     | 155 (0.5)     | 26 (0.4)                       | 989 (0.7)       | 120 (0.9)     | 306 (1.0)     | 341 (0.5)     |       |
| DC                                     | 29 (0.1)      | 8 (0.0)       | 8 (0.1)                        | 180 (0.1)       | 10 (0.1)      | 19 (0.1)      | 50 (0.1)      |       |
| DE                                     | 18 (0.0)      | 37 (0.1)      | 7 (0.1)                        | 119 (0.1)       | 30 (0.2)      | 12 (0.0)      | 64 (0.1)      |       |
| FL                                     | 4612 (12.5)   | 4283 (14.7)   | 651 (10.4)                     | 14055 (10.0)    | 1688 (13.2)   | 3441 (11.6)   | 7864 (10.7)   |       |
| GA                                     | 2172 (5.9)    | 2379 (8.1)    | 300 (4.8)                      | 9390 (6.7)      | 642 (5.0)     | 1812 (6.1)    | 6477 (8.8)    |       |
| HI                                     | 61 (0.2)      | 66 (0.2)      | 9 (0.1)                        | 162 (0.1)       | 12 (0.1)      | 25 (0.1)      | 103 (0.1)     |       |
| IA                                     | 279 (0.8)     | 66 (0.2)      | 62 (1.0)                       | 1463 (1.0)      | 116 (0.9)     | 166 (0.6)     | 410 (0.6)     |       |
| ID                                     | 152 (0.4)     | 160 (0.5)     | 22 (0.4)                       | 628 (0.4)       | 40 (0.3)      | 110 (0.4)     | 280 (0.4)     |       |
| IL                                     | 717 (2.0)     | 325 (1.1)     | 240 (3.8)                      | 3323 (2.4)      | 296 (2.3)     | 386 (1.3)     | 1080 (1.5)    |       |
| IN                                     | 770 (2.1)     | 340 (1.2)     | 257 (4.1)                      | 3992 (2.8)      | 331 (2.6)     | 499 (1.7)     | 1795 (2.4)    |       |
| KS                                     | 113 (0.3)     | 118 (0.4)     | 65 (1.0)                       | 970 (0.7)       | 97 (0.8)      | 138 (0.5)     | 289 (0.4)     |       |
| KY                                     | 294 (0.8)     | 108 (0.4)     | 78 (1.2)                       | 1364 (1.0)      | 182 (1.4)     | 370 (1.3)     | 686 (0.9)     |       |
| LA                                     | 302 (0.8)     | 560 (1.9)     | 186 (3.0)                      | 1876 (1.3)      | 225 (1.8)     | 624 (2.1)     | 825 (1.1)     |       |
| MA                                     | 237 (0.6)     | 107 (0.4)     | 35 (0.6)                       | 787 (0.6)       | 67 (0.5)      | 84 (0.3)      | 292 (0.4)     |       |
| MD                                     | 281 (0.8)     | 456 (1.6)     | 87 (1.4)                       | 2316 (1.6)      | 520 (4.1)     | 314 (1.1)     | 500 (0.7)     |       |
| ME                                     | 54 (0.1)      | 10 (0.0)      | 1 (0.0)                        | 282 (0.2)       | 8 (0.1)       | 12 (0.0)      | 83 (0.1)      |       |
| MI                                     | 150 (0.4)     | 127 (0.4)     | 83 (1.3)                       | 1248 (0.9)      | 159 (1.2)     | 258 (0.9)     | 235 (0.3)     |       |
| MN                                     | 202 (0.5)     | 160 (0.5)     | 98 (1.6)                       | 2288 (1.6)      | 109 (0.9)     | 536 (1.8)     | 559 (0.8)     |       |
| MO                                     | 1285 (3.5)    | 699 (2.4)     | 250 (4.0)                      | 5253 (3.7)      | 412 (3.2)     | 744 (2.5)     | 2711 (3.7)    |       |
| MS                                     | 124 (0.3)     | 212 (0.7)     | 46 (0.7)                       | 872 (0.6)       | 85 (0.7)      | 296 (1.0)     | 526 (0.7)     |       |
| MT                                     | 15 (0.0)      | 9 (0.0)       | 4 (0.1)                        | 81 (0.1)        | 10 (0.1)      | 37 (0.1)      | 33 (0.0)      |       |
| NC                                     | 1953 (5.3)    | 1100 (3.8)    | 355 (5.7)                      | 7689 (5.5)      | 689 (5.4)     | 1603 (5.4)    | 4244 (5.8)    |       |
| ND                                     | 15 (0.0)      | 8 (0.0)       | 7 (0.1)                        | 94 (0.1)        | 8 (0.1)       | 3 (0.0)       | 29 (0.0)      |       |
| NE                                     | 118 (0.3)     | 88 (0.3)      | 37 (0.6)                       | 1189 (0.8)      | 143 (1.1)     | 52 (0.2)      | 315 (0.4)     |       |
| NH                                     | 49 (0.1)      | 24 (0.1)      | 10 (0.2)                       | 257 (0.2)       | 19 (0.1)      | 12 (0.0)      | 99 (0.1)      |       |
| NJ                                     | 250 (0.7)     | 210 (0.7)     | 48 (0.8)                       | 1341 (1.0)      | 234 (1.8)     | 86 (0.3)      | 659 (0.9)     |       |
| NM                                     | 373 (1.0)     | 154 (0.5)     | 49 (0.8)                       | 649 (0.5)       | 41 (0.3)      | 196 (0.7)     | 458 (0.6)     |       |
| NV                                     | 396 (1.1)     | 519 (1.8)     | 18 (0.3)                       | 862 (0.6)       | 43 (0.3)      | 217 (0.7)     | 763 (1.0)     |       |
| NY                                     | 893 (2.4)     | 317 (1.1)     | 105 (1.7)                      | 2683 (1.9)      | 271 (2.1)     | 318 (1.1)     | 1401 (1.9)    |       |
| OH                                     | 1111 (3.0)    | 802 (2.7)     | 605 (9.6)                      | 7406 (5.3)      | 799 (6.2)     | 2248 (7.6)    | 3633 (5.0)    |       |
| OK                                     | 709 (1.9)     | 790 (2.7)     | 206 (3.3)                      | 3003 (2.1)      | 237 (1.9)     | 400 (1.4)     | 1658 (2.3)    |       |
| OR                                     | 481 (1.3)     | 163 (0.6)     | 23 (0.4)                       | 1875 (1.3)      | 114 (0.9)     | 304 (1.0)     | 818 (1.1)     |       |
| PA                                     | 282 (0.8)     | 234 (0.8)     | 53 (0.8)                       | 1342 (1.0)      | 153 (1.2)     | 255 (0.9)     | 350 (0.5)     |       |
| RI                                     | 236 (0.6)     | 259 (0.9)     | 44 (0.7)                       | 1217 (0.9)      | 132 (1.0)     | 191 (0.6)     | 231 (0.3)     |       |

|                              | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|------------------------------|--------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| SC                           | 897 (2.4)    | 371 (1.3)    | 101 (1.6)                      | 3735 (2.7)      | 153 (1.2)   | 231 (0.8)     | 2084 (2.8)   |       |
| SD                           | 16 (0.0)     | 8 (0.0)      | 3 (0.0)                        | 63 (0.0)        | 7 (0.1)     | 5 (0.0)       | 11 (0.0)     |       |
| TN                           | 994 (2.7)    | 659 (2.3)    | 211 (3.4)                      | 3238 (2.3)      | 269 (2.1)   | 1073 (3.6)    | 2100 (2.9)   |       |
| TX                           | 4280 (11.6)  | 3416 (11.7)  | 597 (9.5)                      | 15537 (11.0)    | 1486 (11.6) | 3437 (11.6)   | 10342 (14.1) |       |
| UT                           | 434 (1.2)    | 477 (1.6)    | 62 (1.0)                       | 1722 (1.2)      | 124 (1.0)   | 378 (1.3)     | 1037 (1.4)   |       |
| VA                           | 569 (1.5)    | 314 (1.1)    | 166 (2.6)                      | 2663 (1.9)      | 325 (2.5)   | 503 (1.7)     | 1076 (1.5)   |       |
| VT                           | 31 (0.1)     | 6 (0.0)      | 1 (0.0)                        | 67 (0.0)        | 2 (0.0)     | 18 (0.1)      | 41 (0.1)     |       |
| WA                           | 938 (2.6)    | 316 (1.1)    | 25 (0.4)                       | 2917 (2.1)      | 94 (0.7)    | 1163 (3.9)    | 1636 (2.2)   |       |
| WI                           | 939 (2.6)    | 281 (1.0)    | 139 (2.2)                      | 4000 (2.8)      | 305 (2.4)   | 287 (1.0)     | 2658 (3.6)   |       |
| WV                           | 47 (0.1)     | 56 (0.2)     | 9 (0.1)                        | 366 (0.3)       | 56 (0.4)    | 90 (0.3)      | 133 (0.2)    |       |
| WY                           | 12 (0.0)     | 17 (0.1)     | 12 (0.2)                       | 151 (0.1)       | 17 (0.1)    | 16 (0.1)      | 27 (0.0)     |       |
| Year                         |              |              |                                |                 |             |               |              | 0.723 |
| 2004                         | 200 (0.5)    | 735 (2.5)    | 174 (2.8)                      | 1786 (1.3)      | 606 (4.7)   | 374 (1.3)     | 537 (0.7)    |       |
| 2005                         | 490 (1.3)    | 1553 (5.3)   | 356 (5.7)                      | 4131 (2.9)      | 1062 (8.3)  | 821 (2.8)     | 1108 (1.5)   |       |
| 2006                         | 731 (2.0)    | 2498 (8.6)   | 420 (6.7)                      | 6267 (4.5)      | 1465 (11.5) | 1346 (4.6)    | 1452 (2.0)   |       |
| 2007                         | 876 (2.4)    | 2652 (9.1)   | 413 (6.6)                      | 6773 (4.8)      | 1464 (11.5) | 1575 (5.3)    | 1671 (2.3)   |       |
| 2008                         | 823 (2.2)    | 2792 (9.6)   | 360 (5.7)                      | 7607 (5.4)      | 1383 (10.8) | 1580 (5.3)    | 1720 (2.3)   |       |
| 2009                         | 1010 (2.7)   | 2891 (9.9)   | 422 (6.7)                      | 8718 (6.2)      | 1130 (8.8)  | 1862 (6.3)    | 1934 (2.6)   |       |
| 2010                         | 1176 (3.2)   | 2887 (9.9)   | 498 (7.9)                      | 9373 (6.7)      | 1038 (8.1)  | 2254 (7.6)    | 2078 (2.8)   |       |
| 2011                         | 1350 (3.7)   | 2833 (9.7)   | 505 (8.1)                      | 11007 (7.8)     | 1005 (7.9)  | 2778 (9.4)    | 2534 (3.5)   |       |
| 2012                         | 1718 (4.7)   | 2489 (8.5)   | 576 (9.2)                      | 11867 (8.4)     | 925 (7.2)   | 3077 (10.4)   | 3103 (4.2)   |       |
| 2013                         | 2175 (5.9)   | 1886 (6.5)   | 476 (7.6)                      | 11329 (8.1)     | 776 (6.1)   | 2649 (9.0)    | 3725 (5.1)   |       |
| 2014                         | 3300 (9.0)   | 1144 (3.9)   | 291 (4.6)                      | 6045 (4.3)      | 504 (3.9)   | 1817 (6.1)    | 5853 (8.0)   |       |
| 2015                         | 3656 (9.9)   | 1040 (3.6)   | 312 (5.0)                      | 6020 (4.3)      | 382 (3.0)   | 1763 (6.0)    | 7372 (10.1)  |       |
| 2016                         | 4707 (12.8)  | 1205 (4.1)   | 336 (5.4)                      | 6900 (4.9)      | 379 (3.0)   | 2078 (7.0)    | 10256 (14.0) |       |
| 2017                         | 5199 (14.1)  | 1600 (5.5)   | 418 (6.7)                      | 17856 (12.7)    | 312 (2.4)   | 2287 (7.7)    | 10561 (14.4) |       |
| 2018                         | 4911 (13.4)  | 547 (1.9)    | 385 (6.1)                      | 13270 (9.4)     | 174 (1.4)   | 1597 (5.4)    | 9821 (13.4)  |       |
| 2019                         | 4443 (12.1)  | 450 (1.5)    | 328 (5.2)                      | 11783 (8.4)     | 181 (1.4)   | 1691 (5.7)    | 9561 (13.0)  |       |
| <b>Comorbidities (n (%))</b> |              |              |                                |                 |             |               |              |       |
| Opioid dependence            | 3021 (8.2)   | 1026 (3.5)   | 302 (4.8)                      | 6659 (4.7)      | 377 (2.9)   | 1782 (6.0)    | 5955 (8.1)   | 0.110 |
| Opioid abuse                 | 177 (0.5)    | 115 (0.4)    | 27 (0.4)                       | 482 (0.3)       | 27 (0.2)    | 147 (0.5)     | 307 (0.4)    | 0.019 |
| Alcohol abuse                | 898 (2.4)    | 457 (1.6)    | 109 (1.7)                      | 2710 (1.9)      | 181 (1.4)   | 737 (2.5)     | 1420 (1.9)   | 0.036 |
| Tobacco use                  | 7676 (20.9)  | 4447 (15.2)  | 1094 (17.4)                    | 27846 (19.8)    | 1692 (13.2) | 5837 (19.8)   | 15585 (21.3) | 0.095 |
| Other drug abuse             | 1222 (3.3)   | 917 (3.1)    | 212 (3.4)                      | 3672 (2.6)      | 363 (2.8)   | 1199 (4.1)    | 2370 (3.2)   | 0.030 |
| Anxiety                      | 9085 (24.7)  | 5839 (20.0)  | 1374 (21.9)                    | 30930 (22.0)    | 2245 (17.6) | 6563 (22.2)   | 18576 (25.3) | 0.077 |
| Bipolar disorder             | 1794 (4.9)   | 979 (3.4)    | 260 (4.1)                      | 5481 (3.9)      | 422 (3.3)   | 1204 (4.1)    | 3697 (5.0)   | 0.041 |
| Bone fracture                | 2883 (7.8)   | 1539 (5.3)   | 362 (5.8)                      | 9576 (6.8)      | 786 (6.1)   | 2104 (7.1)    | 5233 (7.1)   | 0.044 |
| Cancer                       | 2888 (7.9)   | 1371 (4.7)   | 285 (4.5)                      | 8731 (6.2)      | 731 (5.7)   | 1686 (5.7)    | 4420 (6.0)   | 0.053 |
| Chronic renal insufficiency  | 3886 (10.6)  | 1067 (3.7)   | 304 (4.8)                      | 9510 (6.8)      | 468 (3.7)   | 1702 (5.8)    | 6806 (9.3)   | 0.130 |
| Congestive heart failure     | 2993 (8.1)   | 1125 (3.9)   | 296 (4.7)                      | 8224 (5.8)      | 508 (4.0)   | 1559 (5.3)    | 5197 (7.1)   | 0.083 |
| COPD/asthma/oxygen           | 9269 (25.2)  | 4988 (17.1)  | 1116 (17.8)                    | 29312 (20.8)    | 2024 (15.8) | 5580 (18.9)   | 18143 (24.8) | 0.110 |
| Dementia                     | 1529 (4.2)   | 351 (1.2)    | 104 (1.7)                      | 2816 (2.0)      | 206 (1.6)   | 643 (2.2)     | 1915 (2.6)   | 0.071 |
| Depression                   | 8332 (22.7)  | 5838 (20.0)  | 1347 (21.5)                    | 29232 (20.8)    | 2844 (22.2) | 6691 (22.6)   | 15842 (21.6) | 0.029 |
| Diabetes                     | 10187 (27.7) | 4906 (16.8)  | 1213 (19.3)                    | 33313 (23.7)    | 2082 (16.3) | 6145 (20.8)   | 19835 (27.1) | 0.137 |
| Epilepsy                     | 1025 (2.8)   | 593 (2.0)    | 144 (2.3)                      | 2781 (2.0)      | 267 (2.1)   | 665 (2.3)     | 1606 (2.2)   | 0.020 |
| HIV                          | 198 (0.5)    | 108 (0.4)    | 22 (0.4)                       | 694 (0.5)       | 42 (0.3)    | 115 (0.4)     | 391 (0.5)    | 0.016 |
| Intentional self-harm        | 39 (0.1)     | 22 (0.1)     | 3 (0.0)                        | 131 (0.1)       | 8 (0.1)     | 17 (0.1)      | 66 (0.1)     | 0.009 |
| Liver disease                | 2731 (7.4)   | 1514 (5.2)   | 324 (5.2)                      | 8836 (6.3)      | 628 (4.9)   | 1783 (6.0)    | 4781 (6.5)   | 0.045 |
| Musculoskeletal injury       | 2850 (7.8)   | 2687 (9.2)   | 653 (10.4)                     | 14036 (10.0)    | 1328 (10.4) | 2900 (9.8)    | 6060 (8.3)   | 0.043 |
| Multiple sclerosis           | 1089 (3.0)   | 153 (0.5)    | 24 (0.4)                       | 829 (0.6)       | 92 (0.7)    | 146 (0.5)     | 704 (1.0)    | 0.073 |
| Obesity                      | 6204 (16.9)  | 2451 (8.4)   | 670 (10.7)                     | 20131 (14.3)    | 1036 (8.1)  | 3933 (13.3)   | 12883 (17.6) | 0.142 |
| Pneumonia                    | 1065 (2.9)   | 760 (2.6)    | 137 (2.2)                      | 3720 (2.6)      | 358 (2.8)   | 833 (2.8)     | 1673 (2.3)   | 0.021 |

|                                                | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|------------------------------------------------|--------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| Psychosis                                      | 800 (2.2)    | 306 (1.0)    | 91 (1.5)                       | 2043 (1.5)      | 125 (1.0)   | 470 (1.6)     | 1301 (1.8)   | 0.041 |
| Renal dysfunction                              | 4619 (12.6)  | 1787 (6.1)   | 444 (7.1)                      | 12486 (8.9)     | 828 (6.5)   | 2443 (8.3)    | 7962 (10.9)  | 0.100 |
| Spasticity                                     | 9611 (26.1)  | 4563 (15.6)  | 1047 (16.7)                    | 23710 (16.8)    | 2242 (17.5) | 5440 (18.4)   | 14500 (19.8) | 0.094 |
| Urinary calculus                               | 1353 (3.7)   | 788 (2.7)    | 224 (3.6)                      | 4826 (3.4)      | 401 (3.1)   | 988 (3.3)     | 2421 (3.3)   | 0.021 |
| Urinary tract infection                        | 4588 (12.5)  | 2665 (9.1)   | 606 (9.7)                      | 14365 (10.2)    | 1313 (10.3) | 3010 (10.2)   | 7427 (10.1)  | 0.035 |
| <b>Pain conditions (n (%))</b>                 |              |              |                                |                 |             |               |              |       |
| Abdominal pain                                 | 6610 (18.0)  | 4455 (15.3)  | 1098 (17.5)                    | 25173 (17.9)    | 2289 (17.9) | 5149 (17.4)   | 12527 (17.1) | 0.026 |
| Back and neck pain                             | 27539 (74.9) | 20238 (69.3) | 4688 (74.8)                    | 102251 (72.7)   | 9508 (74.4) | 22549 (76.3)  | 58882 (80.3) | 0.090 |
| Back pain without radiculopathy                | 24800 (67.5) | 18759 (64.2) | 4302 (68.6)                    | 93570 (66.5)    | 8786 (68.7) | 20812 (70.4)  | 53082 (72.4) | 0.069 |
| Back pain with radiculopathy                   | 11280 (30.7) | 6985 (23.9)  | 1650 (26.3)                    | 36838 (26.2)    | 3359 (26.3) | 9002 (30.5)   | 25243 (34.4) | 0.094 |
| Dental pain                                    | 317 (0.9)    | 291 (1.0)    | 69 (1.1)                       | 1273 (0.9)      | 96 (0.8)    | 256 (0.9)     | 591 (0.8)    | 0.015 |
| Diabetic neuropathy                            | 3512 (9.6)   | 1016 (3.5)   | 255 (4.1)                      | 8928 (6.3)      | 395 (3.1)   | 1464 (5.0)    | 6509 (8.9)   | 0.131 |
| Fibromyalgia                                   | 5259 (14.3)  | 4462 (15.3)  | 1059 (16.9)                    | 19948 (14.2)    | 2419 (18.9) | 4471 (15.1)   | 11389 (15.5) | 0.051 |
| Headache                                       | 5851 (15.9)  | 4814 (16.5)  | 1279 (20.4)                    | 23553 (16.7)    | 2318 (18.1) | 4922 (16.7)   | 12632 (17.2) | 0.043 |
| Osteoarthritis                                 | 11425 (31.1) | 6467 (22.1)  | 1644 (26.2)                    | 40313 (28.6)    | 3045 (23.8) | 8107 (27.4)   | 23554 (32.1) | 0.101 |
| Rheumatoid arthritis                           | 2100 (5.7)   | 1279 (4.4)   | 329 (5.2)                      | 8072 (5.7)      | 716 (5.6)   | 1533 (5.2)    | 4362 (6.0)   | 0.027 |
| Postherpetic neuralgia                         | 177 (0.5)    | 67 (0.2)     | 17 (0.3)                       | 409 (0.3)       | 45 (0.4)    | 94 (0.3)      | 250 (0.3)    | 0.016 |
| Other arthritis                                | 22802 (62.0) | 15145 (51.9) | 3529 (56.3)                    | 82774 (58.8)    | 7241 (56.6) | 17498 (59.2)  | 45062 (61.5) | 0.084 |
| Other neuropathy                               | 17365 (47.2) | 10949 (37.5) | 2442 (38.9)                    | 56380 (40.1)    | 5223 (40.8) | 13405 (45.4)  | 36748 (50.1) | 0.115 |
| Other unspecified pain                         | 23194 (63.1) | 10461 (35.8) | 2930 (46.7)                    | 70815 (50.3)    | 4555 (35.6) | 15151 (51.3)  | 48385 (66.0) | 0.295 |
| <b>Other prescription fills (n (%))</b>        |              |              |                                |                 |             |               |              |       |
| Antibiotics                                    | 20534 (55.9) | 16152 (55.3) | 3505 (55.9)                    | 79094 (56.2)    | 7325 (57.3) | 16470 (55.7)  | 40236 (54.9) | 0.017 |
| Anticonvulsants                                | 4367 (11.9)  | 2495 (8.5)   | 618 (9.9)                      | 12293 (8.7)     | 1353 (10.6) | 2767 (9.4)    | 8210 (11.2)  | 0.051 |
| Antidepressants, SSRIs                         | 9920 (27.0)  | 7048 (24.1)  | 1640 (26.2)                    | 36275 (25.8)    | 3443 (26.9) | 7666 (25.9)   | 19403 (26.5) | 0.025 |
| Antidepressants, SNRIs                         | 6696 (18.2)  | 3841 (13.2)  | 976 (15.6)                     | 20835 (14.8)    | 2221 (17.4) | 4454 (15.1)   | 13526 (18.5) | 0.065 |
| Antidepressants, TCAs                          | 3538 (9.6)   | 2499 (8.6)   | 602 (9.6)                      | 12099 (8.6)     | 1182 (9.2)  | 2651 (9.0)    | 6798 (9.3)   | 0.018 |
| Antidepressants, other                         | 7514 (20.4)  | 4255 (14.6)  | 981 (15.6)                     | 23495 (16.7)    | 2054 (16.1) | 5109 (17.3)   | 14652 (20.0) | 0.069 |
| Antidiabetics                                  | 7996 (21.7)  | 3818 (13.1)  | 958 (15.3)                     | 26509 (18.8)    | 1640 (12.8) | 4896 (16.6)   | 15797 (21.6) | 0.120 |
| Antipsychotics, atypical                       | 2773 (7.5)   | 1523 (5.2)   | 377 (6.0)                      | 7978 (5.7)      | 694 (5.4)   | 1751 (5.9)    | 5257 (7.2)   | 0.042 |
| Antipsychotics, typical                        | 932 (2.5)    | 584 (2.0)    | 128 (2.0)                      | 2798 (2.0)      | 272 (2.1)   | 565 (1.9)     | 1086 (1.5)   | 0.025 |
| Barbiturates                                   | 88 (0.2)     | 189 (0.6)    | 27 (0.4)                       | 478 (0.3)       | 83 (0.6)    | 138 (0.5)     | 156 (0.2)    | 0.033 |
| Benzodiazepines                                | 14007 (38.1) | 12426 (42.6) | 2311 (36.9)                    | 48695 (34.6)    | 4843 (37.9) | 10269 (34.8)  | 27496 (37.5) | 0.062 |
| CNS stimulants                                 | 1347 (3.7)   | 1304 (4.5)   | 255 (4.1)                      | 4862 (3.5)      | 544 (4.3)   | 1183 (4.0)    | 2645 (3.6)   | 0.023 |
| Dementia agents                                | 808 (2.2)    | 206 (0.7)    | 51 (0.8)                       | 1528 (1.1)      | 103 (0.8)   | 349 (1.2)     | 1113 (1.5)   | 0.053 |
| Gabapentinoids                                 | 15029 (40.9) | 6579 (22.5)  | 1637 (26.1)                    | 41543 (29.5)    | 3204 (25.1) | 9151 (31.0)   | 29238 (39.9) | 0.186 |
| Lithium                                        | 173 (0.5)    | 169 (0.6)    | 36 (0.6)                       | 603 (0.4)       | 61 (0.5)    | 140 (0.5)     | 373 (0.5)    | 0.009 |
| Multiple sclerosis agents                      | 442 (1.2)    | 44 (0.2)     | 4 (0.1)                        | 268 (0.2)       | 44 (0.3)    | 53 (0.2)      | 293 (0.4)    | 0.057 |
| NSAIDs                                         | 12871 (35.0) | 10097 (34.6) | 2736 (43.6)                    | 56899 (40.4)    | 5560 (43.5) | 12217 (41.3)  | 28174 (38.4) | 0.092 |
| Other sedative hypnotics                       | 4850 (13.2)  | 5461 (18.7)  | 996 (15.9)                     | 21992 (15.6)    | 2706 (21.2) | 4675 (15.8)   | 10143 (13.8) | 0.087 |
| Smoking cessation                              | 3061 (8.3)   | 2090 (7.2)   | 456 (7.3)                      | 11475 (8.2)     | 1087 (8.5)  | 2355 (8.0)    | 6256 (8.5)   | 0.025 |
| Triptans                                       | 1492 (4.1)   | 1448 (5.0)   | 348 (5.6)                      | 6473 (4.6)      | 833 (6.5)   | 1290 (4.4)    | 3414 (4.7)   | 0.044 |
| Other CNS depressants                          | 297 (0.8)    | 151 (0.5)    | 31 (0.5)                       | 761 (0.5)       | 91 (0.7)    | 142 (0.5)     | 606 (0.8)    | 0.022 |
| <b>Prescription opioid utilization (n (%))</b> |              |              |                                |                 |             |               |              |       |
| Prescription opioid on index date              |              |              |                                |                 |             |               |              |       |
| Buprenorphine                                  | 221 (0.6)    | 92 (0.3)     | 32 (0.5)                       | 540 (0.4)       | 56 (0.4)    | 207 (0.7)     | 430 (0.6)    | 0.024 |
| Butorphanol                                    | 69 (0.2)     | 105 (0.4)    | 34 (0.5)                       | 428 (0.3)       | 60 (0.5)    | 89 (0.3)      | 184 (0.3)    | 0.025 |
| Codeine                                        | 1155 (3.1)   | 1184 (4.1)   | 287 (4.6)                      | 5838 (4.1)      | 518 (4.1)   | 1184 (4.0)    | 2379 (3.2)   | 0.031 |
| Dihydrocodeine                                 | 11 (0.0)     | 16 (0.1)     | 5 (0.1)                        | 69 (0.0)        | 10 (0.1)    | 14 (0.0)      | 26 (0.0)     | 0.010 |
| Fentanyl                                       | 2471 (6.7)   | 1635 (5.6)   | 318 (5.1)                      | 6731 (4.8)      | 919 (7.2)   | 1598 (5.4)    | 4025 (5.5)   | 0.043 |
| Hydrocodone                                    | 17132 (46.6) | 17701 (60.6) | 3491 (55.7)                    | 77439 (55.0)    | 6866 (53.7) | 16226 (54.9)  | 35334 (48.2) | 0.112 |
| Hydromorphone                                  | 1185 (3.2)   | 765 (2.6)    | 121 (1.9)                      | 3032 (2.2)      | 284 (2.2)   | 868 (2.9)     | 1923 (2.6)   | 0.035 |
| Levorphanol                                    | 13 (0.0)     | 2 (0.0)      | 3 (0.0)                        | 31 (0.0)        | 1 (0.0)     | 4 (0.0)       | 31 (0.0)     | 0.013 |

