## Characteristics of reviewed studies: Efficacy of pharmacological interventions

### Comparisons Included in this Clinical Question

(Opiate antagonist + anaesthesia) versus pharmacological with minimal sedation

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
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<tbody>
<tr>
<td>ARNOLDREED2005</td>
<td>Buprenorphine versus adrenergic agonist</td>
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<tr>
<td>COLLINS2005</td>
<td>Buprenorphine versus dihydrocodeine</td>
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<tr>
<td>DEJONG2005</td>
<td>Buprenorphine versus methadone</td>
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<td>FAVRAT2006</td>
<td>CHESKIN1994</td>
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<td>KRABBE2003</td>
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<td>SEOANE1997</td>
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<td>COLLINS2005</td>
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<td>FAVRAT2006</td>
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<td>KRABBE2003</td>
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<td>SEOANE1997</td>
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<td>PONIZOVSKY2006</td>
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<td>RAISTRICK2005</td>
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</tr>
<tr>
<td>COLINS2005</td>
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<td>FAVRAT2006</td>
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<td>KRABBE2003</td>
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<td>RAISTRICK2005</td>
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</tr>
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<td>UMBRICH2003</td>
<td>Buprenorphine versus other pharmacological treatment</td>
</tr>
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<td>JANIRI1994</td>
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<td>SCHNEIDER2000</td>
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<td></td>
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<td>GHERDE1994</td>
<td>Methadone versus (methadone + adrenergic agonist)</td>
</tr>
<tr>
<td>SAN1994</td>
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<td>GERRA2000</td>
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<td>JIANG1993</td>
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<td>KLEBER1985</td>
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<td>SAN1990</td>
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<td>WASHTON1980</td>
</tr>
<tr>
<td>BESWICK2003A</td>
<td>Methadone versus adrenergic agonist</td>
</tr>
<tr>
<td>GERRA1995</td>
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<td>GERRA2000</td>
<td>SORENSEN1982</td>
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<td>OCONNOR1997</td>
<td>TENNANT1975</td>
</tr>
<tr>
<td>UMBRICH1999</td>
<td>TENNANT1978</td>
</tr>
<tr>
<td></td>
<td>Methadone versus other opiate agonist</td>
</tr>
<tr>
<td></td>
<td>Methadone versus other pharmacological treatment</td>
</tr>
</tbody>
</table>

### Characteristics of Included Studies

#### Methods

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type: RCT (randomised controlled trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNOLDREED2005</td>
<td>Type of Analysis: Per protocol</td>
</tr>
<tr>
<td></td>
<td>Blinding: Open</td>
</tr>
<tr>
<td></td>
<td>Duration (days): Range 1-10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 80</td>
</tr>
<tr>
<td>Age: Mean 30  Range 16-50</td>
</tr>
<tr>
<td>Sex: 51 males  29 females</td>
</tr>
<tr>
<td>Diagnosis: 100% opiate dependence by DSM-IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Used</td>
</tr>
<tr>
<td>Abstinence: 1 month</td>
</tr>
<tr>
<td>Completion</td>
</tr>
<tr>
<td>Withdrawal severity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 N = 41</td>
</tr>
<tr>
<td>Opiate antagonist: naloxone with inpatient - Rapid detoxification: IV naloxone (~800 micrograms) over 5-8 min interspersed with IV clonidine (150 micrograms in 10 ml saline)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
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<tbody>
<tr>
<td>Study quality: 1+</td>
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</tbody>
</table>
**BEARN1996**

<table>
<thead>
<tr>
<th>Data Used</th>
<th>Opiate antagonist: naltrexone - 20-30 min after IV protocol, oral doses of 4, 8, 15 and 23mg naltrexone at 30 min intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic - Subcutaneous octreotide (0.1mg) and IV ondansetron (2mg) premedication; also oral flunitrazepam depending level of opioid use prior to treatment</td>
</tr>
<tr>
<td></td>
<td>Midazolam hydrochloride during IV detox protocol depending on level of arousal/discomfort experienced</td>
</tr>
</tbody>
</table>

