**TITLE: Comparative effectiveness of dual vs single-action antidepressants on HIV clinical outcomes in HIV-infected people with depression**

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**Table 1. Intent-to-treat inverse probability of treatment weight model.**

|  |  |  |
| --- | --- | --- |
| Variable | Odds Ratio | 95% Confidence Interval |
| Site FENWAY vs UW | 0.79 | 0.50 | 1.25 |
| Site JH vs UW | 1.29 | 0.79 | 2.10 |
| Site UAB vs UW | 0.85 | 0.57 | 1.27 |
| Site UCSD vs UW | 0.54 | 0.35 | 0.83 |
| Site UCSF vs UW | 0.86 | 0.56 | 1.32 |
| Age | 1.02 | 1.01 | 1.03 |
| Male | 1.28 | 0.91 | 1.79 |
| White | 1.36 | 0.89 | 2.07 |
| Black | 0.95 | 0.59 | 1.55 |
| Appointment with psychiatrist in washout period | 1.75 | 1.30 | 2.34 |
| Prior single-action treatment | 0.75 | 0.52 | 1.08 |
| Prior dual-action treatment | 3.20 | 2.12 | 4.84 |
| On ART at index date | 1.20 | 0.83 | 1.74 |
| CD4 T-cell count | 1.00 | 1.00 | 1.00 |
| Viral suppression | 1.30 | 0.96 | 1.76 |
| AIDS Defining Illness | 1.27 | 0.97 | 1.66 |
| Anxiety | 0.79 | 0.59 | 1.06 |
| Alcohol use | 1.14 | 0.82 | 1.58 |
| Drug use | 1.20 | 0.92 | 1.58 |
| Smoking history | 1.05 | 0.81 | 1.36 |

**Table 2. Intent-to-treat inverse probability of treatment weight model diagnostics**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Minimum | Maximum | Mean |
| Predicted probability for receiving dual-action antidepressant treatment | 0.058894 | 0.803181 | 0.296454 |
| Inverse probability of treatment weights | 0.370637 | 3.574592 | 1.000242 |

**Table 3. Intent-to-treat treatment episode medications**

|  |  |  |
| --- | --- | --- |
| Antidepressant | Frequency | Percent |
| BUPROPION | 186 | 13.19 |
| CITALOPRAM | 407 | 28.87 |
| DESVENLAFAXINE | 2 | 0.14 |
| DULOXETINE | 59 | 4.18 |
| ESCITALOPRAM | 161 | 11.42 |
| FLUOXETINE | 136 | 9.65 |
| FLUVOXAMINE | 1 | 0.07 |
| MIRTAZAPINE | 113 | 8.01 |
| PAROXETINE | 148 | 10.5 |
| SERTRALINE HCL | 139 | 9.86 |
| VENLAFAXINE | 58 | 4.11 |

**Table 4. Per-protocol inverse probability of treatment weight model**

|  |  |  |
| --- | --- | --- |
| Variable | Odds Ratio | 95% Confidence Interval |
| Site FENWAY vs UW | 1.114 | 0.359 | 3.456 |
| Site JH vs UW | 1.62 | 0.465 | 5.64 |
| Site UAB vs UW | 1.069 | 0.363 | 3.15 |
| Site UCSD vs UW | 1.098 | 0.372 | 3.237 |
| Site UCSF vs UW | 0.634 | 0.196 | 2.049 |
| Age | 1.039 | 1.01 | 1.068 |
| Male | 1.429 | 0.725 | 2.816 |
| White | 1.14 | 0.662 | 1.965 |
| CD4 T-cell count | 1 | 0.999 | 1.001 |
| Viral suppression | 1.567 | 0.847 | 2.897 |
| Prior dual-action treatment | 3.769 | 1.802 | 7.885 |
| On ART at index date | 1.278 | 0.612 | 2.671 |
| Anxiety | 0.51 | 0.271 | 0.958 |
| Alcohol use | 1.004 | 0.506 | 1.993 |
| Drug use | 1.406 | 0.84 | 2.351 |