|                                                                                       | Baclofen          | Carisoprodol      | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone        | Methocarbamol     | Tizanidine        | SMD   |
|---------------------------------------------------------------------------------------|-------------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|-------------------|-------|
| Meperidine                                                                            | 44 (0.1)          | 123 (0.4)         | 12 (0.2)                       | 302 (0.2)         | 41 (0.3)          | 88 (0.3)          | 96 (0.1)          | 0.027 |
| Methadone                                                                             | 1520 (4.1)        | 1132 (3.9)        | 181 (2.9)                      | 3768 (2.7)        | 418 (3.3)         | 895 (3.0)         | 2494 (3.4)        | 0.035 |
| Morphine                                                                              | 3744 (10.2)       | 2213 (7.6)        | 398 (6.3)                      | 9432 (6.7)        | 900 (7.0)         | 2293 (7.8)        | 6988 (9.5)        | 0.062 |
| Opium                                                                                 | 12 (0.0)          | 5 (0.0)           | 1 (0.0)                        | 57 (0.0)          | 4 (0.0)           | 13 (0.0)          | 10 (0.0)          | 0.009 |
| Oxycodone                                                                             | 13425 (36.5)      | 10947 (37.5)      | 2067 (33.0)                    | 48160 (34.2)      | 4250 (33.2)       | 11066 (37.4)      | 27043 (36.9)      | 0.049 |
| Oxymorphone                                                                           | 557 (1.5)         | 400 (1.4)         | 64 (1.0)                       | 1366 (1.0)        | 184 (1.4)         | 313 (1.1)         | 1215 (1.7)        | 0.029 |
| Pentazocine                                                                           | 21 (0.1)          | 51 (0.2)          | 25 (0.4)                       | 183 (0.1)         | 36 (0.3)          | 51 (0.2)          | 67 (0.1)          | 0.031 |
| Propoxyphene                                                                          | 100 (0.3)         | 408 (1.4)         | 88 (1.4)                       | 1308 (0.9)        | 242 (1.9)         | 253 (0.9)         | 208 (0.3)         | 0.075 |
| Tapentadol                                                                            | 328 (0.9)         | 125 (0.4)         | 60 (1.0)                       | 814 (0.6)         | 96 (0.8)          | 260 (0.9)         | 758 (1.0)         | 0.030 |
| Tramadol                                                                              | 6450 (17.5)       | 3868 (13.2)       | 1375 (21.9)                    | 29263 (20.8)      | 2902 (22.7)       | 5902 (20.0)       | 13039 (17.8)      | 0.099 |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 175.46 (14.88)    | 174.30 (16.42)    | 174.88 (15.65)                 | 174.61 (15.95)    | 173.61 (17.15)    | 174.10 (16.43)    | 175.84 (14.29)    | 0.060 |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                   |                   |                                |                   |                   |                   |                   |       |
| (Index - 180) to (index - 151)                                                        | 2121.14 (3274.27) | 2358.81 (3782.31) | 1871.66 (2992.89)              | 1745.96 (2807.82) | 1965.82 (3263.65) | 1841.99 (2946.14) | 2009.16 (2975.36) | 0.075 |
| (Index - 150) to (index - 121)                                                        | 2164.79 (3288.32) | 2442.72 (3735.94) | 1921.22 (3039.58)              | 1792.27 (2820.50) | 2028.34 (3237.51) | 1902.59 (2991.53) | 2049.50 (2997.21) | 0.077 |
| (Index - 120) to (index - 91)                                                         | 2321.81 (3402.44) | 2652.60 (3888.15) | 2047.60 (3021.90)              | 1920.84 (2868.87) | 2194.51 (3368.42) | 2047.91 (2997.13) | 2180.17 (3060.61) | 0.083 |
| (Index - 90) to (index - 61)                                                          | 2312.15 (3340.34) | 2663.63 (3903.58) | 2066.12 (3135.43)              | 1931.14 (2875.97) | 2229.62 (3393.16) | 2056.87 (3005.05) | 2169.66 (3055.88) | 0.082 |
| (Index - 60) to (index - 31)                                                          | 2301.29 (3359.11) | 2694.70 (3934.81) | 2085.28 (3173.76)              | 1934.93 (2873.58) | 2236.01 (3355.67) | 2086.26 (3068.03) | 2145.21 (3013.61) | 0.081 |
| (Index - 30) to index                                                                 | 2796.90 (4102.91) | 3504.62 (5195.75) | 2453.76 (3683.44)              | 2299.16 (3469.44) | 2668.04 (3974.18) | 2486.34 (3552.45) | 2664.65 (3813.63) | 0.101 |
| <b>Healthcare utilization (mean (SD))</b>                                             |                   |                   |                                |                   |                   |                   |                   |       |
| Number of physician visits                                                            | 8.77 (6.41)       | 7.22 (5.92)       | 8.03 (6.15)                    | 7.92 (6.00)       | 8.15 (6.31)       | 8.19 (6.13)       | 8.57 (5.78)       | 0.095 |
| Number of distinct prescribed medications                                             | 12.51 (6.02)      | 10.69 (5.56)      | 11.32 (5.85)                   | 11.56 (5.81)      | 11.48 (5.72)      | 11.45 (5.71)      | 12.29 (5.99)      | 0.122 |
| Number of hospitalizations                                                            | 0.37 (3.50)       | 0.21 (0.86)       | 0.20 (0.84)                    | 0.26 (1.68)       | 0.24 (1.06)       | 0.34 (1.84)       | 0.23 (1.68)       | 0.043 |
| Number of hospitalization days                                                        | 1.06 (68.14)      | 0.92 (3.47)       | 0.89 (3.51)                    | 1.11 (4.29)       | 1.09 (4.00)       | 1.50 (5.12)       | 0.99 (4.19)       | 0.042 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 9. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in Optum© Clinformatics® Data Mart, 2004-2019 (post-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 5144.37       | 5103.86       | 5166.71                        | 5137.31         | 5126.98       | 5130.42       | 5217.48       |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 51.77 (13.62) | 53.17 (12.76) | 53.52 (13.21)                  | 53.32 (12.86)   | 52.71 (12.82) | 53.69 (13.15) | 51.14 (13.24) | 0.085 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.015 |
| Unknown                                | 1.0 (0.0)     | 1.1 (0.0)     | 0.9 (0.0)                      | 1.1 (0.0)       | 0.7 (0.0)     | 1.2 (0.0)     | 1.3 (0.0)     |       |
| Male                                   | 2142.9 (41.7) | 2018.0 (39.5) | 2059.1 (39.9)                  | 2049.6 (39.9)   | 2033.6 (39.7) | 2049.0 (39.9) | 2090.4 (40.1) |       |
| Female                                 | 3000.5 (58.3) | 3084.7 (60.4) | 3106.6 (60.1)                  | 3086.7 (60.1)   | 3092.7 (60.3) | 3080.2 (60.0) | 3125.8 (59.9) |       |
| State                                  |               |               |                                |                 |               |               |               | 0.090 |
| AK                                     | 0.3 (0.0)     | 1.6 (0.0)     | 1.0 (0.0)                      | 0.8 (0.0)       | 1.4 (0.0)     | 0.6 (0.0)     | 1.5 (0.0)     |       |
| AL                                     | 132.0 (2.6)   | 174.5 (3.4)   | 194.9 (3.8)                    | 181.2 (3.5)     | 170.9 (3.3)   | 203.1 (4.0)   | 155.4 (3.0)   |       |
| AR                                     | 60.8 (1.2)    | 58.7 (1.2)    | 53.2 (1.0)                     | 56.2 (1.1)      | 53.3 (1.0)    | 62.0 (1.2)    | 68.4 (1.3)    |       |
| AZ                                     | 200.2 (3.9)   | 179.3 (3.5)   | 179.4 (3.5)                    | 187.3 (3.6)     | 189.8 (3.7)   | 186.8 (3.6)   | 159.3 (3.1)   |       |
| CA                                     | 137.6 (2.7)   | 155.0 (3.0)   | 153.0 (3.0)                    | 152.9 (3.0)     | 151.3 (3.0)   | 159.0 (3.1)   | 125.5 (2.4)   |       |
| CO                                     | 176.5 (3.4)   | 190.1 (3.7)   | 185.4 (3.6)                    | 186.5 (3.6)     | 192.7 (3.8)   | 178.9 (3.5)   | 200.7 (3.8)   |       |
| CT                                     | 24.3 (0.5)    | 25.0 (0.5)    | 25.4 (0.5)                     | 25.2 (0.5)      | 31.0 (0.6)    | 26.1 (0.5)    | 27.6 (0.5)    |       |
| DC                                     | 6.3 (0.1)     | 3.9 (0.1)     | 3.9 (0.1)                      | 4.6 (0.1)       | 4.5 (0.1)     | 5.3 (0.1)     | 3.1 (0.1)     |       |
| DE                                     | 5.5 (0.1)     | 7.1 (0.1)     | 5.4 (0.1)                      | 5.9 (0.1)       | 6.2 (0.1)     | 6.7 (0.1)     | 8.3 (0.2)     |       |
| FL                                     | 600.4 (11.7)  | 584.3 (11.4)  | 604.4 (11.7)                   | 604.4 (11.8)    | 584.4 (11.4)  | 610.0 (11.9)  | 645.3 (12.4)  |       |
| GA                                     | 274.3 (5.3)   | 265.0 (5.2)   | 268.6 (5.2)                    | 263.7 (5.1)     | 248.9 (4.9)   | 272.7 (5.3)   | 282.0 (5.4)   |       |
| HI                                     | 5.1 (0.1)     | 7.9 (0.2)     | 9.0 (0.2)                      | 8.2 (0.2)       | 7.3 (0.1)     | 8.5 (0.2)     | 5.8 (0.1)     |       |
| IA                                     | 48.7 (0.9)    | 49.4 (1.0)    | 48.1 (0.9)                     | 48.2 (0.9)      | 49.1 (1.0)    | 47.7 (0.9)    | 50.6 (1.0)    |       |
| ID                                     | 20.6 (0.4)    | 19.9 (0.4)    | 20.2 (0.4)                     | 18.7 (0.4)      | 18.5 (0.4)    | 18.5 (0.4)    | 21.5 (0.4)    |       |
| IL                                     | 172.9 (3.4)   | 167.2 (3.3)   | 160.9 (3.1)                    | 166.1 (3.2)     | 165.4 (3.2)   | 163.0 (3.2)   | 141.5 (2.7)   |       |
| IN                                     | 192.5 (3.7)   | 160.4 (3.1)   | 180.2 (3.5)                    | 169.9 (3.3)     | 168.5 (3.3)   | 171.2 (3.3)   | 191.1 (3.7)   |       |
| KS                                     | 43.4 (0.8)    | 34.0 (0.7)    | 37.9 (0.7)                     | 40.1 (0.8)      | 41.7 (0.8)    | 36.5 (0.7)    | 48.6 (0.9)    |       |
| KY                                     | 95.2 (1.9)    | 70.2 (1.4)    | 66.1 (1.3)                     | 66.6 (1.3)      | 72.3 (1.4)    | 63.9 (1.2)    | 77.4 (1.5)    |       |
| LA                                     | 138.5 (2.7)   | 107.5 (2.1)   | 116.0 (2.2)                    | 115.2 (2.2)     | 116.2 (2.3)   | 100.5 (2.0)   | 133.4 (2.6)   |       |
| MA                                     | 37.1 (0.7)    | 34.3 (0.7)    | 32.2 (0.6)                     | 31.2 (0.6)      | 30.3 (0.6)    | 28.3 (0.6)    | 33.2 (0.6)    |       |
| MD                                     | 79.5 (1.5)    | 80.3 (1.6)    | 80.3 (1.6)                     | 81.2 (1.6)      | 90.1 (1.8)    | 78.9 (1.5)    | 98.6 (1.9)    |       |
| ME                                     | 1.2 (0.0)     | 1.5 (0.0)     | 1.0 (0.0)                      | 1.0 (0.0)       | 0.8 (0.0)     | 0.8 (0.0)     | 0.9 (0.0)     |       |
| MI                                     | 52.5 (1.0)    | 53.0 (1.0)    | 53.7 (1.0)                     | 57.3 (1.1)      | 63.8 (1.2)    | 48.6 (0.9)    | 68.0 (1.3)    |       |
| MN                                     | 72.9 (1.4)    | 76.5 (1.5)    | 67.6 (1.3)                     | 68.6 (1.3)      | 81.0 (1.6)    | 67.1 (1.3)    | 78.7 (1.5)    |       |
| MO                                     | 179.6 (3.5)   | 210.8 (4.1)   | 217.7 (4.2)                    | 205.5 (4.0)     | 206.6 (4.0)   | 220.4 (4.3)   | 200.4 (3.8)   |       |
| MS                                     | 42.5 (0.8)    | 35.3 (0.7)    | 37.8 (0.7)                     | 38.5 (0.7)      | 36.8 (0.7)    | 33.9 (0.7)    | 46.1 (0.9)    |       |
| MT                                     | 4.4 (0.1)     | 4.5 (0.1)     | 2.5 (0.0)                      | 3.9 (0.1)       | 3.9 (0.1)     | 3.4 (0.1)     | 5.1 (0.1)     |       |
| NC                                     | 274.1 (5.3)   | 312.0 (6.1)   | 310.1 (6.0)                    | 315.1 (6.1)     | 289.2 (5.6)   | 305.0 (5.9)   | 270.2 (5.2)   |       |
| ND                                     | 3.7 (0.1)     | 4.2 (0.1)     | 2.8 (0.1)                      | 2.9 (0.1)       | 3.4 (0.1)     | 1.7 (0.0)     | 2.8 (0.1)     |       |
| NE                                     | 30.2 (0.6)    | 33.2 (0.7)    | 29.3 (0.6)                     | 30.5 (0.6)      | 30.0 (0.6)    | 31.5 (0.6)    | 31.2 (0.6)    |       |
| NH                                     | 8.0 (0.2)     | 8.6 (0.2)     | 8.7 (0.2)                      | 7.7 (0.1)       | 9.3 (0.2)     | 8.5 (0.2)     | 9.7 (0.2)     |       |
| NJ                                     | 45.8 (0.9)    | 47.4 (0.9)    | 44.4 (0.9)                     | 43.1 (0.8)      | 46.4 (0.9)    | 45.7 (0.9)    | 50.6 (1.0)    |       |
| NM                                     | 37.5 (0.7)    | 35.3 (0.7)    | 39.5 (0.8)                     | 34.6 (0.7)      | 34.3 (0.7)    | 34.3 (0.7)    | 26.5 (0.5)    |       |
| NV                                     | 13.0 (0.3)    | 15.6 (0.3)    | 16.6 (0.3)                     | 16.7 (0.3)      | 16.3 (0.3)    | 16.1 (0.3)    | 16.1 (0.3)    |       |
| NY                                     | 97.3 (1.9)    | 100.0 (2.0)   | 95.7 (1.9)                     | 92.8 (1.8)      | 97.1 (1.9)    | 101.9 (2.0)   | 102.4 (2.0)   |       |
| OH                                     | 406.9 (7.9)   | 389.0 (7.6)   | 394.1 (7.6)                    | 386.1 (7.5)     | 389.1 (7.6)   | 380.1 (7.4)   | 423.2 (8.1)   |       |
| OK                                     | 169.2 (3.3)   | 154.7 (3.0)   | 145.9 (2.8)                    | 156.3 (3.0)     | 154.9 (3.0)   | 144.6 (2.8)   | 155.9 (3.0)   |       |
| OR                                     | 22.2 (0.4)    | 26.3 (0.5)    | 23.0 (0.4)                     | 23.1 (0.5)      | 22.7 (0.4)    | 22.1 (0.4)    | 21.7 (0.4)    |       |
| PA                                     | 50.8 (1.0)    | 52.3 (1.0)    | 49.8 (1.0)                     | 49.9 (1.0)      | 52.2 (1.0)    | 46.0 (0.9)    | 59.5 (1.1)    |       |
| RI                                     | 34.0 (0.7)    | 44.6 (0.9)    | 43.8 (0.8)                     | 42.1 (0.8)      | 42.0 (0.8)    | 45.6 (0.9)    | 36.3 (0.7)    |       |

|                              | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| SC                           | 78.8 (1.5)    | 72.1 (1.4)    | 82.6 (1.6)                     | 74.6 (1.5)      | 65.8 (1.3)    | 85.3 (1.7)    | 84.6 (1.6)    |       |
| SD                           | 3.4 (0.1)     | 2.4 (0.0)     | 2.5 (0.0)                      | 2.8 (0.1)       | 3.7 (0.1)     | 3.4 (0.1)     | 2.3 (0.0)     |       |
| TN                           | 176.4 (3.4)   | 163.0 (3.2)   | 181.3 (3.5)                    | 165.9 (3.2)     | 167.3 (3.3)   | 170.7 (3.3)   | 174.0 (3.3)   |       |
| TX                           | 529.5 (10.3)  | 520.8 (10.2)  | 530.8 (10.3)                   | 543.1 (10.6)    | 553.1 (10.8)  | 532.3 (10.4)  | 527.0 (10.1)  |       |
| UT                           | 58.4 (1.1)    | 57.3 (1.1)    | 52.6 (1.0)                     | 52.7 (1.0)      | 56.9 (1.1)    | 56.2 (1.1)    | 60.2 (1.2)    |       |
| VA                           | 137.5 (2.7)   | 143.0 (2.8)   | 141.0 (2.7)                    | 141.3 (2.7)     | 139.9 (2.7)   | 134.1 (2.6)   | 133.1 (2.6)   |       |
| VT                           | 0.8 (0.0)     | 0.9 (0.0)     | 1.0 (0.0)                      | 0.9 (0.0)       | 1.3 (0.0)     | 0.9 (0.0)     | 1.0 (0.0)     |       |
| WA                           | 24.6 (0.5)    | 25.5 (0.5)    | 24.1 (0.5)                     | 24.4 (0.5)      | 25.5 (0.5)    | 26.1 (0.5)    | 19.6 (0.4)    |       |
| WI                           | 122.5 (2.4)   | 126.8 (2.5)   | 128.2 (2.5)                    | 126.7 (2.5)     | 124.0 (2.4)   | 121.8 (2.4)   | 114.4 (2.2)   |       |
| WV                           | 8.5 (0.2)     | 7.2 (0.1)     | 9.0 (0.2)                      | 9.0 (0.2)       | 10.1 (0.2)    | 9.0 (0.2)     | 10.3 (0.2)    |       |
| WY                           | 6.1 (0.1)     | 4.6 (0.1)     | 4.3 (0.1)                      | 5.8 (0.1)       | 5.7 (0.1)     | 4.9 (0.1)     | 6.8 (0.1)     |       |
| Year                         |               |               |                                |                 |               |               |               | 0.036 |
| 2004                         | 125.1 (2.4)   | 129.0 (2.5)   | 125.3 (2.4)                    | 124.9 (2.4)     | 132.3 (2.6)   | 129.3 (2.5)   | 128.9 (2.5)   |       |
| 2005                         | 266.0 (5.2)   | 268.7 (5.3)   | 276.7 (5.4)                    | 277.3 (5.4)     | 282.9 (5.5)   | 284.4 (5.5)   | 281.6 (5.4)   |       |
| 2006                         | 340.0 (6.6)   | 353.0 (6.9)   | 349.3 (6.8)                    | 340.7 (6.6)     | 344.7 (6.7)   | 330.6 (6.4)   | 361.8 (6.9)   |       |
| 2007                         | 354.2 (6.9)   | 371.8 (7.3)   | 357.8 (6.9)                    | 351.5 (6.8)     | 363.6 (7.1)   | 348.5 (6.8)   | 378.8 (7.3)   |       |
| 2008                         | 322.7 (6.3)   | 338.1 (6.6)   | 320.7 (6.2)                    | 321.1 (6.3)     | 324.9 (6.3)   | 316.3 (6.2)   | 324.8 (6.2)   |       |
| 2009                         | 399.3 (7.8)   | 391.0 (7.7)   | 375.8 (7.3)                    | 380.2 (7.4)     | 381.6 (7.4)   | 372.7 (7.3)   | 402.4 (7.7)   |       |
| 2010                         | 448.6 (8.7)   | 450.2 (8.8)   | 448.6 (8.7)                    | 446.8 (8.7)     | 444.3 (8.7)   | 446.8 (8.7)   | 464.9 (8.9)   |       |
| 2011                         | 480.1 (9.3)   | 470.2 (9.2)   | 467.7 (9.1)                    | 462.8 (9.0)     | 461.4 (9.0)   | 469.7 (9.2)   | 488.2 (9.4)   |       |
| 2012                         | 543.3 (10.6)  | 499.2 (9.8)   | 522.5 (10.1)                   | 519.3 (10.1)    | 519.4 (10.1)  | 524.0 (10.2)  | 540.5 (10.4)  |       |
| 2013                         | 445.4 (8.7)   | 437.1 (8.6)   | 438.4 (8.5)                    | 436.9 (8.5)     | 440.8 (8.6)   | 436.5 (8.5)   | 447.2 (8.6)   |       |
| 2014                         | 263.2 (5.1)   | 261.9 (5.1)   | 275.7 (5.3)                    | 280.6 (5.5)     | 270.4 (5.3)   | 271.9 (5.3)   | 255.0 (4.9)   |       |
| 2015                         | 253.5 (4.9)   | 260.7 (5.1)   | 272.9 (5.3)                    | 276.8 (5.4)     | 267.7 (5.2)   | 273.6 (5.3)   | 247.4 (4.7)   |       |
| 2016                         | 271.0 (5.3)   | 275.7 (5.4)   | 289.8 (5.6)                    | 297.3 (5.8)     | 276.9 (5.4)   | 289.4 (5.6)   | 266.1 (5.1)   |       |
| 2017                         | 296.4 (5.8)   | 264.5 (5.2)   | 299.3 (5.8)                    | 288.3 (5.6)     | 286.6 (5.6)   | 293.6 (5.7)   | 296.7 (5.7)   |       |
| 2018                         | 167.4 (3.3)   | 163.6 (3.2)   | 170.7 (3.3)                    | 166.3 (3.2)     | 165.4 (3.2)   | 173.6 (3.4)   | 165.3 (3.2)   |       |
| 2019                         | 168.1 (3.3)   | 169.1 (3.3)   | 175.6 (3.4)                    | 166.6 (3.2)     | 164.1 (3.2)   | 169.4 (3.3)   | 168.0 (3.2)   |       |
| <b>Comorbidities (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Opioid dependence            | 237.5 (4.6)   | 225.4 (4.4)   | 219.6 (4.3)                    | 215.6 (4.2)     | 221.0 (4.3)   | 223.9 (4.4)   | 229.1 (4.4)   | 0.008 |
| Opioid abuse                 | 19.4 (0.4)    | 19.1 (0.4)    | 18.4 (0.4)                     | 18.1 (0.4)      | 14.1 (0.3)    | 15.6 (0.3)    | 18.8 (0.4)    | 0.008 |
| Alcohol abuse                | 89.1 (1.7)    | 89.3 (1.7)    | 85.5 (1.7)                     | 86.4 (1.7)      | 77.8 (1.5)    | 84.9 (1.7)    | 77.4 (1.5)    | 0.009 |
| Tobacco use                  | 862.6 (16.8)  | 818.2 (16.0)  | 841.9 (16.3)                   | 836.3 (16.3)    | 806.7 (15.7)  | 843.8 (16.4)  | 844.3 (16.2)  | 0.010 |
| Other drug abuse             | 219.9 (4.3)   | 181.6 (3.6)   | 173.6 (3.4)                    | 173.5 (3.4)     | 183.0 (3.6)   | 180.3 (3.5)   | 187.5 (3.6)   | 0.016 |
| Anxiety                      | 1104.3 (21.5) | 1061.5 (20.8) | 1073.3 (20.8)                  | 1057.6 (20.6)   | 1068.7 (20.8) | 1065.8 (20.8) | 1102.0 (21.1) | 0.008 |
| Bipolar disorder             | 216.3 (4.2)   | 210.8 (4.1)   | 200.1 (3.9)                    | 195.9 (3.8)     | 189.3 (3.7)   | 211.7 (4.1)   | 214.0 (4.1)   | 0.012 |
| Bone fracture                | 292.2 (5.7)   | 284.7 (5.6)   | 302.6 (5.9)                    | 296.8 (5.8)     | 291.7 (5.7)   | 298.2 (5.8)   | 299.8 (5.7)   | 0.005 |
| Cancer                       | 278.4 (5.4)   | 258.7 (5.1)   | 253.8 (4.9)                    | 255.1 (5.0)     | 253.6 (4.9)   | 254.9 (5.0)   | 222.6 (4.3)   | 0.017 |
| Chronic renal insufficiency  | 214.0 (4.2)   | 226.2 (4.4)   | 248.5 (4.8)                    | 237.8 (4.6)     | 226.6 (4.4)   | 248.3 (4.8)   | 199.1 (3.8)   | 0.021 |
| Congestive heart failure     | 226.5 (4.4)   | 229.6 (4.5)   | 243.9 (4.7)                    | 237.1 (4.6)     | 221.3 (4.3)   | 254.4 (5.0)   | 199.1 (3.8)   | 0.021 |
| COPD/asthma/oxygen           | 895.3 (17.4)  | 890.4 (17.4)  | 936.2 (18.1)                   | 902.6 (17.6)    | 865.1 (16.9)  | 948.7 (18.5)  | 865.7 (16.6)  | 0.021 |
| Dementia                     | 88.6 (1.7)    | 86.7 (1.7)    | 87.4 (1.7)                     | 86.0 (1.7)      | 85.2 (1.7)    | 87.1 (1.7)    | 80.1 (1.5)    | 0.005 |
| Depression                   | 1179.1 (22.9) | 1128.4 (22.1) | 1134.8 (22.0)                  | 1115.1 (21.7)   | 1127.5 (22.0) | 1113.1 (21.7) | 1171.1 (22.4) | 0.012 |
| Diabetes                     | 919.3 (17.9)  | 942.4 (18.5)  | 1008.3 (19.5)                  | 980.0 (19.1)    | 921.5 (18.0)  | 1030.7 (20.1) | 879.7 (16.9)  | 0.035 |
| Epilepsy                     | 138.5 (2.7)   | 114.0 (2.2)   | 115.7 (2.2)                    | 115.6 (2.3)     | 117.2 (2.3)   | 118.9 (2.3)   | 126.3 (2.4)   | 0.011 |
| HIV                          | 23.1 (0.4)    | 16.6 (0.3)    | 17.6 (0.3)                     | 18.1 (0.4)      | 20.3 (0.4)    | 19.6 (0.4)    | 16.6 (0.3)    | 0.009 |
| Intentional self-harm        | 2.6 (0.1)     | 2.0 (0.0)     | 3.0 (0.1)                      | 2.8 (0.1)       | 2.4 (0.0)     | 2.4 (0.0)     | 3.0 (0.1)     | 0.004 |
| Liver disease                | 271.8 (5.3)   | 262.4 (5.1)   | 267.5 (5.2)                    | 266.0 (5.2)     | 250.8 (4.9)   | 268.2 (5.2)   | 256.6 (4.9)   | 0.008 |
| Musculoskeletal injury       | 512.3 (10.0)  | 508.4 (10.0)  | 517.9 (10.0)                   | 508.8 (9.9)     | 498.6 (9.7)   | 513.0 (10.0)  | 516.6 (9.9)   | 0.004 |
| Multiple sclerosis           | 27.9 (0.5)    | 20.0 (0.4)    | 22.2 (0.4)                     | 21.6 (0.4)      | 25.2 (0.5)    | 19.0 (0.4)    | 25.3 (0.5)    | 0.011 |
| Obesity                      | 484.6 (9.4)   | 480.1 (9.4)   | 523.9 (10.1)                   | 513.2 (10.0)    | 507.9 (9.9)   | 538.2 (10.5)  | 490.1 (9.4)   | 0.017 |
| Pneumonia                    | 129.9 (2.5)   | 122.4 (2.4)   | 122.6 (2.4)                    | 124.0 (2.4)     | 124.4 (2.4)   | 125.6 (2.4)   | 119.7 (2.3)   | 0.005 |