**BESWICK2003A**

<table>
<thead>
<tr>
<th>Data Used</th>
<th>Opiate antagonist: naloxone - 0.8 mg - 0.8 mg naloxone solution days 3 - 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Opiate agonist: methadone with inpatient - Variable initial dose, tapered over 10 days at a linear rate</td>
</tr>
<tr>
<td></td>
<td>Placebo - Placebo tablet</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepine: diazepam with inpatient - For those also dependent on benzodiazepines: 3 days' stabilisation then tapered over 21 days</td>
</tr>
</tbody>
</table>

**Notes**: Randomisation procedure not reported, Setting: London, UK, Duration (days): Mean 20, Study Type: RCT (randomised controlled trial), Study Description: Double dummy design, Blindness: Double blind, Setting: Specialist drug dependency units in London, Exclusions: - on >100 mg MMT - history of epilepsy - severe liver disease - pregnancy - psychotropic medication - alcohol dependence, Type of Analysis: Per protocol for follow-up analyses, Followup: 6 months, Info on Screening Process: 220 invited; 91 randomised and 46 assigned to methadone group, Ethnicity: 89% White, Baseline: 'No differences between the randomised groups' - but did not make clear what differences there might have, Patients who refused randomisation or met exclusion criteria were retained in a non-randomised methadone control group (not described here), Study quality: 1+
### CARNWATH1998

**Study Type:** RCT (randomised controlled trial)  
**Study Description:** Drugs prepared in identical capsules  
**Blindness:** Double blind  
**Duration (days):** Mean 28  
**Notes:** RANDOMISATION: By pharmacy

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Group Description</th>
<th>Data Used</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 2     | 46 | Alpha2 adrenergic agonist: lofexidine with inpatient: drug dependence unit (DDU) -  
As described in Bearn (1998): 1.8 mg in three divided doses on day 1, 1 mg twice daily for 3 days, then 0.6 mg twice daily on days 5-6. Additional 0.4 mg available during any 24-hour period on patient request.  
Placebo - Placebo solution days 3-6 | Withdrawal: Short Opiate Withdrawal Scale  
Withdrawal severity  
Completion | Study quality 1+ |

**n = 50**  
**Age:** Mean 28  
**Sex:** 35 males  15 females  
**Diagnosis:**  
100% opiate misuse  
Exclusions: Not stabilised on <=40 mg per day methadone  
Notes: PRIMARY DIAGNOSIS: Users of methadone or other opiates  
Baseline: (GROUPS: lofexidine / clonidine)  
Previous detoxification experience: 57% / 75%  
Employed: 17% / 17%

### CHESKIN1994

**Study Type:** RCT (randomised controlled trial)  
**Study Description:** Double dummy design  
Type of Analysis: Per protocol  
**Blindness:** Double blind  
**Duration (days):** Mean 10  
**Followup:** 8 day placebo/follow-up phase  
**Setting:** US closed research ward  
**Notes:** Randomisation stratified on Clinical Institute Narcotics Assessment (CINA) score

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Group Description</th>
<th>Data Used</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1     | 26 | Alpha2 adrenergic agonist: lofexidine. Mean dose 0.2 mg - 0.2 mg per capsule, increased to max 8 capsules per day over 3 days, tapered over last 3 days. Duration of medication unclear | Withdrawal severity  
Completion | Study quality 1+ |

**n = 25**  
**Age:** Range 21-45  
**Sex:** 9 males  16 females  
**Diagnosis:**  
100% opiate dependence by clinical assessment  
Exclusions: - not presenting three consecutive non-methadone, opiate-positive urines  
- self-reported history inconsistent with opiate addiction, or lack of fresh needle marks  
- participation in structured buprenorphine or clonidine research programme in past 12 months  
- ASI psychiatric score >=7  
- active psychosis or schizophrenia  
- active cardiovascular or hepatic disease  
- used methadone >7 days in past 4 months  
- sitting systolic BP <110 mmHg or diastolic <70 mmHg  
- reported hypersensitivity to study medications  
Notes: Reported baseline data are for completers only  
Baseline: GROUPS: clonidine / buprenorphine  
CINA score: 33.2 / 30.1  
Years of opiate use: 12.6 / 10.7

### COLLINS2005

**Study Type:** RCT (randomised controlled trial)  
**Study Description:** Patients not blinded  
Type of Analysis: ITT  
**Blindness:** Single blind  
**Duration (days):** Mean 84  
**Setting:** US

