**Supplementary Digital Content A. Additional methods**

**Study Selection**

Studies that used one of the medications as an interim treatment were eligible; studies that did not transition directly between buprenorphine and methadone were excluded. Studies were required to use the medications as part of MOUD. To maximize real-world utility of results, laboratory studies that returned patients to their initial medication before a period of stabilization were excluded. Studies that discontinued the second medication after a post-transfer stabilization period were eligible. Attempts to contact study authors were made when questions arose.

**Data Extraction and ROB Assessment**

For RCTs, ROB was assessed using the Cochrane Collaboration’s tool.43 For observational studies, relevant questions were drawn from the RTI Item Bank on ROB and Precision of Observational Studies.44 There is no established guidance on ROB assessment for interventional studies that have a single treatment group but are not quasi-experimental (i.e., outcome measurements are not compared pre- and post-intervention). For such studies, general ROB assessment questions were drawn from the RTI Item Bank. In all assessments, ROB was allowed to vary by outcome.

**Supplementary Digital Content B. Search strategy**

**MEDLINE via PubMed**

|  |  |  |
| --- | --- | --- |
| Search | Query | Items Found |
| #1 | "Buprenorphine"[Mesh] OR "Buprenorphine, Naloxone Drug Combination"[Mesh] OR anorfin[tiab] OR belbuca[tiab] OR buprenex[tiab] OR buprenorphine[tiab] OR buprex[tiab] OR buprine[tiab] OR butrans[tiab] OR "cl 112, 302"[tiab] OR "cl 112302"[tiab] OR "cl112, 302"[tiab] OR cl112302[tiab] OR finibron[tiab] OR lepetan[tiab] OR "nih 8805"[tiab] OR nih8805[tiab] OR norphin[tiab] OR pentorel[tiab] OR prefin[tiab] OR probuphine[tiab] OR "rx 6029 m"[tiab] OR "rx 6029m"[tiab] OR rx6029m[tiab] OR "6029 M"[tiab] OR 6029M[tiab] OR subutex[tiab] OR transtec[tiab] OR "um 952"[tiab] OR um952[tiab] OR bunavail[tiab] OR "buprenorphine/naloxone"[tiab] OR "naloxone/buprenorphine"[tiab] OR suboxone[tiab] OR zubsolv[tiab] OR 52485-79-7[rn] OR 53152-21-9[rn] | 7,108 |
| #2 | "Methadone"[Mesh] OR "1, 1 diphenyl 1 (2 dimethylaminopropyl) 2 butanone"[tiab] OR "4, 4 diphenyl 6 dimethylamino 3 heptanone"[tiab] OR "6 dimethylamino 4, 4 diphenyl 3 heptanone"[tiab] OR "l-polamidon"[tiab] OR 1095-90-5[rn] OR 125-56-4[rn] OR 23142-53-2[rn] OR 297-88-1[rn] OR 76-99-3[rn] OR adanon[tiab] OR algidon[tiab] OR algolysin[tiab] OR algoxale[tiab] OR althose[tiab] OR amidon[tiab] OR amidona[tiab] OR amidone[tiab] OR amidosan[tiab] OR "an 148"[tiab] OR an148[tiab] OR anadon[tiab] OR biodone[tiab] OR butalgin[tiab] OR deamin[tiab] OR depridol[tiab] OR diaminon[tiab] OR dianone[tiab] OR dolafin[tiab] OR dolamid[tiab] OR dolesone[tiab] OR dolmed[tiab] OR dolophine[tiab] OR dorex[tiab] OR dorexol[tiab] OR eptadone[tiab] OR fenadon[tiab] OR gobbidona[tiab] OR heptadon[tiab] OR heptanon[tiab] OR "hoe 10820"[tiab] OR hoe10820[tiab] OR ketalgin[tiab] OR mecodin[tiab] OR mepecton[tiab] OR mephenon[tiab] OR metadol[tiab] OR metadon[tiab] OR metasedin[tiab] OR methaddict[tiab] OR methadon[tiab] OR methadone[tiab] OR methadose[tiab] OR "methaforte mix"[tiab] OR methex[tiab] OR miadone[tiab] OR moheptan[tiab] OR pallidone[tiab] OR phenadon[tiab] OR phenadone[tiab] OR phymet[tiab] OR physepton[tiab] OR physeptone[tiab] OR pinadone[tiab] OR polamidon[tiab] OR polamivet[tiab] OR polamivit[tiab] OR sinalgin[tiab] OR symoron[tiab] OR westadone[tiab] | 16,402 |
| #3 | #1 AND #2 | 2,224 |
| #4 | #3 NOT (animals[mh] NOT humans[mh]) | 2,121 |
| #5 | #4 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) | 1,948 |
| #6 | #5 AND ("Opiate Substitution Treatment"[Mesh] OR "Opioid-Related Disorders/drug therapy"[Mesh] OR substitut\*[tiab] OR swtich\*[tiab] OR transfer\*[tiab] OR transition\*[tiab] OR initiate[tiab] OR initiating[tiab] OR induction[tiab]) | 1,080 |