|                                                | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|------------------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| Psychosis                                      | 69.5 (1.4)    | 70.9 (1.4)    | 71.9 (1.4)                     | 66.5 (1.3)      | 67.5 (1.3)    | 74.1 (1.4)    | 65.4 (1.3)    | 0.007 |
| Renal dysfunction                              | 341.4 (6.6)   | 346.9 (6.8)   | 377.2 (7.3)                    | 367.0 (7.1)     | 364.3 (7.1)   | 385.7 (7.5)   | 321.4 (6.2)   | 0.022 |
| Spasticity                                     | 965.4 (18.8)  | 884.9 (17.3)  | 897.2 (17.4)                   | 888.5 (17.3)    | 895.9 (17.5)  | 883.2 (17.2)  | 924.7 (17.7)  | 0.014 |
| Urinary calculus                               | 179.9 (3.5)   | 167.2 (3.3)   | 174.0 (3.4)                    | 172.2 (3.4)     | 178.4 (3.5)   | 173.6 (3.4)   | 173.3 (3.3)   | 0.005 |
| Urinary tract infection                        | 517.1 (10.1)  | 507.7 (9.9)   | 513.6 (9.9)                    | 508.3 (9.9)     | 518.4 (10.1)  | 514.2 (10.0)  | 510.0 (9.8)   | 0.004 |
| <b>Pain conditions (n (%))</b>                 |               |               |                                |                 |               |               |               |       |
| Abdominal pain                                 | 927.6 (18.0)  | 886.1 (17.4)  | 894.6 (17.3)                   | 889.7 (17.3)    | 866.3 (16.9)  | 912.1 (17.8)  | 910.8 (17.5)  | 0.011 |
| Back and neck pain                             | 3927.4 (76.3) | 3788.5 (74.2) | 3828.8 (74.1)                  | 3818.2 (74.3)   | 3784.4 (73.8) | 3823.5 (74.5) | 3947.4 (75.7) | 0.024 |
| Back pain without radiculopathy                | 3577.2 (69.5) | 3479.2 (68.2) | 3525.0 (68.2)                  | 3511.3 (68.3)   | 3456.5 (67.4) | 3513.5 (68.5) | 3595.0 (68.9) | 0.017 |
| Back pain with radiculopathy                   | 1451.1 (28.2) | 1342.0 (26.3) | 1368.2 (26.5)                  | 1351.6 (26.3)   | 1330.9 (26.0) | 1342.4 (26.2) | 1459.0 (28.0) | 0.023 |
| Dental pain                                    | 52.2 (1.0)    | 48.7 (1.0)    | 51.4 (1.0)                     | 49.5 (1.0)      | 51.4 (1.0)    | 56.1 (1.1)    | 47.7 (0.9)    | 0.007 |
| Diabetic neuropathy                            | 192.6 (3.7)   | 185.4 (3.6)   | 213.8 (4.1)                    | 194.7 (3.8)     | 176.6 (3.4)   | 215.1 (4.2)   | 176.0 (3.4)   | 0.020 |
| Fibromyalgia                                   | 982.6 (19.1)  | 937.3 (18.4)  | 903.0 (17.5)                   | 886.7 (17.3)    | 924.0 (18.0)  | 898.9 (17.5)  | 1014.6 (19.4) | 0.026 |
| Headache                                       | 1040.8 (20.2) | 986.0 (19.3)  | 964.7 (18.7)                   | 963.1 (18.7)    | 983.5 (19.2)  | 969.7 (18.9)  | 1085.0 (20.8) | 0.023 |
| Osteoarthritis                                 | 1228.0 (23.9) | 1289.0 (25.3) | 1336.1 (25.9)                  | 1324.5 (25.8)   | 1272.1 (24.8) | 1342.3 (26.2) | 1243.6 (23.8) | 0.026 |
| Rheumatoid arthritis                           | 258.2 (5.0)   | 275.4 (5.4)   | 279.1 (5.4)                    | 277.3 (5.4)     | 271.5 (5.3)   | 267.1 (5.2)   | 257.4 (4.9)   | 0.010 |
| Postherpetic neuralgia                         | 16.4 (0.3)    | 15.1 (0.3)    | 14.5 (0.3)                     | 15.3 (0.3)      | 15.6 (0.3)    | 15.7 (0.3)    | 15.4 (0.3)    | 0.003 |
| Other arthritis                                | 2867.6 (55.7) | 2893.9 (56.7) | 2934.2 (56.8)                  | 2914.8 (56.7)   | 2885.9 (56.3) | 2909.0 (56.7) | 2943.8 (56.4) | 0.008 |
| Other neuropathy                               | 2202.6 (42.8) | 2057.7 (40.3) | 2055.5 (39.8)                  | 2033.9 (39.6)   | 2033.4 (39.7) | 2031.1 (39.6) | 2206.5 (42.3) | 0.030 |
| Other unspecified pain                         | 2388.9 (46.4) | 2290.3 (44.9) | 2347.4 (45.4)                  | 2322.8 (45.2)   | 2290.0 (44.7) | 2322.3 (45.3) | 2376.4 (45.5) | 0.013 |
| <b>Other prescription fills (n (%))</b>        |               |               |                                |                 |               |               |               |       |
| Antibiotics                                    | 2847.3 (55.3) | 2858.5 (56.0) | 2891.4 (56.0)                  | 2870.1 (55.9)   | 2883.9 (56.2) | 2870.0 (55.9) | 2883.3 (55.3) | 0.008 |
| Anticonvulsants                                | 554.9 (10.8)  | 531.8 (10.4)  | 510.6 (9.9)                    | 506.3 (9.9)     | 519.5 (10.1)  | 506.6 (9.9)   | 581.2 (11.1)  | 0.019 |
| Antidepressants, SSRIs                         | 1339.4 (26.0) | 1340.0 (26.3) | 1354.5 (26.2)                  | 1347.6 (26.2)   | 1338.2 (26.1) | 1354.7 (26.4) | 1354.1 (26.0) | 0.004 |
| Antidepressants, SNRIs                         | 844.5 (16.4)  | 839.7 (16.5)  | 827.5 (16.0)                   | 810.7 (15.8)    | 823.6 (16.1)  | 809.2 (15.8)  | 880.1 (16.9)  | 0.013 |
| Antidepressants, TCAs                          | 549.6 (10.7)  | 499.0 (9.8)   | 492.3 (9.5)                    | 480.7 (9.4)     | 479.7 (9.4)   | 490.3 (9.6)   | 511.6 (9.8)   | 0.016 |
| Antidepressants, other                         | 790.9 (15.4)  | 830.2 (16.3)  | 816.6 (15.8)                   | 806.5 (15.7)    | 822.6 (16.0)  | 808.8 (15.8)  | 839.3 (16.1)  | 0.010 |
| Antidiabetics                                  | 725.5 (14.1)  | 740.5 (14.5)  | 800.1 (15.5)                   | 769.3 (15.0)    | 727.4 (14.2)  | 812.6 (15.8)  | 697.2 (13.4)  | 0.030 |
| Antipsychotics, atypical                       | 309.9 (6.0)   | 307.2 (6.0)   | 304.0 (5.9)                    | 295.4 (5.7)     | 296.9 (5.8)   | 317.9 (6.2)   | 322.0 (6.2)   | 0.009 |
| Antipsychotics, typical                        | 114.9 (2.2)   | 110.7 (2.2)   | 108.1 (2.1)                    | 104.3 (2.0)     | 106.0 (2.1)   | 109.7 (2.1)   | 119.4 (2.3)   | 0.008 |
| Barbiturates                                   | 27.2 (0.5)    | 23.0 (0.5)    | 21.8 (0.4)                     | 22.5 (0.4)      | 24.6 (0.5)    | 22.4 (0.4)    | 24.0 (0.5)    | 0.006 |
| Benzodiazepines                                | 1976.3 (38.4) | 1927.2 (37.8) | 1895.2 (36.7)                  | 1883.4 (36.7)   | 1912.6 (37.3) | 1897.8 (37.0) | 1991.4 (38.2) | 0.018 |
| CNS stimulants                                 | 223.4 (4.3)   | 209.0 (4.1)   | 213.7 (4.1)                    | 214.2 (4.2)     | 224.9 (4.4)   | 211.3 (4.1)   | 241.6 (4.6)   | 0.011 |
| Dementia agents                                | 42.4 (0.8)    | 42.6 (0.8)    | 44.8 (0.9)                     | 42.7 (0.8)      | 36.3 (0.7)    | 46.8 (0.9)    | 39.1 (0.7)    | 0.009 |
| Gabapentinoids                                 | 1452.4 (28.2) | 1368.1 (26.8) | 1370.1 (26.5)                  | 1348.7 (26.3)   | 1354.3 (26.4) | 1334.8 (26.0) | 1431.9 (27.4) | 0.020 |
| Lithium                                        | 32.7 (0.6)    | 29.4 (0.6)    | 28.9 (0.6)                     | 26.7 (0.5)      | 26.5 (0.5)    | 31.5 (0.6)    | 28.4 (0.5)    | 0.007 |
| Multiple sclerosis agents                      | 5.7 (0.1)     | 3.4 (0.1)     | 4.0 (0.1)                      | 4.0 (0.1)       | 5.3 (0.1)     | 4.2 (0.1)     | 4.4 (0.1)     | 0.006 |
| NSAIDs                                         | 2109.1 (41.0) | 2148.6 (42.1) | 2171.6 (42.0)                  | 2160.7 (42.1)   | 2146.4 (41.9) | 2189.4 (42.7) | 2177.9 (41.7) | 0.011 |
| Other sedative hypnotics                       | 912.2 (17.7)  | 883.6 (17.3)  | 865.0 (16.7)                   | 861.2 (16.8)    | 871.7 (17.0)  | 872.5 (17.0)  | 932.7 (17.9)  | 0.014 |
| Smoking cessation                              | 388.4 (7.6)   | 401.4 (7.9)   | 384.0 (7.4)                    | 384.7 (7.5)     | 398.0 (7.8)   | 374.6 (7.3)   | 407.2 (7.8)   | 0.010 |
| Triptans                                       | 293.5 (5.7)   | 285.7 (5.6)   | 274.0 (5.3)                    | 277.5 (5.4)     | 283.1 (5.5)   | 273.7 (5.3)   | 320.7 (6.1)   | 0.014 |
| Other CNS depressants                          | 27.1 (0.5)    | 28.6 (0.6)    | 27.1 (0.5)                     | 26.1 (0.5)      | 25.8 (0.5)    | 27.6 (0.5)    | 28.6 (0.5)    | 0.003 |
| <b>Prescription opioid utilization (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Prescription opioid on index date              |               |               |                                |                 |               |               |               |       |
| Buprenorphine                                  | 30.1 (0.6)    | 31.3 (0.6)    | 23.9 (0.5)                     | 25.3 (0.5)      | 27.3 (0.5)    | 25.3 (0.5)    | 32.8 (0.6)    | 0.011 |
| Butorphanol                                    | 28.7 (0.6)    | 31.4 (0.6)    | 25.4 (0.5)                     | 23.6 (0.5)      | 25.0 (0.5)    | 21.6 (0.4)    | 27.0 (0.5)    | 0.011 |
| Codeine                                        | 211.1 (4.1)   | 210.1 (4.1)   | 203.2 (3.9)                    | 206.5 (4.0)     | 208.6 (4.1)   | 206.4 (4.0)   | 193.7 (3.7)   | 0.008 |
| Dihydrocodeine                                 | 4.3 (0.1)     | 5.7 (0.1)     | 3.8 (0.1)                      | 4.0 (0.1)       | 4.4 (0.1)     | 4.2 (0.1)     | 3.8 (0.1)     | 0.005 |
| Fentanyl                                       | 336.8 (6.5)   | 311.0 (6.1)   | 286.8 (5.6)                    | 284.7 (5.5)     | 301.6 (5.9)   | 275.8 (5.4)   | 327.8 (6.3)   | 0.022 |
| Hydrocodone                                    | 2752.1 (53.5) | 2782.5 (54.5) | 2856.6 (55.3)                  | 2847.0 (55.4)   | 2815.2 (54.9) | 2824.2 (55.0) | 2805.4 (53.8) | 0.018 |
| Hydromorphone                                  | 131.4 (2.6)   | 114.1 (2.2)   | 109.8 (2.1)                    | 105.8 (2.1)     | 115.1 (2.2)   | 104.5 (2.0)   | 119.5 (2.3)   | 0.014 |
| Levorphanol                                    | 1.3 (0.0)     | 0.6 (0.0)     | 0.5 (0.0)                      | 0.5 (0.0)       | 0.6 (0.0)     | 0.4 (0.0)     | 1.1 (0.0)     | 0.006 |

|                                                                                       | Baclofen          | Carisoprodol      | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine   | Metaxalone        | Methocarbamol     | Tizanidine        | SMD   |
|---------------------------------------------------------------------------------------|-------------------|-------------------|--------------------------------|-------------------|-------------------|-------------------|-------------------|-------|
| Meperidine                                                                            | 9.0 (0.2)         | 13.3 (0.3)        | 11.3 (0.2)                     | 11.1 (0.2)        | 10.7 (0.2)        | 11.4 (0.2)        | 12.8 (0.2)        | 0.007 |
| Methadone                                                                             | 186.4 (3.6)       | 167.1 (3.3)       | 163.4 (3.2)                    | 158.4 (3.1)       | 167.3 (3.3)       | 161.6 (3.1)       | 182.4 (3.5)       | 0.013 |
| Morphine                                                                              | 428.7 (8.3)       | 356.3 (7.0)       | 348.3 (6.7)                    | 342.8 (6.7)       | 355.1 (6.9)       | 355.1 (6.9)       | 386.6 (7.4)       | 0.023 |
| Opium                                                                                 | 1.0 (0.0)         | 1.4 (0.0)         | 1.0 (0.0)                      | 0.9 (0.0)         | 1.0 (0.0)         | 0.7 (0.0)         | 0.5 (0.0)         | 0.005 |
| Oxycodone                                                                             | 1877.3 (36.5)     | 1736.5 (34.0)     | 1728.4 (33.5)                  | 1713.1 (33.3)     | 1731.2 (33.8)     | 1696.8 (33.1)     | 1842.4 (35.3)     | 0.030 |
| Oxymorphone                                                                           | 72.3 (1.4)        | 61.3 (1.2)        | 60.4 (1.2)                     | 60.8 (1.2)        | 62.6 (1.2)        | 60.5 (1.2)        | 75.0 (1.4)        | 0.011 |
| Pentazocine                                                                           | 14.5 (0.3)        | 11.7 (0.2)        | 12.8 (0.2)                     | 11.1 (0.2)        | 10.5 (0.2)        | 12.2 (0.2)        | 11.8 (0.2)        | 0.006 |
| Propoxyphene                                                                          | 61.7 (1.2)        | 63.6 (1.2)        | 58.3 (1.1)                     | 60.7 (1.2)        | 59.3 (1.2)        | 65.1 (1.3)        | 60.9 (1.2)        | 0.006 |
| Tapentadol                                                                            | 48.2 (0.9)        | 49.2 (1.0)        | 47.8 (0.9)                     | 47.1 (0.9)        | 47.4 (0.9)        | 43.3 (0.8)        | 50.4 (1.0)        | 0.005 |
| Tramadol                                                                              | 984.1 (19.1)      | 1076.1 (21.1)     | 1093.6 (21.2)                  | 1092.5 (21.3)     | 1070.5 (20.9)     | 1084.0 (21.1)     | 1071.6 (20.5)     | 0.019 |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 174.75 (15.71)    | 174.92 (15.47)    | 174.71 (15.88)                 | 174.66 (15.74)    | 174.63 (15.85)    | 174.69 (15.49)    | 174.85 (15.62)    | 0.008 |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                   |                   |                                |                   |                   |                   |                   |       |
| (Index - 180) to (index - 151)                                                        | 2169.28 (3497.37) | 2049.85 (3223.61) | 1947.87 (3120.02)              | 1941.92 (3216.52) | 1975.75 (3249.19) | 1945.76 (3187.36) | 2090.57 (3253.36) | 0.031 |
| (Index - 150) to (index - 121)                                                        | 2208.45 (3437.79) | 2099.95 (3118.91) | 2012.60 (3201.16)              | 1993.23 (3211.08) | 2036.90 (3299.10) | 2004.61 (3213.19) | 2150.40 (3320.89) | 0.030 |
| (Index - 120) to (index - 91)                                                         | 2381.93 (3516.46) | 2255.05 (3238.40) | 2148.19 (3169.90)              | 2135.32 (3283.26) | 2163.25 (3341.55) | 2141.12 (3235.98) | 2283.73 (3304.14) | 0.032 |
| (Index - 90) to (index - 61)                                                          | 2383.50 (3450.90) | 2266.35 (3240.14) | 2166.13 (3293.29)              | 2154.67 (3294.73) | 2213.00 (3422.23) | 2150.02 (3255.54) | 2322.57 (3370.32) | 0.032 |
| (Index - 60) to (index - 31)                                                          | 2435.91 (3637.49) | 2281.67 (3267.55) | 2186.84 (3308.33)              | 2170.19 (3324.13) | 2223.44 (3394.87) | 2166.56 (3268.18) | 2331.44 (3355.77) | 0.034 |
| (Index - 30) to index                                                                 | 2911.30 (4017.48) | 2733.04 (3721.45) | 2593.01 (3889.28)              | 2578.71 (3980.61) | 2606.28 (3903.44) | 2573.31 (3801.76) | 2800.15 (3883.22) | 0.039 |
| <b>Healthcare utilization (mean (SD))</b>                                             |                   |                   |                                |                   |                   |                   |                   |       |
| Number of physician visits                                                            | 8.16 (6.12)       | 8.00 (6.35)       | 7.99 (6.11)                    | 7.96 (6.18)       | 8.01 (6.07)       | 7.97 (6.03)       | 8.18 (6.08)       | 0.016 |
| Number of distinct prescribed medications                                             | 11.29 (5.75)      | 11.39 (5.94)      | 11.36 (5.82)                   | 11.28 (5.69)      | 11.28 (5.64)      | 11.42 (5.71)      | 11.16 (5.70)      | 0.018 |
| Number of hospitalizations                                                            | 0.21 (0.78)       | 0.21 (0.71)       | 0.21 (0.90)                    | 0.21 (0.72)       | 0.21 (0.74)       | 0.23 (0.70)       | 0.19 (0.75)       | 0.017 |
| Number of hospitalization days                                                        | 1.12 (4.54)       | 0.96 (3.58)       | 0.93 (3.60)                    | 0.95 (3.53)       | 0.97 (3.49)       | 1.01 (3.22)       | 0.89 (3.74)       | 0.022 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 10. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in IBM® MarketScan® Research Database, 2003-2018 (pre-matching weights)**

|                                        | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|----------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| n                                      | 35213         | 55301         | 14755                          | 240755          | 37513         | 56655         | 71402         |       |
| <b>Demographic information (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Age (mean (SD))                        | 52.82 (13.40) | 50.58 (12.58) | 52.30 (13.54)                  | 51.68 (12.63)   | 53.03 (13.32) | 52.26 (13.02) | 50.86 (12.44) | 0.088 |
| Sex                                    |               |               |                                |                 |               |               |               | 0.046 |
| Male                                   | 14821 (42.1)  | 23349 (42.2)  | 5707 (38.7)                    | 95629 (39.7)    | 14032 (37.4)  | 23809 (42.0)  | 28178 (39.5)  |       |
| Female                                 | 20392 (57.9)  | 31952 (57.8)  | 9048 (61.3)                    | 145126 (60.3)   | 23481 (62.6)  | 32846 (58.0)  | 43224 (60.5)  |       |
| State                                  |               |               |                                |                 |               |               |               | 0.474 |
| AK                                     | 26 (0.1)      | 40 (0.1)      | 7 (0.0)                        | 197 (0.1)       | 14 (0.0)      | 25 (0.0)      | 135 (0.2)     |       |
| AL                                     | 759 (2.2)     | 1306 (2.4)    | 338 (2.3)                      | 5498 (2.3)      | 943 (2.5)     | 3244 (5.7)    | 2413 (3.4)    |       |
| AR                                     | 208 (0.6)     | 615 (1.1)     | 101 (0.7)                      | 1906 (0.8)      | 270 (0.7)     | 434 (0.8)     | 633 (0.9)     |       |
| AZ                                     | 672 (1.9)     | 1489 (2.7)    | 166 (1.1)                      | 3264 (1.4)      | 489 (1.3)     | 987 (1.7)     | 954 (1.3)     |       |
| CA                                     | 3917 (11.1)   | 9083 (16.4)   | 372 (2.5)                      | 17463 (7.3)     | 1690 (4.5)    | 5001 (8.8)    | 2829 (4.0)    |       |
| CO                                     | 314 (0.9)     | 596 (1.1)     | 158 (1.1)                      | 2796 (1.2)      | 402 (1.1)     | 637 (1.1)     | 711 (1.0)     |       |
| CT                                     | 292 (0.8)     | 578 (1.0)     | 80 (0.5)                       | 2318 (1.0)      | 525 (1.4)     | 794 (1.4)     | 415 (0.6)     |       |
| DC                                     | 8 (0.0)       | 11 (0.0)      | 3 (0.0)                        | 64 (0.0)        | 12 (0.0)      | 7 (0.0)       | 8 (0.0)       |       |
| DE                                     | 137 (0.4)     | 405 (0.7)     | 57 (0.4)                       | 1487 (0.6)      | 362 (1.0)     | 100 (0.2)     | 574 (0.8)     |       |
| FL                                     | 2103 (6.0)    | 2879 (5.2)    | 715 (4.8)                      | 10862 (4.5)     | 2005 (5.3)    | 3192 (5.6)    | 3922 (5.5)    |       |
| GA                                     | 1510 (4.3)    | 3276 (5.9)    | 489 (3.3)                      | 10886 (4.5)     | 1549 (4.1)    | 2835 (5.0)    | 4468 (6.3)    |       |
| HI                                     | 12 (0.0)      | 9 (0.0)       | 1 (0.0)                        | 32 (0.0)        | 1 (0.0)       | 6 (0.0)       | 9 (0.0)       |       |
| IA                                     | 286 (0.8)     | 153 (0.3)     | 103 (0.7)                      | 2177 (0.9)      | 396 (1.1)     | 313 (0.6)     | 415 (0.6)     |       |
| ID                                     | 358 (1.0)     | 470 (0.8)     | 80 (0.5)                       | 1822 (0.8)      | 120 (0.3)     | 598 (1.1)     | 509 (0.7)     |       |
| IL                                     | 988 (2.8)     | 1024 (1.9)    | 990 (6.7)                      | 8001 (3.3)      | 1283 (3.4)    | 907 (1.6)     | 1433 (2.0)    |       |
| IN                                     | 1400 (4.0)    | 1314 (2.4)    | 1016 (6.9)                     | 11546 (4.8)     | 1933 (5.2)    | 1517 (2.7)    | 3149 (4.4)    |       |
| KS                                     | 267 (0.8)     | 335 (0.6)     | 183 (1.2)                      | 2089 (0.9)      | 315 (0.8)     | 336 (0.6)     | 517 (0.7)     |       |
| KY                                     | 1464 (4.2)    | 749 (1.4)     | 448 (3.0)                      | 7648 (3.2)      | 1249 (3.3)    | 2103 (3.7)    | 3541 (5.0)    |       |
| LA                                     | 778 (2.2)     | 1275 (2.3)    | 539 (3.7)                      | 5376 (2.2)      | 607 (1.6)     | 1895 (3.3)    | 2408 (3.4)    |       |
| MA                                     | 283 (0.8)     | 234 (0.4)     | 92 (0.6)                       | 1752 (0.7)      | 167 (0.4)     | 236 (0.4)     | 487 (0.7)     |       |
| MD                                     | 359 (1.0)     | 973 (1.8)     | 167 (1.1)                      | 3922 (1.6)      | 1059 (2.8)    | 427 (0.8)     | 790 (1.1)     |       |
| ME                                     | 140 (0.4)     | 96 (0.2)      | 30 (0.2)                       | 1394 (0.6)      | 107 (0.3)     | 145 (0.3)     | 179 (0.3)     |       |
| MI                                     | 2364 (6.7)    | 3236 (5.9)    | 1474 (10.0)                    | 17360 (7.2)     | 3527 (9.4)    | 3515 (6.2)    | 2865 (4.0)    |       |
| MN                                     | 95 (0.3)      | 54 (0.1)      | 48 (0.3)                       | 1028 (0.4)      | 54 (0.1)      | 237 (0.4)     | 284 (0.4)     |       |
| MO                                     | 836 (2.4)     | 1183 (2.1)    | 460 (3.1)                      | 5972 (2.5)      | 835 (2.2)     | 940 (1.7)     | 1613 (2.3)    |       |
| MS                                     | 364 (1.0)     | 772 (1.4)     | 168 (1.1)                      | 2906 (1.2)      | 501 (1.3)     | 852 (1.5)     | 1443 (2.0)    |       |
| MT                                     | 94 (0.3)      | 79 (0.1)      | 48 (0.3)                       | 753 (0.3)       | 119 (0.3)     | 263 (0.5)     | 148 (0.2)     |       |
| NC                                     | 976 (2.8)     | 1298 (2.3)    | 483 (3.3)                      | 7997 (3.3)      | 1445 (3.9)    | 1625 (2.9)    | 2313 (3.2)    |       |
| ND                                     | 10 (0.0)      | 4 (0.0)       | 3 (0.0)                        | 106 (0.0)       | 5 (0.0)       | 14 (0.0)      | 16 (0.0)      |       |
| NE                                     | 53 (0.2)      | 55 (0.1)      | 25 (0.2)                       | 626 (0.3)       | 138 (0.4)     | 38 (0.1)      | 113 (0.2)     |       |
| NH                                     | 94 (0.3)      | 81 (0.1)      | 42 (0.3)                       | 745 (0.3)       | 115 (0.3)     | 91 (0.2)      | 227 (0.3)     |       |
| NJ                                     | 327 (0.9)     | 499 (0.9)     | 136 (0.9)                      | 2605 (1.1)      | 645 (1.7)     | 222 (0.4)     | 819 (1.1)     |       |
| NM                                     | 687 (2.0)     | 438 (0.8)     | 160 (1.1)                      | 1816 (0.8)      | 139 (0.4)     | 569 (1.0)     | 574 (0.8)     |       |
| NV                                     | 341 (1.0)     | 1566 (2.8)    | 64 (0.4)                       | 1972 (0.8)      | 253 (0.7)     | 636 (1.1)     | 767 (1.1)     |       |
| NY                                     | 2026 (5.8)    | 1771 (3.2)    | 436 (3.0)                      | 9568 (4.0)      | 1637 (4.4)    | 1852 (3.3)    | 2729 (3.8)    |       |
| OH                                     | 1557 (4.4)    | 1657 (3.0)    | 1265 (8.6)                     | 14575 (6.1)     | 2182 (5.8)    | 3169 (5.6)    | 6048 (8.5)    |       |
| OK                                     | 729 (2.1)     | 1663 (3.0)    | 460 (3.1)                      | 5625 (2.3)      | 625 (1.7)     | 836 (1.5)     | 1935 (2.7)    |       |
| OR                                     | 417 (1.2)     | 335 (0.6)     | 65 (0.4)                       | 3057 (1.3)      | 279 (0.7)     | 680 (1.2)     | 744 (1.0)     |       |
| PA                                     | 1327 (3.8)    | 2053 (3.7)    | 493 (3.3)                      | 10300 (4.3)     | 1556 (4.1)    | 1797 (3.2)    | 1514 (2.1)    |       |
| RI                                     | 49 (0.1)      | 68 (0.1)      | 11 (0.1)                       | 418 (0.2)       | 57 (0.2)      | 46 (0.1)      | 67 (0.1)      |       |
| SC                                     | 1022 (2.9)    | 1820 (3.3)    | 469 (3.2)                      | 8910 (3.7)      | 1220 (3.3)    | 1220 (2.2)    | 2882 (4.0)    |       |

|                              | Baclofen    | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone  | Methocarbamol | Tizanidine   | SMD   |
|------------------------------|-------------|--------------|--------------------------------|-----------------|-------------|---------------|--------------|-------|
| SD                           | 41 (0.1)    | 23 (0.0)     | 19 (0.1)                       | 258 (0.1)       | 22 (0.1)    | 25 (0.0)      | 38 (0.1)     |       |
| TN                           | 1364 (3.9)  | 2071 (3.7)   | 561 (3.8)                      | 7744 (3.2)      | 1254 (3.3)  | 2692 (4.8)    | 2781 (3.9)   |       |
| TX                           | 2156 (6.1)  | 5451 (9.9)   | 1008 (6.8)                     | 17897 (7.4)     | 3268 (8.7)  | 5098 (9.0)    | 6550 (9.2)   |       |
| UT                           | 165 (0.5)   | 464 (0.8)    | 66 (0.4)                       | 1373 (0.6)      | 165 (0.4)   | 489 (0.9)     | 544 (0.8)    |       |
| VA                           | 565 (1.6)   | 554 (1.0)    | 336 (2.3)                      | 4718 (2.0)      | 816 (2.2)   | 914 (1.6)     | 1100 (1.5)   |       |
| VT                           | 21 (0.1)    | 10 (0.0)     | 2 (0.0)                        | 113 (0.0)       | 5 (0.0)     | 41 (0.1)      | 23 (0.0)     |       |
| WA                           | 580 (1.6)   | 599 (1.1)    | 52 (0.4)                       | 4193 (1.7)      | 277 (0.7)   | 2270 (4.0)    | 940 (1.3)    |       |
| WI                           | 414 (1.2)   | 254 (0.5)    | 114 (0.8)                      | 2975 (1.2)      | 384 (1.0)   | 214 (0.4)     | 963 (1.3)    |       |
| WV                           | 227 (0.6)   | 295 (0.5)    | 131 (0.9)                      | 2370 (1.0)      | 451 (1.2)   | 535 (0.9)     | 822 (1.2)    |       |
| WY                           | 31 (0.1)    | 38 (0.1)     | 21 (0.1)                       | 275 (0.1)       | 41 (0.1)    | 36 (0.1)      | 41 (0.1)     |       |
| Year                         |             |              |                                |                 |             |               |              | 0.394 |
| 2003                         | 402 (1.1)   | 1567 (2.8)   | 335 (2.3)                      | 3172 (1.3)      | 1147 (3.1)  | 729 (1.3)     | 968 (1.4)    |       |
| 2004                         | 933 (2.6)   | 3308 (6.0)   | 706 (4.8)                      | 7416 (3.1)      | 2432 (6.5)  | 1641 (2.9)    | 1992 (2.8)   |       |
| 2005                         | 1180 (3.4)  | 3441 (6.2)   | 789 (5.3)                      | 9370 (3.9)      | 2782 (7.4)  | 1941 (3.4)    | 2272 (3.2)   |       |
| 2006                         | 1057 (3.0)  | 3174 (5.7)   | 763 (5.2)                      | 9299 (3.9)      | 2964 (7.9)  | 1831 (3.2)    | 2432 (3.4)   |       |
| 2007                         | 1210 (3.4)  | 3733 (6.8)   | 928 (6.3)                      | 11412 (4.7)     | 3431 (9.1)  | 2340 (4.1)    | 2928 (4.1)   |       |
| 2008                         | 1674 (4.8)  | 5070 (9.2)   | 1097 (7.4)                     | 16222 (6.7)     | 3828 (10.2) | 3119 (5.5)    | 3823 (5.4)   |       |
| 2009                         | 2374 (6.7)  | 6272 (11.3)  | 1270 (8.6)                     | 21817 (9.1)     | 3715 (9.9)  | 4151 (7.3)    | 4935 (6.9)   |       |
| 2010                         | 2693 (7.6)  | 6547 (11.8)  | 1269 (8.6)                     | 24045 (10.0)    | 3351 (8.9)  | 4886 (8.6)    | 5298 (7.4)   |       |
| 2011                         | 3329 (9.5)  | 6590 (11.9)  | 1416 (9.6)                     | 27523 (11.4)    | 3364 (9.0)  | 6076 (10.7)   | 6472 (9.1)   |       |
| 2012                         | 3818 (10.8) | 5546 (10.0)  | 1615 (10.9)                    | 28098 (11.7)    | 3104 (8.3)  | 6745 (11.9)   | 7532 (10.5)  |       |
| 2013                         | 3224 (9.2)  | 3476 (6.3)   | 1085 (7.4)                     | 20902 (8.7)     | 2275 (6.1)  | 5152 (9.1)    | 6149 (8.6)   |       |
| 2014                         | 3639 (10.3) | 2655 (4.8)   | 1009 (6.8)                     | 19662 (8.2)     | 1775 (4.7)  | 5134 (9.1)    | 6733 (9.4)   |       |
| 2015                         | 3005 (8.5)  | 1571 (2.8)   | 809 (5.5)                      | 14148 (5.9)     | 1207 (3.2)  | 3918 (6.9)    | 5865 (8.2)   |       |
| 2016                         | 2949 (8.4)  | 1250 (2.3)   | 712 (4.8)                      | 12788 (5.3)     | 1063 (2.8)  | 4062 (7.2)    | 6145 (8.6)   |       |
| 2017                         | 1999 (5.7)  | 681 (1.2)    | 474 (3.2)                      | 8038 (3.3)      | 598 (1.6)   | 2682 (4.7)    | 4269 (6.0)   |       |
| 2018                         | 1727 (4.9)  | 420 (0.8)    | 478 (3.2)                      | 6843 (2.8)      | 477 (1.3)   | 2248 (4.0)    | 3589 (5.0)   |       |
| <b>Comorbidities (n (%))</b> |             |              |                                |                 |             |               |              |       |
| Opioid dependence            | 1561 (4.4)  | 1060 (1.9)   | 380 (2.6)                      | 5209 (2.2)      | 589 (1.6)   | 2480 (4.4)    | 2809 (3.9)   | 0.085 |
| Opioid abuse                 | 121 (0.3)   | 123 (0.2)    | 28 (0.2)                       | 490 (0.2)       | 57 (0.2)    | 216 (0.4)     | 201 (0.3)    | 0.020 |
| Alcohol abuse                | 608 (1.7)   | 546 (1.0)    | 149 (1.0)                      | 2783 (1.2)      | 349 (0.9)   | 1037 (1.8)    | 774 (1.1)    | 0.036 |
| Tobacco use                  | 3380 (9.6)  | 4319 (7.8)   | 1279 (8.7)                     | 22992 (9.5)     | 2288 (6.1)  | 5919 (10.4)   | 6338 (8.9)   | 0.060 |
| Other drug abuse             | 1217 (3.5)  | 1260 (2.3)   | 362 (2.5)                      | 5141 (2.1)      | 693 (1.8)   | 1931 (3.4)    | 2023 (2.8)   | 0.047 |
| Anxiety                      | 5853 (16.6) | 6879 (12.4)  | 2034 (13.8)                    | 33646 (14.0)    | 4020 (10.7) | 8842 (15.6)   | 11532 (16.2) | 0.074 |
| Bipolar disorder             | 1052 (3.0)  | 1409 (2.5)   | 391 (2.6)                      | 5957 (2.5)      | 892 (2.4)   | 1584 (2.8)    | 2025 (2.8)   | 0.017 |
| Bone fracture                | 1985 (5.6)  | 2524 (4.6)   | 709 (4.8)                      | 12120 (5.0)     | 1870 (5.0)  | 3321 (5.9)    | 3228 (4.5)   | 0.028 |
| Cancer                       | 2764 (7.8)  | 2420 (4.4)   | 709 (4.8)                      | 13158 (5.5)     | 1904 (5.1)  | 2887 (5.1)    | 3133 (4.4)   | 0.052 |
| Chronic renal insufficiency  | 1173 (3.3)  | 1036 (1.9)   | 376 (2.5)                      | 6425 (2.7)      | 860 (2.3)   | 1601 (2.8)    | 1791 (2.5)   | 0.034 |
| Congestive heart failure     | 1171 (3.3)  | 1288 (2.3)   | 431 (2.9)                      | 6128 (2.5)      | 1020 (2.7)  | 1548 (2.7)    | 1598 (2.2)   | 0.027 |
| COPD/asthma/oxygen           | 4601 (13.1) | 6486 (11.7)  | 1722 (11.7)                    | 28628 (11.9)    | 4295 (11.4) | 7053 (12.4)   | 8182 (11.5)  | 0.021 |
| Dementia                     | 687 (2.0)   | 368 (0.7)    | 138 (0.9)                      | 2117 (0.9)      | 364 (1.0)   | 563 (1.0)     | 729 (1.0)    | 0.036 |
| Depression                   | 7003 (19.9) | 8393 (15.2)  | 2345 (15.9)                    | 39781 (16.5)    | 5878 (15.7) | 9895 (17.5)   | 12974 (18.2) | 0.052 |
| Diabetes                     | 5671 (16.1) | 7312 (13.2)  | 2267 (15.4)                    | 37662 (15.6)    | 5398 (14.4) | 8949 (15.8)   | 10448 (14.6) | 0.033 |
| Epilepsy                     | 758 (2.2)   | 887 (1.6)    | 237 (1.6)                      | 3401 (1.4)      | 557 (1.5)   | 870 (1.5)     | 1210 (1.7)   | 0.020 |
| HIV                          | 120 (0.3)   | 163 (0.3)    | 29 (0.2)                       | 685 (0.3)       | 83 (0.2)    | 152 (0.3)     | 180 (0.3)    | 0.011 |
| Intentional self-harm        | 22 (0.1)    | 21 (0.0)     | 7 (0.0)                        | 103 (0.0)       | 11 (0.0)    | 38 (0.1)      | 25 (0.0)     | 0.008 |
| Liver disease                | 1763 (5.0)  | 2086 (3.8)   | 518 (3.5)                      | 10035 (4.2)     | 1313 (3.5)  | 2323 (4.1)    | 2697 (3.8)   | 0.030 |
| Musculoskeletal injury       | 2622 (7.4)  | 5000 (9.0)   | 1369 (9.3)                     | 23576 (9.8)     | 3362 (9.0)  | 5189 (9.2)    | 5706 (8.0)   | 0.033 |
| Multiple sclerosis           | 1514 (4.3)  | 259 (0.5)    | 72 (0.5)                       | 1232 (0.5)      | 215 (0.6)   | 272 (0.5)     | 806 (1.1)    | 0.089 |
| Obesity                      | 2752 (7.8)  | 2772 (5.0)   | 868 (5.9)                      | 17750 (7.4)     | 1840 (4.9)  | 4696 (8.3)    | 5578 (7.8)   | 0.068 |
| Pneumonia                    | 1047 (3.0)  | 1410 (2.5)   | 352 (2.4)                      | 5797 (2.4)      | 970 (2.6)   | 1330 (2.3)    | 1439 (2.0)   | 0.022 |
| Psychosis                    | 427 (1.2)   | 427 (0.8)    | 120 (0.8)                      | 1688 (0.7)      | 264 (0.7)   | 492 (0.9)     | 485 (0.7)    | 0.021 |