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Group Description</th>
<th>Data Used</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1     | 37 | Opiate partial agonist: buprenorphine with inpatient. Mean dose 17 mg - Total 17 mg sublingual in divided doses, three times daily over 3 days  
Placebo - Oral placebo capsule three times daily for 18 days | Withdrawal: OOWS (Objective Opiate Withdrawal)  
Withdrawal: Subjective Opiate Withdrawal Scale  
Completion  
Retention: duration in treatment | Study quality 1++ |

**n = 106**  
**Age:** Mean 36 Range 21-50  
**Sex:** 76 males  30 females  
**Diagnosis:**  
100% opiate dependence by DSM-IV  
Exclusions: - age outside 21-50 range

**Additional symptomatic medications available for specific symptoms, but were not requested by any participant throughout study**  
Study quality 1++
3 days' inpatient phase followed by 12 weeks' outpatient phase

Notes: RANDOMISATION: Blocks of 12 with computer-generated assignments
ALLOCATION: Staff remained unaware of randomisation sequence

Info on Screening Process: 169 screened; 35 met exclusion criteria and 28 lost to follow-up or refused consent; 106 enrolled and randomised

- poor general health or acute medical illness
- DSM-IV criteria for dependence on alcohol or non-opiate drugs
- pregnancy or lactation or failure to use adequate birth control
- history of significant violent behaviour
- schizophrenia and/or major mood disorder
- suicide risk
- current psychotropic medication, MAO inhibitors, protease inhibitors
- positive cocaine urinalysis on admission
- BMI > 40
- Blood glucose concentration > 160 mg/dL
- history of food or drug allergy, sensitivity to study medication

Notes: PRIMARY DIAGNOSIS: Opiate dependence >=6 months and seeking treatment
ETHNICITY: 53% White

Baseline: (GROUPS: ultrarapid / buprenorphine / clonidine)
Heroin use (days in past 30): 30 / 29 / 29
Lifetime heroin use disorder (years): 7.6 / 7.4 / 6.4
Previous inpatient detoxification attempts: 1.74 / 1.59 / 1.21
Previous inpatient rehabilitation attempts: 0.57 / 0.54 / 0.56
Previous outpatient detoxification attempts: 0.17 / 0.11 / 0.29
Previous MMT: 0.66 / 0.57 / 0.53

Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed
Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy
Opiate antagonist: naltrexone with inpatient - Induced at 12.5 mg on day 2, 25 mg on day 3, then increased to maintenance dose of 50 mg on subsequent days
Alpha2 adrenergic agonist: clonidine with inpatient - As needed

Group 2 N=34
Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed
Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy
Opiate antagonist: naltrexone with outpatient - Initial 12.5 mg dose on day 6, followed by 25 mg next day and 50 mg maintenance dose on subsequent days
Alpha2 adrenergic agonist: clonidine with inpatient - As needed

Group 3 N=35
Symptomatic with inpatient - As required: clonazepam, up to 2 mg every 8 hours; ketorolac, 30 mg intramuscularly every 6 hours; ondansetron, 8 mg orally every 8 hours or prochlorperazine, 10 mg orally/intramuscularly every 8 hours; octreotide, 100 mcg every 8 hours; and so on
Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed
Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy
Anaesthetic: propofol with inpatient - 25-150 mcg/kg per min; anaesthesia maintained for 2-4 hours
Opiate antagonist: naltrexone with inpatient - Mean dose 50 mg - Induced on 50 mg then maintained throughout outpatient phase
Alpha2 adrenergic agonist: clonidine with inpatient - As needed, up to 0.2 mg every 4 hours (max 1.2 mg/day)