**Table 5. Per protocol inverse probability of treatment weight model diagnostics**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Minimum | Maximum | Mean |
| Predicted probability for receiving dual-action antidepressant treatment | 0.038775 | 0.713237 | 0.233259 |
| Inverse probability of treatment weights | 0.355553 | 3.162937 | 1.0004646 |

**Table 6. Per protocol treatment episode medications**

|  |  |  |
| --- | --- | --- |
| Antidepressant | Frequency | Percent |
| BUPROPION | 47 | 10.85 |
| CITALOPRAM | 121 | 27.94 |
| DULOXETINE | 12 | 2.77 |
| ESCITALOPRAM | 51 | 11.78 |
| FLUOXETINE | 51 | 11.78 |
| FLUVOXAMINE | 1 | 0.23 |
| MIRTAZAPINE | 27 | 6.24 |
| PAROXETINE | 64 | 14.78 |
| SERTRALINE HCL | 44 | 10.16 |
| VENLAFAXINE | 15 | 3.46 |

**Table 7. Per protocol treatment episode characteristics (n=433)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Unweighted |  | IPT Weighted |
|  | Total(n=433) | Dual-action (n=101) | Single- action (n=332) | STD |  | Dual-action (n=101) | Single- action (n=332) | STD |
|  | % | % | % |  |  | % | % |  |
| Prior single-action\*  | 16 | 20 | 15 | 0.120 |  | 16 | 17 | 0.032 |
| Prior dual-action\* | 9 | 18 | 7 | 0.376 |  | 10 | 10 | 0.003 |
| Psychiatrist appointment in washout period₮ | 17 | 22 | 16 | 0.163 |  | 23 | 16 | 0.187 |
| Demographics |  |  |  |  |  |  |  |  |
|  Age, mean (SD) | 40 (9) | 42 (8) | 39 (9) | 0.316 |  | 39 (9) | 40 (9) | 0.023 |
|  Male | 81 | 85 | 80 | 0.143 |  | 81 | 81 | 0.016 |
|  White | 60 | 63 | 59 | 0.094 |  | 61 | 60 | 0.032 |
|  Black  | 30 | 27 | 30 | 0.081 |  | 30 | 30 | 0.013 |
|  Other/unknown  | 11 | 10 | 11 | 0.031 |  | 9 | 10 | 0.033 |
|  Hispanic | 20 | 17 | 21 | 0.099 |  | 15 | 20 | 0.126 |
| Health status |  |  |  |  |  |  |  |  |
|  Viral suppression(<200 copies/mL)₮ | 70 | 78 | 67 | 0.247 |  | 67 | 69 | 0.049 |
|  CD4 T-cell count, mean₮ (SD) | 490 (279) | 506 (284) | 485 (278) | 0.075 |  | 487 (291) | 492 (283) | 0.019 |
|  Anxiety | 23 | 19 | 24 | 0.119 |  | 21 | 22 | 0.031 |
|  ADI | 32 | 37 | 31 | 0.120 |  | 38 | 31 | 0.138 |
|  At risk drinking | 14 | 15 | 14 | 0.029 |  | 16 | 14 | 0.061 |
|  Drug use | 30 | 36 | 28 | 0.160 |  | 30 | 30 | 0.002 |
|  Smoker ever | 34 | 31 | 36 | 0.102 |  | 37 | 37 | 0.004 |
| On ART at index | 83 | 86 | 82 | 0.104 |  | 83 | 83 | 0.009 |
| Clinic |  |  |  |  |  |  |  |  |
|  A | 16 | 19 | 15 | 0.111 |  | 15 | 16 | 0.014 |
|  B | 10 | 12 | 9 | 0.096 |  | 9 | 10 | 0.042 |
|  C | 29 | 27 | 29 | 0.055 |  | 33 | 29 | 0.085 |
|  D | 24 | 25 | 25 | 0.022 |  | 25 | 24 | 0.022 |
|  E | 16 | 12 | 12 | 0.152 |  | 13 | 16 | 0.068 |
|  F | 6 | 6 | 6 | 0.009 |  | 5 | 6 | 0.029 |
| Psychiatrist appointment – follow-up | 25 | 30 | 24 | 0.129 |  | 31 | 24 | 0.150 |
| On ART continuously – follow-up | 78 | 84 | 77 | 0.186 |  | 82 | 77 | 0.112 |
| Viral suppression(<200 copies/mL) – follow-up | 77 | 86 | 75 | 0.236 |  | 82 | 80 | 0.046 |
| CD4 T-cell count, mean (SD) - follow-up | 523 (273) | 542 (271) | 517 (275) | 0.091 |  | 520 (283) | 522 (281) | 0.007 |
|  |  |  |  |  |  |  |  |  |