|                                                | Baclofen     | Carisoprodol | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone   | Methocarbamol | Tizanidine   | SMD   |
|------------------------------------------------|--------------|--------------|--------------------------------|-----------------|--------------|---------------|--------------|-------|
| Renal dysfunction                              | 2077 (5.9)   | 2126 (3.8)   | 700 (4.7)                      | 11561 (4.8)     | 1711 (4.6)   | 2811 (5.0)    | 3060 (4.3)   | 0.035 |
| Spasticity                                     | 7855 (22.3)  | 5962 (10.8)  | 1800 (12.2)                    | 27559 (11.4)    | 4343 (11.6)  | 7513 (13.3)   | 10128 (14.2) | 0.110 |
| Urinary calculus                               | 995 (2.8)    | 1369 (2.5)   | 435 (2.9)                      | 6747 (2.8)      | 941 (2.5)    | 1600 (2.8)    | 1947 (2.7)   | 0.013 |
| Urinary tract infection                        | 3435 (9.8)   | 4120 (7.5)   | 1283 (8.7)                     | 19498 (8.1)     | 2958 (7.9)   | 4521 (8.0)    | 5503 (7.7)   | 0.031 |
| <b>Pain conditions (n (%))</b>                 |              |              |                                |                 |              |               |              |       |
| Abdominal pain                                 | 5880 (16.7)  | 7842 (14.2)  | 2315 (15.7)                    | 37305 (15.5)    | 5512 (14.7)  | 8668 (15.3)   | 10387 (14.5) | 0.028 |
| Back and neck pain                             | 24619 (69.9) | 35677 (64.5) | 9714 (65.8)                    | 158492 (65.8)   | 24798 (66.1) | 40650 (71.8)  | 53176 (74.5) | 0.095 |
| Back pain without radiculopathy                | 21778 (61.8) | 32770 (59.3) | 8893 (60.3)                    | 144722 (60.1)   | 22388 (59.7) | 37263 (65.8)  | 46836 (65.6) | 0.065 |
| Back pain with radiculopathy                   | 8501 (24.1)  | 10971 (19.8) | 2809 (19.0)                    | 48686 (20.2)    | 7208 (19.2)  | 14683 (25.9)  | 19363 (27.1) | 0.096 |
| Dental pain                                    | 225 (0.6)    | 432 (0.8)    | 107 (0.7)                      | 1646 (0.7)      | 183 (0.5)    | 350 (0.6)     | 398 (0.6)    | 0.015 |
| Diabetic neuropathy                            | 1096 (3.1)   | 943 (1.7)    | 362 (2.5)                      | 5740 (2.4)      | 727 (1.9)    | 1508 (2.7)    | 1897 (2.7)   | 0.037 |
| Fibromyalgia                                   | 5178 (14.7)  | 6446 (11.7)  | 1978 (13.4)                    | 29150 (12.1)    | 5008 (13.4)  | 6570 (11.6)   | 11727 (16.4) | 0.061 |
| Headache                                       | 5379 (15.3)  | 7797 (14.1)  | 2327 (15.8)                    | 34687 (14.4)    | 5108 (13.6)  | 7818 (13.8)   | 12090 (16.9) | 0.040 |
| Osteoarthritis                                 | 6744 (19.2)  | 9628 (17.4)  | 2836 (19.2)                    | 48926 (20.3)    | 7399 (19.7)  | 11799 (20.8)  | 13618 (19.1) | 0.032 |
| Rheumatoid arthritis                           | 1390 (3.9)   | 2027 (3.7)   | 658 (4.5)                      | 11238 (4.7)     | 1852 (4.9)   | 2288 (4.0)    | 3121 (4.4)   | 0.027 |
| Postherpetic neuralgia                         | 119 (0.3)    | 84 (0.2)     | 35 (0.2)                       | 494 (0.2)       | 73 (0.2)     | 139 (0.2)     | 187 (0.3)    | 0.014 |
| Other arthritis                                | 18357 (52.1) | 25361 (45.9) | 7381 (50.0)                    | 121426 (50.4)   | 18141 (48.4) | 29088 (51.3)  | 35968 (50.4) | 0.048 |
| Other neuropathy                               | 14595 (41.4) | 17718 (32.0) | 4652 (31.5)                    | 78386 (32.6)    | 12009 (32.0) | 22314 (39.4)  | 30374 (42.5) | 0.118 |
| Other unspecified pain                         | 14555 (41.3) | 12420 (22.5) | 4415 (29.9)                    | 71892 (29.9)    | 8526 (22.7)  | 20331 (35.9)  | 29363 (41.1) | 0.206 |
| <b>Other prescription fills (n (%))</b>        |              |              |                                |                 |              |               |              |       |
| Antibiotics                                    | 19745 (56.1) | 31458 (56.9) | 8554 (58.0)                    | 136800 (56.8)   | 21818 (58.2) | 31807 (56.1)  | 38942 (54.5) | 0.030 |
| Anticonvulsants                                | 4408 (12.5)  | 4772 (8.6)   | 1451 (9.8)                     | 20166 (8.4)     | 3746 (10.0)  | 5022 (8.9)    | 8503 (11.9)  | 0.063 |
| Antidepressants, SSRIs                         | 9397 (26.7)  | 13760 (24.9) | 3787 (25.7)                    | 61399 (25.5)    | 10143 (27.0) | 14660 (25.9)  | 18395 (25.8) | 0.020 |
| Antidepressants, SNRIs                         | 6836 (19.4)  | 8040 (14.5)  | 2396 (16.2)                    | 37399 (15.5)    | 6534 (17.4)  | 9092 (16.0)   | 14146 (19.8) | 0.063 |
| Antidepressants, TCAs                          | 3816 (10.8)  | 4721 (8.5)   | 1392 (9.4)                     | 20413 (8.5)     | 3399 (9.1)   | 4861 (8.6)    | 7301 (10.2)  | 0.037 |
| Antidepressants, other                         | 6050 (17.2)  | 7681 (13.9)  | 2261 (15.3)                    | 34816 (14.5)    | 5815 (15.5)  | 9058 (16.0)   | 11743 (16.4) | 0.038 |
| Antidiabetics                                  | 4825 (13.7)  | 6459 (11.7)  | 2029 (13.8)                    | 33091 (13.7)    | 4927 (13.1)  | 7828 (13.8)   | 9121 (12.8)  | 0.026 |
| Antipsychotics, atypical                       | 2175 (6.2)   | 2687 (4.9)   | 744 (5.0)                      | 10930 (4.5)     | 1915 (5.1)   | 3002 (5.3)    | 4011 (5.6)   | 0.028 |
| Antipsychotics, typical                        | 1090 (3.1)   | 1137 (2.1)   | 310 (2.1)                      | 4680 (1.9)      | 756 (2.0)    | 1031 (1.8)    | 1178 (1.6)   | 0.032 |
| Barbiturates                                   | 221 (0.6)    | 459 (0.8)    | 122 (0.8)                      | 1362 (0.6)      | 308 (0.8)    | 398 (0.7)     | 355 (0.5)    | 0.020 |
| Benzodiazepines                                | 15604 (44.3) | 27008 (48.8) | 6441 (43.7)                    | 98822 (41.0)    | 15929 (42.5) | 24075 (42.5)  | 30578 (42.8) | 0.054 |
| CNS stimulants                                 | 1735 (4.9)   | 2358 (4.3)   | 680 (4.6)                      | 9299 (3.9)      | 1491 (4.0)   | 2419 (4.3)    | 3433 (4.8)   | 0.024 |
| Dementia agents                                | 400 (1.1)    | 306 (0.6)    | 146 (1.0)                      | 1482 (0.6)      | 344 (0.9)    | 415 (0.7)     | 508 (0.7)    | 0.029 |
| Gabapentinoids                                 | 12664 (36.0) | 11617 (21.0) | 3594 (24.4)                    | 58165 (24.2)    | 9195 (24.5)  | 16067 (28.4)  | 23456 (32.9) | 0.141 |
| Lithium                                        | 153 (0.4)    | 260 (0.5)    | 63 (0.4)                       | 1003 (0.4)      | 169 (0.5)    | 246 (0.4)     | 298 (0.4)    | 0.003 |
| Multiple sclerosis agents                      | 775 (2.2)    | 102 (0.2)    | 33 (0.2)                       | 536 (0.2)       | 87 (0.2)     | 108 (0.2)     | 382 (0.5)    | 0.066 |
| NSAIDs                                         | 13241 (37.6) | 21376 (38.7) | 7019 (47.6)                    | 104532 (43.4)   | 17081 (45.5) | 24929 (44.0)  | 29174 (40.9) | 0.090 |
| Other sedative hypnotics                       | 6331 (18.0)  | 11243 (20.3) | 2636 (17.9)                    | 44146 (18.3)    | 7813 (20.8)  | 9903 (17.5)   | 13421 (18.8) | 0.038 |
| Smoking cessation                              | 3249 (9.2)   | 4653 (8.4)   | 1329 (9.0)                     | 20861 (8.7)     | 3523 (9.4)   | 4923 (8.7)    | 6525 (9.1)   | 0.015 |
| Triptans                                       | 1965 (5.6)   | 3053 (5.5)   | 922 (6.2)                      | 13360 (5.5)     | 2396 (6.4)   | 2989 (5.3)    | 4894 (6.9)   | 0.029 |
| Other CNS depressants                          | 154 (0.4)    | 241 (0.4)    | 64 (0.4)                       | 887 (0.4)       | 188 (0.5)    | 180 (0.3)     | 311 (0.4)    | 0.010 |
| <b>Prescription opioid utilization (n (%))</b> |              |              |                                |                 |              |               |              |       |
| Prescription opioid on index date              |              |              |                                |                 |              |               |              |       |
| Buprenorphine                                  | 353 (1.0)    | 304 (0.5)    | 116 (0.8)                      | 1118 (0.5)      | 185 (0.5)    | 593 (1.0)     | 702 (1.0)    | 0.035 |
| Butorphanol                                    | 90 (0.3)     | 246 (0.4)    | 85 (0.6)                       | 987 (0.4)       | 155 (0.4)    | 154 (0.3)     | 321 (0.4)    | 0.021 |
| Codeine                                        | 1145 (3.3)   | 2872 (5.2)   | 786 (5.3)                      | 11003 (4.6)     | 1703 (4.5)   | 2442 (4.3)    | 2230 (3.1)   | 0.051 |
| Dihydrocodeine                                 | 13 (0.0)     | 49 (0.1)     | 19 (0.1)                       | 160 (0.1)       | 51 (0.1)     | 31 (0.1)      | 51 (0.1)     | 0.015 |
| Fentanyl                                       | 3334 (9.5)   | 3555 (6.4)   | 887 (6.0)                      | 13506 (5.6)     | 2804 (7.5)   | 3331 (5.9)    | 5515 (7.7)   | 0.061 |
| Hydrocodone                                    | 17280 (49.1) | 35460 (64.1) | 8677 (58.8)                    | 143263 (59.5)   | 21095 (56.2) | 33859 (59.8)  | 36744 (51.5) | 0.126 |
| Hydromorphone                                  | 1214 (3.4)   | 1309 (2.4)   | 262 (1.8)                      | 4796 (2.0)      | 656 (1.7)    | 1428 (2.5)    | 1834 (2.6)   | 0.044 |
| Levorphanol                                    | 15 (0.0)     | 4 (0.0)      | 2 (0.0)                        | 18 (0.0)        | 8 (0.0)      | 14 (0.0)      | 31 (0.0)     | 0.012 |
| Meperidine                                     | 74 (0.2)     | 284 (0.5)    | 50 (0.3)                       | 681 (0.3)       | 126 (0.3)    | 183 (0.3)     | 187 (0.3)    | 0.018 |

|                                                                                       | Baclofen             | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine      | Metaxalone           | Methocarbamol        | Tizanidine           | SMD   |
|---------------------------------------------------------------------------------------|----------------------|----------------------|--------------------------------|----------------------|----------------------|----------------------|----------------------|-------|
| Methadone                                                                             | 1669 (4.7)           | 1669 (3.0)           | 348 (2.4)                      | 5618 (2.3)           | 924 (2.5)            | 1477 (2.6)           | 2659 (3.7)           | 0.056 |
| Morphine                                                                              | 3460 (9.8)           | 3336 (6.0)           | 816 (5.5)                      | 13000 (5.4)          | 2175 (5.8)           | 3590 (6.3)           | 5811 (8.1)           | 0.070 |
| Opium                                                                                 | 20 (0.1)             | 15 (0.0)             | 7 (0.0)                        | 113 (0.0)            | 18 (0.0)             | 27 (0.0)             | 26 (0.0)             | 0.005 |
| Oxycodone                                                                             | 12530 (35.6)         | 18505 (33.5)         | 4033 (27.3)                    | 73660 (30.6)         | 10709 (28.5)         | 19154 (33.8)         | 25195 (35.3)         | 0.085 |
| Oxymorphone                                                                           | 703 (2.0)            | 629 (1.1)            | 206 (1.4)                      | 2408 (1.0)           | 405 (1.1)            | 694 (1.2)            | 1465 (2.1)           | 0.041 |
| Pentazocine                                                                           | 53 (0.2)             | 169 (0.3)            | 55 (0.4)                       | 455 (0.2)            | 105 (0.3)            | 116 (0.2)            | 140 (0.2)            | 0.019 |
| Propoxyphene                                                                          | 227 (0.6)            | 912 (1.6)            | 315 (2.1)                      | 3443 (1.4)           | 864 (2.3)            | 666 (1.2)            | 575 (0.8)            | 0.065 |
| Tapentadol                                                                            | 461 (1.3)            | 338 (0.6)            | 143 (1.0)                      | 1858 (0.8)           | 270 (0.7)            | 593 (1.0)            | 1024 (1.4)           | 0.038 |
| Tramadol                                                                              | 6153 (17.5)          | 8652 (15.6)          | 3531 (23.9)                    | 53994 (22.4)         | 9392 (25.0)          | 12126 (21.4)         | 13576 (19.0)         | 0.106 |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 174.30 (16.41)       | 173.66 (17.26)       | 174.09 (16.42)                 | 173.54 (17.20)       | 173.47 (17.20)       | 173.62 (17.14)       | 174.68 (15.88)       | 0.032 |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                      |                      |                                |                      |                      |                      |                      |       |
| (Index - 180) to (index - 151)                                                        | 2314.76<br>(3690.25) | 2184.26<br>(3681.84) | 1753.54<br>(2961.42)           | 1662.88<br>(2880.18) | 1763.95<br>(3021.84) | 1696.56<br>(2841.05) | 2159.33<br>(3456.29) | 0.097 |
| (Index - 150) to (index - 121)                                                        | 2392.23<br>(3686.29) | 2240.78<br>(3675.07) | 1817.53<br>(2987.70)           | 1718.33<br>(2891.30) | 1828.26<br>(3066.69) | 1763.14<br>(2901.34) | 2208.11<br>(3458.22) | 0.097 |
| (Index - 120) to (index - 91)                                                         | 2606.62<br>(3828.70) | 2443.18<br>(3813.10) | 1956.33<br>(3080.29)           | 1861.83<br>(2941.53) | 1987.92<br>(3153.21) | 1903.69<br>(2972.87) | 2389.77<br>(3533.11) | 0.105 |
| (Index - 90) to (index - 61)                                                          | 2610.62<br>(3780.29) | 2480.63<br>(3838.87) | 1933.82<br>(2983.01)           | 1881.01<br>(2980.35) | 2012.16<br>(3186.87) | 1923.74<br>(2955.03) | 2399.94<br>(3568.43) | 0.106 |
| (Index - 60) to (index - 31)                                                          | 2628.48<br>(3882.65) | 2481.34<br>(3844.58) | 1958.86<br>(3080.37)           | 1883.49<br>(2982.83) | 2006.52<br>(3209.15) | 1942.80<br>(2976.12) | 2386.75<br>(3559.27) | 0.104 |
| (Index - 30) to index                                                                 | 3236.83<br>(4696.30) | 3181.01<br>(4867.46) | 2301.38<br>(3616.53)           | 2254.17<br>(3544.75) | 2417.00<br>(3822.20) | 2362.37<br>(3524.88) | 3038.92<br>(4528.87) | 0.123 |
| <b>Healthcare utilization (mean (SD))</b>                                             |                      |                      |                                |                      |                      |                      |                      |       |
| Number of physician visits                                                            | 8.91 (6.92)          | 7.70 (6.28)          | 7.74 (6.25)                    | 7.69 (6.16)          | 7.97 (6.48)          | 8.09 (6.17)          | 8.32 (6.18)          | 0.078 |
| Number of distinct prescribed medications                                             | 11.79 (5.79)         | 10.94 (5.64)         | 11.63 (5.75)                   | 11.14 (5.58)         | 11.85 (5.97)         | 11.40 (5.61)         | 11.28 (5.67)         | 0.073 |
| Number of hospitalizations                                                            | 0.23 (0.60)          | 0.19 (0.52)          | 0.15 (0.48)                    | 0.19 (0.52)          | 0.18 (0.51)          | 0.27 (0.60)          | 0.15 (0.48)          | 0.090 |
| Number of hospitalization days                                                        | 1.38 (4.88)          | 0.91 (3.31)          | 0.78 (3.04)                    | 0.94 (3.51)          | 0.91 (3.41)          | 1.33 (3.95)          | 0.77 (3.25)          | 0.074 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 11. Characteristics of patients who initiated skeletal muscle relaxants while on long-term opioid therapy in IBM® MarketScan® Research Database, 2003-2018 (post-matching weights)**

|                                        | Baclofen          | Carisoprodol   | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone     | Methocarbamol  | Tizanidine     | SMD   |
|----------------------------------------|-------------------|----------------|--------------------------------|-----------------|----------------|----------------|----------------|-------|
| n                                      | 12330.77          | 12488.71       | 12568.51                       | 12564.91        | 12529.55       | 12538.98       | 12419.28       |       |
| <b>Demographic information (n (%))</b> |                   |                |                                |                 |                |                |                |       |
| Age (mean (SD))                        | 51.93 (13.48)     | 52.26 (12.56)  | 52.25 (13.46)                  | 52.32 (12.78)   | 52.10 (13.17)  | 52.20 (13.25)  | 51.91 (12.86)  | 0.015 |
| Sex                                    |                   |                |                                |                 |                |                |                | 0.004 |
| Male                                   | 4866.57<br>(39.5) | 4963.41 (39.7) | 5017.11 (39.9)                 | 5007.21 (39.9)  | 4946.45 (39.5) | 4980.88 (39.7) | 4929.48 (39.7) |       |
| Female                                 | 7464.2 (60.5)     | 7525.3 (60.3)  | 7551.4 (60.1)                  | 7557.7 (60.1)   | 7583.1 (60.5)  | 7558.1 (60.3)  | 7489.8 (60.3)  |       |
| State                                  |                   |                |                                |                 |                |                |                | 0.041 |
| AK                                     | 6.9 (0.1)         | 6.6 (0.1)      | 6.9 (0.1)                      | 6.8 (0.1)       | 6.9 (0.1)      | 6.7 (0.1)      | 7.3 (0.1)      |       |
| AL                                     | 302.4 (2.5)       | 306.2 (2.5)    | 317.4 (2.5)                    | 321.4 (2.6)     | 319.7 (2.6)    | 310.8 (2.5)    | 311.4 (2.5)    |       |
| AR                                     | 88.1 (0.7)        | 97.8 (0.8)     | 93.5 (0.7)                     | 93.2 (0.7)      | 92.4 (0.7)     | 98.8 (0.8)     | 96.9 (0.8)     |       |
| AZ                                     | 161.9 (1.3)       | 163.1 (1.3)    | 165.4 (1.3)                    | 165.2 (1.3)     | 173.4 (1.4)    | 179.4 (1.4)    | 148.7 (1.2)    |       |
| CA                                     | 371.8 (3.0)       | 384.8 (3.1)    | 371.8 (3.0)                    | 373.8 (3.0)     | 381.7 (3.0)    | 404.7 (3.2)    | 343.6 (2.8)    |       |
| CO                                     | 138.9 (1.1)       | 148.9 (1.2)    | 139.9 (1.1)                    | 143.4 (1.1)     | 150.2 (1.2)    | 134.7 (1.1)    | 146.8 (1.2)    |       |
| CT                                     | 67.0 (0.5)        | 84.3 (0.7)     | 79.1 (0.6)                     | 80.4 (0.6)      | 83.8 (0.7)     | 74.3 (0.6)     | 77.6 (0.6)     |       |
| DC                                     | 3.0 (0.0)         | 2.6 (0.0)      | 3.0 (0.0)                      | 2.8 (0.0)       | 3.8 (0.0)      | 2.0 (0.0)      | 2.5 (0.0)      |       |
| DE                                     | 49.5 (0.4)        | 51.4 (0.4)     | 52.5 (0.4)                     | 53.7 (0.4)      | 55.3 (0.4)     | 53.1 (0.4)     | 55.6 (0.4)     |       |
| FL                                     | 684.7 (5.6)       | 667.8 (5.3)    | 687.3 (5.5)                    | 689.3 (5.5)     | 666.2 (5.3)    | 675.8 (5.4)    | 691.9 (5.6)    |       |
| GA                                     | 459.1 (3.7)       | 469.3 (3.8)    | 473.8 (3.8)                    | 478.2 (3.8)     | 467.8 (3.7)    | 481.6 (3.8)    | 486.9 (3.9)    |       |
| HI                                     | 0.8 (0.0)         | 0.7 (0.0)      | 0.9 (0.0)                      | 0.8 (0.0)       | 1.0 (0.0)      | 1.0 (0.0)      | 1.0 (0.0)      |       |
| IA                                     | 89.8 (0.7)        | 98.0 (0.8)     | 95.7 (0.8)                     | 92.6 (0.7)      | 92.6 (0.7)     | 90.7 (0.7)     | 89.0 (0.7)     |       |
| ID                                     | 80.4 (0.7)        | 79.5 (0.6)     | 76.6 (0.6)                     | 77.0 (0.6)      | 75.7 (0.6)     | 76.4 (0.6)     | 79.9 (0.6)     |       |
| IL                                     | 534.6 (4.3)       | 573.0 (4.6)    | 574.5 (4.6)                    | 560.2 (4.5)     | 560.7 (4.5)    | 579.3 (4.6)    | 544.0 (4.4)    |       |
| IN                                     | 778.3 (6.3)       | 745.7 (6.0)    | 758.1 (6.0)                    | 748.8 (6.0)     | 752.2 (6.0)    | 763.4 (6.1)    | 756.7 (6.1)    |       |
| KS                                     | 142.9 (1.2)       | 142.4 (1.1)    | 137.2 (1.1)                    | 138.4 (1.1)     | 140.0 (1.1)    | 126.7 (1.0)    | 139.7 (1.1)    |       |
| KY                                     | 452.1 (3.7)       | 399.3 (3.2)    | 419.0 (3.3)                    | 411.9 (3.3)     | 411.1 (3.3)    | 417.7 (3.3)    | 422.2 (3.4)    |       |
| LA                                     | 428.3 (3.5)       | 378.2 (3.0)    | 399.5 (3.2)                    | 407.5 (3.2)     | 392.7 (3.1)    | 399.3 (3.2)    | 412.7 (3.3)    |       |
| MA                                     | 77.2 (0.6)        | 96.4 (0.8)     | 88.5 (0.7)                     | 85.7 (0.7)      | 84.5 (0.7)     | 86.6 (0.7)     | 84.2 (0.7)     |       |
| MD                                     | 152.4 (1.2)       | 158.9 (1.3)    | 154.9 (1.2)                    | 155.1 (1.2)     | 154.6 (1.2)    | 150.7 (1.2)    | 155.3 (1.3)    |       |
| ME                                     | 29.7 (0.2)        | 33.0 (0.3)     | 29.1 (0.2)                     | 29.6 (0.2)      | 31.9 (0.3)     | 28.7 (0.2)     | 28.4 (0.2)     |       |
| MI                                     | 1151.3 (9.3)      | 1145.9 (9.2)   | 1223.3 (9.7)                   | 1223.2 (9.7)    | 1186.2 (9.5)   | 1154.4 (9.2)   | 1170.0 (9.4)   |       |
| MN                                     | 31.6 (0.3)        | 33.3 (0.3)     | 37.2 (0.3)                     | 33.7 (0.3)      | 34.4 (0.3)     | 36.6 (0.3)     | 32.1 (0.3)     |       |
| MO                                     | 374.9 (3.0)       | 404.7 (3.2)    | 398.7 (3.2)                    | 395.7 (3.1)     | 408.4 (3.3)    | 406.0 (3.2)    | 389.5 (3.1)    |       |
| MS                                     | 139.7 (1.1)       | 150.1 (1.2)    | 156.2 (1.2)                    | 158.0 (1.3)     | 156.6 (1.2)    | 151.9 (1.2)    | 160.3 (1.3)    |       |
| MT                                     | 44.5 (0.4)        | 43.0 (0.3)     | 41.5 (0.3)                     | 42.5 (0.3)      | 42.2 (0.3)     | 39.0 (0.3)     | 41.4 (0.3)     |       |
| NC                                     | 437.8 (3.6)       | 445.6 (3.6)    | 440.5 (3.5)                    | 437.9 (3.5)     | 433.4 (3.5)    | 424.4 (3.4)    | 424.3 (3.4)    |       |
| ND                                     | 2.8 (0.0)         | 2.8 (0.0)      | 2.5 (0.0)                      | 2.5 (0.0)       | 2.5 (0.0)      | 2.9 (0.0)      | 2.9 (0.0)      |       |
| NE                                     | 18.3 (0.1)        | 21.6 (0.2)     | 21.1 (0.2)                     | 20.6 (0.2)      | 20.7 (0.2)     | 22.1 (0.2)     | 22.5 (0.2)     |       |
| NH                                     | 37.6 (0.3)        | 42.1 (0.3)     | 38.4 (0.3)                     | 37.6 (0.3)      | 40.2 (0.3)     | 38.0 (0.3)     | 39.2 (0.3)     |       |
| NJ                                     | 118.5 (1.0)       | 127.9 (1.0)    | 121.6 (1.0)                    | 122.9 (1.0)     | 123.7 (1.0)    | 127.8 (1.0)    | 125.3 (1.0)    |       |
| NM                                     | 122.8 (1.0)       | 123.0 (1.0)    | 126.4 (1.0)                    | 128.7 (1.0)     | 127.0 (1.0)    | 122.9 (1.0)    | 112.3 (0.9)    |       |
| NV                                     | 62.8 (0.5)        | 61.7 (0.5)     | 64.0 (0.5)                     | 65.5 (0.5)      | 58.9 (0.5)     | 60.1 (0.5)     | 57.4 (0.5)     |       |
| NY                                     | 458.3 (3.7)       | 430.9 (3.5)    | 432.3 (3.4)                    | 431.2 (3.4)     | 434.0 (3.5)    | 441.1 (3.5)    | 411.1 (3.3)    |       |
| OH                                     | 830.9 (6.7)       | 853.3 (6.8)    | 874.3 (7.0)                    | 880.1 (7.0)     | 856.2 (6.8)    | 900.2 (7.2)    | 876.3 (7.1)    |       |
| OK                                     | 365.0 (3.0)       | 362.9 (2.9)    | 374.9 (3.0)                    | 372.2 (3.0)     | 386.3 (3.1)    | 388.6 (3.1)    | 372.4 (3.0)    |       |
| OR                                     | 62.7 (0.5)        | 68.8 (0.6)     | 64.0 (0.5)                     | 64.7 (0.5)      | 69.8 (0.6)     | 65.9 (0.5)     | 65.0 (0.5)     |       |
| PA                                     | 482.5 (3.9)       | 504.4 (4.0)    | 470.9 (3.7)                    | 476.0 (3.8)     | 482.5 (3.9)    | 459.0 (3.7)    | 476.5 (3.8)    |       |
| RI                                     | 9.0 (0.1)         | 12.0 (0.1)     | 11.0 (0.1)                     | 10.9 (0.1)      | 10.7 (0.1)     | 11.8 (0.1)     | 11.2 (0.1)     |       |