**EMBASE**

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| --- | --- | --- |
| Search | Query | Items Found |
| #1 | 'buprenorphine'/exp OR 'buprenorphine plus naloxone'/exp OR anorfin:ti,ab OR belbuca:ti,ab OR buprenex:ti,ab OR buprenorphine:ti,ab OR buprex:ti,ab OR buprine:ti,ab OR butrans:ti,ab OR 'cl 112, 302':ti,ab OR 'cl 112302':ti,ab OR 'cl112, 302':ti,ab OR cl112302:ti,ab OR finibron:ti,ab OR lepetan:ti,ab OR 'nih 8805':ti,ab OR nih8805:ti,ab OR norphin:ti,ab OR pentorel:ti,ab OR prefin:ti,ab OR probuphine:ti,ab OR 'rx 6029 m':ti,ab OR 'rx 6029m':ti,ab OR rx6029m:ti,ab OR '6029 m':ti,ab OR 6029m:ti,ab OR subutex:ti,ab OR transtec:ti,ab OR 'um 952':ti,ab OR um952:ti,ab OR bunavail:ti,ab OR 'buprenorphine/naloxone':ti,ab OR 'naloxone/buprenorphine':ti,ab OR suboxone:ti,ab OR zubsolv:ti,ab OR '52485 79 7':rn OR '53152 21 9':rn | 17,916 |
| #2 | 'methadone'/exp OR '1, 1 diphenyl 1 (2 dimethylaminopropyl) 2 butanone':ti,ab OR '4, 4 diphenyl 6 dimethylamino 3 heptanone':ti,ab OR '6 dimethylamino 4, 4 diphenyl 3 heptanone':ti,ab OR 'l-polamidon':ti,ab OR '1095 90 5':rn OR '125 56 4':rn OR '23142 53 2':rn OR '297 88 1':rn OR '76 99 3':rn OR adanon:ti,ab OR algidon:ti,ab OR algolysin:ti,ab OR algoxale:ti,ab OR althose:ti,ab OR amidon:ti,ab OR amidona:ti,ab OR amidone:ti,ab OR amidosan:ti,ab OR 'an 148':ti,ab OR an148:ti,ab OR anadon:ti,ab OR biodone:ti,ab OR butalgin:ti,ab OR deamin:ti,ab OR depridol:ti,ab OR diaminon:ti,ab OR dianone:ti,ab OR dolafin:ti,ab OR dolamid:ti,ab OR dolesone:ti,ab OR dolmed:ti,ab OR dolophine:ti,ab OR dorex:ti,ab OR dorexol:ti,ab OR eptadone:ti,ab OR fenadon:ti,ab OR gobbidona:ti,ab OR heptadon:ti,ab OR heptanon:ti,ab OR 'hoe 10820':ti,ab OR hoe10820:ti,ab OR ketalgin:ti,ab OR mecodin:ti,ab OR mepecton:ti,ab OR mephenon:ti,ab OR metadol:ti,ab OR metadon:ti,ab OR metasedin:ti,ab OR methaddict:ti,ab OR methadon:ti,ab OR methadone:ti,ab OR methadose:ti,ab OR 'methaforte mix':ti,ab OR methex:ti,ab OR miadone:ti,ab OR moheptan:ti,ab OR pallidone:ti,ab OR phenadon:ti,ab OR phenadone:ti,ab OR phymet:ti,ab OR physepton:ti,ab OR physeptone:ti,ab OR pinadone:ti,ab OR polamidon:ti,ab OR polamivet:ti,ab OR polamivit:ti,ab OR sinalgin:ti,ab OR symoron:ti,ab OR westadone:ti,ab | 34,078 |
| #3 | #1 AND #2 | 6,833 |
| #4 | #3 AND [humans]/lim | 6,228 |
| #5 | #4 NOT ('case report'/exp OR 'editorial'/exp OR 'letter'/exp) | 5,655 |
| #6 | #5 AND ('opiate substitution treatment'/exp OR substitut\*:ti,ab OR swtich\*:ti,ab OR transfer\*:ti,ab OR transition\*:ti,ab OR initiate:ti,ab OR initiating:ti,ab OR induction:ti,ab) | 1,264 |

**Cochrane Library**

|  |  |  |
| --- | --- | --- |
| Search | Query | Items Found |
| #1 | anorfin or belbuca or buprenex or buprenorphine or buprex or buprine or butrans or finibron or lepetan or norphin or pentorel or prefin or probuphine or subutex or transtec or bunavail or "buprenorphine-naloxone" or "naloxone- buprenorphine" or suboxone or zubsolv:ti,ab,kw (Word variations have been searched) | 2,352 |
| #2 | [mh Buprenorphine] OR [mh "Buprenorphine, Naloxone Drug Combination"] | 1,025 |
| #3 | #1 OR #2 | 2,352 |
| #4 | adanon or algidon or algolysin or algoxale or althose or amidon or amidona or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolmed or dolophine or dorex or dorexol or eptadone or fenadon or gobbidona or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metadon or metasedin or methaddict or methadon or methadone or methadose or "methaforte mix" or methex or miadone or moheptan or pallidone or phenadon or phenadone or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron or westadone:ti,ab,kw (Word variations have been searched) | 2,933 |
| #5 | [mh Methadone] | 1,170 |
| #6 | #4 OR #5 | 2,944 |
| #7 | #3 AND #6 | 594 |
| #8 | substitut\* or swtich\* or transfer\* or transition\* or initiate or initiating or induction:ti,ab,kw (Word variations have been searched) | 91,933 |
| #9 | [mh "Opiate Substitution Treatment"] OR [mh "Opioid-Related Disorders"/DT] | 699 |
| #10 | #7 AND #9  in Cochrane Reviews (Reviews and Protocols) and Trials | 254 |

**Web of Science**

|  |  |  |
| --- | --- | --- |
| Search | Query | Items Found |
| #1 | TS=(anorfin or belbuca or buprenex or buprenorphine or buprex or buprine or butrans or finibron or lepetan or norphin or pentorel or prefin or probuphine or subutex or transtec or bunavail or (buprenorphine AND naloxone) or suboxone or zubsolv) OR TI=(anorfin or belbuca or buprenex or buprenorphine or buprex or buprine or butrans or finibron or lepetan or norphin or pentorel or prefin or probuphine or subutex or transtec or bunavail or (buprenorphine AND naloxone) or suboxone or zubsolv) | 8,456 |
| #2 | TS=(adanon or algidon or algolysin or algoxale or althose or amidon or amidona or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolmed or dolophine or dorex or dorexol or eptadone or fenadon or gobbidona or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metadon or metasedin or methaddict or methadon or methadone or methadose or "methaforte mix" or methex or miadone or moheptan or pallidone or phenadon or phenadone or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron or westadone) OR TI=(adanon or algidon or algolysin or algoxale or althose or amidon or amidona or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolmed or dolophine or dorex or dorexol or eptadone or fenadon or gobbidona or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metadon or metasedin or methaddict or methadon or methadone or methadose or "methaforte mix" or methex or miadone or moheptan or pallidone or phenadon or phenadone or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron or westadone) | 17,704 |
| #3 | #2 AND #1 | 3,356 |
| #4 | TS=(substitut\* or swtich\* or transfer\* or transition\* or initiate or initiating or induction) OR TI=(substitut\* or swtich\* or transfer\* or transition\* or initiate or initiating or induction) | 4,860,234 |
| #5 | #3 AND #4 | 951 |