STD, standardized difference; SD, standard deviation, ART, antiretroviral therapy.

\* Antidepressant treatment received prior to the current treatment episode; includes periods of treatment that did not have at least a 90-day washout period

₮Measure taken or event occurred in the washout period but not more than 6 months prior to the treatment episode index date

**Table 8. Per protocol weighted GEE intent-to-treat analysis – HIV clinical outcomes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Probability of viral suppression (<200 copies/mL) |  |  | CD4 T-cell count |  |
|  | RR | 95% CI |  | Mean difference | 95% CI |
| Baseline difference: dual vs single-action antidepressants | 0.97 | (0.80,1.17) |  | -5 | (-79,68) |
| Initiation of antidepressants\* | 1.18¥ | (0.1.11,1.25) |  | 31¥ | (-14,49) |
| Difference-in-difference: dual vs single-action antidepressants\*\* | 1.06 | (0.89,1.26) |  | 3 | (-40,47) |

GEE, generalizing estimating equations; RR, risk ratio; CI, confidence interval.

\*Estimated change from baseline in GEE model without interaction term

\*\*Interaction between treatment group and study period. This is the comparative effectiveness difference-in-difference estimate which represents the change in the outcome from baseline for dual-action antidepressants minus the same difference for single-action antidepressants.

¥ P value <0.001

**Table 9. Secondary analysis - intent-to-treat inverse probability of treatment weight model**

|  |  |  |
| --- | --- | --- |
| Variable | Odds Ratio | 95% Confidence Interval |
| Age | 1.009 | 0.990 | 1.028 |
| Male | 1.317 | 0.758 | 2.291 |
| White | 0.739 | 0.498 | 1.097 |
| Appointment with psychiatrist in washout period | 2.689 | 1.791 | 4.038 |
| Prior single-action | 3.687 | 2.073 | 6.559 |
| Prior dual-action | 0.478 | 0.265 | 0.861 |
| On ART at index date | 1.131 | 0.594 | 2.157 |
| CD4 T-cell count in washout period | 1.001 | 1.000 | 1.001 |
| Viral suppression in washout period | 0.603 | 0.374 | 0.971 |
| PHQ-9 in washout period | 0.949 | 0.914 | 0.985 |
| PHQ-9 < 5 in washout period (remission) | 0.567 | 0.313 | 1.029 |

**Table 10. Secondary analysis - intent-to-treat inverse probability of observations weight model**

|  |  |  |
| --- | --- | --- |
| Variable | Odds Ratio | 95% Confidence Interval |
| Dual-action treatment episode (ref: single-action) | 0.985 | 0.616 | 1.573 |
| Age | 1.005 | 0.985 | 1.025 |
| Male | 1.878 | 1.092 | 3.230 |
| White | 0.390 | 0.251 | 0.605 |
| Appointment with psychiatrist in washout period | 2.924 | 1.671 | 5.117 |
| Prior single-action | 0.863 | 0.465 | 1.601 |
| Prior dual-action | 1.317 | 0.735 | 2.359 |
| On ART at index date | 1.781 | 0.951 | 3.336 |
| CD4 T-cell count in washout period | 1.000 | 0.999 | 1.001 |
| Viral suppression in washout period | 1.355 | 0.810 | 2.267 |
| PHQ-9 in washout period | 0.983 | 0.948 | 1.020 |
| PHQ-9 < 5 in washout period (remission) | 0.880 | 0.470 | 1.646 |