|                              | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| SC                           | 426.5 (3.5)   | 447.2 (3.6)   | 433.0 (3.4)                    | 432.7 (3.4)     | 422.0 (3.4)   | 423.0 (3.4)   | 442.9 (3.6)   |       |
| SD                           | 13.7 (0.1)    | 15.8 (0.1)    | 14.8 (0.1)                     | 14.3 (0.1)      | 13.8 (0.1)    | 13.6 (0.1)    | 11.6 (0.1)    |       |
| TN                           | 517.6 (4.2)   | 516.7 (4.1)   | 526.7 (4.2)                    | 528.1 (4.2)     | 521.6 (4.2)   | 544.7 (4.3)   | 524.7 (4.2)   |       |
| TX                           | 917.9 (7.4)   | 948.3 (7.6)   | 947.0 (7.5)                    | 944.2 (7.5)     | 962.2 (7.7)   | 940.8 (7.5)   | 945.4 (7.6)   |       |
| UT                           | 60.3 (0.5)    | 64.2 (0.5)    | 62.9 (0.5)                     | 62.6 (0.5)      | 67.6 (0.5)    | 63.1 (0.5)    | 63.2 (0.5)    |       |
| VA                           | 261.6 (2.1)   | 278.9 (2.2)   | 268.2 (2.1)                    | 270.4 (2.2)     | 278.8 (2.2)   | 268.0 (2.1)   | 276.4 (2.2)   |       |
| VT                           | 1.7 (0.0)     | 2.0 (0.0)     | 2.0 (0.0)                      | 2.0 (0.0)       | 2.0 (0.0)     | 1.8 (0.0)     | 2.4 (0.0)     |       |
| WA                           | 49.8 (0.4)    | 53.3 (0.4)    | 52.0 (0.4)                     | 51.9 (0.4)      | 54.2 (0.4)    | 53.3 (0.4)    | 47.1 (0.4)    |       |
| WI                           | 104.8 (0.8)   | 100.7 (0.8)   | 104.3 (0.8)                    | 105.0 (0.8)     | 105.1 (0.8)   | 100.4 (0.8)   | 97.0 (0.8)    |       |
| WV                           | 111.4 (0.9)   | 123.0 (1.0)   | 115.7 (0.9)                    | 117.4 (0.9)     | 114.4 (0.9)   | 118.3 (0.9)   | 117.5 (0.9)   |       |
| WY                           | 14.9 (0.1)    | 16.7 (0.1)    | 18.4 (0.1)                     | 16.4 (0.1)      | 15.9 (0.1)    | 17.4 (0.1)    | 19.2 (0.2)    |       |
| Year                         |               |               |                                |                 |               |               |               | 0.029 |
| 2003                         | 232.0 (1.9)   | 238.4 (1.9)   | 243.1 (1.9)                    | 232.2 (1.8)     | 236.3 (1.9)   | 230.4 (1.8)   | 238.4 (1.9)   |       |
| 2004                         | 492.3 (4.0)   | 541.6 (4.3)   | 517.5 (4.1)                    | 514.9 (4.1)     | 530.2 (4.2)   | 510.3 (4.1)   | 523.3 (4.2)   |       |
| 2005                         | 576.4 (4.7)   | 645.7 (5.2)   | 619.1 (4.9)                    | 620.5 (4.9)     | 638.6 (5.1)   | 594.1 (4.7)   | 617.6 (5.0)   |       |
| 2006                         | 549.4 (4.5)   | 623.6 (5.0)   | 586.6 (4.7)                    | 591.9 (4.7)     | 598.9 (4.8)   | 586.2 (4.7)   | 597.4 (4.8)   |       |
| 2007                         | 675.5 (5.5)   | 727.6 (5.8)   | 719.9 (5.7)                    | 713.5 (5.7)     | 711.1 (5.7)   | 703.1 (5.6)   | 697.5 (5.6)   |       |
| 2008                         | 866.6 (7.0)   | 915.9 (7.3)   | 893.0 (7.1)                    | 900.2 (7.2)     | 898.6 (7.2)   | 887.0 (7.1)   | 882.3 (7.1)   |       |
| 2009                         | 1102.0 (8.9)  | 1113.8 (8.9)  | 1113.3 (8.9)                   | 1114.1 (8.9)    | 1090.2 (8.7)  | 1097.3 (8.8)  | 1087.4 (8.8)  |       |
| 2010                         | 1129.5 (9.2)  | 1163.2 (9.3)  | 1159.4 (9.2)                   | 1160.6 (9.2)    | 1162.5 (9.3)  | 1147.5 (9.2)  | 1100.0 (8.9)  |       |
| 2011                         | 1297.4 (10.5) | 1298.8 (10.4) | 1319.5 (10.5)                  | 1317.9 (10.5)   | 1308.5 (10.4) | 1348.2 (10.8) | 1290.0 (10.4) |       |
| 2012                         | 1444.4 (11.7) | 1445.7 (11.6) | 1476.6 (11.7)                  | 1481.4 (11.8)   | 1478.8 (11.8) | 1504.2 (12.0) | 1432.7 (11.5) |       |
| 2013                         | 979.5 (7.9)   | 990.1 (7.9)   | 1009.4 (8.0)                   | 1017.4 (8.1)    | 1006.0 (8.0)  | 1018.2 (8.1)  | 991.8 (8.0)   |       |
| 2014                         | 937.4 (7.6)   | 896.9 (7.2)   | 929.5 (7.4)                    | 926.2 (7.4)     | 919.7 (7.3)   | 936.8 (7.5)   | 926.3 (7.5)   |       |
| 2015                         | 720.0 (5.8)   | 678.7 (5.4)   | 689.5 (5.5)                    | 699.1 (5.6)     | 687.1 (5.5)   | 701.2 (5.6)   | 717.4 (5.8)   |       |
| 2016                         | 631.3 (5.1)   | 566.5 (4.5)   | 611.5 (4.9)                    | 607.4 (4.8)     | 597.7 (4.8)   | 598.8 (4.8)   | 623.7 (5.0)   |       |
| 2017                         | 390.4 (3.2)   | 353.4 (2.8)   | 371.0 (3.0)                    | 369.8 (2.9)     | 370.7 (3.0)   | 373.0 (3.0)   | 388.6 (3.1)   |       |
| 2018                         | 306.9 (2.5)   | 288.7 (2.3)   | 309.7 (2.5)                    | 297.9 (2.4)     | 294.6 (2.4)   | 302.7 (2.4)   | 304.8 (2.5)   |       |
| <b>Comorbidities (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Opioid dependence            | 332.3 (2.7)   | 322.4 (2.6)   | 313.9 (2.5)                    | 312.7 (2.5)     | 316.7 (2.5)   | 320.5 (2.6)   | 328.4 (2.6)   | 0.006 |
| Opioid abuse                 | 29.3 (0.2)    | 23.0 (0.2)    | 25.6 (0.2)                     | 25.4 (0.2)      | 22.0 (0.2)    | 24.7 (0.2)    | 24.7 (0.2)    | 0.005 |
| Alcohol abuse                | 139.1 (1.1)   | 131.0 (1.0)   | 132.9 (1.1)                    | 132.7 (1.1)     | 128.1 (1.0)   | 129.4 (1.0)   | 133.0 (1.1)   | 0.004 |
| Tobacco use                  | 1073.9 (8.7)  | 1057.8 (8.5)  | 1063.0 (8.5)                   | 1073.7 (8.5)    | 1054.2 (8.4)  | 1090.0 (8.7)  | 1077.7 (8.7)  | 0.005 |
| Other drug abuse             | 337.1 (2.7)   | 322.3 (2.6)   | 313.2 (2.5)                    | 317.9 (2.5)     | 315.7 (2.5)   | 329.3 (2.6)   | 321.8 (2.6)   | 0.006 |
| Anxiety                      | 1756.0 (14.2) | 1697.5 (13.6) | 1722.0 (13.7)                  | 1732.0 (13.8)   | 1717.1 (13.7) | 1775.1 (14.2) | 1747.7 (14.1) | 0.009 |
| Bipolar disorder             | 337.4 (2.7)   | 345.3 (2.8)   | 329.0 (2.6)                    | 331.4 (2.6)     | 329.6 (2.6)   | 346.0 (2.8)   | 332.9 (2.7)   | 0.005 |
| Bone fracture                | 612.7 (5.0)   | 601.8 (4.8)   | 595.3 (4.7)                    | 598.1 (4.8)     | 591.6 (4.7)   | 595.0 (4.7)   | 595.9 (4.8)   | 0.004 |
| Cancer                       | 617.2 (5.0)   | 640.9 (5.1)   | 614.3 (4.9)                    | 632.0 (5.0)     | 624.3 (5.0)   | 633.8 (5.1)   | 635.5 (5.1)   | 0.005 |
| Chronic renal insufficiency  | 305.5 (2.5)   | 312.8 (2.5)   | 319.6 (2.5)                    | 320.0 (2.5)     | 310.7 (2.5)   | 330.6 (2.6)   | 306.3 (2.5)   | 0.004 |
| Congestive heart failure     | 349.8 (2.8)   | 336.9 (2.7)   | 359.5 (2.9)                    | 357.7 (2.8)     | 360.7 (2.9)   | 390.2 (3.1)   | 345.8 (2.8)   | 0.008 |
| COPD/asthma/oxygen           | 1449.5 (11.8) | 1491.1 (11.9) | 1494.0 (11.9)                  | 1486.5 (11.8)   | 1483.3 (11.8) | 1524.2 (12.2) | 1471.9 (11.9) | 0.004 |
| Dementia                     | 122.0 (1.0)   | 124.0 (1.0)   | 117.0 (0.9)                    | 122.1 (1.0)     | 118.4 (0.9)   | 126.5 (1.0)   | 121.2 (1.0)   | 0.003 |
| Depression                   | 2097.6 (17.0) | 2086.0 (16.7) | 2037.1 (16.2)                  | 2040.1 (16.2)   | 2056.0 (16.4) | 2044.6 (16.3) | 2057.8 (16.6) | 0.009 |
| Diabetes                     | 1855.3 (15.0) | 1890.2 (15.1) | 1917.0 (15.3)                  | 1927.6 (15.3)   | 1888.3 (15.1) | 1943.9 (15.5) | 1866.6 (15.0) | 0.006 |
| Epilepsy                     | 206.5 (1.7)   | 208.6 (1.7)   | 206.6 (1.6)                    | 206.3 (1.6)     | 205.0 (1.6)   | 212.7 (1.7)   | 210.5 (1.7)   | 0.002 |
| HIV                          | 27.8 (0.2)    | 30.7 (0.2)    | 26.0 (0.2)                     | 26.7 (0.2)      | 28.7 (0.2)    | 27.4 (0.2)    | 25.9 (0.2)    | 0.003 |
| Intentional self-harm        | 5.9 (0.0)     | 4.6 (0.0)     | 4.9 (0.0)                      | 5.5 (0.0)       | 4.5 (0.0)     | 6.0 (0.0)     | 5.8 (0.0)     | 0.003 |
| Liver disease                | 449.3 (3.6)   | 451.7 (3.6)   | 460.0 (3.7)                    | 458.4 (3.6)     | 451.4 (3.6)   | 472.5 (3.8)   | 455.8 (3.7)   | 0.003 |
| Musculoskeletal injury       | 1087.4 (8.8)  | 1055.5 (8.5)  | 1093.1 (8.7)                   | 1090.6 (8.7)    | 1070.2 (8.5)  | 1120.5 (8.9)  | 1089.5 (8.8)  | 0.007 |
| Multiple sclerosis           | 72.8 (0.6)    | 65.9 (0.5)    | 67.9 (0.5)                     | 68.0 (0.5)      | 70.0 (0.6)    | 58.7 (0.5)    | 76.7 (0.6)    | 0.008 |
| Obesity                      | 780.5 (6.3)   | 730.3 (5.8)   | 750.1 (6.0)                    | 749.6 (6.0)     | 747.4 (6.0)   | 766.3 (6.1)   | 742.2 (6.0)   | 0.007 |
| Pneumonia                    | 320.2 (2.6)   | 305.1 (2.4)   | 310.0 (2.5)                    | 303.6 (2.4)     | 302.4 (2.4)   | 329.1 (2.6)   | 297.5 (2.4)   | 0.007 |

|                                                | Baclofen      | Carisoprodol  | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine | Metaxalone    | Methocarbamol | Tizanidine    | SMD   |
|------------------------------------------------|---------------|---------------|--------------------------------|-----------------|---------------|---------------|---------------|-------|
| Psychosis                                      | 100.0 (0.8)   | 113.0 (0.9)   | 103.0 (0.8)                    | 103.8 (0.8)     | 101.6 (0.8)   | 110.3 (0.9)   | 102.2 (0.8)   | 0.004 |
| Renal dysfunction                              | 581.1 (4.7)   | 594.2 (4.8)   | 602.4 (4.8)                    | 602.7 (4.8)     | 588.4 (4.7)   | 625.9 (5.0)   | 574.0 (4.6)   | 0.006 |
| Spasticity                                     | 1673.2 (13.6) | 1624.9 (13.0) | 1608.3 (12.8)                  | 1609.9 (12.8)   | 1624.4 (13.0) | 1575.3 (12.6) | 1641.8 (13.2) | 0.011 |
| Urinary calculus                               | 356.5 (2.9)   | 348.2 (2.8)   | 348.7 (2.8)                    | 355.1 (2.8)     | 348.8 (2.8)   | 381.2 (3.0)   | 346.8 (2.8)   | 0.006 |
| Urinary tract infection                        | 1058.1 (8.6)  | 1075.8 (8.6)  | 1068.3 (8.5)                   | 1074.8 (8.6)    | 1053.1 (8.4)  | 1106.0 (8.8)  | 1067.0 (8.6)  | 0.005 |
| <b>Pain conditions (n (%))</b>                 |               |               |                                |                 |               |               |               |       |
| Abdominal pain                                 | 1908.3 (15.5) | 1907.1 (15.3) | 1926.4 (15.3)                  | 1945.8 (15.5)   | 1944.9 (15.5) | 1983.8 (15.8) | 1932.3 (15.6) | 0.006 |
| Back and neck pain                             | 8491.1 (68.9) | 8277.1 (66.3) | 8397.4 (66.8)                  | 8396.2 (66.8)   | 8356.7 (66.7) | 8416.5 (67.1) | 8364.5 (67.4) | 0.019 |
| Back pain without radiculopathy                | 7659.4 (62.1) | 7515.1 (60.2) | 7623.3 (60.7)                  | 7634.7 (60.8)   | 7563.8 (60.4) | 7652.1 (61.0) | 7577.3 (61.0) | 0.015 |
| Back pain with radiculopathy                   | 2658.7 (21.6) | 2453.6 (19.6) | 2518.0 (20.0)                  | 2523.1 (20.1)   | 2491.0 (19.9) | 2503.2 (20.0) | 2558.7 (20.6) | 0.017 |
| Dental pain                                    | 83.2 (0.7)    | 85.8 (0.7)    | 86.5 (0.7)                     | 86.8 (0.7)      | 84.7 (0.7)    | 88.0 (0.7)    | 86.5 (0.7)    | 0.001 |
| Diabetic neuropathy                            | 304.9 (2.5)   | 298.9 (2.4)   | 297.2 (2.4)                    | 297.3 (2.4)     | 288.7 (2.3)   | 302.3 (2.4)   | 285.6 (2.3)   | 0.005 |
| Fibromyalgia                                   | 1788.6 (14.5) | 1718.7 (13.8) | 1718.1 (13.7)                  | 1699.2 (13.5)   | 1730.1 (13.8) | 1729.8 (13.8) | 1773.7 (14.3) | 0.012 |
| Headache                                       | 1957.2 (15.9) | 1916.0 (15.3) | 1904.8 (15.2)                  | 1889.1 (15.0)   | 1900.9 (15.2) | 1913.9 (15.3) | 1974.8 (15.9) | 0.011 |
| Osteoarthritis                                 | 2359.3 (19.1) | 2369.5 (19.0) | 2402.9 (19.1)                  | 2394.7 (19.1)   | 2345.8 (18.7) | 2389.7 (19.1) | 2353.6 (19.0) | 0.004 |
| Rheumatoid arthritis                           | 527.2 (4.3)   | 540.8 (4.3)   | 543.1 (4.3)                    | 542.7 (4.3)     | 540.5 (4.3)   | 546.4 (4.4)   | 546.9 (4.4)   | 0.002 |
| Postherpetic neuralgia                         | 31.3 (0.3)    | 24.7 (0.2)    | 27.3 (0.2)                     | 29.4 (0.2)      | 30.7 (0.2)    | 28.2 (0.2)    | 28.0 (0.2)    | 0.005 |
| Other arthritis                                | 6223.5 (50.5) | 6175.9 (49.5) | 6243.2 (49.7)                  | 6233.9 (49.6)   | 6190.8 (49.4) | 6253.7 (49.9) | 6209.5 (50.0) | 0.009 |
| Other neuropathy                               | 4351.0 (35.3) | 4068.6 (32.6) | 4148.9 (33.0)                  | 4157.3 (33.1)   | 4130.6 (33.0) | 4116.9 (32.8) | 4238.6 (34.1) | 0.022 |
| Other unspecified pain                         | 3948.8 (32.0) | 3784.3 (30.3) | 3804.4 (30.3)                  | 3805.8 (30.3)   | 3775.3 (30.1) | 3871.1 (30.9) | 3839.6 (30.9) | 0.016 |
| <b>Other prescription fills (n (%))</b>        |               |               |                                |                 |               |               |               |       |
| Antibiotics                                    | 7097.5 (57.6) | 7194.3 (57.6) | 7205.1 (57.3)                  | 7210.7 (57.4)   | 7205.5 (57.5) | 7239.6 (57.7) | 7164.1 (57.7) | 0.004 |
| Anticonvulsants                                | 1303.8 (10.6) | 1291.7 (10.3) | 1241.7 (9.9)                   | 1236.0 (9.8)    | 1270.1 (10.1) | 1252.5 (10.0) | 1311.5 (10.6) | 0.012 |
| Antidepressants, SSRIs                         | 3182.3 (25.8) | 3228.2 (25.8) | 3233.1 (25.7)                  | 3231.9 (25.7)   | 3211.8 (25.6) | 3211.4 (25.6) | 3231.0 (26.0) | 0.004 |
| Antidepressants, SNRIs                         | 2071.1 (16.8) | 2099.4 (16.8) | 2076.8 (16.5)                  | 2074.3 (16.5)   | 2111.8 (16.9) | 2089.9 (16.7) | 2134.1 (17.2) | 0.007 |
| Antidepressants, TCAs                          | 1214.8 (9.9)  | 1233.4 (9.9)  | 1182.1 (9.4)                   | 1171.3 (9.3)    | 1184.9 (9.5)  | 1148.4 (9.2)  | 1202.8 (9.7)  | 0.011 |
| Antidepressants, other                         | 1924.8 (15.6) | 1977.0 (15.8) | 1906.2 (15.2)                  | 1906.6 (15.2)   | 1932.8 (15.4) | 1895.9 (15.1) | 1930.2 (15.5) | 0.009 |
| Antidiabetics                                  | 1633.4 (13.2) | 1686.4 (13.5) | 1698.2 (13.5)                  | 1710.0 (13.6)   | 1669.7 (13.3) | 1704.8 (13.6) | 1653.1 (13.3) | 0.005 |
| Antipsychotics, atypical                       | 669.2 (5.4)   | 649.6 (5.2)   | 645.1 (5.1)                    | 643.7 (5.1)     | 650.2 (5.2)   | 657.8 (5.2)   | 653.1 (5.3)   | 0.005 |
| Antipsychotics, typical                        | 261.9 (2.1)   | 278.6 (2.2)   | 263.4 (2.1)                    | 259.5 (2.1)     | 267.8 (2.1)   | 261.1 (2.1)   | 262.8 (2.1)   | 0.004 |
| Barbiturates                                   | 91.5 (0.7)    | 107.7 (0.9)   | 94.3 (0.8)                     | 94.3 (0.8)      | 94.7 (0.8)    | 89.7 (0.7)    | 99.0 (0.8)    | 0.006 |
| Benzodiazepines                                | 5485.7 (44.5) | 5576.8 (44.7) | 5514.5 (43.9)                  | 5515.0 (43.9)   | 5514.9 (44.0) | 5512.8 (44.0) | 5545.6 (44.7) | 0.008 |
| CNS stimulants                                 | 586.2 (4.8)   | 594.0 (4.8)   | 573.4 (4.6)                    | 575.1 (4.6)     | 576.6 (4.6)   | 566.1 (4.5)   | 595.5 (4.8)   | 0.006 |
| Dementia agents                                | 123.5 (1.0)   | 116.4 (0.9)   | 116.8 (0.9)                    | 117.0 (0.9)     | 114.3 (0.9)   | 117.3 (0.9)   | 105.8 (0.9)   | 0.005 |
| Gabapentinoids                                 | 3298.6 (26.8) | 3255.7 (26.1) | 3207.1 (25.5)                  | 3213.0 (25.6)   | 3199.1 (25.5) | 3188.6 (25.4) | 3269.5 (26.3) | 0.013 |
| Lithium                                        | 52.5 (0.4)    | 56.8 (0.5)    | 52.7 (0.4)                     | 53.7 (0.4)      | 52.1 (0.4)    | 59.0 (0.5)    | 53.4 (0.4)    | 0.003 |
| Multiple sclerosis agents                      | 41.0 (0.3)    | 30.6 (0.2)    | 31.6 (0.3)                     | 30.2 (0.2)      | 30.1 (0.2)    | 24.9 (0.2)    | 33.4 (0.3)    | 0.009 |
| NSAIDs                                         | 5547.5 (45.0) | 5654.9 (45.3) | 5608.7 (44.6)                  | 5610.0 (44.6)   | 5595.3 (44.7) | 5612.0 (44.8) | 5566.6 (44.8) | 0.005 |
| Other sedative hypnotics                       | 2282.6 (18.5) | 2290.6 (18.3) | 2286.3 (18.2)                  | 2282.4 (18.2)   | 2291.4 (18.3) | 2289.6 (18.3) | 2286.8 (18.4) | 0.004 |
| Smoking cessation                              | 1125.1 (9.1)  | 1129.5 (9.0)  | 1118.1 (8.9)                   | 1112.9 (8.9)    | 1123.9 (9.0)  | 1129.8 (9.0)  | 1125.7 (9.1)  | 0.004 |
| Triptans                                       | 761.7 (6.2)   | 757.3 (6.1)   | 731.7 (5.8)                    | 731.6 (5.8)     | 751.9 (6.0)   | 723.5 (5.8)   | 777.9 (6.3)   | 0.010 |
| Other CNS depressants                          | 53.8 (0.4)    | 52.7 (0.4)    | 52.6 (0.4)                     | 53.2 (0.4)      | 56.4 (0.4)    | 50.5 (0.4)    | 56.6 (0.5)    | 0.003 |
| <b>Prescription opioid utilization (n (%))</b> |               |               |                                |                 |               |               |               |       |
| Prescription opioid on index date              |               |               |                                |                 |               |               |               |       |
| Buprenorphine                                  | 102.6 (0.8)   | 99.7 (0.8)    | 94.5 (0.8)                     | 94.5 (0.8)      | 95.2 (0.8)    | 95.7 (0.8)    | 101.3 (0.8)   | 0.004 |
| Butorphanol                                    | 58.6 (0.5)    | 50.7 (0.4)    | 50.6 (0.4)                     | 54.5 (0.4)      | 53.5 (0.4)    | 58.1 (0.5)    | 56.0 (0.5)    | 0.005 |
| Codeine                                        | 547.9 (4.4)   | 598.9 (4.8)   | 575.3 (4.6)                    | 570.8 (4.5)     | 566.5 (4.5)   | 585.8 (4.7)   | 558.5 (4.5)   | 0.007 |
| Dihydrocodeine                                 | 10.1 (0.1)    | 8.5 (0.1)     | 10.9 (0.1)                     | 10.4 (0.1)      | 10.8 (0.1)    | 11.6 (0.1)    | 11.2 (0.1)    | 0.003 |
| Fentanyl                                       | 863.7 (7.0)   | 825.6 (6.6)   | 797.4 (6.3)                    | 808.8 (6.4)     | 826.3 (6.6)   | 799.2 (6.4)   | 813.7 (6.6)   | 0.010 |
| Hydrocodone                                    | 7086.6 (57.5) | 7224.1 (57.8) | 7313.8 (58.2)                  | 7331.6 (58.3)   | 7290.4 (58.2) | 7285.5 (58.1) | 7148.1 (57.6) | 0.008 |
| Hydromorphone                                  | 261.5 (2.1)   | 259.6 (2.1)   | 239.6 (1.9)                    | 237.9 (1.9)     | 243.3 (1.9)   | 234.7 (1.9)   | 255.6 (2.1)   | 0.009 |
| Levorphanol                                    | 1.4 (0.0)     | 1.3 (0.0)     | 2.0 (0.0)                      | 1.3 (0.0)       | 1.2 (0.0)     | 1.4 (0.0)     | 2.1 (0.0)     | 0.003 |

|                                                                                       | Baclofen             | Carisoprodol         | Chlorzoxazone/<br>orphenadrine | Cyclobenzaprine      | Metaxalone           | Methocarbamol        | Tizanidine           | SMD   |
|---------------------------------------------------------------------------------------|----------------------|----------------------|--------------------------------|----------------------|----------------------|----------------------|----------------------|-------|
| Meperidine                                                                            | 39.4 (0.3)           | 40.7 (0.3)           | 41.5 (0.3)                     | 40.0 (0.3)           | 37.9 (0.3)           | 40.5 (0.3)           | 40.2 (0.3)           | 0.002 |
| Methadone                                                                             | 363.6 (2.9)          | 342.9 (2.7)          | 327.1 (2.6)                    | 324.1 (2.6)          | 331.6 (2.6)          | 330.6 (2.6)          | 342.7 (2.8)          | 0.009 |
| Morphine                                                                              | 804.9 (6.5)          | 781.3 (6.3)          | 748.5 (6.0)                    | 743.3 (5.9)          | 770.7 (6.2)          | 741.0 (5.9)          | 791.0 (6.4)          | 0.012 |
| Opium                                                                                 | 7.2 (0.1)            | 7.1 (0.1)            | 5.7 (0.0)                      | 5.4 (0.0)            | 5.0 (0.0)            | 5.8 (0.0)            | 6.2 (0.1)            | 0.004 |
| Oxycodone                                                                             | 3756.0 (30.5)        | 3674.4 (29.4)        | 3642.1 (29.0)                  | 3653.0 (29.1)        | 3640.8 (29.1)        | 3623.3 (28.9)        | 3703.8 (29.8)        | 0.014 |
| Oxymorphone                                                                           | 198.0 (1.6)          | 194.3 (1.6)          | 183.8 (1.5)                    | 182.1 (1.4)          | 179.9 (1.4)          | 186.4 (1.5)          | 191.0 (1.5)          | 0.006 |
| Pentazocine                                                                           | 34.3 (0.3)           | 40.5 (0.3)           | 36.7 (0.3)                     | 36.5 (0.3)           | 37.4 (0.3)           | 38.7 (0.3)           | 36.8 (0.3)           | 0.003 |
| Propoxyphene                                                                          | 173.6 (1.4)          | 177.7 (1.4)          | 183.9 (1.5)                    | 174.8 (1.4)          | 172.9 (1.4)          | 173.4 (1.4)          | 168.8 (1.4)          | 0.003 |
| Tapentadol                                                                            | 125.6 (1.0)          | 123.6 (1.0)          | 119.8 (1.0)                    | 122.6 (1.0)          | 129.6 (1.0)          | 119.2 (1.0)          | 133.1 (1.1)          | 0.005 |
| Tramadol                                                                              | 2628.8 (21.3)        | 2726.7 (21.8)        | 2795.1 (22.2)                  | 2790.0 (22.2)        | 2772.1 (22.1)        | 2761.5 (22.0)        | 2752.5 (22.2)        | 0.008 |
| Number of days covered by prescription opioids in 180 days pre-index date (mean (SD)) | 174.23 (16.32)       | 174.17 (16.52)       | 174.08 (16.47)                 | 174.05 (16.51)       | 174.04 (16.49)       | 174.05 (16.50)       | 174.10 (16.60)       | 0.005 |
| Total dispensed MMEs per interval (days) (mean (SD))                                  |                      |                      |                                |                      |                      |                      |                      |       |
| (Index - 180) to (index - 151)                                                        | 1923.50<br>(3146.57) | 1909.52<br>(3097.92) | 1821.03<br>(3032.69)           | 1820.88<br>(3161.35) | 1834.65<br>(3142.29) | 1840.29<br>(3218.79) | 1883.15<br>(3100.16) | 0.016 |
| (Index - 150) to (index - 121)                                                        | 2000.20<br>(3164.38) | 1980.75<br>(3140.23) | 1878.61<br>(3016.02)           | 1881.94<br>(3177.29) | 1901.31<br>(3199.04) | 1907.86<br>(3267.16) | 1954.55<br>(3171.24) | 0.019 |
| (Index - 120) to (index - 91)                                                         | 2155.64<br>(3237.11) | 2125.10<br>(3176.81) | 2027.13<br>(3114.94)           | 2029.39<br>(3234.85) | 2053.15<br>(3302.87) | 2064.59<br>(3439.49) | 2110.18<br>(3178.51) | 0.019 |
| (Index - 90) to (index - 61)                                                          | 2130.92<br>(3122.39) | 2112.01<br>(3118.67) | 2016.49<br>(3061.53)           | 2017.86<br>(3205.50) | 2036.40<br>(3229.28) | 2043.65<br>(3319.69) | 2088.68<br>(3149.42) | 0.018 |
| (Index - 60) to (index - 31)                                                          | 2150.24<br>(3229.27) | 2122.85<br>(3128.46) | 2036.30<br>(3135.57)           | 2038.40<br>(3265.09) | 2053.55<br>(3286.32) | 2064.79<br>(3370.99) | 2106.53<br>(3195.79) | 0.017 |
| (Index - 30) to index                                                                 | 2571.13<br>(3724.72) | 2542.33<br>(3602.70) | 2419.97<br>(3744.72)           | 2423.68<br>(3836.42) | 2448.35<br>(3850.06) | 2440.46<br>(3862.76) | 2513.39<br>(3642.53) | 0.019 |
| <b>Healthcare utilization (mean (SD))</b>                                             |                      |                      |                                |                      |                      |                      |                      |       |
| Number of physician visits                                                            | 8.03 (6.09)          | 7.85 (6.30)          | 7.81 (6.25)                    | 7.82 (6.28)          | 7.82 (6.24)          | 7.91 (6.21)          | 7.92 (6.03)          | 0.014 |
| Number of distinct prescribed medications                                             | 11.57 (5.69)         | 11.64 (5.92)         | 11.48 (5.70)                   | 11.48 (5.73)         | 11.53 (5.74)         | 11.54 (5.70)         | 11.59 (5.82)         | 0.012 |
| Number of hospitalizations                                                            | 0.16 (0.47)          | 0.16 (0.45)          | 0.16 (0.50)                    | 0.16 (0.46)          | 0.16 (0.47)          | 0.17 (0.44)          | 0.17 (0.49)          | 0.008 |
| Number of hospitalization days                                                        | 0.86 (3.19)          | 0.83 (3.28)          | 0.82 (3.18)                    | 0.82 (3.17)          | 0.83 (3.10)          | 0.88 (3.10)          | 0.84 (3.20)          | 0.008 |

Abbreviations: SD, standard deviation; SMD, standardized mean difference; MMEs, morphine milligram equivalents