**PsycInfo**

|  |  |  |
| --- | --- | --- |
| Search | Query | Items Found |
| #1 | DE "Buprenorphine" OR TI (anorfin or belbuca or buprenex or buprenorphine or buprex or buprine or butrans or finibron or lepetan or norphin or pentorel or prefin or probuphine or subutex or transtec or bunavail or "buprenorphine-naloxone" or "naloxone-buprenorphine" or suboxone or zubsolv) OR AB (anorfin or belbuca or buprenex or buprenorphine or buprex or buprine or butrans or finibron or lepetan or norphin or pentorel or prefin or probuphine or subutex or transtec or bunavail or "buprenorphine-naloxone" or "naloxone- buprenorphine" or suboxone or zubsolv) | 2,819 |
| #2 | DE "Methadone" OR TI (adanon or algidon or algolysin or algoxale or althose or amidon or amidona or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolmed or dolophine or dorex or dorexol or eptadone or fenadon or gobbidona or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metadon or metasedin or methaddict or methadon or methadone or methadose or "methaforte mix" or methex or miadone or moheptan or pallidone or phenadon or phenadone or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron or westadone) OR AB (adanon or algidon or algolysin or algoxale or althose or amidon or amidona or amidone or amidosan or anadon or biodone or butalgin or deamin or depridol or diaminon or dianone or dolafin or dolamid or dolesone or dolmed or dolophine or dorex or dorexol or eptadone or fenadon or gobbidona or heptadon or heptanon or ketalgin or mecodin or mepecton or mephenon or metadol or metadon or metasedin or methaddict or methadon or methadone or methadose or "methaforte mix" or methex or miadone or moheptan or pallidone or phenadon or phenadone or phymet or physepton or physeptone or pinadone or polamidon or polamivet or polamivit or sinalgin or symoron or westadone) | 7,874 |
| #3 | #1 AND #2 | 1,242 |
| #4 | TI (substitut\* or swtich\* or transfer\* or transition\* or initiate or initiating or induction) OR AB (substitut\* or swtich\* or transfer\* or transition\* or initiate or initiating or induction) | 200,415 |
| #5 | #3 AND #4 | 298 |

**World Health Organization International Clinical Trials Registry Protocol**

Buprenorphine AND methadone AND transfer: 9 records for 6 trials

Buprenorphine AND methadone AND switch: 4 records for 3 trials

Buprenorphine AND methadone AND transition: No results.

**Cochrane Central Register of Controlled Trials (CENTRAL): Issue 8 of 12, August 2019**

'buprenorphine AND methadone AND (switch OR transfer OR transition) in Title, Abstract, Keywords in Trials': 38 results from 1,560,300 trials

**Supplementary Digital Content B. Extracted Data**

**Table B-1. Characteristics of included studies**

| **First author, year**  **ROB**  **No. of patients** | **Country**  **Years of data collection**  **Study design** | **Setting** | **Study duration** | **Inclusion criteria** | **Exclusion criteria** |
| --- | --- | --- | --- | --- | --- |
|  | | | | | |
|  |  |  |  |  |  |
|  | | | | | |
| Bouchez, 199824  High ROB  N=10 | France  NR  Non-comparative trial | NR | Unclear | NR | NR |
| Breen, 200325  Medium ROB for transfer completion and relapse, high ROB for withdrawal  N=38 | Australia  1999  RCT | Outpatient; 4 clinics that provided take-home doses | 19 days\* | ≤40 mg METH; ≥6 months in METH treatment; eligible for METH take-home doses; no heroin use in last 2 weeks (by urine and self-report); daily attendance for 2 weeks; Global Assessment of Functioning score ≥61 | Serious medical or psychiatric conditions; pregnancy; breastfeeding; concurrent alcohol or benzodiazepine dependence |
| Clark, 200629  Medium ROB  N=30 | Australia  NR  RCT | Inpatient; residential detoxification facility | 3 months | Oral METH for treatment of heroin dependence with a stable dose between 40 mg and 100 mg for the last 4 weeks; eligible for admission to one of the study residential detoxification facilities; ≥18 years; mentally capable of consent; able to understand written or spoken English; support from METH prescribing doctor to participate | Currently dependent on alcohol, benzodiazepines (excluding prescribed benzodiazepines), cannabis, cocaine, or amphetamines; any serious concomitant medical or psychiatric illnesses, including a) hepatic serum transaminase levels >4 times normal or b) serum creatinine levels >1.5 mg/dL; known hypersensitivity or serious adverse effects from BUP or clonidine; pregnant or breastfeeding |
| Conroy, 201335  Medium ROB  N=39 | United Kingdom  NR  Non-comparative cohort | Outpatient; addiction service in a Scottish National Health System board | 1-2 days | Methadone dose currently stable at >30 mg/day currently treated by addiction services and with a reason for wanting transfer to BUP | NR |
| Glasper, 200527  Low ROB  N=23 | United Kingdom  2001-2003  Non-comparative trial | Inpatient; dedicated drug dependence unit | 8 days | DSM-IV criteria for opioid dependence; METH dose between 30 and 70 mg/day on the third day of admission | Codependence on any other psychotropic drug; use of any prescribed psychotropic medication, other than opiates; serious physical illness necessitating non-standard detoxification treatment (e.g., severe hepatic impairment); psychiatric illness detected on clinical examination; pregnancy |
| Gonzalez-Saiz., 200830 & Gonzalez-Saiz, 200931  Medium ROB  N=46 | Spain  NR  Non-comparative trial | Inpatient; public residential treatment center | 3 months | ≤80 mg METH/day and with a clinical evaluation suggestive of the possibility of starting a gradual reduction to 40 mg; DSM-IV diagnosis of OUD | Those with pending legal charges and expected to start serving sentence within the next 6 months; pregnant or breastfeeding; METH >80 mg/day |
| Greenwald, 200326  Low ROB  N=5 | United States  NR  Non-comparative trial | Outpatient; no further details provided | Varied; (range 22-109 days) | Free of chronic diseases and prescribed medications; urine test positive for opioids or METH and negative for cocaine, benzodiazepines, and barbiturates; expired breath sample negative for alcohol | Current DSM-IV Axis I disorder or drug dependence besides opioids and nicotine; cognitive impairment |
| Hess, 201134  Medium ROB  N=11 | Switzerland  NR  Non-comparative trial | Inpatient; no further details provided | 60 days | Age 18-60; in METH treatment ≥3 months; daily METH dose between 60 mg and 100 mg; German fluency; ability to give informed consent | NR |
| Levin, 199723    Medium ROB  N=19 | United States  NR  Crossover trial | Inpatient; hospital-based clinical research center | Approx. 3 weeks | Current history of nonmedical IV cocaine use; no current severe psychiatric disorders; satisfactory physical health, as determined by physical exam, lab tests, electrocardiogram, chest X-ray, and stress test; ability to perform study procedures | Physiologic dependence on drugs other than METH, cocaine, and nicotine; requesting treatment for cocaine addiction; pregnancy; history of seizures or seizure disorder; pseudocholinesterase deficiency; history of significantly violent behavior |
| Lintzeris, 201838  Low ROB  N=33 | Australia, New Zealand  NR  Prospective cohort | Specialist drug and alcohol settings:  61% inpatient;  39% outpatient | 3 months | Age 18 and older; in METH treatment ≥1 month; seeking transfer from METH to BUP at a participating site; able to give consent | NR |
| Lukas, 198421  Medium ROB  N=3 | United States  NR  Non-comparative trial | Inpatient; no further details reported | 67 days\* | NR | NR |
| Naumovski, 201536  Low ROB  N=29 | Australia  NR  Non-comparative trial | Outpatient; no further details provided | Varied | Stable in METH treatment for >1 year (compliant with dosing and not using illicit drugs including additional opioids or benzodiazepines as determined by physical exam and urine drug screen) | Interferon treatment for hepatitis C, housing or family instability, awaiting medical procedures involving opioid analgesia, suicidality, pregnancy, or comorbidities (including depression, psychosis, severe liver damage) |
| Oretti, 201537  Medium ROB  N=7 | United Kingdom  2007-2014  Case series | Inpatient; community addiction unit ward | Varied (range 53 days to 15 months) | METH ≥6 months; desire to switch to BUP and deemed “high risk of [transfer] failure” (e.g., with polysubstance use, significant psychiatric history, METH dose >30 mg) | NR |
| Rosen, 199522  Medium ROB  N=14 | United States  NR  Non-comparative trial | Outpatient; no further details reported | 30 days | NR | NR |
| Salsitz, 201032  Medium ROB  N=25 | United States  2003-2008  Non-comparative cohort | Outpatient; office-based methadone maintenance program | Varied (mean direction of follow-up was 30 months) | ≤80 mg METH/day; ≥4 years of enrollment in a traditional METH maintenance treatment program; ≥3 years of illicit drug abstinence; no excessive drinking; employment; emotional stability | NR |
| Stein, 200528  Medium ROB  N=16‡ | United States  2003-2004  Non-comparative cohort | Outpatient; hospital primary care clinic | 180 days | Opioid addiction6 mo or 35 mg METH/day; alcohol use < NIAAA hazardous levels; cocaine use no more than twice weekly; no benzodiazepine dependence; willingness to remain in treatment ≥6 months | NR |
| Terasaki, 201939  High ROB  N=2† | United States  2019  Case series | Inpatient; hospital | Varied (3 month follow-up in 1; follow-up duration NR in the other) | Hospitalized adult patients with OUD who were initially stabilized on METH and wished to start BUP | NR |
| Whitley, 201033  Medium ROB  N=32 | United States  2005-2008  Non-comparative cohort | Outpatient; treatment was given in the context of general primary care; induction took place either at the office or at home | 30 days | ≥18 years old; DSM-IV OUD diagnosis; insured by a health plan accepted at the health center or able to pay for treatment on a sliding scale fee | Hypersensitivity to BUP or NLX; pregnancy; DSM-IV alcohol dependence; serum aspartate aminotransferase or alanine aminotransferase levels >5 times normal; severe, untreated psychiatric illness; taking >60 mg METH daily during past month |