DEJONG2005
Study Type: RCT (randomised controlled trial)
Study Description: 7 days' inpatient treatment followed by 10 months' outpatient community reinforcement approach

n= 272
Age: Mean 36
Sex: 223 males 49 females

Data Used
Withdrawal: Subjective Opiate Withdrawal Scale
Urinalysis

Group 1 N=137
Symptomatic with inpatient - As per ultrarapid group

Study quality: 1++

APPENDIX 15(a)
<table>
<thead>
<tr>
<th>Diagnosis:</th>
<th>Opiate use Withdrawal: COWS (Clinical Opiate Withdrawal) Abstinence: 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusions:</td>
<td>Opiate antagonist: naltrexone with inpatient - 12.5 mg on day 1, 25 mg on day 2, 50 mg on day 3</td>
</tr>
<tr>
<td>Alpha2 adrenergic agonist: clonidine with inpatient - As per ultrarapid group</td>
<td></td>
</tr>
<tr>
<td>8am: diclofenac, ondansetron, diazepam, transdermal nicotine (for smokers) Post-naltrexone: octreotide, ondansetron, butylscopolamine, diazepam; haloperidol and midazolam as necessary</td>
<td></td>
</tr>
<tr>
<td>Anaesthetic: propofol with inpatient. Mean dose 5000 ng/ml - Anaesthesia induced on first signs of opiate withdrawal, using target controlled infusion method, and maintained for 4 hours</td>
<td></td>
</tr>
<tr>
<td>Psychosocial: CRA (community reinforcement approach) with outpatient - As per ultrarapid group</td>
<td></td>
</tr>
<tr>
<td>2 N= 135 Group Symptomatic with inpatient - All participants treated with same medications at same dosages: Sams: diltiazem, ondansetron, diazepam, transdermal nicotine (for smokers) Post-naltrexone: octreotide, ondansetron, butylscopolamine, diazepam; haloperidol and midazolam as necessary</td>
<td></td>
</tr>
<tr>
<td>Anaesthetic: propofol with inpatient. Mean dose 5000 ng/ml - Anaesthesia induced on first signs of opiate withdrawal, using target controlled infusion method, and maintained for 4 hours</td>
<td></td>
</tr>
<tr>
<td>Psychosocial: CRA (community reinforcement approach) with outpatient - 23 sessions over 10 months: 10 monitoring naltrexone compliance, addictive behaviours and craving; 13 working on drug-refusal behaviour, relational issues, problem solving, social skills training and craving management with accompanying non drug user</td>
<td></td>
</tr>
<tr>
<td>Opiate antagonist: naltrexone with inpatient - Administered at 9 am to precipitate withdrawal. At the end of anaesthesia, 100 mg administered through orogastric tube. Continued on maintenance dose (50 mg) for 10 months Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 0.3 mg - Administered at 9 am to prevent high blood pressure</td>
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</tr>
<tr>
<td>Post-naltrexone: 0.15 mg subcutaneously at five intervals over the day</td>
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</tbody>
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**APPENDIX 15(a)**

**DRUMMOND1989**

<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
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</thead>
<tbody>
<tr>
<td>Study quality 1+</td>
</tr>
<tr>
<td>Setting: Double blind</td>
</tr>
<tr>
<td>Duration (days): Mean 14</td>
</tr>
<tr>
<td>Setting: Inpatient detoxification at three Glasgow hospitals</td>
</tr>
<tr>
<td>Notes: RANDOMISATION: Participants randomly assigned to one of two groups. Pharmacy department disguised preparations.</td>
</tr>
<tr>
<td>Info on Screening Process: 33 screened, 9 excluded, 24 met inclusion criteria</td>
</tr>
<tr>
<td>n= 24</td>
</tr>
<tr>
<td>Age: Mean 25</td>
</tr>
<tr>
<td>Sex: 13 males 11 females</td>
</tr>
<tr>
<td>Diagnosis: 85% opiate dependence by urinalysis</td>
</tr>
<tr>
<td>Notes: Primary drug: heroin</td>
</tr>
<tr>
<td>3 participants took benzodiazepine on a regular basis</td>
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<tr>
<td>13 participants reported occasional use of cannabis</td>
</tr>
<tr>
<td>Baseline: Mean duration of drug use: 4.7 years (SD = 2.2) Mean daily dose of heroin 0.8 g (SD = 0.6)</td>
</tr>
<tr>
<td>Data Used Urinalysis Withdrawal: Subjective Opiate Withdrawal Scale Withdrawal: OOWS (Objective Opiate Withdrawal)</td>
</tr>
<tr>
<td>Group 1 N= 13 Opiate agonist: methadone with inpatient. Mean dose 20 mg - Participants received methadone linctus 20 mg orally in the first 24 hours and placebo tablets together. Thereafter they could receive 30 mg more if needed</td>
</tr>
<tr>
<td>Group 2 N= 11 Benzodiazepine: chlordiazepoxide with inpatient. Mean dose 200 mg - Patients received 200 mg of chlordiazepoxide orally in the first 24 hours with the option of a further 300 mg if needed</td>
</tr>
</tbody>
</table>