**eTable 12. Hazard ratio of opioid overdose for patients who initiated skeletal muscle relaxants while on long-term opioid therapy, 30-day intention-to-treat analysis (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 36                          | 24,487                | 686,051                     | 19.17 (13.83, 26.57)                       | 2.13 (1.44, 3.14) | 3.16 (0.80, 12.49)   |
|                                                | Tizanidine                                          | 14                          | 18,440                | 531,674                     | 9.62 (5.70, 16.24)                         | 0.99 (0.56, 1.75) | 1.32 (0.27, 6.41)    |
|                                                | Carisoprodol                                        | 26                          | 21,726                | 628,196                     | 15.12 (10.29, 22.20)                       | 1.91 (1.26, 2.90) | 1.65 (0.37, 7.43)    |
|                                                | Metaxalone                                          | 6                           | 12,686                | 368,141                     | 5.95 (2.67, 13.25)                         | 0.71 (0.33, 1.55) | 0.75 (0.12, 4.58)    |
|                                                | Methocarbamol                                       | 14                          | 19,118                | 542,619                     | 9.42 (5.58, 15.91)                         | 1.45 (0.89, 2.36) | 1.42 (0.30, 6.73)    |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 8,017                 | 232,281                     | 7.86 (3.27, 18.89)                         | 0.81 (0.33, 2.00) | 0.95 (0.17, 5.22)    |
|                                                | Cyclobenzaprine                                     | 54                          | 93,997                | 2,698,132                   | 7.31 (5.60, 9.54)                          | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 136                         | 40,185                | 1,084,968                   | 45.78 (38.70, 54.16)                       | 3.54 (2.72, 4.62) | 2.89 (0.69, 12.05)   |
|                                                | Tizanidine                                          | 53                          | 51,710                | 1,478,501                   | 13.09 (10.00, 17.14)                       | 1.05 (0.76, 1.46) | 0.98 (0.17, 5.60)    |
|                                                | Carisoprodol                                        | 14                          | 11,404                | 332,198                     | 15.39 (9.12, 25.99)                        | 1.39 (0.84, 2.31) | 1.31 (0.26, 6.61)    |
|                                                | Metaxalone                                          | 2                           | 4,450                 | 123,369                     | 5.92 (1.48, 23.68)                         | 0.62 (0.20, 1.95) | 0.31 (0.03, 3.87)    |
|                                                | Methocarbamol                                       | 15                          | 19,340                | 542,760                     | 10.09 (6.09, 16.74)                        | 0.75 (0.44, 1.28) | 0.95 (0.16, 5.49)    |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 3,110                 | 87,941                      | 4.15 (0.59, 29.49)                         | 0.29 (0.04, 2.08) | 0.15 (0.01, 4.37)    |
|                                                | Cyclobenzaprine                                     | 75                          | 77,165                | 2,156,702                   | 12.70 (10.13, 15.93)                       | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 52                          | 36,765                | 1,055,225                   | 18.00 (13.72, 23.62)                       | 2.92 (2.04, 4.18) | 1.06 (0.17, 6.61)    |
|                                                | Tizanidine                                          | 54                          | 73,286                | 2,143,825                   | 9.20 (7.05, 12.01)                         | 1.50 (1.05, 2.14) | 1.30 (0.23, 7.40)    |
|                                                | Carisoprodol                                        | 31                          | 29,202                | 856,253                     | 13.22 (9.30, 18.80)                        | 2.15 (1.41, 3.29) | 2.52 (0.53, 11.89)   |
|                                                | Metaxalone                                          | 3                           | 12,786                | 373,674                     | 2.93 (0.95, 9.09)                          | 0.48 (0.15, 1.52) | 0.44 (0.04, 4.73)    |
|                                                | Methocarbamol                                       | 14                          | 29,549                | 857,177                     | 5.97 (3.53, 10.07)                         | 0.97 (0.55, 1.72) | 1.05 (0.17, 6.56)    |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 6,270                 | 183,412                     | 9.96 (4.14, 23.92)                         | 1.62 (0.65, 4.02) | 1.80 (0.35, 9.23)    |
|                                                | Cyclobenzaprine                                     | 69                          | 140,732               | 4,096,144                   | 6.15 (4.86, 7.79)                          | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 42                          | 35,213                | 1,028,603                   | 14.91 (11.02, 20.18)                       | 3.61 (2.49, 5.25) | 2.65 (0.92, 7.67)    |
|                                                | Tizanidine                                          | 23                          | 71,402                | 2,103,337                   | 3.99 (2.65, 6.01)                          | 0.97 (0.61, 1.54) | 0.85 (0.22, 3.22)    |
|                                                | Carisoprodol                                        | 29                          | 55,301                | 1,632,072                   | 6.49 (4.51, 9.34)                          | 1.58 (1.03, 2.41) | 1.40 (0.43, 4.57)    |
|                                                | Metaxalone                                          | 7                           | 37,513                | 1,108,180                   | 2.31 (1.10, 4.84)                          | 0.56 (0.26, 1.21) | 0.37 (0.07, 2.10)    |
|                                                | Methocarbamol                                       | 20                          | 56,655                | 1,668,041                   | 4.38 (2.83, 6.79)                          | 1.06 (0.65, 1.73) | 0.75 (0.19, 2.98)    |
|                                                | Chlorzoxazone/orphenadrine                          | 7                           | 14,755                | 434,748                     | 5.88 (2.80, 12.34)                         | 1.43 (0.66, 3.09) | 1.47 (0.46, 4.74)    |
|                                                | Cyclobenzaprine                                     | 80                          | 240,755               | 7,085,866                   | 4.12 (3.31, 5.13)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 266                         | 136,650               |                             |                                            | 3.29 (2.77, 3.90) | 2.52 (1.29, 4.90)    |
|                                                | Tizanidine                                          | 144                         | 214,838               |                             |                                            | 1.19 (0.97, 1.45) | 1.07 (0.49, 2.33)    |
|                                                | Carisoprodol                                        | 100                         | 117,633               |                             |                                            | 1.76 (1.40, 2.21) | 1.64 (0.81, 3.34)    |
|                                                | Metaxalone                                          | 18                          | 67,435                |                             |                                            | 0.59 (0.37, 0.95) | 0.46 (0.17, 1.24)    |
|                                                | Methocarbamol                                       | 63                          | 124,662               |                             |                                            | 1.00 (0.76, 1.32) | 1.00 (0.45, 2.20)    |
|                                                | Chlorzoxazone/orphenadrine                          | 18                          | 32,152                |                             |                                            | 1.15 (0.71, 1.85) | 1.14 (0.53, 2.46)    |
|                                                | Cyclobenzaprine                                     | 278                         | 552,649               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 12 (continued). Hazard ratio of opioid overdose for patients who initiated skeletal muscle relaxants while on long-term opioid therapy, 30-day intention-to-treat analysis (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Nominal (unadjusted) p-value | Adjusted p-value |
|------------------------------------------------|-----------------------------------------------------|------------------------------|------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 0.1008                       | 0.6048           |
|                                                | Tizanidine                                          | 0.7300                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.5167                       | > 0.99           |
|                                                | Metaxalone                                          | 0.7549                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.6562                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.9559                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 0.1461                       | 0.8766           |
|                                                | Tizanidine                                          | 0.9830                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.7475                       | > 0.99           |
|                                                | Metaxalone                                          | 0.3656                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.9505                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.2729                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Optum© Clinformatics® Data Mart                | Baclofen                                            | 0.9502                       | > 0.99           |
|                                                | Tizanidine                                          | 0.7664                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.2434                       | > 0.99           |
|                                                | Metaxalone                                          | 0.4985                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.9614                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.4805                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| IBM® MarketScan® Research Database             | Baclofen                                            | 0.0715                       | 0.4290           |
|                                                | Tizanidine                                          | 0.8101                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.5744                       | > 0.99           |
|                                                | Metaxalone                                          | 0.2625                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.6831                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.5161                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Pooled                                         | Baclofen                                            | 0.0066                       | 0.0396           |
|                                                | Tizanidine                                          | 0.8737                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.1730                       | > 0.99           |
|                                                | Metaxalone                                          | 0.1245                       | 0.7500           |
|                                                | Methocarbamol                                       | 0.9895                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.7362                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |

**eTable 13. Hazard ratio of opioid overdose for patients who initiated skeletal muscle relaxants while on long-term opioid therapy, as-treated analysis (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) | Median follow-up time (interquartile range) (days) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|----------------------------------------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 55                          | 24,487                | 1,388,391                   | 14.47 (11.11, 18.85)                       | 2.26 (1.59, 3.21) | 1.98 (0.61, 6.44)    | 43 (32)                                            |
|                                                | Tizanidine                                          | 27                          | 18,440                | 1,130,050                   | 8.73 (5.98, 12.73)                         | 1.38 (0.89, 2.15) | 1.06 (0.29, 3.91)    | 43 (43)                                            |
|                                                | Carisoprodol                                        | 51                          | 21,726                | 1,664,694                   | 11.19 (8.50, 14.72)                        | 1.86 (1.29, 2.68) | 1.46 (0.44, 4.84)    | 43 (66)                                            |
|                                                | Metaxalone                                          | 10                          | 12,686                | 506,177                     | 7.22 (3.88, 13.41)                         | 1.06 (0.55, 2.06) | 1.03 (0.25, 4.23)    | 27 (25)                                            |
|                                                | Methocarbamol                                       | 17                          | 19,118                | 768,497                     | 8.08 (5.02, 13.00)                         | 1.20 (0.71, 2.03) | 1.44 (0.39, 5.31)    | 26 (25)                                            |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 8,017                 | 305,337                     | 5.98 (2.49, 14.37)                         | 0.88 (0.35, 2.17) | 0.72 (0.15, 3.47)    | 23 (24)                                            |
|                                                | Cyclobenzaprine                                     | 73                          | 93,997                | 3,985,370                   | 6.69 (5.32, 8.42)                          | Ref               | Ref                  | 27 (24)                                            |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 200                         | 40,185                | 2,187,051                   | 33.40 (29.08, 38.37)                       | 3.29 (2.60, 4.15) | 2.87 (0.86, 9.58)    | 43 (27)                                            |
|                                                | Tizanidine                                          | 104                         | 51,710                | 3,103,361                   | 12.24 (10.10, 14.83)                       | 1.23 (0.94, 1.61) | 1.16 (0.29, 4.62)    | 43 (43)                                            |
|                                                | Carisoprodol                                        | 27                          | 11,404                | 1,038,199                   | 9.50 (6.51, 13.85)                         | 1.06 (0.69, 1.62) | 0.96 (0.24, 3.83)    | 43 (72)                                            |
|                                                | Metaxalone                                          | 5                           | 4,450                 | 184,876                     | 9.88 (4.11, 23.73)                         | 0.90 (0.37, 2.20) | 0.60 (0.10, 3.53)    | 29 (23)                                            |
|                                                | Methocarbamol                                       | 18                          | 19,340                | 903,315                     | 7.28 (4.59, 11.55)                         | 0.69 (0.42, 1.13) | 0.80 (0.17, 3.91)    | 33 (23)                                            |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 3,110                 | 135,544                     | 8.08 (2.61, 25.07)                         | 0.75 (0.24, 2.35) | 0.60 (0.10, 3.45)    | 28 (23)                                            |
|                                                | Cyclobenzaprine                                     | 108                         | 77,165                | 3,763,803                   | 10.48 (8.68, 12.66)                        | Ref               | Ref                  | 33 (22)                                            |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 90                          | 36,765                | 2,254,456                   | 14.58 (11.86, 17.83)                       | 2.75 (2.07, 3.65) | 1.14 (0.28, 4.68)    | 43 (40)                                            |
|                                                | Tizanidine                                          | 116                         | 73,296                | 4,653,376                   | 9.11 (7.59, 10.92)                         | 1.72 (1.32, 2.25) | 1.50 (0.40, 5.69)    | 43 (42)                                            |
|                                                | Carisoprodol                                        | 54                          | 29,202                | 2,031,874                   | 9.71 (7.43, 12.67)                         | 1.84 (1.32, 2.57) | 2.13 (0.61, 7.47)    | 43 (45)                                            |
|                                                | Metaxalone                                          | 6                           | 12,786                | 511,595                     | 4.28 (1.92, 9.54)                          | 0.75 (0.33, 1.72) | 0.63 (0.10, 3.81)    | 33 (20)                                            |
|                                                | Methocarbamol                                       | 15                          | 29,549                | 1,294,235                   | 4.23 (2.55, 7.02)                          | 0.76 (0.44, 1.30) | 0.72 (0.13, 3.91)    | 33 (22)                                            |
|                                                | Chlorzoxazone/orphenadrine                          | 6                           | 6,270                 | 281,151                     | 7.79 (3.50, 17.35)                         | 1.40 (0.61, 3.18) | 1.62 (0.41, 6.42)    | 33 (22)                                            |
|                                                | Cyclobenzaprine                                     | 102                         | 140,732               | 6,740,270                   | 5.53 (4.55, 6.71)                          | Ref               | Ref                  | 33 (20)                                            |
| IBM® MarketScan® Research Database             | Baclofen                                            | 58                          | 35,213                | 2,117,872                   | 10.00 (7.73, 12.94)                        | 3.05 (2.21, 4.21) | 2.22 (0.89, 5.55)    | 43 (36)                                            |
|                                                | Tizanidine                                          | 47                          | 71,402                | 4,518,580                   | 3.80 (2.85, 5.06)                          | 1.16 (0.82, 1.64) | 1.02 (0.36, 2.89)    | 43 (42)                                            |
|                                                | Carisoprodol                                        | 77                          | 55,301                | 3,770,247                   | 7.46 (5.97, 9.33)                          | 2.26 (1.68, 3.05) | 1.97 (0.79, 4.95)    | 43 (47)                                            |
|                                                | Metaxalone                                          | 13                          | 37,513                | 1,652,803                   | 2.87 (1.67, 4.95)                          | 0.84 (0.47, 1.49) | 0.68 (0.20, 2.36)    | 33 (20)                                            |
|                                                | Methocarbamol                                       | 23                          | 56,655                | 2,478,024                   | 3.39 (2.25, 5.10)                          | 0.98 (0.62, 1.54) | 0.62 (0.17, 2.22)    | 33 (22)                                            |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 14,755                | 671,624                     | 2.72 (1.13, 6.53)                          | 0.79 (0.32, 1.94) | 0.80 (0.25, 2.58)    | 33 (20)                                            |
|                                                | Cyclobenzaprine                                     | 105                         | 240,755               | 11,183,585                  | 3.43 (2.83, 4.15)                          | Ref               | Ref                  | 33 (20)                                            |
| Pooled                                         | Baclofen                                            | 403                         | 136,650               |                             |                                            | 2.98 (2.58, 3.43) | 2.07 (1.18, 3.64)    |                                                    |
|                                                | Tizanidine                                          | 294                         | 214,838               |                             |                                            | 1.39 (1.19, 1.62) | 1.15 (0.62, 2.14)    |                                                    |
|                                                | Carisoprodol                                        | 209                         | 117,633               |                             |                                            | 1.80 (1.52, 2.13) | 1.66 (0.94, 2.94)    |                                                    |
|                                                | Metaxalone                                          | 34                          | 67,435                |                             |                                            | 0.88 (0.62, 1.25) | 0.74 (0.35, 1.56)    |                                                    |
|                                                | Methocarbamol                                       | 73                          | 124,662               |                             |                                            | 0.87 (0.68, 1.12) | 0.87 (0.43, 1.75)    |                                                    |
|                                                | Chlorzoxazone/orphenadrine                          | 19                          | 32,152                |                             |                                            | 0.94 (0.59, 1.48) | 0.90 (0.45, 1.81)    |                                                    |
|                                                | Cyclobenzaprine                                     | 388                         | 552,649               |                             |                                            | Ref               | Ref                  |                                                    |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 13 (continued). Hazard ratio of opioid overdose for patients who initiated skeletal muscle relaxants while on long-term opioid therapy, as-treated analysis (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Nominal (unadjusted) p-value | Adjusted p-value |
|------------------------------------------------|-----------------------------------------------------|------------------------------|------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 0.2576                       | > 0.99           |
|                                                | Tizanidine                                          | 0.9280                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.5349                       | > 0.99           |
|                                                | Metaxalone                                          | 0.9636                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.5851                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.6826                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 0.0865                       | 0.5190           |
|                                                | Tizanidine                                          | 0.8377                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.9486                       | > 0.99           |
|                                                | Metaxalone                                          | 0.5675                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.7869                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.5661                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Optum© Clinformatics® Data Mart                | Baclofen                                            | 0.8589                       | > 0.99           |
|                                                | Tizanidine                                          | 0.5495                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.2378                       | > 0.99           |
|                                                | Metaxalone                                          | 0.6129                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.7019                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.4948                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| IBM® MarketScan® Research Database             | Baclofen                                            | 0.0880                       | 0.5280           |
|                                                | Tizanidine                                          | 0.9761                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.1472                       | 0.8832           |
|                                                | Metaxalone                                          | 0.5475                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.4621                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.7066                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Pooled                                         | Baclofen                                            | 0.0115                       | 0.0690           |
|                                                | Tizanidine                                          | 0.6594                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.0809                       | 0.4854           |
|                                                | Metaxalone                                          | 0.4246                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.6873                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.7699                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |

**eTable 14. Hazard ratio of sepsis for patients who initiated skeletal muscle relaxants while on long-term opioid therapy (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 69                          | 24,487                | 685,780                     | 36.75 (29.03, 46.53)                       | 1.64 (1.24, 2.17) | 0.72 (0.24, 2.15)    |
|                                                | Tizanidine                                          | 22                          | 18,440                | 531,469                     | 15.12 (9.96, 22.96)                        | 0.68 (0.43, 1.06) | 0.85 (0.30, 2.39)    |
|                                                | Carisoprodol                                        | 28                          | 21,726                | 628,275                     | 16.28 (11.24, 23.58)                       | 0.73 (0.49, 1.09) | 1.15 (0.44, 2.99)    |
|                                                | Metaxalone                                          | 18                          | 12,686                | 367,912                     | 17.87 (11.26, 28.36)                       | 0.80 (0.49, 1.30) | 0.87 (0.31, 2.42)    |
|                                                | Methocarbamol                                       | 41                          | 19,118                | 542,123                     | 27.62 (20.34, 37.52)                       | 1.23 (0.88, 1.74) | 1.00 (0.37, 2.70)    |
|                                                | Chlorzoxazone/orphenadrine                          | 18                          | 8,017                 | 232,051                     | 28.33 (17.85, 44.97)                       | 1.27 (0.78, 2.07) | 1.57 (0.64, 3.83)    |
|                                                | Cyclobenzaprine                                     | 165                         | 93,997                | 2,696,589                   | 22.35 (19.19, 26.03)                       | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 514                         | 40,185                | 1,080,713                   | 173.72 (159.33, 189.40)                    | 1.65 (1.47, 1.86) | 1.49 (0.83, 2.68)    |
|                                                | Tizanidine                                          | 389                         | 51,710                | 1,474,095                   | 96.39 (87.27, 106.46)                      | 0.92 (0.81, 1.05) | 0.88 (0.45, 1.70)    |
|                                                | Carisoprodol                                        | 59                          | 11,404                | 331,716                     | 64.96 (50.33, 83.85)                       | 0.63 (0.48, 0.82) | 0.79 (0.40, 1.55)    |
|                                                | Metaxalone                                          | 28                          | 4,450                 | 123,093                     | 83.08 (57.37, 120.33)                      | 0.79 (0.54, 1.16) | 0.79 (0.40, 1.56)    |
|                                                | Methocarbamol                                       | 153                         | 19,340                | 541,084                     | 103.28 (88.15, 121.01)                     | 0.99 (0.83, 1.18) | 1.02 (0.54, 1.93)    |
|                                                | Chlorzoxazone/orphenadrine                          | 21                          | 3,110                 | 87,740                      | 87.42 (57.00, 134.08)                      | 0.84 (0.54, 1.29) | 0.89 (0.46, 1.72)    |
|                                                | Cyclobenzaprine                                     | 616                         | 77,165                | 2,149,868                   | 104.65 (96.71, 113.26)                     | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 195                         | 36,765                | 1,053,084                   | 67.63 (58.78, 77.82)                       | 1.52 (1.28, 1.79) | 1.01 (0.48, 2.15)    |
|                                                | Tizanidine                                          | 280                         | 73,286                | 2,141,103                   | 47.77 (42.49, 53.70)                       | 1.07 (0.93, 1.24) | 0.83 (0.38, 1.82)    |
|                                                | Carisoprodol                                        | 53                          | 29,202                | 856,045                     | 22.61 (17.28, 29.60)                       | 0.51 (0.38, 0.67) | 0.90 (0.42, 1.95)    |
|                                                | Metaxalone                                          | 32                          | 12,786                | 373,264                     | 31.31 (22.14, 44.28)                       | 0.70 (0.49, 1.01) | 1.00 (0.47, 2.12)    |
|                                                | Methocarbamol                                       | 87                          | 29,549                | 855,954                     | 37.12 (30.09, 45.81)                       | 0.83 (0.66, 1.05) | 0.81 (0.36, 1.78)    |
|                                                | Chlorzoxazone/orphenadrine                          | 13                          | 6,270                 | 183,312                     | 25.90 (15.04, 44.61)                       | 0.58 (0.34, 1.01) | 0.74 (0.33, 1.66)    |
|                                                | Cyclobenzaprine                                     | 499                         | 140,732               | 4,089,546                   | 44.57 (40.82, 48.65)                       | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 129                         | 35,213                | 1,027,360                   | 45.86 (38.59, 54.50)                       | 1.68 (1.38, 2.03) | 0.94 (0.54, 1.64)    |
|                                                | Tizanidine                                          | 79                          | 71,402                | 2,102,550                   | 13.72 (11.01, 17.11)                       | 0.50 (0.40, 0.64) | 0.51 (0.26, 0.99)    |
|                                                | Carisoprodol                                        | 71                          | 55,301                | 1,631,569                   | 15.89 (12.60, 20.06)                       | 0.58 (0.45, 0.75) | 0.66 (0.36, 1.21)    |
|                                                | Metaxalone                                          | 63                          | 37,513                | 1,107,434                   | 20.78 (16.23, 26.60)                       | 0.76 (0.59, 0.99) | 0.82 (0.46, 1.46)    |
|                                                | Methocarbamol                                       | 118                         | 56,655                | 1,666,590                   | 25.86 (21.59, 30.97)                       | 0.95 (0.78, 1.16) | 0.82 (0.46, 1.45)    |
|                                                | Chlorzoxazone/orphenadrine                          | 34                          | 14,755                | 434,426                     | 28.59 (20.43, 40.01)                       | 1.05 (0.74, 1.48) | 1.21 (0.72, 2.03)    |
|                                                | Cyclobenzaprine                                     | 530                         | 240,755               | 7,079,280                   | 27.34 (25.11, 29.78)                       | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 907                         | 136,650               |                             |                                            | 1.60 (1.48, 1.74) | 1.09 (0.78, 1.52)    |
|                                                | Tizanidine                                          | 770                         | 214,838               |                             |                                            | 0.88 (0.81, 0.96) | 0.72 (0.50, 1.05)    |
|                                                | Carisoprodol                                        | 211                         | 117,633               |                             |                                            | 0.59 (0.51, 0.68) | 0.80 (0.56, 1.15)    |
|                                                | Metaxalone                                          | 141                         | 67,435                |                             |                                            | 0.77 (0.64, 0.91) | 0.85 (0.60, 1.22)    |
|                                                | Methocarbamol                                       | 399                         | 124,662               |                             |                                            | 0.96 (0.86, 1.07) | 0.90 (0.63, 1.27)    |
|                                                | Chlorzoxazone/orphenadrine                          | 86                          | 32,152                |                             |                                            | 0.92 (0.74, 1.14) | 1.06 (0.76, 1.49)    |
|                                                | Cyclobenzaprine                                     | 1,810                       | 552,649               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 14 (continued). Hazard ratio of sepsis for patients who initiated skeletal muscle relaxants while on long-term opioid therapy (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Nominal (unadjusted) p-value | Adjusted p-value |
|------------------------------------------------|-----------------------------------------------------|------------------------------|------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 0.5505                       | > 0.99           |
|                                                | Tizanidine                                          | 0.7590                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.7741                       | > 0.99           |
|                                                | Metaxalone                                          | 0.7914                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.9932                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.3247                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 0.1835                       | > 0.99           |
|                                                | Tizanidine                                          | 0.6998                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.4857                       | > 0.99           |
|                                                | Metaxalone                                          | 0.4934                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.9484                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.7290                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Optum© Clinformatics® Data Mart                | Baclofen                                            | 0.9717                       | > 0.99           |
|                                                | Tizanidine                                          | 0.6398                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.7899                       | > 0.99           |
|                                                | Metaxalone                                          | 0.9946                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.5926                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.4620                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| IBM® MarketScan® Research Database             | Baclofen                                            | 0.8393                       | > 0.99           |
|                                                | Tizanidine                                          | 0.0451                       | > 0.99           |
|                                                | Carisoprodol                                        | 0.1789                       | > 0.99           |
|                                                | Metaxalone                                          | 0.5013                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.4957                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.4704                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |
| Pooled                                         | Baclofen                                            | 0.6217                       | > 0.99           |
|                                                | Tizanidine                                          | 0.0841                       | 0.5046           |
|                                                | Carisoprodol                                        | 0.2292                       | > 0.99           |
|                                                | Metaxalone                                          | 0.3829                       | > 0.99           |
|                                                | Methocarbamol                                       | 0.5379                       | > 0.99           |
|                                                | Chlorzoxazone/orphenadrine                          | 0.7181                       | > 0.99           |
|                                                | Cyclobenzaprine                                     | Ref                          | Ref              |