**Table 11. Secondary analysis - intent-to-treatment inverse probability of treatment and observation weight model diagnostics**a

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Minimum | Maximum | Mean |
| Predicted probability for receiving dual-action antidepressant treatment | 0.0396885 | 0.8140032 | 0.2810463 |
| Inverse probability of treatment weights | 0.3452637 | 3.0114992 | 1.0001589 |
| Predicted probability for missing a PHQ-9 in the follow-up period | 0.2967138 | 0.9585934 | 0.7646971 |
| Inverse probability of observations weights | 0.3345638 | 3.5592954 | 0.9943877 |
| Inverse probability of treatment and observation weightsb | 0.2665783 | 6.044988 | 0.9961067 |

aThe inverse probability of treatment and observation weights were only used in the depression models because the PHQ-9 was the only outcome with missing values in the follow-up. Only the inverse probability of treatment weights were used for the HIV clinical outcome models because there were no missing HIV viral load or CD4 T-cell count values in the follow-up period.

b Equals the product of the inverse probability of treatment weights and the inverse probability of the missing observation weights

**Table 1 2. Secondary analysis - intent-to-treat treatment episode medications**

| **Medication name** | **Frequency** | **Percent** | **CumulativeFrequency** | **CumulativePercent** |
| --- | --- | --- | --- | --- |
| **BUPROPION** | 42 | 13.73 | 42 | 13.73 |
| **CITALOPRAM** | 127 | 41.50 | 169 | 55.23 |
| **DESVENLAFAXINE** | 1 | 0.33 | 170 | 55.56 |
| **DULOXETINE** | 10 | 3.27 | 180 | 58.82 |
| **ESCITALOPRAM** | 33 | 10.78 | 213 | 69.61 |
| **FLUOXETINE** | 20 | 6.54 | 233 | 76.14 |
| **MIRTAZAPINE** | 21 | 6.86 | 254 | 83.01 |
| **PAROXETINE** | 24 | 7.84 | 278 | 90.85 |
| **SERTRALINE HCL** | 16 | 5.23 | 294 | 96.08 |
| **VENLAFAXINE** | 12 | 3.92 | 306 | 100.00 |