**FAVRAT2006**
## DRUG MISUSE: OPIOID DETOXIFICATION

### Study Type: RCT (randomised controlled trial)

**Setting:** Switzerland

**Notes:** Randomisation by pharmacist

---

### Study Description: Randomisation by pharmacist

**Blindness:** No mention

**Duration (days):** Range 1-7

**Notes:** Randomisation procedure not described

---

### Notes on Screening Process: 113 eligible, 43 refused to participate but agreed to be followed up; 70 randomised

---

### GERRA1995

**Study Type:** RCT (randomised controlled trial)

**Type of Analysis:** Per protocol

**Blindness:** Double blind

**Duration (days):** Mean 4

**Followup:** 3 and 6 months

**Setting:** Italy

**Notes:** Randomisation procedure not described

---

### Data Used

**ASI (Addiction Severity Index)**

**Compliance**

**Abstinence:** 12 months

**Abstinence:** 3 months

Notes: Completion defined as 3 days of retention in treatment for anaesthesia without drug consumption and 7 days for clonidine

**FOLLOW-UPS:** At 3, 6 and 12 months

---

### GROUP 1 N=34

**Psychosocial:** individual therapy with outpatient - As per ultrarapid group

**Symptomatic with inpatient:** Limited to one drug at one dosage per indication: loperamide 4 mg, tolperisone 150 mg, ondansetron 4 mg, zolpidem 10 mg, olanzapine 5 mg, paracetamol 500 mg

**Alpha2 adrenergic agonist:** clonidine with inpatient - 0.600 mg/day for first 3 days, 0.300 mg on day 4, 0.225 mg on day 5, 0.150 mg on day 6 and 0.075 mg on day 7 (in divided 0.075 mg doses)

---

### GROUP 2 N=36

**Psychosocial:** individual therapy with outpatient - One week of "intensive" psychosocial support following discharge

**Symptomatic with inpatient:** During anaesthesia, octreotide. After anaesthesia, during recovery phase: 30 mg intravenous ketorolac, glycopyrrolate if needed and 5 mg droperidol for delirium if needed.

**Anaesthetic:** propofol with inpatient - Monitored and maintained at bispectral index 45-60 by propofol infusion (around 5-6 hours)

**Opiate antagonist:** naltrexone with inpatient. Mean dose 100 mg - Oral, with 30 mg oral sodium citrate to precipitate withdrawal. Before leaving ICU, 24 hours after start of treatment, initiation of maintenance dose (50 mg) oral naltrexone

**Alpha2 adrenergic agonist:** clonidine with inpatient - During anaesthesia, clonidine or lidocaine used to deepen anaesthesia and control withdrawal signs

---

### Data Used

**Withdrawal severity**

**Urinalysis**

**Completion**

Notes: DROP OUTS: 2/33 clonidine, 2/42 clonidine-naltrexone, 1/58 clonidine-naloxone, 5/19 placebo

---

### GROUP 1 N=33

**Psychosocial:** individual therapy - Psychotherapy - no further details

**Placebo with outpatient:** Placebo tablets for 3 months

**Alpha2 adrenergic agonist:** clonidine with outpatient. Mean dose 0.15 mg - Intravenous clonidine three times daily for 4 days

---

### GROUP 2 N=42

**Psychosocial:** individual therapy - Psychotherapy - no further details

**Opiate antagonist:** naltrexone with outpatient. Mean dose 50 mg - daily beginning on day 2. Maintained on naltrexone for following 3 months

**Alpha2 adrenergic agonist:** clonidine with outpatient - As per clonidine group

---

### Study Quality: 1++

**Data Used**

**ASI (Addiction Severity Index)**

**Completion**

**Abstinence:** 12 months

**Abstinence:** 3 months

Notes: Completion defined as 3 days of retention in treatment for anaesthesia without drug consumption and 7 days for clonidine