**eTable 15. Hazard ratio of opioid overdose for patients who initiated skeletal muscle relaxants indicated for spasticity while on long-term opioid therapy (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 36                          | 24,487                | 686,051                     | 19.17 (13.83, 26.57)                       | 1.98 (1.07, 3.68) | 1.56 (0.70, 3.50)    |
|                                                | Tizanidine                                          | 14                          | 18,440                | 531,674                     | 9.62 (5.70, 16.24)                         | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 136                         | 40,185                | 1,084,968                   | 45.78 (38.70, 54.16)                       | 3.43 (2.49, 4.70) | 3.34 (2.28, 4.89)    |
|                                                | Tizanidine                                          | 53                          | 51,710                | 1,478,501                   | 13.09 (10.00, 17.14)                       | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 52                          | 36,765                | 1,055,225                   | 18.00 (13.72, 23.62)                       | 1.95 (1.33, 2.85) | 1.63 (1.03, 2.56)    |
|                                                | Tizanidine                                          | 54                          | 73,286                | 2,143,825                   | 9.20 (7.05, 12.01)                         | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 42                          | 35,213                | 1,028,603                   | 14.91 (11.02, 20.18)                       | 3.73 (2.24, 6.20) | 3.04 (1.62, 5.72)    |
|                                                | Tizanidine                                          | 23                          | 71,402                | 2,103,337                   | 3.99 (2.65, 6.01)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 266                         | 136,650               |                             |                                            | 2.79 (2.27, 3.43) | 2.50 (1.95, 3.21)    |
|                                                | Tizanidine                                          | 144                         | 214,838               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 16. Hazard ratio of opioid overdose for patients who initiated skeletal muscle relaxants indicated for muscle spasm while on long-term opioid therapy (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Carisoprodol                                        | 26                          | 21,726                | 628,196                     | 15.12 (10.29, 22.20)                       | 2.07 (1.30, 3.30) | 1.67 (0.41, 6.82)    |
|                                                | Metaxalone                                          | 6                           | 12,686                | 368,141                     | 5.95 (2.67, 13.25)                         | 0.82 (0.35, 1.90) | 0.78 (0.15, 4.17)    |
|                                                | Methocarbamol                                       | 14                          | 19,118                | 542,619                     | 9.42 (5.58, 15.91)                         | 1.29 (0.72, 2.32) | 1.59 (0.38, 6.60)    |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 8,017                 | 232,281                     | 7.86 (3.27, 18.89)                         | 1.08 (0.43, 2.69) | 1.3 (0.30, 5.69)     |
|                                                | Cyclobenzaprine                                     | 54                          | 93,997                | 2,698,132                   | 7.31 (5.60, 9.54)                          | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Carisoprodol                                        | 14                          | 11,404                | 332,198                     | 15.39 (9.12, 25.99)                        | 1.22 (0.69, 2.16) | 1.3 (0.26, 6.57)     |
|                                                | Metaxalone                                          | 2                           | 4,450                 | 123,369                     | 5.92 (1.48, 23.68)                         | 0.47 (0.11, 1.90) | 0.32 (0.03, 3.85)    |
|                                                | Methocarbamol                                       | 15                          | 19,340                | 542,760                     | 10.09 (6.09, 16.74)                        | 0.8 (0.46, 1.39)  | 0.95 (0.17, 5.49)    |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 3,110                 | 87,941                      | 4.15 (0.59, 29.49)                         | 0.33 (0.05, 2.35) | 0.16 (0.01, 4.26)    |
|                                                | Cyclobenzaprine                                     | 75                          | 77,165                | 2,156,702                   | 12.70 (10.13, 15.93)                       | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Carisoprodol                                        | 31                          | 29,202                | 856,253                     | 13.22 (9.30, 18.80)                        | 2.15 (1.41, 3.29) | 2.84 (0.62, 13.02)   |
|                                                | Metaxalone                                          | 3                           | 12,786                | 373,674                     | 2.93 (0.95, 9.09)                          | 0.48 (0.15, 1.52) | 0.45 (0.04, 4.72)    |
|                                                | Methocarbamol                                       | 14                          | 29,549                | 857,177                     | 5.97 (3.53, 10.07)                         | 0.97 (0.55, 1.72) | 1.02 (0.16, 6.47)    |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 6,270                 | 183,412                     | 9.96 (4.14, 23.92)                         | 1.62 (0.65, 4.02) | 1.93 (0.39, 9.65)    |
|                                                | Cyclobenzaprine                                     | 69                          | 140,732               | 4,096,144                   | 6.15 (4.86, 7.79)                          | Ref               | Ref                  |
| IBM® MarketScan® Research Database Pooled      | Carisoprodol                                        | 29                          | 55,301                | 1,632,072                   | 6.49 (4.51, 9.34)                          | 1.58 (1.03, 2.41) | 1.45 (0.47, 4.51)    |
|                                                | Metaxalone                                          | 7                           | 37,513                | 1,108,180                   | 2.31 (1.10, 4.84)                          | 0.56 (0.26, 1.21) | 0.37 (0.07, 1.98)    |
|                                                | Methocarbamol                                       | 20                          | 56,655                | 1,668,041                   | 4.38 (2.83, 6.79)                          | 1.06 (0.65, 1.73) | 0.71 (0.18, 2.76)    |
|                                                | Chlorzoxazone/orphenadrine                          | 7                           | 14,755                | 434,748                     | 5.88 (2.80, 12.34)                         | 1.43 (0.66, 3.09) | 1.38 (0.44, 4.33)    |
|                                                | Cyclobenzaprine                                     | 80                          | 240,755               | 7,085,866                   | 4.12 (3.31, 5.13)                          | Ref               | Ref                  |
| Pooled                                         | Carisoprodol                                        | 100                         | 117,633               |                             |                                            | 1.74 (1.39, 2.19) | 1.72 (0.87, 3.40)    |
|                                                | Metaxalone                                          | 18                          | 67,435                |                             |                                            | 0.58 (0.36, 0.94) | 0.47 (0.18, 1.23)    |
|                                                | Methocarbamol                                       | 63                          | 124,662               |                             |                                            | 1.01 (0.77, 1.32) | 1.02 (0.48, 2.21)    |
|                                                | Chlorzoxazone/orphenadrine                          | 18                          | 32,152                |                             |                                            | 1.13 (0.70, 1.82) | 1.21 (0.58, 2.53)    |
|                                                | Cyclobenzaprine                                     | 278                         | 552,649               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 17. Hazard ratio of opioid overdose for patients without prior recorded substance abuse who initiated skeletal muscle relaxants while on long-term opioid therapy (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 19                          | 19,685                | 551,147                     | 12.59 (8.03, 19.74)                        | 2.79 (1.54, 5.04) | 2.95 (0.38, 23.02)   |
|                                                | Tizanidine                                          | 11                          | 14,760                | 425,966                     | 9.43 (5.22, 17.03)                         | 2.10 (1.04, 4.24) | 2.07 (0.24, 17.79)   |
|                                                | Carisoprodol                                        | 19                          | 17,585                | 509,622                     | 13.62 (8.69, 21.35)                        | 3.03 (1.68, 5.47) | 2.30 (0.28, 19.00)   |
|                                                | Metaxalone                                          | 5                           | 10,427                | 302,982                     | 6.03 (2.51, 14.48)                         | 1.34 (0.52, 3.49) | 1.47 (0.15, 14.34)   |
|                                                | Methocarbamol                                       | 6                           | 14,472                | 411,230                     | 5.33 (2.39, 11.86)                         | 1.18 (0.49, 2.87) | 1.66 (0.18, 15.47)   |
|                                                | Chlorzoxazone/orphenadrine                          | 2                           | 6,298                 | 182,720                     | 4.00 (1.00, 15.99)                         | 0.89 (0.21, 3.75) | 0.97 (0.08, 11.89)   |
|                                                | Cyclobenzaprine                                     | 26                          | 73,381                | 2,110,223                   | 4.50 (3.06, 6.61)                          | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 69                          | 27,608                | 736,016                     | 34.24 (27.04, 43.35)                       | 3.80 (2.55, 5.67) | 2.78 (0.41, 18.82)   |
|                                                | Tizanidine                                          | 23                          | 34,691                | 987,020                     | 8.51 (5.66, 12.81)                         | 0.96 (0.57, 1.61) | 0.80 (0.07, 9.28)    |
|                                                | Carisoprodol                                        | 6                           | 8,078                 | 235,474                     | 9.31 (4.18, 20.72)                         | 1.06 (0.45, 2.50) | 0.75 (0.06, 8.92)    |
|                                                | Metaxalone                                          | 1                           | 3,303                 | 90,984                      | 4.01 (0.57, 28.50)                         | 0.45 (0.06, 3.27) | 0.21 (< 0.01, 10.70) |
|                                                | Methocarbamol                                       | 8                           | 13,312                | 372,224                     | 7.85 (3.93, 15.70)                         | 0.88 (0.41, 1.89) | 1.19 (0.13, 10.92)   |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 2,247                 | 63,554                      | 5.75 (0.81, 40.80)                         | 0.65 (0.09, 4.71) | 0.31 (0.01, 8.82)    |
|                                                | Cyclobenzaprine                                     | 37                          | 54,513                | 1,515,376                   | 8.92 (6.46, 12.31)                         | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 20                          | 25,973                | 743,645                     | 9.82 (6.34, 15.23)                         | 2.56 (1.47, 4.48) | 1.32 (0.09, 18.75)   |
|                                                | Tizanidine                                          | 28                          | 51,494                | 1,507,258                   | 6.79 (4.68, 9.83)                          | 1.78 (1.07, 2.96) | 1.52 (0.12, 19.81)   |
|                                                | Carisoprodol                                        | 18                          | 23,332                | 684,951                     | 9.60 (6.05, 15.23)                         | 2.52 (1.41, 4.49) | 3.31 (0.34, 32.40)   |
|                                                | Metaxalone                                          | 1                           | 10,514                | 307,228                     | 1.19 (0.17, 8.44)                          | 0.31 (0.04, 2.28) | 0.30 (< 0.01, 19.52) |
|                                                | Methocarbamol                                       | 8                           | 21,668                | 629,264                     | 4.64 (2.32, 9.29)                          | 1.22 (0.56, 2.64) | 1.02 (0.06, 17.01)   |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 4,805                 | 140,746                     | 7.79 (2.51, 24.14)                         | 2.04 (0.63, 6.67) | 2.74 (0.27, 28.23)   |
|                                                | Cyclobenzaprine                                     | 32                          | 105,100               | 3,062,360                   | 3.82 (2.70, 5.40)                          | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 29                          | 29,519                | 862,197                     | 12.29 (8.54, 17.68)                        | 3.56 (2.28, 5.56) | 2.52 (0.69, 9.16)    |
|                                                | Tizanidine                                          | 17                          | 60,895                | 1,794,558                   | 3.46 (2.15, 5.57)                          | 1.00 (0.58, 1.72) | 0.65 (0.11, 3.70)    |
|                                                | Carisoprodol                                        | 20                          | 48,980                | 1,446,210                   | 5.05 (3.26, 7.83)                          | 1.47 (0.88, 2.44) | 1.42 (0.34, 5.90)    |
|                                                | Metaxalone                                          | 7                           | 34,026                | 1,005,302                   | 2.54 (1.21, 5.33)                          | 0.74 (0.34, 1.62) | 0.56 (0.09, 3.44)    |
|                                                | Methocarbamol                                       | 11                          | 47,342                | 1,395,320                   | 2.88 (1.59, 5.20)                          | 0.84 (0.44, 1.59) | 0.75 (0.14, 3.95)    |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 12,844                | 378,647                     | 2.89 (0.93, 8.97)                          | 0.84 (0.26, 2.68) | 0.93 (0.19, 4.45)    |
|                                                | Cyclobenzaprine                                     | 58                          | 208,552               | 6,142,968                   | 3.45 (2.67, 4.46)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 137                         | 102,785               |                             |                                            | 3.34 (2.64, 4.22) | 2.48 (1.02, 6.04)    |
|                                                | Tizanidine                                          | 79                          | 161,840               |                             |                                            | 1.28 (0.98, 1.69) | 1.06 (0.37, 2.97)    |
|                                                | Carisoprodol                                        | 63                          | 97,975                |                             |                                            | 1.92 (1.43, 2.57) | 1.70 (0.66, 4.36)    |
|                                                | Metaxalone                                          | 14                          | 58,270                |                             |                                            | 0.75 (0.44, 1.30) | 0.61 (0.18, 2.06)    |
|                                                | Methocarbamol                                       | 33                          | 96,794                |                             |                                            | 0.98 (0.67, 1.43) | 1.04 (0.37, 2.97)    |
|                                                | Chlorzoxazone/orphenadrine                          | 9                           | 26,194                |                             |                                            | 1.01 (0.52, 1.98) | 1.06 (0.37, 3.00)    |
|                                                | Cyclobenzaprine                                     | 153                         | 441,546               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 18. Hazard ratio of opioid overdose for patients prescribed low opioid dosages (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI)  | Weighted HR (95% CI)  |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|--------------------|-----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 9                           | 11,269                | 318,351                     | 10.33 (5.37, 19.85)                        | 2.51 (1.11, 5.69)  | 1.24 (0.04, 37.21)    |
|                                                | Tizanidine                                          | 3                           | 7,584                 | 218,362                     | 5.02 (1.62, 15.56)                         | 1.22 (0.36, 4.20)  | 1.47 (0.06, 37.96)    |
|                                                | Carisoprodol                                        | 8                           | 9,283                 | 266,833                     | 10.95 (5.48, 21.90)                        | 2.67 (1.14, 6.24)  | 2.51 (0.13, 48.71)    |
|                                                | Metaxalone                                          | 0                           | 6,181                 | 179,825                     | 0.00 (N/A)                                 | 0.00 (N/A)         | 0.00 (N/A)            |
|                                                | Methocarbamol                                       | 8                           | 10,645                | 300,653                     | 9.72 (4.86, 19.43)                         | 2.37 (1.01, 5.53)  | 2.81 (0.15, 52.16)    |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 4,310                 | 124,443                     | 8.81 (2.84, 27.30)                         | 2.15 (0.63, 7.37)  | 2.06 (0.10, 43.38)    |
|                                                | Cyclobenzaprine                                     | 16                          | 49,655                | 1,424,590                   | 4.10 (2.51, 6.70)                          | Ref                | Ref                   |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 41                          | 19,792                | 528,282                     | 28.35 (20.87, 38.50)                       | 5.59 (3.09, 10.09) | 6.90 (0.18, 259.20)   |
|                                                | Tizanidine                                          | 14                          | 24,097                | 685,236                     | 7.46 (4.42, 12.60)                         | 1.50 (0.72, 3.10)  | 1.72 (0.02, 120.23)   |
|                                                | Carisoprodol                                        | 3                           | 4,137                 | 120,260                     | 9.11 (2.94, 28.25)                         | 1.84 (0.53, 6.37)  | 3.07 (0.06, 147.83)   |
|                                                | Metaxalone                                          | 0                           | 2,312                 | 63,707                      | 0.00 (N/A)                                 | 0.00 (N/A)         | 0.00 (N/A)            |
|                                                | Methocarbamol                                       | 1                           | 9,420                 | 262,669                     | 1.39 (0.20, 9.87)                          | 0.28 (0.04, 2.11)  | 0.35 (< 0.01, 261.72) |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 1,602                 | 45,022                      | 8.11 (1.14, 57.59)                         | 1.62 (0.21, 12.28) | 1.57 (0.02, 117.93)   |
|                                                | Cyclobenzaprine                                     | 15                          | 39,302                | 1,094,266                   | 5.01 (3.02, 8.31)                          | Ref                | Ref                   |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 16                          | 17,406                | 497,581                     | 11.74 (7.20, 19.17)                        | 3.50 (1.82, 6.76)  | 1.12 (0.04, 32.27)    |
|                                                | Tizanidine                                          | 10                          | 34,636                | 1,012,227                   | 3.61 (1.94, 6.71)                          | 1.08 (0.51, 2.31)  | 0.64 (0.01, 31.30)    |
|                                                | Carisoprodol                                        | 6                           | 11,947                | 351,372                     | 6.24 (2.80, 13.88)                         | 1.87 (0.75, 4.67)  | 3.14 (0.19, 52.16)    |
|                                                | Metaxalone                                          | 1                           | 6,383                 | 186,619                     | 1.96 (0.28, 13.89)                         | 0.59 (0.08, 4.38)  | 0.29 (< 0.01, 51.34)  |
|                                                | Methocarbamol                                       | 6                           | 14,692                | 425,169                     | 5.15 (2.32, 11.47)                         | 1.54 (0.62, 3.84)  | 1.37 (0.06, 34.07)    |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 3,316                 | 96,944                      | 3.77 (0.53, 26.75)                         | 1.13 (0.15, 8.42)  | 1.09 (0.04, 31.86)    |
|                                                | Cyclobenzaprine                                     | 20                          | 75,199                | 2,188,056                   | 3.34 (2.15, 5.17)                          | Ref                | Ref                   |
| IBM® MarketScan® Research Database             | Baclofen                                            | 10                          | 13,975                | 407,940                     | 8.95 (4.82, 16.64)                         | 7.94 (3.37, 18.69) | 7.66 (0.44, 134.04)   |
|                                                | Tizanidine                                          | 3                           | 28,684                | 845,076                     | 1.30 (0.42, 4.02)                          | 1.15 (0.32, 4.13)  | 2.23 (0.09, 57.18)    |
|                                                | Carisoprodol                                        | 6                           | 21,681                | 640,480                     | 3.42 (1.54, 7.62)                          | 3.04 (1.13, 8.22)  | 2.10 (0.08, 55.24)    |
|                                                | Metaxalone                                          | 3                           | 18,644                | 550,998                     | 1.99 (0.64, 6.17)                          | 1.77 (0.49, 6.34)  | 1.07 (0.03, 45.15)    |
|                                                | Methocarbamol                                       | 3                           | 26,676                | 786,483                     | 1.39 (0.45, 4.32)                          | 1.24 (0.35, 4.44)  | 0.61 (0.01, 48.06)    |
|                                                | Chlorzoxazone/orphenadrine                          | 0                           | 7,486                 | 220,786                     | 0.00 (N/A)                                 | 0.00 (N/A)         | 0.00 (N/A)            |
|                                                | Cyclobenzaprine                                     | 11                          | 121,136               | 3,568,891                   | 1.13 (0.62, 2.03)                          | Ref                | Ref                   |
| Pooled                                         | Baclofen                                            | 76                          | 62,442                |                             |                                            | 4.53 (3.22, 6.38)  | 3.71 (0.81, 16.96)    |
|                                                | Tizanidine                                          | 30                          | 95,001                |                             |                                            | 1.27 (0.82, 1.97)  | 1.44 (0.25, 8.31)     |
|                                                | Carisoprodol                                        | 23                          | 47,048                |                             |                                            | 2.36 (1.46, 3.80)  | 2.68 (0.56, 12.98)    |
|                                                | Metaxalone                                          | 4                           | 33,520                |                             |                                            | 0.63 (0.23, 1.73)  | 0.35 (0.03, 4.90)     |
|                                                | Methocarbamol                                       | 18                          | 61,433                |                             |                                            | 1.35 (0.80, 2.27)  | 1.43 (0.25, 8.26)     |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 16,714                |                             |                                            | 1.40 (0.56, 3.49)  | 1.18 (0.19, 7.30)     |
|                                                | Cyclobenzaprine                                     | 62                          | 285,292               |                             |                                            | Ref                | Ref                   |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 19. Hazard ratio of opioid overdose for patients prescribed high opioid dosages (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 27                          | 13,218                | 367,700                     | 26.82 (18.39, 39.11)                       | 2.2 (1.39, 3.48)  | 3.68 (0.77, 17.56)   |
|                                                | Tizanidine                                          | 11                          | 10,856                | 313,312                     | 12.82 (7.10, 23.16)                        | 0.95 (0.49, 1.84) | 1.34 (0.22, 8.32)    |
|                                                | Carisoprodol                                        | 18                          | 12,443                | 361,363                     | 18.19 (11.46, 28.88)                       | 1.65 (1.00, 2.74) | 1.36 (0.22, 8.33)    |
|                                                | Metaxalone                                          | 6                           | 6,505                 | 188,316                     | 11.64 (5.23, 25.90)                        | 1.01 (0.46, 2.23) | 1.04 (0.15, 7.16)    |
|                                                | Methocarbamol                                       | 6                           | 8,473                 | 241,966                     | 9.06 (4.07, 20.16)                         | 1.12 (0.57, 2.21) | 0.96 (0.13, 6.91)    |
|                                                | Chlorzoxazone/orphenadrine                          | 2                           | 3,707                 | 107,838                     | 6.77 (1.69, 27.09)                         | 0.5 (0.12, 2.07)  | 0.54 (0.05, 5.54)    |
|                                                | Cyclobenzaprine                                     | 38                          | 44,342                | 1,273,542                   | 10.90 (7.93, 14.98)                        | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 95                          | 20,393                | 556,686                     | 62.33 (50.98, 76.21)                       | 3 (2.17, 4.14)    | 1.99 (0.39, 10.19)   |
|                                                | Tizanidine                                          | 39                          | 27,613                | 793,265                     | 17.96 (13.12, 24.58)                       | 0.88 (0.59, 1.31) | 0.73 (0.10, 5.61)    |
|                                                | Carisoprodol                                        | 11                          | 7,267                 | 211,938                     | 18.96 (10.50, 34.23)                       | 0.93 (0.49, 1.77) | 1.24 (0.21, 7.33)    |
|                                                | Metaxalone                                          | 2                           | 2,138                 | 59,662                      | 12.24 (3.06, 48.96)                        | 0.59 (0.15, 2.43) | 0.36 (0.03, 4.79)    |
|                                                | Methocarbamol                                       | 14                          | 9,920                 | 280,091                     | 18.26 (10.81, 30.83)                       | 0.89 (0.50, 1.59) | 0.89 (0.13, 6.12)    |
|                                                | Chlorzoxazone/orphenadrine                          | 0                           | 1,508                 | 42,919                      | 0 (N/A)                                    | 0 (N/A)           | 0 (N/A)              |
|                                                | Cyclobenzaprine                                     | 60                          | 37,863                | 1,062,436                   | 20.63 (16.02, 26.57)                       | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 36                          | 19,359                | 557,644                     | 23.58 (17.01, 32.69)                       | 2.51 (1.63, 3.86) | 1.09 (0.12, 9.99)    |
|                                                | Tizanidine                                          | 44                          | 38,650                | 1,131,598                   | 14.20 (10.57, 19.08)                       | 1.52 (1.01, 2.28) | 1.67 (0.22, 12.58)   |
|                                                | Carisoprodol                                        | 25                          | 17,255                | 504,881                     | 18.09 (12.22, 26.77)                       | 1.93 (1.19, 3.13) | 2.32 (0.34, 15.78)   |
|                                                | Metaxalone                                          | 2                           | 6,403                 | 187,055                     | 3.91 (0.98, 15.62)                         | 0.42 (0.10, 1.71) | 0.54 (0.04, 8.12)    |
|                                                | Methocarbamol                                       | 8                           | 14,857                | 432,008                     | 6.76 (3.38, 13.53)                         | 0.72 (0.34, 1.52) | 1.01 (0.11, 9.73)    |
|                                                | Chlorzoxazone/orphenadrine                          | 4                           | 2,954                 | 86,468                      | 16.90 (6.34, 45.02)                        | 1.8 (0.65, 5.00)  | 2.01 (0.28, 14.26)   |
|                                                | Cyclobenzaprine                                     | 49                          | 65,533                | 1,908,088                   | 9.38 (7.09, 12.41)                         | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 32                          | 21,238                | 620,663                     | 18.83 (13.32, 26.63)                       | 2.63 (1.73, 3.99) | 1.95 (0.60, 6.34)    |
|                                                | Tizanidine                                          | 20                          | 42,718                | 1,258,261                   | 5.81 (3.75, 9.00)                          | 0.81 (0.49, 1.33) | 0.68 (0.15, 3.06)    |
|                                                | Carisoprodol                                        | 23                          | 33,620                | 991,592                     | 8.47 (5.63, 12.75)                         | 1.18 (0.74, 1.90) | 1.24 (0.34, 4.48)    |
|                                                | Metaxalone                                          | 4                           | 18,869                | 557,182                     | 2.62 (0.98, 6.99)                          | 0.37 (0.13, 1.00) | 0.23 (0.03, 2.09)    |
|                                                | Methocarbamol                                       | 17                          | 29,979                | 881,558                     | 7.04 (4.38, 11.33)                         | 0.98 (0.58, 1.67) | 0.71 (0.16, 3.14)    |
|                                                | Chlorzoxazone/orphenadrine                          | 7                           | 7,269                 | 213,962                     | 11.95 (5.70, 25.07)                        | 1.67 (0.77, 3.63) | 1.66 (0.50, 5.58)    |
|                                                | Cyclobenzaprine                                     | 69                          | 119,619               | 3,516,975                   | 7.17 (5.66, 9.07)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 190                         | 74,208                |                             |                                            | 2.75 (2.26, 3.35) | 2.17 (1.02, 4.62)    |
|                                                | Tizanidine                                          | 114                         | 119,837               |                             |                                            | 1.08 (0.87, 1.33) | 0.98 (0.40, 2.37)    |
|                                                | Carisoprodol                                        | 77                          | 70,585                |                             |                                            | 1.4 (1.08, 1.81)  | 1.43 (0.63, 3.21)    |
|                                                | Metaxalone                                          | 14                          | 33,915                |                             |                                            | 0.57 (0.33, 0.98) | 0.47 (0.16, 1.42)    |
|                                                | Methocarbamol                                       | 45                          | 63,229                |                             |                                            | 0.88 (0.64, 1.21) | 0.85 (0.34, 2.13)    |
|                                                | Chlorzoxazone/orphenadrine                          | 13                          | 15,438                |                             |                                            | 1 (0.62, 1.89)    | 1.12 (0.48, 2.64)    |
|                                                | Cyclobenzaprine                                     | 216                         | 267,357               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 20. Hazard ratio of opioid overdose for patients co-prescribed benzodiazepines on the cohort entry date (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 27                          | 8,306                 | 230,658                     | 42.75 (29.32, 62.35)                       | 3.41 (2.08, 5.60) | 4.49 (0.80, 25.13)   |
|                                                | Tizanidine                                          | 10                          | 8,424                 | 242,938                     | 15.03 (8.09, 27.94)                        | 1.20 (0.60, 2.42) | 1.36 (0.18, 10.48)   |
|                                                | Carisoprodol                                        | 20                          | 11,494                | 332,278                     | 21.98 (14.18, 34.08)                       | 1.76 (1.02, 3.04) | 2.08 (0.32, 13.72)   |
|                                                | Metaxalone                                          | 4                           | 5,369                 | 155,776                     | 9.38 (3.52, 24.99)                         | 0.75 (0.27, 2.11) | 1.05 (0.12, 9.07)    |
|                                                | Methocarbamol                                       | 9                           | 8,117                 | 230,943                     | 14.23 (7.41, 27.36)                        | 1.14 (0.55, 2.36) | 1.48 (0.20, 11.01)   |
|                                                | Chlorzoxazone/orphenadrine                          | 4                           | 3,607                 | 104,521                     | 13.98 (5.25, 37.24)                        | 1.12 (0.40, 3.14) | 1.27 (0.16, 10.07)   |
|                                                | Cyclobenzaprine                                     | 37                          | 37,677                | 1,082,097                   | 12.49 (9.05, 17.24)                        | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 37                          | 10,260                | 275,471                     | 49.06 (35.54, 67.71)                       | 2.40 (1.48, 3.91) | 1.71 (0.14, 21.46)   |
|                                                | Tizanidine                                          | 22                          | 13,666                | 388,266                     | 20.70 (13.63, 31.43)                       | 1.03 (0.59, 1.79) | 0.88 (0.05, 16.41)   |
|                                                | Carisoprodol                                        | 6                           | 3,879                 | 112,758                     | 19.44 (8.73, 43.26)                        | 0.97 (0.40, 2.33) | 1.13 (0.07, 17.37)   |
|                                                | Metaxalone                                          | 0                           | 1,099                 | 30,461                      | 0.00 (N/A)                                 | 0.00 (N/A)        | 0.00 (N/A)           |
|                                                | Methocarbamol                                       | 8                           | 4,860                 | 134,082                     | 21.79 (10.90, 43.58)                       | 1.08 (0.49, 2.35) | 1.09 (0.07, 17.58)   |
|                                                | Chlorzoxazone/orphenadrine                          | 0                           | 759                   | 21,401                      | 0.00 (N/A)                                 | 0.00 (N/A)        | 0.00 (N/A)           |
|                                                | Cyclobenzaprine                                     | 29                          | 18,879                | 522,744                     | 20.26 (14.08, 29.16)                       | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 14                          | 10,124                | 291,625                     | 17.53 (10.38, 29.61)                       | 1.92 (1.00, 3.69) | 0.69 (0.03, 18.17)   |
|                                                | Tizanidine                                          | 18                          | 19,692                | 576,761                     | 11.40 (7.18, 18.09)                        | 1.25 (0.68, 2.29) | 0.64 (0.02, 17.84)   |
|                                                | Carisoprodol                                        | 16                          | 9,223                 | 269,880                     | 21.65 (13.27, 35.35)                       | 2.37 (1.27, 4.44) | 3.33 (0.31, 35.88)   |
|                                                | Metaxalone                                          | 1                           | 3,370                 | 98,351                      | 3.71 (0.52, 26.37)                         | 0.41 (0.06, 3.00) | 0.20 (< 0.01, 32.68) |
|                                                | Methocarbamol                                       | 5                           | 7,250                 | 210,532                     | 8.67 (3.61, 20.84)                         | 0.95 (0.36, 2.48) | 1.21 (0.07, 20.25)   |
|                                                | Chlorzoxazone/orphenadrine                          | 2                           | 1,670                 | 48,890                      | 14.94 (3.74, 59.75)                        | 1.64 (0.39, 6.91) | 1.35 (0.09, 21.09)   |
|                                                | Cyclobenzaprine                                     | 25                          | 34,379                | 999,387                     | 9.14 (6.17, 13.52)                         | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 18                          | 11,079                | 323,978                     | 20.29 (12.79, 32.21)                       | 3.18 (1.80, 5.59) | 2.12 (0.41, 11.00)   |
|                                                | Tizanidine                                          | 9                           | 21,621                | 635,859                     | 5.17 (2.69, 9.94)                          | 0.81 (0.39, 1.68) | 0.47 (0.04, 5.18)    |
|                                                | Carisoprodol                                        | 19                          | 20,293                | 597,705                     | 11.61 (7.41, 18.20)                        | 1.82 (1.04, 3.17) | 1.85 (0.35, 9.95)    |
|                                                | Metaxalone                                          | 3                           | 11,168                | 330,340                     | 3.32 (1.07, 10.28)                         | 0.52 (0.16, 1.69) | 0.34 (0.02, 4.99)    |
|                                                | Methocarbamol                                       | 6                           | 17,227                | 507,064                     | 4.32 (1.94, 9.62)                          | 0.68 (0.29, 1.61) | 0.61 (0.07, 5.49)    |
|                                                | Chlorzoxazone/orphenadrine                          | 4                           | 4,682                 | 137,760                     | 10.61 (3.98, 28.26)                        | 1.66 (0.59, 4.67) | 1.90 (0.36, 10.12)   |
|                                                | Cyclobenzaprine                                     | 36                          | 70,050                | 2,060,138                   | 6.38 (4.60, 8.85)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 96                          | 39,769                |                             |                                            | 2.72 (2.08, 3.56) | 2.49 (0.93, 6.71)    |
|                                                | Tizanidine                                          | 59                          | 63,403                |                             |                                            | 1.10 (0.80, 1.50) | 0.82 (0.24, 2.85)    |
|                                                | Carisoprodol                                        | 61                          | 44,889                |                             |                                            | 1.74 (1.28, 2.36) | 2.03 (0.74, 5.62)    |
|                                                | Metaxalone                                          | 8                           | 21,006                |                             |                                            | 0.52 (0.25, 1.06) | 0.47 (0.11, 2.03)    |
|                                                | Methocarbamol                                       | 28                          | 37,454                |                             |                                            | 0.96 (0.63, 1.44) | 1.04 (0.32, 3.34)    |
|                                                | Chlorzoxazone/orphenadrine                          | 10                          | 10,718                |                             |                                            | 1.17 (0.61, 2.23) | 1.30 (0.43, 3.94)    |
|                                                | Cyclobenzaprine                                     | 127                         | 160,985               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 21. Hazard ratio of opioid overdose for patients not co-prescribed benzodiazepines on the cohort entry date (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 9                           | 16,181                | 455,393                     | 7.22 (3.76, 13.87)                         | 1.87 (0.84, 4.20) | 1.15 (0.07, 18.31)   |
|                                                | Tizanidine                                          | 4                           | 10,016                | 288,736                     | 5.06 (1.90, 13.48)                         | 1.32 (0.44, 3.92) | 1.22 (0.08, 18.05)   |
|                                                | Carisoprodol                                        | 6                           | 10,232                | 295,918                     | 7.41 (3.33, 16.48)                         | 1.93 (0.76, 4.89) | 1.34 (0.10, 18.56)   |
|                                                | Metaxalone                                          | 2                           | 7,317                 | 212,365                     | 3.44 (0.86, 13.75)                         | 0.90 (0.21, 3.88) | 0.46 (0.01, 15.86)   |
|                                                | Methocarbamol                                       | 5                           | 11,001                | 311,676                     | 5.86 (2.44, 14.08)                         | 1.52 (0.56, 4.13) | 1.50 (0.11, 19.65)   |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 4,410                 | 127,760                     | 2.86 (0.40, 20.30)                         | 0.75 (0.10, 5.60) | 0.43 (0.01, 15.86)   |
|                                                | Cyclobenzaprine                                     | 17                          | 56,320                | 1,616,035                   | 3.84 (2.39, 6.18)                          | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 99                          | 29,925                | 809,497                     | 44.67 (36.68, 54.40)                       | 4.29 (3.03, 6.09) | 3.05 (0.52, 17.87)   |
|                                                | Tizanidine                                          | 31                          | 38,044                | 1,090,235                   | 10.39 (7.30, 14.77)                        | 1.02 (0.64, 1.60) | 0.84 (0.09, 8.09)    |
|                                                | Carisoprodol                                        | 8                           | 7,525                 | 219,440                     | 13.32 (6.66, 26.63)                        | 1.31 (0.62, 2.78) | 1.36 (0.18, 10.09)   |
|                                                | Metaxalone                                          | 2                           | 3,351                 | 92,908                      | 7.86 (1.97, 31.44)                         | 0.76 (0.19, 3.14) | 0.46 (0.03, 7.03)    |
|                                                | Methocarbamol                                       | 7                           | 14,480                | 408,678                     | 6.26 (2.98, 13.12)                         | 0.61 (0.28, 1.35) | 0.49 (0.03, 7.02)    |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 2,351                 | 66,540                      | 5.49 (0.77, 38.97)                         | 0.54 (0.07, 3.88) | 0.28 (0.01, 7.32)    |
|                                                | Cyclobenzaprine                                     | 46                          | 58,286                | 1,633,958                   | 10.28 (7.70, 13.73)                        | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 38                          | 26,641                | 763,600                     | 18.18 (13.23, 24.98)                       | 3.49 (2.26, 5.39) | 1.40 (0.14, 14.01)   |
|                                                | Tizanidine                                          | 36                          | 53,594                | 1,567,064                   | 8.39 (6.05, 11.63)                         | 1.62 (1.04, 2.51) | 1.51 (0.16, 14.49)   |
|                                                | Carisoprodol                                        | 15                          | 19,979                | 586,373                     | 9.34 (5.63, 15.50)                         | 1.80 (1.00, 3.24) | 2.18 (0.26, 18.33)   |
|                                                | Metaxalone                                          | 2                           | 9,416                 | 275,323                     | 2.65 (0.66, 10.61)                         | 0.51 (0.12, 2.11) | 0.45 (0.02, 10.64)   |
|                                                | Methocarbamol                                       | 9                           | 22,299                | 646,645                     | 5.08 (2.65, 9.77)                          | 0.98 (0.48, 2.00) | 0.99 (0.08, 12.02)   |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 4,600                 | 134,522                     | 8.15 (2.63, 25.26)                         | 1.57 (0.49, 5.06) | 1.95 (0.23, 16.94)   |
|                                                | Cyclobenzaprine                                     | 44                          | 106,353               | 3,096,757                   | 5.19 (3.86, 6.97)                          | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 24                          | 24,134                | 704,625                     | 12.44 (8.34, 18.56)                        | 3.88 (2.36, 6.39) | 3.18 (0.77, 13.02)   |
|                                                | Tizanidine                                          | 14                          | 49,781                | 1,467,478                   | 3.48 (2.06, 5.88)                          | 1.09 (0.60, 1.99) | 1.10 (0.20, 6.02)    |
|                                                | Carisoprodol                                        | 10                          | 35,008                | 1,034,367                   | 3.53 (1.90, 6.56)                          | 1.11 (0.56, 2.20) | 0.93 (0.16, 5.46)    |
|                                                | Metaxalone                                          | 4                           | 26,345                | 777,840                     | 1.88 (0.70, 5.00)                          | 0.59 (0.21, 1.64) | 0.39 (0.04, 3.96)    |
|                                                | Methocarbamol                                       | 14                          | 39,428                | 1,160,977                   | 4.40 (2.61, 7.44)                          | 1.38 (0.76, 2.51) | 0.91 (0.15, 5.38)    |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 10,073                | 296,988                     | 3.69 (1.19, 11.44)                         | 1.15 (0.36, 3.72) | 1.18 (0.22, 6.24)    |
|                                                | Cyclobenzaprine                                     | 44                          | 170,705               | 5,025,728                   | 3.20 (2.38, 4.30)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 170                         | 96,881                |                             |                                            | 3.79 (3.03, 4.74) | 2.49 (0.99, 6.25)    |
|                                                | Tizanidine                                          | 85                          | 151,435               |                             |                                            | 1.23 (0.94, 1.60) | 1.13 (0.39, 3.28)    |
|                                                | Carisoprodol                                        | 39                          | 72,744                |                             |                                            | 1.47 (1.03, 2.09) | 1.35 (0.49, 3.74)    |
|                                                | Metaxalone                                          | 10                          | 46,429                |                             |                                            | 0.65 (0.34, 1.23) | 0.43 (0.11, 1.77)    |
|                                                | Methocarbamol                                       | 35                          | 87,208                |                             |                                            | 1.03 (0.71, 1.48) | 0.90 (0.29, 2.78)    |
|                                                | Chlorzoxazone/orphenadrine                          | 8                           | 21,434                |                             |                                            | 1.05 (0.51, 2.13) | 0.98 (0.33, 2.95)    |
|                                                | Cyclobenzaprine                                     | 151                         | 391,664               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 22. Hazard ratio of opioid overdose for patients prescribed oxycodone on the cohort entry date (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 15                          | 7,100                 | 197,674                     | 27.72 (16.71, 45.98)                       | 2.69 (1.41, 5.16) | 3.95 (0.52, 29.83)   |
|                                                | Tizanidine                                          | 6                           | 6,177                 | 177,628                     | 12.34 (5.54, 27.47)                        | 1.21 (0.49, 2.96) | 1.09 (0.09, 13.11)   |
|                                                | Carisoprodol                                        | 10                          | 7,208                 | 207,870                     | 17.57 (9.45, 32.66)                        | 1.72 (0.82, 3.61) | 1.41 (0.14, 14.71)   |
|                                                | Metaxalone                                          | 2                           | 4,029                 | 116,159                     | 6.29 (1.57, 25.15)                         | 0.62 (0.15, 2.61) | 0.34 (0.01, 11.81)   |
|                                                | Methocarbamol                                       | 3                           | 5,603                 | 157,734                     | 6.95 (2.24, 21.54)                         | 0.68 (0.20, 2.25) | 0.91 (0.07, 12.30)   |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 2,158                 | 62,064                      | 17.66 (5.69, 54.74)                        | 1.72 (0.52, 5.74) | 1.14 (0.10, 13.25)   |
|                                                | Cyclobenzaprine                                     | 23                          | 28,745                | 819,993                     | 10.24 (6.81, 15.42)                        | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 58                          | 11,991                | 327,284                     | 64.73 (50.04, 83.73)                       | 3.44 (2.25, 5.25) | 2.63 (0.31, 22.33)   |
|                                                | Tizanidine                                          | 22                          | 16,821                | 482,594                     | 16.65 (10.96, 25.29)                       | 0.90 (0.53, 1.54) | 0.91 (0.07, 12.58)   |
|                                                | Carisoprodol                                        | 4                           | 3,540                 | 103,025                     | 14.18 (5.32, 37.79)                        | 0.77 (0.27, 2.17) | 1.07 (0.09, 13.48)   |
|                                                | Metaxalone                                          | 2                           | 1,410                 | 39,576                      | 18.46 (4.62, 73.81)                        | 0.99 (0.24, 4.12) | 1.22 (0.11, 14.22)   |
|                                                | Methocarbamol                                       | 7                           | 6,204                 | 175,293                     | 14.59 (6.95, 30.60)                        | 0.78 (0.35, 1.77) | 0.91 (0.07, 12.66)   |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 868                   | 24,624                      | 14.83 (2.09, 105.31)                       | 0.80 (0.11, 5.83) | 0.22 (< 0.01, 16.30) |
|                                                | Cyclobenzaprine                                     | 34                          | 23,720                | 666,277                     | 18.64 (13.32, 26.09)                       | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 25                          | 13,425                | 385,127                     | 23.71 (16.02, 35.09)                       | 2.45 (1.47, 4.06) | 1.06 (0.07, 15.18)   |
|                                                | Tizanidine                                          | 30                          | 27,043                | 789,891                     | 13.87 (9.70, 19.84)                        | 1.44 (0.89, 2.33) | 1.54 (0.13, 17.70)   |
|                                                | Carisoprodol                                        | 21                          | 10,947                | 319,837                     | 23.98 (15.64, 36.78)                       | 2.49 (1.46, 4.25) | 3.08 (0.34, 27.76)   |
|                                                | Metaxalone                                          | 2                           | 4,250                 | 123,846                     | 5.90 (1.48, 23.59)                         | 0.61 (0.15, 2.54) | 0.52 (0.02, 13.65)   |
|                                                | Methocarbamol                                       | 4                           | 11,066                | 320,738                     | 4.56 (6.94, 22.63)                         | 0.47 (0.17, 1.32) | 0.64 (0.03, 13.60)   |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 2,067                 | 60,265                      | 18.18 (5.86, 56.38)                        | 1.88 (0.58, 6.11) | 2.04 (0.20, 20.90)   |
|                                                | Cyclobenzaprine                                     | 37                          | 48,160                | 1,397,991                   | 9.67 (7.00, 13.34)                         | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 25                          | 12,530                | 365,703                     | 24.97 (16.87, 36.95)                       | 3.28 (2.01, 5.35) | 2.48 (0.59, 10.47)   |
|                                                | Tizanidine                                          | 12                          | 25,195                | 742,118                     | 5.91 (3.35, 10.40)                         | 0.78 (0.41, 1.47) | 0.62 (0.09, 4.43)    |
|                                                | Carisoprodol                                        | 9                           | 18,505                | 545,704                     | 6.02 (3.13, 11.58)                         | 0.79 (0.39, 1.62) | 0.78 (0.12, 4.88)    |
|                                                | Metaxalone                                          | 3                           | 10,709                | 316,296                     | 3.46 (1.12, 10.74)                         | 0.46 (0.14, 1.47) | 0.26 (0.02, 3.75)    |
|                                                | Methocarbamol                                       | 14                          | 19,154                | 562,309                     | 9.09 (5.39, 15.35)                         | 1.20 (0.66, 2.18) | 0.97 (0.17, 5.47)    |
|                                                | Chlorzoxazone/orphenadrine                          | 4                           | 4,033                 | 118,140                     | 12.37 (4.64, 32.95)                        | 1.63 (0.59, 4.52) | 1.52 (0.32, 7.28)    |
|                                                | Cyclobenzaprine                                     | 45                          | 73,660                | 2,162,353                   | 7.60 (5.68, 10.18)                         | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 123                         | 45,046                |                             |                                            | 3.04 (2.38, 3.89) | 2.54 (0.99, 6.54)    |
|                                                | Tizanidine                                          | 70                          | 75,236                |                             |                                            | 1.06 (0.79, 1.41) | 0.93 (0.30, 2.94)    |
|                                                | Carisoprodol                                        | 44                          | 40,200                |                             |                                            | 1.43 (1.02, 2.01) | 1.36 (0.48, 3.91)    |
|                                                | Metaxalone                                          | 9                           | 20,398                |                             |                                            | 0.60 (0.31, 1.18) | 0.50 (0.13, 2.00)    |
|                                                | Methocarbamol                                       | 28                          | 42,027                |                             |                                            | 0.84 (0.56, 1.26) | 0.89 (0.28, 2.89)    |
|                                                | Chlorzoxazone/orphenadrine                          | 11                          | 9,126                 |                             |                                            | 1.57 (0.85, 2.90) | 1.29 (0.44, 3.73)    |
|                                                | Cyclobenzaprine                                     | 139                         | 174,285               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 23. Hazard ratio of opioid overdose for patients not prescribed oxycodone on the cohort entry date (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 21                          | 17,387                | 488,390                     | 15.71 (10.24, 24.09)                       | 2.60 (1.49, 4.52) | 2.57 (0.35, 18.81)   |
|                                                | Tizanidine                                          | 8                           | 12,263                | 354,033                     | 8.25 (4.13, 16.50)                         | 1.37 (0.63, 2.98) | 1.58 (0.18, 13.50)   |
|                                                | Carisoprodol                                        | 16                          | 14,518                | 420,326                     | 13.90 (8.52, 22.69)                        | 2.31 (1.26, 4.22) | 2.01 (0.26, 15.66)   |
|                                                | Metaxalone                                          | 4                           | 8,657                 | 251,982                     | 5.80 (3.02, 17.41)                         | 0.96 (0.34, 2.73) | 1.06 (0.10, 10.89)   |
|                                                | Methocarbamol                                       | 11                          | 13,515                | 384,885                     | 10.44 (5.78, 18.85)                        | 1.73 (0.87, 3.44) | 1.83 (0.23, 14.71)   |
|                                                | Chlorzoxazone/orphenadrine                          | 2                           | 5,859                 | 170,217                     | 4.29 (1.07, 17.16)                         | 0.71 (0.17, 2.98) | 0.67 (0.05, 9.40)    |
|                                                | Cyclobenzaprine                                     | 31                          | 65,252                | 1,878,139                   | 6.03 (4.24, 8.57)                          | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 78                          | 28,194                | 757,684                     | 37.60 (30.12, 46.94)                       | 3.71 (2.54, 5.41) | 2.80 (0.39, 20.29)   |
|                                                | Tizanidine                                          | 31                          | 34,889                | 995,907                     | 11.37 (8.00, 16.17)                        | 1.14 (0.71, 1.81) | 0.96 (0.09, 10.77)   |
|                                                | Carisoprodol                                        | 10                          | 7,864                 | 229,173                     | 15.94 (8.58, 29.62)                        | 1.60 (0.80, 3.20) | 1.49 (0.17, 13.12)   |
|                                                | Metaxalone                                          | 0                           | 3,040                 | 83,793                      | 0.00 (N/A)                                 | 0.00 (N/A)        | 0.00 (N/A)           |
|                                                | Methocarbamol                                       | 8                           | 13,136                | 367,467                     | 7.95 (3.98, 15.90)                         | 0.79 (0.37, 1.69) | 0.74 (0.06, 9.92)    |
|                                                | Chlorzoxazone/orphenadrine                          | 0                           | 2,242                 | 63,317                      | 0.00 (N/A)                                 | 0.00 (N/A)        | 0.00 (N/A)           |
|                                                | Cyclobenzaprine                                     | 41                          | 53,445                | 1,490,425                   | 10.05 (7.40, 13.65)                        | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 27                          | 23,340                | 670,098                     | 14.72 (10.09, 21.46)                       | 3.39 (2.03, 5.66) | 0.95 (0.06, 14.59)   |
|                                                | Tizanidine                                          | 24                          | 46,243                | 1,353,934                   | 6.47 (4.34, 9.66)                          | 1.50 (0.88, 2.54) | 1.02 (0.07, 14.75)   |
|                                                | Carisoprodol                                        | 10                          | 18,255                | 536,416                     | 6.81 (3.66, 12.66)                         | 1.57 (0.77, 3.20) | 2.41 (0.25, 23.32)   |
|                                                | Metaxalone                                          | 1                           | 8,536                 | 249,828                     | 1.46 (0.21, 10.38)                         | 0.34 (0.05, 2.47) | 0.48 (0.02, 13.70)   |
|                                                | Methocarbamol                                       | 10                          | 18,483                | 536,439                     | 6.81 (3.66, 12.65)                         | 1.57 (0.77, 3.20) | 1.76 (0.16, 19.21)   |
|                                                | Chlorzoxazone/orphenadrine                          | 2                           | 4,203                 | 123,147                     | 5.93 (1.48, 23.72)                         | 1.37 (0.33, 5.72) | 1.10 (0.08, 15.23)   |
|                                                | Cyclobenzaprine                                     | 32                          | 92,572                | 2,698,153                   | 4.33 (3.06, 6.13)                          | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 17                          | 22,683                | 662,900                     | 9.37 (5.82, 15.07)                         | 3.60 (2.02, 6.43) | 2.93 (0.60, 14.31)   |
|                                                | Tizanidine                                          | 11                          | 46,207                | 1,361,219                   | 2.95 (1.63, 5.33)                          | 1.14 (0.58, 2.24) | 1.19 (0.19, 7.64)    |
|                                                | Carisoprodol                                        | 20                          | 36,796                | 1,086,368                   | 6.72 (4.34, 10.42)                         | 2.59 (1.50, 4.49) | 2.08 (0.39, 10.98)   |
|                                                | Metaxalone                                          | 4                           | 26,804                | 791,884                     | 1.84 (0.69, 4.92)                          | 0.71 (0.25, 2.00) | 0.47 (0.04, 5.28)    |
|                                                | Methocarbamol                                       | 6                           | 37,501                | 1,105,732                   | 1.98 (0.89, 4.41)                          | 0.76 (0.32, 1.82) | 0.37 (0.03, 5.15)    |
|                                                | Chlorzoxazone/orphenadrine                          | 3                           | 10,722                | 316,608                     | 3.46 (1.12, 10.73)                         | 1.33 (0.41, 4.34) | 1.46 (0.25, 8.59)    |
|                                                | Cyclobenzaprine                                     | 35                          | 167,095               | 4,923,513                   | 2.60 (1.86, 3.62)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 143                         | 91,604                |                             |                                            | 3.47 (2.73, 4.40) | 2.45 (0.93, 6.46)    |
|                                                | Tizanidine                                          | 74                          | 139,602               |                             |                                            | 1.27 (0.95, 1.69) | 1.20 (0.40, 3.60)    |
|                                                | Carisoprodol                                        | 56                          | 77,433                |                             |                                            | 2.05 (1.50, 2.79) | 1.99 (0.73, 5.38)    |
|                                                | Metaxalone                                          | 9                           | 47,037                |                             |                                            | 0.59 (0.30, 1.16) | 0.50 (0.12, 2.05)    |
|                                                | Methocarbamol                                       | 35                          | 82,635                |                             |                                            | 1.14 (0.79, 1.66) | 1.05 (0.34, 3.27)    |
|                                                | Chlorzoxazone/orphenadrine                          | 7                           | 23,026                |                             |                                            | 0.85 (0.40, 1.81) | 0.87 (0.26, 2.86)    |
|                                                | Cyclobenzaprine                                     | 139                         | 378,364               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 24. Hazard ratio of opioid overdose for patients prescribed hydrocodone on the cohort entry date (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 20                          | 12,597                | 357,475                     | 20.43 (13.18, 31.67)                       | 2.84 (1.63, 4.94) | 3.17 (0.56, 18.04)   |
|                                                | Tizanidine                                          | 11                          | 10,554                | 305,110                     | 13.17 (7.29, 23.78)                        | 1.83 (0.93, 3.63) | 1.76 (0.27, 11.64)   |
|                                                | Carisoprodol                                        | 15                          | 14,298                | 413,656                     | 13.24 (7.98, 21.97)                        | 1.84 (1.00, 3.39) | 1.57 (0.23, 10.89)   |
|                                                | Metaxalone                                          | 3                           | 7,444                 | 217,069                     | 5.05 (1.63, 15.65)                         | 0.70 (0.22, 2.29) | 0.72 (0.07, 7.33)    |
|                                                | Methocarbamol                                       | 8                           | 11,919                | 338,578                     | 8.63 (4.32, 17.26)                         | 1.20 (0.55, 2.60) | 1.44 (0.20, 10.29)   |
|                                                | Chlorzoxazone/orphenadrine                          | 4                           | 5,256                 | 152,263                     | 9.60 (3.60, 25.57)                         | 1.34 (0.47, 3.77) | 0.86 (0.09, 7.91)    |
|                                                | Cyclobenzaprine                                     | 33                          | 58,218                | 1,676,808                   | 7.19 (5.11, 10.11)                         | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 65                          | 20,534                | 561,289                     | 42.30 (33.17, 53.94)                       | 3.46 (2.32, 5.14) | 3.09 (0.41, 23.46)   |
|                                                | Tizanidine                                          | 26                          | 26,946                | 774,548                     | 12.26 (8.35, 30.52)                        | 1.02 (0.62, 1.67) | 0.95 (0.08, 11.75)   |
|                                                | Carisoprodol                                        | 9                           | 7,076                 | 206,988                     | 15.88 (8.26, 30.52)                        | 1.32 (0.64, 2.73) | 1.46 (0.15, 14.06)   |
|                                                | Metaxalone                                          | 0                           | 2,134                 | 59,609                      | 0.00 (N/A)                                 | 0.00 (N/A)        | 0.00 (N/A)           |
|                                                | Methocarbamol                                       | 6                           | 10,851                | 307,512                     | 7.13 (3.20, 15.86)                         | 0.59 (0.25, 1.39) | 1.13 (0.10, 12.52)   |
|                                                | Chlorzoxazone/orphenadrine                          | 0                           | 1,669                 | 47,687                      | 0.00 (N/A)                                 | 0.00 (N/A)        | 0.00 (N/A)           |
|                                                | Cyclobenzaprine                                     | 39                          | 41,566                | 1,174,917                   | 12.12 (8.86, 16.59)                        | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 23                          | 17,132                | 494,989                     | 16.97 (11.28, 25.54)                       | 3.28 (1.92, 5.60) | 0.91 (0.06, 13.21)   |
|                                                | Tizanidine                                          | 21                          | 35,334                | 1,035,144                   | 7.41 (4.83, 11.36)                         | 1.43 (0.83, 2.49) | 1.23 (0.10, 14.73)   |
|                                                | Carisoprodol                                        | 12                          | 17,701                | 520,022                     | 8.43 (4.79, 14.84)                         | 1.63 (0.84, 3.17) | 2.32 (0.25, 21.31)   |
|                                                | Metaxalone                                          | 2                           | 6,866                 | 201,355                     | 3.63 (0.91, 14.51)                         | 0.70 (0.17, 2.93) | 0.76 (0.05, 12.72)   |
|                                                | Methocarbamol                                       | 7                           | 16,226                | 471,940                     | 5.42 (2.58, 11.36)                         | 1.05 (0.46, 2.37) | 1.23 (0.10, 14.87)   |
|                                                | Chlorzoxazone/orphenadrine                          | 5                           | 3,491                 | 102,109                     | 17.89 (7.44, 42.97)                        | 3.46 (1.35, 8.89) | 3.54 (0.44, 28.74)   |
|                                                | Cyclobenzaprine                                     | 32                          | 77,439                | 2,260,260                   | 5.17 (3.66, 7.31)                          | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 14                          | 17,280                | 506,139                     | 10.10 (5.98, 17.06)                        | 2.71 (1.48, 4.96) | 2.80 (0.64, 12.31)   |
|                                                | Tizanidine                                          | 10                          | 36,744                | 1,082,337                   | 3.37 (1.82, 6.27)                          | 0.91 (0.46, 1.81) | 0.98 (0.16, 5.96)    |
|                                                | Carisoprodol                                        | 20                          | 35,460                | 1,046,678                   | 6.98 (4.50, 10.82)                         | 1.88 (1.10, 3.19) | 1.85 (0.38, 8.93)    |
|                                                | Metaxalone                                          | 4                           | 21,095                | 623,645                     | 2.34 (0.88, 6.24)                          | 0.63 (0.23, 1.76) | 0.48 (0.05, 4.46)    |
|                                                | Methocarbamol                                       | 9                           | 33,859                | 998,326                     | 3.29 (1.71, 6.33)                          | 0.89 (0.43, 1.82) | 0.57 (0.07, 4.67)    |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 8,677                 | 255,647                     | 1.43 (0.20, 10.14)                         | 0.38 (0.05, 2.79) | 0.42 (0.04, 4.32)    |
|                                                | Cyclobenzaprine                                     | 43                          | 143,263               | 4,220,904                   | 3.72 (2.76, 5.02)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 122                         | 67,543                |                             |                                            | 3.24 (2.54, 4.14) | 2.62 (1.05, 6.50)    |
|                                                | Tizanidine                                          | 68                          | 109,578               |                             |                                            | 1.20 (0.90, 1.60) | 1.22 (0.43, 3.46)    |
|                                                | Carisoprodol                                        | 56                          | 74,535                |                             |                                            | 1.69 (1.24, 2.30) | 1.78 (0.68, 4.68)    |
|                                                | Metaxalone                                          | 9                           | 37,539                |                             |                                            | 0.58 (0.30, 1.14) | 0.50 (0.13, 1.90)    |
|                                                | Methocarbamol                                       | 30                          | 72,855                |                             |                                            | 0.90 (0.60, 1.33) | 1.02 (0.34, 3.02)    |
|                                                | Chlorzoxazone/orphenadrine                          | 10                          | 19,093                |                             |                                            | 1.15 (0.61, 2.19) | 1.00 (0.33, 2.97)    |
|                                                | Cyclobenzaprine                                     | 147                         | 320,486               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 25. Hazard ratio of opioid overdose for patients not prescribed hydrocodone on the cohort entry date (by database and pooled)**