\*Study included an additional period of buprenorphine reduction after stabilization.

†A third case was not included in this review because the patient was not stable on METH before transferring to BUP.

‡Of the 41 total patients described, 16 patients transferred from methadone to buprenorphine.

Abbreviations: Approx.=approximately; BUP=buprenorphine; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; IV=intravenous; METH=methadone; mg=milligrams; NIAAA=National Institute on Alcohol Abuse and Alcoholism; NLX=naloxone; NR=not reported; OUD=opioid use disorder; RCT=randomized controlled trial; ROB=risk of bias.

**Table B-2. Included studies’ strategies for transferring from methadone to buprenorphine**

| **First author, year**  ***(Group, if applicable)***  **No. of patients** | **Stable METH dose;**  **METH transfer dose**  **(range or SD), mg/daya** | **Waiting period, hours**  **Presence of withdrawal symptoms at transfer** | **Concomitant medications** | **BUP formulation** | **First day of BUP**  **Initial dose (mg)**  **Total first-day dose (mg)**  **Add’l days of BUP** | **Final total BUP dose, mg/day**  **Time from first to stable BUP dose** |
| --- | --- | --- | --- | --- | --- | --- |
| Bouchez, 199824  *Low METH dose*  N=5 | 42 (30-50);  42 (30-50) | Mean 32 hours  (range 18-72)  NR | NR | sl BUP mono | 2 or 4  (mean 2.4)  8-16  (mean 12)  NA; results from initial BUP dose only | 2-16  1 day |
| Bouchez, 199824  *High METH dose*  N=5 | 75 (60-90);  75 (60-90) | Mean 13 hours  (range 6-24)  NR | NR | sl or IV BUP mono | 4 or 8  4 or 8  NA; results from initial BUP dose only | 4 or 8  1 day |
| Breen, 200325  *Transfer at 30 mg*  N=19 | 34.2 (4.9);  30 (0)b | 24 hours  Required: None  Observed: Mean SOWS prior to first dose of BUP ~7 | For symptoms PRN | sl BUP mono tablet | 4  4-8  Day 2: 0-16c  Day 3: 0-24c  Days 4-5: 0-24c | 0-24 (mean 10.9)  1-5 days |
| Breen, 200325  *Transfer when uncomfortable*  N=19 | 37.2 (7.7);  27 (4.5)d | 24 hours  Required: None  Observed: Mean SOWS prior to first dose of BUP ~11 | For symptoms PRN | sl BUP mono tablet | 4  4-8  Day 2: 0-16c  Day 3: 0-24c  Days 4-5: 0-24c | 0-24 (mean 9.5)  1-5 days |
| Breen, 200325  *Transfer below 30 mg*  N=17 | 19.4 (5.6);  19.1 (6.0) | 24 hours  Required: None  Observed: Mean SOWS prior to first dose of BUP ~4 | For symptoms PRN | sl BUP mono tablet | 4  4-8  Day 2: 0-16c  Day 3: 0-24c  Days 4-5: 0-24c | 0-24 (mean 6.0)  1-5 days |
| Clark, 200629  *Slow transfer*  N=9 | 72.2 (19.9);  72.2 (19.9) | 36-72 hours  Required: “Significant opiate withdrawal”  Observed mean (SD), 1 hour prior to first dose of BUP:  OOWS: 3.3 (2.1)  SubOWS: 15.3 (12.0)  SOWS: 8.4 (6.0) | For symptoms PRN | sl BUP mono tablet | 0.8  3.2  Day 2: 8  Day 3: 16  Days 4-5: 32 | 32  5 days |
| Clark, 200629  *Moderate transfer*  N=10 | 67.3 (17.3);  67.3 (17.3) | 36-72 hours  Required: “Significant opiate withdrawal”  Observed mean (SD), 1 hour prior to first dose of BUP:  OOWS: 4.6 (2.5)  SubOWS: 15.9 (10.2)  SOWS: 8.8 (5.6) | For symptoms PRN | sl BUP mono tablet | 4  4-6  Day 2: 8-12  Day 3: 16  Day 4: 24  Day 5: 32 | 32  5 days |
| Clark, 200629  *Rapid transfer*  N=11 | 72.1 (16.0);  72.1 (16.0) | 36-72 hours  Required: “Significant opiate withdrawal”  Observed mean (SD), 1 hour prior to first dose of BUP:  OOWS: 3.4 (2.8)  SubOWS: 16.2 (16.3)  SOWS: 7.7 (7.6) | For symptoms PRN | sl BUP mono tablet | 8  32  Days 2-5: 32 | 32  1 day |
| Conroy, 201335  N=39 | NR (35-120);  NR (35-120) | 36-48 hours  Required: “In a state of withdrawal” | None allowed | BUP/NLX, formulation NR for first 3 doses; sl tablet for doses 4-5 | 2/0.5  16/4-24/6  NA; single-day transfer | 16/4-24/6  1 day |
| Glasper, 200527  *Intermediate METH dose*  N=11 | 37 (30-49);  31.4 (NR) | 24 hours  Required: “When withdrawal symptoms were already evident” | Lofexidine PRN | BUP mono, formulation NR | 4  4-8 (mean 8.0)  Day 2: 4-12e  (mean 11.5)  Day 3: 4-16e  (mean 14.0)  Day 4: 4-16e  (mean 13.1) | 4-16 (mean 13.1)  1-4 days |