**FOLLOW-UPS:** At 3, 6 and 12 months

---

### Notes: RANDOMISATION: Computer-generated numbers

**Setting:** Switzerland

**Duration (days):** Range 1-7

**Blindness:** No mention

**Study Type:** RCT (randomised controlled trial)

**Type of Analysis:** Per protocol

**Study Description:** Randomisation by pharmacist

---

### Notes on Screening Process: 113 eligible, 43 refused to participate but agreed to be followed up; 70 randomised

---

### Info on Screening Process: 113 eligible, 43 refused to participate but agreed to be followed up; 70 randomised

---

### Study Quality: 1++

**Data Used**

**ASI (Addiction Severity Index)**

**Completion**

**Abstinence:** 12 months

**Abstinence:** 3 months

Notes: Completion defined as 3 days of retention in treatment for anaesthesia without drug consumption and 7 days for clonidine

**FOLLOW-UPS:** At 3, 6 and 12 months

---

### Notes: DROP OUTS: 2/33 clonidine, 2/42 clonidine-naltrexone, 1/58 clonidine-naloxone, 5/19 placebo

---

### Study Quality: 1++
<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>Type of Analysis: Per protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (days): Mean 10</td>
<td>Blindness: No mention</td>
</tr>
<tr>
<td>Follow up: 6 months</td>
<td>Study Type: RCT (randomised controlled trial)</td>
</tr>
<tr>
<td>Setting: Italy</td>
<td>Blindness: Single blind</td>
</tr>
<tr>
<td></td>
<td>Duration (days): Mean 3</td>
</tr>
<tr>
<td></td>
<td>Setting: Italy</td>
</tr>
<tr>
<td></td>
<td>Info on Screening Process: All those asked gave consent and were randomised</td>
</tr>
</tbody>
</table>

### GERRA2000

**n = 98**

**Age:** Range 18-36

**Sex:** 71 males, 27 females

**Diagnosis:**
- 100% opiate dependence by DSM-III-R
- 100% opiate misuse by DSM-IV

**Exclusions:**
- Polydrug dependence or prolonged use of drugs other than heroin
- Severe chronic liver, renal or other physical disorders
- Psychosis
- Recent weight loss or obesity
- Endocrinopathies
- Immunodeficiencies

**Notes:** PRIMARY DIAGNOSIS confirmed by urinalysis

**Baseline:** Years of heroin use: 2-6

**Data Used**

- Entry to further treatment: naltrexone maintenance
- Withdrawal severity
- Opiate use

**Group 1 N = 32**

- Alpha2 adrenergic agonist: clonidine with outpatient - Intravenous clonidine 0.15 mg in 100 mL saline three times in the morning and afternoon for 2 days; in following 3 days half doses of clonidine administered (0.15 mg 3 times a day). At 11 pm clonidine orally received every evening for 5 days

**Group 2 N = 32**

- Opiate antagonist: naltrexone with outpatient - Naloxone injections until full dose of 0.04 mg reached. Naltrexone syrup 5 mg orally on day 1, 50 mg on day 2
- Alpha2 adrenergic agonist: clonidine with outpatient - As per clonidine group (group 1)

- Symptomatic - 60 mg oxazepam twice a day, 10 mg oral baclofen twice a day, 400 mg ketoprofene twice a day

**Group 3 N = 34**

- Opiate agonist: methadone with inpatient - Dose tapered from 40 mg to 0 mg in 10 days, administered once daily in syrup

**Study quality 1+**

**Intravenous heroin administered to all participants until 12 hours before treatment**

**All participants admitted to naltrexone maintenance post treatment**

### GERRA2001

**n = 40**

**Age:** Range 20-32

**Sex:** All males

**Diagnosis:**
- 100% opiate dependence

**Exclusions:**
- Female
- Heavy polydrug misuse: long-lasting consumption of alcohol or other drugs
- Psychosis
- Severe chronic liver illness

**Data Used**

- Withdrawal severity
- Urinalysis
- Completion

**Notes:** DROPOUTS: clonidine 15%, llofoxidine 10%

**Group 1 N = 20**

- Alpha2 adrenergic agonist: llofoxidine - 0.2 mg tablets three times in the morning and three times in the afternoon for 3 days. On day 2, additional tablet at 9 am and at 12 pm.
- Benzodiazepine: oxazepam. Mean dose 60 mg - Orally, twice a day
- GABA agonist: baclofen - 10 mg orally three times daily
- Ketoprofene. Mean dose 400 mg - 400 mg intravenous daily, in 1000 mL saline