| Database                                       | Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|------------------------------------------------|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Medicaid Analytic eXtract (MAX)                | Baclofen                                            | 16                          | 11,890                | 328,576                     | 17.79 (10.90, 29.03)                       | 2.36 (1.23, 4.52) | 2.89 (0.29, 29.11)   |
|                                                | Tizanidine                                          | 3                           | 7,886                 | 226,564                     | 4.84 (1.56, 15.00)                         | 0.65 (0.19, 2.16) | 0.63 (0.03, 15.26)   |
|                                                | Carisoprodol                                        | 11                          | 7,428                 | 214,540                     | 18.73 (10.37, 33.82)                       | 2.50 (1.20, 5.18) | 1.92 (0.17, 21.73)   |
|                                                | Metaxalone                                          | 3                           | 5,242                 | 151,072                     | 7.25 (2.34, 22.49)                         | 0.97 (0.29, 3.24) | 0.70 (0.03, 15.01)   |
|                                                | Methocarbamol                                       | 6                           | 7,199                 | 204,041                     | 10.74 (4.83, 23.91)                        | 1.43 (0.58, 3.54) | 1.41 (0.11, 18.52)   |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 2,761                 | 80,018                      | 4.56 (0.64, 32.41)                         | 0.61 (0.08, 4.53) | 0.84 (0.05, 15.30)   |
|                                                | Cyclobenzaprine                                     | 21                          | 35,779                | 1,021,324                   | 7.51 (4.90, 11.52)                         | Ref               | Ref                  |
| Medicare (diabetes, heart failure, and stroke) | Baclofen                                            | 71                          | 19,651                | 523,679                     | 49.52 (39.24, 62.49)                       | 3.66 (2.45, 5.46) | 2.38 (0.30, 18.68)   |
|                                                | Tizanidine                                          | 27                          | 24,764                | 703,953                     | 14.01 (9.61, 20.43)                        | 1.05 (0.64, 1.74) | 0.95 (0.08, 11.15)   |
|                                                | Carisoprodol                                        | 5                           | 4,328                 | 125,210                     | 14.59 (6.07, 35.04)                        | 1.10 (0.43, 2.81) | 1.34 (0.14, 12.99)   |
|                                                | Metaxalone                                          | 2                           | 2,316                 | 63,760                      | 11.46 (2.87, 45.81)                        | 0.85 (0.21, 3.55) | 0.52 (0.03, 9.86)    |
|                                                | Methocarbamol                                       | 9                           | 8,489                 | 235,248                     | 13.97 (7.27, 26.86)                        | 1.05 (0.50, 2.17) | 0.85 (0.07, 10.77)   |
|                                                | Chlorzoxazone/orphenadrine                          | 1                           | 1,441                 | 40,254                      | 9.07 (1.28, 64.42)                         | 0.68 (0.09, 4.96) | 0.31 (0.01, 10.60)   |
|                                                | Cyclobenzaprine                                     | 36                          | 35,599                | 981,785                     | 13.39 (9.66, 18.57)                        | Ref               | Ref                  |
| Optum® Clinformatics® Data Mart                | Baclofen                                            | 29                          | 19,633                | 560,236                     | 18.91 (13.14, 27.21)                       | 2.56 (1.57, 4.16) | 1.09 (0.08, 15.26)   |
|                                                | Tizanidine                                          | 33                          | 37,952                | 1,108,681                   | 10.87 (7.73, 15.29)                        | 1.48 (0.93, 2.37) | 1.19 (0.09, 15.52)   |
|                                                | Carisoprodol                                        | 19                          | 11,501                | 336,231                     | 20.64 (13.17, 32.36)                       | 2.81 (1.62, 4.88) | 2.93 (0.32, 26.58)   |
|                                                | Metaxalone                                          | 1                           | 5,920                 | 172,319                     | 2.12 (0.30, 15.05)                         | 0.29 (0.04, 2.10) | 0.26 (< 0.01, 17.25) |
|                                                | Methocarbamol                                       | 7                           | 13,323                | 385,237                     | 6.64 (3.16, 13.92)                         | 0.90 (0.40, 2.02) | 0.82 (0.05, 14.03)   |
|                                                | Chlorzoxazone/orphenadrine                          | 0                           | 2,779                 | 81,303                      | 0.00 (N/A)                                 | 0.00 (N/A)        | 0.00 (N/A)           |
|                                                | Cyclobenzaprine                                     | 37                          | 63,293                | 1,835,884                   | 7.36 (5.33, 10.16)                         | Ref               | Ref                  |
| IBM® MarketScan® Research Database             | Baclofen                                            | 28                          | 17,933                | 522,464                     | 19.57 (13.52, 28.35)                       | 4.14 (2.54, 6.77) | 2.87 (0.61, 13.62)   |
|                                                | Tizanidine                                          | 13                          | 34,658                | 1,021,000                   | 4.65 (2.70, 8.01)                          | 0.99 (0.52, 1.86) | 0.78 (0.10, 5.89)    |
|                                                | Carisoprodol                                        | 9                           | 19,841                | 585,394                     | 5.62 (2.92, 10.79)                         | 1.19 (0.58, 2.47) | 0.80 (0.11, 5.93)    |
|                                                | Metaxalone                                          | 3                           | 16,418                | 484,535                     | 2.26 (0.73, 7.01)                          | 0.48 (0.15, 1.56) | 0.23 (0.01, 5.03)    |
|                                                | Methocarbamol                                       | 11                          | 22,796                | 669,715                     | 6.00 (3.32, 10.83)                         | 1.27 (0.65, 2.49) | 0.93 (0.14, 6.37)    |
|                                                | Chlorzoxazone/orphenadrine                          | 6                           | 6,078                 | 179,101                     | 12.24 (5.50, 27.24)                        | 2.60 (1.10, 6.15) | 2.70 (0.57, 12.87)   |
|                                                | Cyclobenzaprine                                     | 37                          | 97,492                | 2,864,962                   | 4.72 (3.42, 6.51)                          | Ref               | Ref                  |
| Pooled                                         | Baclofen                                            | 144                         | 69,107                |                             |                                            | 3.26 (2.56, 4.14) | 2.41 (0.89, 6.55)    |
|                                                | Tizanidine                                          | 76                          | 105,260               |                             |                                            | 1.15 (0.87, 1.53) | 0.88 (0.26, 2.98)    |
|                                                | Carisoprodol                                        | 44                          | 43,098                |                             |                                            | 1.90 (1.35, 2.67) | 1.54 (0.53, 4.50)    |
|                                                | Metaxalone                                          | 9                           | 29,896                |                             |                                            | 0.59 (0.30, 1.17) | 0.39 (0.08, 1.89)    |
|                                                | Methocarbamol                                       | 33                          | 51,807                |                             |                                            | 1.13 (0.77, 1.65) | 0.98 (0.30, 3.21)    |
|                                                | Chlorzoxazone/orphenadrine                          | 8                           | 13,059                |                             |                                            | 1.14 (0.56, 2.32) | 1.28 (0.42, 3.89)    |
|                                                | Cyclobenzaprine                                     | 131                         | 232,163               |                             |                                            | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years

**eTable 26. Hazard ratio of opioid overdose after adjustment for socioeconomic status measures and rural-urban continuum codes in Medicaid Analytic eXtract (MAX)**

| Skeletal muscle relaxant co-prescribed with opioids | Number of unweighted events | Number of individuals | Total follow-up time (days) | Crude incidence rate (95% CI) <sup>1</sup> | Crude HR (95% CI) | Weighted HR (95% CI) |
|-----------------------------------------------------|-----------------------------|-----------------------|-----------------------------|--------------------------------------------|-------------------|----------------------|
| Baclofen                                            | 36                          | 23,828                | 667,191                     | 19.71 (14.22, 27.32)                       | 2.73 (1.78, 4.18) | 3.41 (0.84, 13.87)   |
| Tizanidine                                          | 14                          | 17,612                | 507,674                     | 10.07 (5.97, 17.01)                        | 1.40 (0.78, 2.53) | 1.36 (0.27, 6.86)    |
| Carisoprodol                                        | 26                          | 20,802                | 601,226                     | 15.80 (10.75, 23.20)                       | 2.20 (1.37, 3.53) | 1.78 (0.39, 8.23)    |
| Metaxalone                                          | 6                           | 12,054                | 349,814                     | 6.26 (2.81, 13.94)                         | 0.87 (0.37, 2.03) | 0.79 (0.13, 4.97)    |
| Methocarbamol                                       | 14                          | 18,360                | 520,644                     | 9.82 (5.82, 16.48)                         | 1.36 (0.76, 2.46) | 1.41 (0.28, 7.00)    |
| Chlorzoxazone/orphenadrine                          | 5                           | 7,717                 | 223,527                     | 8.17 (3.40, 19.63)                         | 1.14 (0.45, 2.85) | 1.03 (0.19, 5.75)    |
| Cyclobenzaprine                                     | 51                          | 90,258                | 2,589,909                   | 7.19 (5.47, 9.46)                          | Ref               | Ref                  |

Abbreviations: CI, confidence interval; HR, hazard ratio

<sup>1</sup>Crude incidence rate presents the number of events per 1,000 person-years