| Glasper, 200527  *High METH dose*  N=12 | 60 (50-70);  51.1 (NR) | 24 hours  Required: “When withdrawal symptoms were already evident” | Lofexidine PRN | BUP mono, formulation NR | 4  4-8 (mean 7.6)  Day 2: 4-12e  (mean 12.0)  Day 3: 4-16e  (mean 14.2)  Day 4: 4-16e  (mean 14.4) | 4-16 (mean 14.4)  1-4 days |
| Gonzalez-Saiz, 200830 Gonzalez-Saiz, 200931  N=46 | Overall: 46.6 (22)  METH >40 mg: 57.2;  40f | Mean 59 hours  (range 25-72)  Required: “Some withdrawal symptoms”  Observed: Mean (SD) OOWS before induction 2.7 (2.6) | For symptoms PRN, including benzodiazepines | sl BUP mono tablet | Flexible: 1-8f  (mean 3.6)  Day 2: NR  (mean 3.9)  Days 3-5: NR (mean 4.2) | 1-8 (mean 4.2)  3-5 days |
| Greenwald, 200326  N=5 | 60;  45 | 24 hours  NR | NR | sl BUP mono tablet | 8  8  Days 1-6: 8  Days 7-8: 16 | 16  8 days |
| Hess, 201134  N=11 | NR (60-100);  NR (60-100) | 12 hours  NR | NR | BUP mono transdermal patch + NR formulation | 35 µg/hourh  Day 2: patch+4  Day 3: patch+16  Days 4-5: 24 | 24  4 days |
| Levin, 199723  N=19 | 60;  0 | 48 hours  Medication given regardless of withdrawal symptoms;  Observed: mean total SOWS prior to first dose of BUP: ~20 | For symptoms PRN | sl BUP mono liquid | 4  4  Day 2: 8 | 8  2 days |
| Lintzeris, 201838  N=33 | Means approx. based on figure  Low: ~20 (<30)  Medium: ~40 (30-50)  High: ~80 (>50) | ≥24 hours  COWS >12 (moderate withdrawal) | NR | sl BUP/NLX | 2  8-16+  Previous day dose + add’l dose based on symptoms | ≥12 mg  2-3 days |
| Lukas, 198421  N=3 | 47.7 (25-60);  47.7 (25-60) | 24 hours  Medication given regardless of withdrawal symptoms; Observed: mean Himmelsbach and withdrawal scores prior to first dose of BUP were elevated at first BUP dose, compared with at last METH dose | NR | SQ BUP mono liquid | 2  2  ­­­NA; single-day transfer | 2  1 day |
| Naumovski, 201536  N=29 | 86.8 (42.5-140);  61.2 (SE 3.6)i | 48 hours  Required: “If clinical withdrawal signs were evident”  Observed: Mean COWS at time of first dose of BUP: 20.3 | For symptoms PRN | BUP mono, formulation NR | 0.4-4  4-12  Day 2: 16-24  Day 3: 24-32 | 24-32  3 days |
| Oretti, 201537  N=7 | 77.9 (50-120);  77.9 (50-120) | Mean 59 hours  (range 42-76)  Required: COWS >10 (mild to moderate withdrawal) | For symptoms PRN | BUP mono BUP/NLXe, formulations NR | 4 or 4/1  4-32j or 4/1-24/6j  NAj | 16-20e  4/1-20/5e  (mean 16)  ~1 day |
| Rosen, 199522  N=14 | 25;  25 | Within 24 hours  Required: “Mild withdrawal symptoms” | NR | BUP mono, formulation NR | 2-8 (mean 3.1)  2-8 (mean 3.1)  Days 1-5: 2-8k | 2-8f  1-5 days |
| Salsitz, 201032  N=25 | 39 (20);  NRl | 48-72 hours  Required: COWS ≥13, indicating at least moderate withdrawal | NR | sl BUP/NLX | 2/0.5-4/1  2/0.5-4/1  ­­ NRm | Mean 10.9l (SD 7.6)  Up to 7 days |
| Stein, 200528  N=16 | NR (<35);  NR (<35) | NR  Required: “In withdrawal” | NR | BUP/NLX, formulation NR | 4/1  4/1-16/4h  NRh | 12-24h  7-28 days |
| Terasaki, 201939  Patient 2 | 100;  100 (microdosing protocol)  METH was continued at full dose through day 7, after which it was discontinued | None; microdosing study | Pain control | sl BUP/NLX | 1  1  Day 2: 1.5  Day 3: 3  Day 4: 6  Days 5 & 6: 8  Day 7: 12  Days 8 & 9: 16  Day 10: 20  Day 11: 24 | 24  11 days |
| Terasaki, 201939  Patient 3 | 40;  40 (microdosing protocol)  METH was intended to be continued at full dose through day 7, after which it was discontinued | None; microdosing study | Pain control | sl BUP/NLX | 0.5  0.5  Day 2: 1  Day 3: 2  Day 4: 4  Days 5 & 6: 8  Day 7: 12  Day 8: 12 | 12  7 days |
| Whitley, 201033  N=32 | NR (≤60);  NR (≤60) | NR  Required: Mild to moderate withdrawal, generally COWS ≥10 | For symptoms PRN | BUP/NLX, formulation NR | Flexible: 2/0.5o  NRo  NRo | NRi |

aThe transfer dose of METH was the average of the METH dose over the last 5 days before transfer.