**Table 1 3. Secondary analysis - intent-to-treat treatment episode characteristics (n=306)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Unweighted |  |  | IPT Weighted |
|  | Total | Dual-action (n=86) | Single- action (n=220) | STD |  | Total | Dual-action (n=86)  | Single-action (n=220) | STD |
|  | % | % | % |  |  | % | % | % |  |
| Outcome variables |  |  |  |  |  |  |  |  |  |
| Depression (PHQ-9) – in washout, mean (SD) ₮ | 10.5 (7.2) | 9.9 (6.7) | 10.7 (7.4) | 0.111 |  | 10.2 (7.3) | 10.3 (7.3) | 10.1 (7.4) | 0.037 |
| Depression (PHQ-9) – in follow-up, mean (SD) | 7.9 (6.3) | 8.0 (5.7) | 7.9 (6.5) | 0.018 |  | 7.8 (6.3) | 7.6 (5.9) | 7.9 (6.4) | 0.042 |
| Depression remission (PHQ-9 <5) – in washout₮ | 24 | 24 | 24 | 0.008 |  | 26 | 26 | 25 | 0.038 |
| Depression remission (PHQ-9 <5) – in follow-up | 34 | 34 | 34 | 0.011 |  | 35 | 38 | 33 | 0.108 |
| Viral suppression(<200 copies/mL) - in washout₮ | 76 | 73 | 77 | 0.083 |  | 76 | 77 | 76 | 0.016 |
| Viral suppression(<200 copies/mL) - in follow-up | 87 | 90 | 86 | 0.107 |  | 86 | 87 | 86 | 0.032 |
| CD4 T-cell count – in washout, mean (SD)₮  | 526 (299) | 563 (332) | 512 (285) | 0.171 |  | 525 (301) | 523 (319) | 525 (295) | 0.008 |
| CD4 T-cell count – in follow-up ₮ (SD) | 562 (301) | 595 (305) | 549 (298) | 0.152 |  | 565 (316) | 571 (322) | 563 (314) | 0.025 |
| Prior single-action\* | 16 | 15 | 17 | 0.046 |  | 17 | 19 | 17 | 0.055 |
| Prior dual-action\* | 13 | 22 | 10 | 0.358 |  | 12 | 12 | 12 | 0.019 |
| Psychiatrist appointment - in washout₮ | 25 | 38 | 20 | 0.430 |  | 25 | 26 | 25 | 0.022 |
| Demographics |  |  |  |  |  |  |  |  |  |
| Age, mean (SD) | 38 (10) | 38 (10) | 38 (10) | 0.038 |  | 36 | 38 | 37 | 0.013 |
| Male | 85 | 87 | 84 | 0.087 |  | 85 | 84 | 85 | 0.030 |
| White | 57 | 55 | 58 | 0.071 |  | 56 | 54 | 56 | 0.036 |
| Black  | 34 | 30 | 36 | 0.119 |  | 36 | 31 | 38 | 0.141 |
| Other/unknown  | 9 | 15 | 6 | 0.333 |  | 9 | 15 | 6 | 0.306 |
| Hispanic | 16 | 14 | 16 | 0.066 |  | 15 | 15 | 15 | 0.020 |
| Health status – conditions identified any time prior to the index date unless otherwise specified |  |  |  |  |  |  |  |  |  |
| Anxiety | 32 | 33 | 32 | 0.016 |  | 33 | 36 | 32 | 0.075 |
| ADI  | 28 | 31 | 27 | 0.091 |  | 28 | 31 | 27 | 0.081 |
| At risk drinking  | 13 | 21 | 10 | 0.310 |  | 13 | 20 | 11 | 0.286 |
| Drug use  | 25 | 22 | 26 | 0.088 |  | 24 | 19 | 26 | 0.173 |
| Smoker ever | 42 | 51 | 39 | 0.245 |  | 43 | 54 | 40 | 0.289 |
| On ART at index | 90 | 90 | 90 | 0.015 |  | 90 | 89 | 90 | 0.032 |
| Clinic |  |  |  |  |  |  |  |  |  |
| A | 11 | 14 | 10 | 0.126 |  | 11 | 13 | 10 | 0.121 |
| B | 50 | 56 | 48 | 0.153 |  | 52 | 57 | 50 | 0.127 |
| C | 21 | 6 | 27 | 0.538 |  | 20 | 7 | 25 | 0.472 |
| D | 7 | 10 | 5 | 0.221 |  | 6 | 11 | 5 | 0.234 |
| E | 11 | 14 | 10 | 0.142 |  | 11 | 13 | 10 | 0.085 |
| Psychiatrist appointment during follow-up | 41 | 53 | 36 | 0.351 |  | 41 | 46 | 40 | 0.117 |
| # days received treatment during follow-up continuously, mean (SD) | 229 (131) | 200 (200) | 240 (240) | 0.315 |  | 231 (130) | 205 (137) | 242 (125) | 0.286 |
| Per protocol£  | 33 | 21 | 37 | 0.352 |  | 33 | 21 | 38 | 0.350 |
| Switch out€ | 18 | 26 | 15 | 0.291 |  | 17 | 23 | 15 | 0.233 |
| Augmented± | 7 | 16 | 3 | 0.531 |  | 7 | 16 | 3 | 0.551 |
| On ART continuously during follow-up | 74 | 78 | 74 | 0.091 |  | 73 | 74 | 73 | 0.030 |
| # days from index date the PHQ-9 was collected, mean (SD) | 230 (89) | 238 (85) | 226 (91) | 0.127 |  | 226 (89) | 224 (83) | 227 (92) | 0.035 |
| # days from index date the HIV viral load lab result was collected. Mean (SD) | 265 (83) | 280 (81) | 259 (83) | 0.247 |  | 266 (83) | 277 (83) | 261 (82) | 0.198 |
| # days from index date the CD4 T-cell lab result was collected, mean (SD) | 262 (86) | 274 (84) | 257 (87) | 0.204 |  | 261 (86) | 273 (83) | 257 (87) | 0.192 |