b For patients on doses of METH >30 mg, the dose was reduced by 2.5 mg/week until they reached 30 mg.

c Starting on day 2, the morning dose was the previous day’s dose plus 2-4 mg if withdrawal or craving was reported or minus 2-4 mg if intoxication or severe side effects were reported. An additional afternoon dose up to 4 mg was allowed, up to a maximum of 24 mg/day.

d Patients reduced their METH dose by 2.5 mg/week until they reported withdrawal discomfort.

e Morning dose was equal to the total amount given on the previous day. An additional 2-4–mg dose was allowed at least 4 hours later, based on withdrawal symptoms.

f No taper for patients on ≤40 mg METH; for patients between 40 and 80 mg METH, dose was reduced over several weeks to 40 mg/day.

g First-day dose varied by patient and was based largely on prior METH dose. Dosage was as follows: 71% received 4 mg, 16% received 2 mg, 7% received 1 mg, 4% received 6 mg, 4% received 8 mg, and 2% received 3 mg. Overall mean dose was 3.6 mg.

h Buprenorphine patch provided 35 µg/hour over 96 hours. Plasma concentration of 200-300 pg/mL buprenorphine at maximum after 96 hours.

i Dose was reduced twice weekly by 5 mg until each patient felt that they could not tolerate any further dose reduction, reaching the transfer dose.

j BUP monotherapy was used until 2012, when it was replaced by BUP/NLX. Timing of dose escalation varied. Goal was to reach final dose of BUP within 24 hours of COWS scoring. Dose range at discharge was 4 to 20 mg for BUP/NLX and 16 to 20 for BUP monotherapy (calculated overall mean: 16 mg).

k Over the first 5 days, the patients receiving 2 mg could remain the same or be increased to an additional 3, 4, or 6 mg/day. It was not reported how many of those transferring from METH had their doses increased.

l Patients on stable doses of METH from 5-80 mg (mean 39 mg) were given the option of reducing their doses to 30-40 mg before transfer, but it was not reported if any (and, if so, how many) did so. Therefore, final mean dose of METH cannot be determined. For the purpose of basic statistical analyses reported herein, it is assumed that the mean dose remained below 40 mg.

m Patients were stabilized on BUP/NLX over 1 week with frequent follow-up by their clinician during this period. Details of flexible dosing were not reported.

n Usual first-day dose for the full sample (including non-transfers) was 8 mg; 16 mg was frequently used for transfers from METH. Patients were seen 3-4 times during the first week, with prescriptions given for 1-2 days at a time, to be taken once or twice a day as desired. Mean maintenance dose for overall sample (including non-transfers) at week 1 ranged from 17.9 to 19.8 mg/day. Usual stabilization dose was 12-24 mg/day.

o Most (72.2%) received this initial dose (the lowest possible in the study); it is unclear what dose(s) the remainder of the patients received. Additional doses were administered if necessary, but no additional information was reported. When precipitated or protracted withdrawal occurred, physicians tended to increase the dose of BUP fairly rapidly within the first 24-48 hours.

Abbreviations: approx.=approximately; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; IV=intravenous; METH=methadone; mono=monotherapy; NLX=naloxone; NR=not reported; OOWS=Objective Opiate Withdrawal Scale; PRN=as needed; SD=standard deviation; SE=standard error; sl=sublingual; SOWS=Subjective Opiate Withdrawal Scale; SQ=subcutaneous; SubOWS=Subjective Opiate Withdrawal Scale.