IPT, inverse probability of treatment; PHQ-9, patient health questionnaire; STD, standardized difference; SD, standard deviation; ART, antiretroviral therapy.

\* Antidepressant treatment received prior to the current treatment episode; includes periods of treatment that did not have at least a 90-day washout period

₮ Measure taken or event occurred in the washout period but not more than 6 months prior to the treatment episode index date

£ Treatment episode with no switch out, augmentation or discontinuation of antidepressant initiated on the index date during follow-up

€ Addition of a new psychotropic medication with concurrent receipt of the original antidepressant lasting fewer than thirty days

± Addition of a new psychotropic medication with concurrent receipt of the original antidepressant lasting more than thirty days

Depression PHQ-9 ANOVA for repeated measures

 Difference in washout and follow-up value p value <0.001

 Difference in washout and follow-up value for dual-action p value <0.001

Difference in washout and follow-up value for single-action p value <0.001

 Interaction term: dual-action (ref:single-action)\*post(ref:pre) p value 0.54

Depression remission McNemar and Cochran-Mantel-Haenszel tests

 Difference in washout and follow-up value p value 0.01

 Difference in washout and follow-up value for dual-action p value 0.06

Difference in washout and follow-up value for single-action p value 0.05

 Interaction term: dual-action (ref:single-action)\*post(ref:pre) p value 0.53

Viral suppression(<200 copies/mL) McNemar and Cochran-Mantel-Haenszel tests

 Difference in washout and follow-up value p value <0.001

 Difference in washout and follow-up value for dual-action p value <0.001

Difference in washout and follow-up value for single-action p value 0.03

 Interaction term: dual-action (ref:single-action)\*post(ref:pre) p value 0.80

CD4 T-cell count PHQ-9 ANOVA for repeated measures

 Difference in washout and follow-up value p value <0.001

 Difference in washout and follow-up value for dual-action p value <0.001

Difference in washout and follow-up value for single-action p value <0.001

 Interaction term: dual-action (ref:single-action)\*post(ref:pre) p value 0.64

**Table 14. Secondary analysis - weighted GEE intent-to-treat analysis – HIV clinical outcomes\***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Probability of viral suppression (<200 copies/mL) |  |  | CD4 T-cells/mm3 |  |
|  | RR | 95% CI |  | Mean difference | 95% CI |
| Baseline difference: dual vs single-action antidepressants | 1.00 | (0.86,1.16) |  | 5 | (-81,92) |
| Initiation of antidepressants\*\* | 1.13¥ | (1.06,1.21) |  | 40¥ | (19,62) |
| Difference-in-difference: dual vs single-action antidepressants\*\*\* | 1.01 | (0.87,1.17) |  | 10 | (-40,60) |

GEE, generalized estimating equations; RR, risk ratio; CI, confidence interval; PHQ-9, patient health questionnaire.

\* n = 306, both models included at-risk drinking as a covariate in regression equation because the standard difference for at-risk drinking, smoking, race other or unknown and CNICS site after inverse probability of treatment weighting was > 0.25 threshold indicating potential for confounding not addressed with the inverse weighting method.

\*\*Estimated change from baseline in GEE model without interaction term

\*\*\*Interaction between treatment group and study period. This is the comparative effectiveness difference-in-difference estimate which represents the change in the outcome from baseline for dual-action antidepressants minus the same difference for single-action antidepressants.

¥ P value <0.001

± P value <0.01