**Table B-3. Outcomes**

| **First author, year**  **No. enrolled** | **Outcomes** |
| --- | --- |
|  | |
|  |  |
|  | |
| Bouchez, 199824  N=10 | **Precipitated withdrawal**  Timing of measurement unclear.  Precipitated withdrawal among the 5 patients on higher doses of METH (>50 mg), all of whom received a fixed initial dose of either 4 or 8 mg BUP. Mild withdrawal among the 5 patients on doses of METH <50 mg, all of whom received a variable dose of BUP. |
| Breen, 200325  Transfer at 30 mg N=19;  Transfer when uncomfortable N=19;  Transfer <30 mg N=17 | **Transfer completion\***  “Transfer at 30 mg” group: 17/18 (94.4%)  “Transfer when uncomfortable” group: 16/16 (100%)  “Transfer below 30 mg” group: 17/17 (100%)  **Reasons for transfer discontinuation**  1 patient in the transfer at 30 mg group did not stabilize on BUP and returned to METH after 2 days of BUP (receiving a total of 8 mg BUP on day 1 and 12 mg the next day).  **Relapse to opioids (self-reported heroin use or urine screen positive for heroin)**  Including pre-transfer period:  “Transfer at 30 mg” group: 3/19 (15.8%)  “Transfer when uncomfortable” group: 5/19 (26.3%)  “Transfer below 30 mg” group: 2/17 (11.8%)  During 5-day induction period only:  “Transfer at 30 mg” group: 2/18 (11.1%)  “Transfer when uncomfortable” group: 2/16 (12.5%)  “Transfer below 30 mg” group: 2/17 (11.8%) |
| Clark, 200629  Slow transfer N=9;  Moderate transfer  N=10;  Rapid transfer, N=11 | **Precipitated withdrawal (as defined by the study author)**  After the first dose of BUP: OOWS, coefficients (95% CI) from multivariate analysis (including gender, METH dose, and time since METH dose) with moderate transfer group as reference  Not including pre-BUP scores  Slow transfer: -0.78 (-2.1 to 0.56)  Rapid transfer: -0.56 (-1.8 to 0.67)  Including pre-BUP scores  Slow transfer: -0.3 (-1.5 to 0.84)  Rapid transfer: -0.10 (-0.96 to 1.17)  From [the time of first BUP dose], the moderate and rapid groups appear to have experienced some precipitated withdrawal, with a mean increase in approximately one degree on the OOWS scale. The moderate group remained at this level for approximately the next 48 hours, whereas the rapid group had a reduction in OOWS to a fairly comfortable level later that afternoon, which was maintained overnight.  Total clonidine usage post-BUP, mean (SD) mcg  Slow transfer: 969 (614); range 50-1650  Moderate transfer: 1582 (1478); range 0-4800  Rapid transfer: 998 (886); range 0-2700  Difference was not statistically significant  Total diazepam usage post-randomization, mean (SD) mg  Slow transfer: 120 (119); range 25-415  Moderate transfer: 135 (44); range 55-190  Rapid transfer: 74 (56); range 10-180 (p=0.01 vs moderate)  Composite score that incorporated OOWS, medication use, and dropout  Slow transfer: 6.0 (2.8)  Moderate transfer: 9.1 (2.8)  Rapid transfer: 5.2 (4.2)  Composite score: mean (95% CI) absolute difference from moderate group  Slow transfer: 3.1 (0.4 to 5.8)  Rapid transfer: 3.9 (0.6 to 7.2)  Composite measure of OOWS score, medication use, and dropout indicated that the moderate transfer group had significantly more difficulty transferring, compared with the slow and rapid groups.  Waiting an extra day between METH and first BUP was associated with a reduction in OOWS of 1.1 (95% CI 0.2 to 2.0). |
| Clark, 200629 (continued) | **Transfer completion (defined as discharge from residential facility taking BUP with SOWS ≤15 or OOWS ≤3)**  Slow transfer: 9/9 (100%)  Moderate transfer: 7/10 (70%)  Rapid transfer: 11/11 (100%)  **Reasons for transfer discontinuation**  Slow transfer: NA  Moderate transfer: 2 became anxious and returned to METH; 1 relapsed to heroin and left to get a naltrexone implant  Rapid transfer: NA  **Treatment retention (still on BUP)**  At 3 months  Overall: 18/30 (60.0%)  Slow transfer: 6/9 (66.7%); 2 were on METH and 1 was on neither BUP nor METH  Moderate transfer: 4/10 (40%); 3 were on METH and 3 were on neither BUP nor METH  Rapid transfer: 8/11 (72.7%); 2 were on METH and 1 was on neither BUP nor METH  **Abstinence from opioids (self-reported, Opiate Treatment Index)**  Unadjusted, at 1 month:  Slow transfer: 33%  Moderate transfer: 33%  Rapid transfer: 91%; between-groups p=0.01  Unadjusted, at 3 months:  Slow transfer: 33%  Moderate transfer: 40%  Rapid transfer: 82%; between-groups p=0.06  Adjusted change in heroin use from baseline (days in the last month):  Transfer to 32 mg BUP: -5.8 days (range -27 to +1)  Transfer to <32 mg BUP: +18.3 days (range -1 to +25)  Abandoned transfer: +12.5 days (range 0 to +20) |
| Clark, 200629 (continued) | **Relapse to opioids (self-reported days of heroin use in past month, Opiate Treatment Index)**  Unadjusted at 1 month:  Slow transfer: 5.6 days  Moderate transfer: 3.7 days  Rapid transfer: 0.67 days; between-groups p=0.16  Unadjusted difference from baseline at 1 month:  Slow transfer: -5.2 days  Moderate transfer: -3.1 days  Rapid transfer: -1.9 days; between-groups p=NS  Unadjusted at 3 months:  Slow transfer: 2.3 days  Moderate transfer: 2.9 days  Rapid transfer: 0.23 days; between-groups p=NS  Unadjusted difference from baseline at 3 months:  Slow transfer: -8.5 days  Moderate transfer: -3.9 days  Rapid transfer: -1.6 days; between-groups p=NS  **Serious adverse events**  1 patient in slow transfer group left treatment facility early, after 16 mg BUP on day 4 and with a prescription to take 32 mg. One week post-discharge, he was admitted to a hospital psychiatric ward as an involuntary patient for what was thought to be an anxiety-related psychotic reaction possibly in response to BUP. His pharmacy confirmed that he was picking up 16 mg daily prior to this episode. He was admitted to the psychiatric unit with thought disorder and bizarre posturing, and was also diagnosed with anxiety disorder and a possible underlying social phobic disorder. He was discharged 5 days later with no formal thought disorder or delusion. He had received no BUP in this time, only chlorpromazine and diazepam. Following discharge, he subsequently recommenced BUP with no problems. He began picking up 8 mg daily of BUP, which had increased to 16 mg daily at the 3-month follow-up. He had no further delusional or psychotic episodes; however, he was still experiencing quite prominent social phobia. |
| Conroy, 201335  N=39 | **Precipitated withdrawal**  “There is an identifiable spike in the worsening of the withdrawal symptoms [based on SOWS scores] in many of the cases. This generally occurs after 4 mg to 8 mg of buprenorphine administered.”  **Transfer success**  37/39 (94.9%)  **Reasons for transfer discontinuation**  Both patients admitted consumption of heroin just prior to commencing on BUP and therefore experienced a withdrawal. |
| Glasper, 200527  Intermediate dose  N=10;  High dose  N=11 | **Transfer completion**  Overall 21/23 (91.3%)  Intermediate METH dose: 10/11 (90.9%)  High METH dose: 11/12 (91.7%)  **Reasons for transfer discontinuation**  One patient was discharged due to unauthorized benzodiazepine use, and another developed mild but persistent withdrawal and chose to leave study, returning to METH. |
| Gonzalez-Saiz, 200830 & Gonzalez-Saiz, 200931  N=46 | **Transfer completion**  43/46 (93.5%)  **Reasons for transfer discontinuation**  Three patients voluntarily abandoned the transfer after an average of 3.7 days on BUP. Reasons not reported.  **Treatment retention**  Retention at 3 months: The patients assessed at 3 months represented 45.7% of those who began (21 patients). Between the 1-month and 3-month assessments (M1-M2), 14 subjects were released after having completed buprenorphine treatment, 6 left the [treatment center] and were switched back to methadone and 2 subjects were withdrawn for disciplinary reasons. |
| Greenwald, 200326  N=5 | **Precipitated withdrawal**  Significant spike in withdrawal symptoms after first day/dose of BUP (8 mg). Symptoms elevated but not significantly higher after day 2 dose. Withdrawal scores exceeded the “uncomfortable” threshold for all patients following the first BUP dose.  **Transfer completion**  5/5 (100%)  **Abstinence from opioids (negative urine drug screen)**  1/5 (20%) provided a drug-free urine sample on the final test day (day 8) only.  **Relapse to opioids (self-report and positive urine drug screen)**  Volunteers reported using heroin and virtually all urine samples tested opioid positive. However, reported amounts of heroin use decreased by more than half (<2 bags/day) throughout the protocol and did not increase during the transfer. |
| Hess, 201134  N=11 | **Transfer completion**  10/11 (90.9%)  Still on BUP at day 14: 81.8% (N not reported)  **Reasons for transfer discontinuation**  NR  **Treatment retention**  Still on BUP at day 60: 68.6% (N not reported) |
| Levin, 199723  N=19 | **Transfer completion (completed METH taper and received BUP 8 mg for 2 weeks)**  15/18 (83.3%) (the “pilot” subject is not included in this denominator)  **Reasons for transfer discontinuation**  All 3 non-completers were discontinued due to inability to tolerate withdrawal symptoms  1 discontinued after taper from 60 mg to 30 mg METH  1 discontinued after receiving 2 days of BUP (4 mg day 1 and 8 mg day 2)  1 discontinued after receiving 6 days of BUP (4 mg day 1 and 8 mg days 2-6) |
| Lintzeris, 201838  Low METH=9;  Med METH=9;  High METH=15 | **Precipitated withdrawal** (COWS increase ≥6 points within 6 hours of first BUP dose)  Overall: 3/33 (9%)  Low-dose METH: 0/9 (0%)  Medium-dose METH: 0/9 (0%)  High-dose METH: 3/15 (20%)  Between-groups p=NS  One patient’s precipitated withdrawal was caused by medication error (initial BUP dose of 8 mg instead of 2 mg).  Another’s was caused by administration of first BUP dose with COWS=5.  **Transfer completion (remained on BUP at day 7)**  Overall: 26/33 (79%)  Low-dose METH: 8/9 (89%)  Medium-dose METH: 8/9 (89%)  High-dose METH: 10/15 (67%)  Between-groups p=NS  **Reasons for transfer discontinuation**  The 3 patients who experienced precipitated withdrawal requested resumption of METH. Three resumed METH within 2 days of attempted transfer due to side effects with BUP/NLX (anxiety and poor sleep). One dropped out, relapsed, and returned to METH treatment 1 week later.  **Relapse to opioids**  1 patient (3%) stopped BUP/NLX and used heroin for several days. |
| Lukas, 198421  N=3 | **Precipitated withdrawal**  Substitution of buprenorphine for methadone was accompanied by increases in total Himmelsbach scores, primarily because of elevations in number of tremors and emesis, which diminished over the next few days. Withdrawal scores for pulse, sickness, “kicking,” and “How do you feel?” were also elevated at buprenorphine substitution (no taper).  **Transfer completion**  3/3 (100%) |
| Naumovski, 201536  N=29 | **Transfer completion**  23/29 (79.3%)  **Reasons for transfer discontinuation**  2 due to severe precipitated withdrawals having demanded early BUP dosing without objective opioid withdrawals (protocol violation); 1 intoxicated with alcohol on transfer day; 1 did not show signs of withdrawal after 5 days of abstinence; 1 was incarcerated on day 4 and returned to METH in jail; 1 was returned to METH on day 4 because of illicit amphetamine use after finding BUP non-therapeutic. |
| Oretti, 201537  N=7 | **Transfer completion**  6/7 (85.7%)  Positive urine drug screen for BUP at early follow-up (range 13 days to 6 weeks post-discharge): 5/6 (83.3%)  **Reasons for transfer discontinuation**  [The patient] consumed his last dose of methadone 2 days before admission. He experienced withdrawal the morning after the admission and received 4 mg of BUP/NLX. He became anxious and indicated that he was experiencing severe withdrawal and did not wish to continue with the transfer and discharged himself from the ward. He admitted consuming heroin on the morning of admission. He was recommenced on methadone (25 mg) the next day.  **Post-transfer BUP compliance**  Buprenorphine compliant at late follow-up (range 6 months to 15 months): 4/5 (80.0%)  **Abstinence from opioids (negative urine drug screen)**  Early follow-up: 5/6 (83.3%)  Late follow-up: 4/5 (80.0%)  **Relapse to opioids**  Early follow-up: 1/6 (16.7%) relapsed on heroin and was not BUP compliant  Late follow-up: 1/5 (20.0%) relapsed on heroin and was not BUP compliant  **Use or misuse of non-opioid substances (positive urine drug screen)**  Early follow-up  Cocaine: 1/6 (16.7%)  Amphetamine: 1/6 (16.7%)  Cannabis: 2/6 (33.3%)  Benzodiazepine: 2/6 (33.3%)  Late follow-up  Cannabis: 2/5 (40%)  Benzodiazepine: 1/5 (20%) |
| Rosen, 199522  N=14 | **Transfer completion**  14/14 (100%) |
| Salsitz, 201032  N=25 | **Transfer completion**  25/25 (100%)  **Treatment retention**  18/25 (72%) remained in treatment program at an average of 30 months of follow-up  4/25 (16%) transferred maintenance treatment outside of program to other primary care physicians  1/25 (4%) tapered off and discontinued BUP with clinician supervision over 6-month period  1/25 (4%) relapsed on cocaine 18 months post-transfer and dropped out of program  **Relapse**  As above, 1/25 (4%) relapsed on cocaine 18 months post-transfer and dropped out of program  **Death**  1/25 (4%)  Died of liver failure secondary to long-standing chronic hepatitis C infection 42 months after transfer to BUP. |
| Stein, 200528  N=16 | **Treatment retention**  9/16 (56.3%) remained in treatment at 180 days |
| Terasaki, 201939  N=2b | **Precipitated withdrawal**  Possible; vague symptoms reported by patient 3 after first BUP dose (but still on full dose of METH)—mostly anxiety.  **Transfer completion**  2/2 (100%)  **Treatment adherence**  1/2 (50%): Patient 3 requested variable amounts of methadone during the transfer protocol.  **Treatment retention**  1/2 (50%): Patient 2 remained in treatment at follow-up; patient 3 did not.  **Relapse**  1/2 (50%): Patient 3 relapsed on heroin during the 3 months between discharge and follow-up. |
| Whitley, 201033  N=32 | **Precipitated withdrawal**  11/32 (34.3%) of those taking prescribed METH within 30 days had a “complicated induction” (precipitated or protracted withdrawal). Numbers of each for prescribed METH only were not reported.  Of the 10 patients who experienced precipitated withdrawal, 9 reported taking METH (prescribed or non-prescribed) prior to initiating BUP treatment. Of the 9 patients who experienced protracted withdrawal, 7 reported taking METH prior to initiating BUP. |

\*The denominators in 2 of the groups differ from the previous 2 tables for this study because 4 patients (3 in the “transfer when uncomfortable” group and 1 in the “transfer at 30 mg” group) were randomized but remained on METH maintenance due to positive urine drug results for heroin use prior to transfer to BUP.

†A third patient was reported but was eligible for this review because she was not stable on METH before transfer.

Abbreviations: BUP=buprenorphine; CI=confidence interval; COWS=Clinical Opioid Withdrawal Scale; METH=methadone; mg=milligrams; NA=not applicable; NLX=naloxone; NR=not reported; NS=not significant; OOWS=Objective Opiate Withdrawal Scale; SD=standard deviation; SE=standard error; sl=sublingual; SOWS=Subjective Opiate Withdrawal Scale.