**Study quality 1+**
**GROUP B**

- Benzodiazepine: oxazepam. Mean dose 60 mg - Orally, twice per day
- GABA agonist: baclofen. Mean dose 10 mg - 10 mg orally 3 times daily
- Ketoprofene. Mean dose 400 mg - 400 mg intravenous daily, in 1000 ml saline
- Alpha2 adrenergic agonist: clonidine with outpatient. Mean dose 0.15 mg - 0.15 mg tablets 3 times in the morning and 3 times in the afternoon for 3 days. On day 2, additional tablet at 9pm and at 12pm.

**GROUP A**

- Opiate agonist: methadone - Initial dose 40 mg, reduced by 5 mg every other day down to 0
- Placebo with inpatient - Administered identically to clonidine

**GHODSE1994**

- Study Type: RCT (randomised controlled trial)
- blindness: Double blind
- Duration (days): Mean 14
- Followup: 4 weeks
- Setting: Drug dependency unit in UK

<table>
<thead>
<tr>
<th>Data Used</th>
<th>Group 1 N=42</th>
<th>Group 2 N=44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal severity</td>
<td>Opiate agonist: methadone - Initial dose 40 mg, reduced by 5 mg every other day down to 0</td>
<td>Opiate agonist: methadone - Initial dose 40 mg, reduced by 5 mg every other day down to 0</td>
</tr>
<tr>
<td>Completion</td>
<td>Placebo failed to complete detoxification</td>
<td>Placebo with inpatient - Administered identically to clonidine</td>
</tr>
</tbody>
</table>

**HOWELLS2002**

- Study Type: RCT (randomised controlled trial)
- Study Description: Allocation by pharmacist, who oversaw binding procedures throughout study; double dummy design
- Type of Analysis: ITT
- BLINDNESS: Double blind
- Duration (days): Mean 10
- Setting: UK male prison
- Notes: RANDOMISATION: "Simple randomisation procedure" by pharmacist

<table>
<thead>
<tr>
<th>Data Used</th>
<th>Group 1 N=36</th>
<th>Group 2 N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal: WPS (Withdrawal Problems Scale)</td>
<td>Opiate agonist: methadone with prison - 30 mg day 1, 25 mg days 2-3, 20 mg days 4-5, tapered to 0 in 10 days</td>
<td>Alpha2 adrenergic agonist: lofexidine with prison - 0.6 mg day 1, increased by 0.4 mg per day until maximum tolerated dose or 1.2 mg reached. Dose reduced by 0.1 mg if a blood pressure reading &lt; 90/60 mm Hg recorded.</td>
</tr>
<tr>
<td>Withdrawal: Short Opiate Withdrawal Scale SDS (Severity of Dependence Scale)</td>
<td>Placebo - Placebo peach coloured tablets, twice daily for 10 days</td>
<td>Placebo - Placebo green syrup, twice daily for 10 days</td>
</tr>
<tr>
<td>Withdrawal severity Completion</td>
<td>Placebo failed to complete detoxification</td>
<td>Study quality 1++</td>
</tr>
</tbody>
</table>

**JANIRI1994**

- Study Type: RCT (randomised controlled trial)
- Blindness: Double blind
- Duration (days): Mean 6
- Setting: Italy
- Notes: RANDOMISATION: not reported

<table>
<thead>
<tr>
<th>Data Used</th>
<th>Group 1 N=13</th>
<th>Group 2 N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion</td>
<td>Opiate partial agonist: buprenorphine with inpatient - Intramuscularly: 0.9 mg days 1 and 2, 0.45 mg day 3, 0.15 mg day 4</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient - Intramuscularly: 0.3-0.9 mg per day for 6 days</td>
</tr>
</tbody>
</table>

**APPENDIX 15(a)**

**DRUG MISUSE: OPIOID DETOXIFICATION**
### JIANG1993
**Study Type:** RCT (randomised controlled trial)

- **Blindness:** No mention
- **Duration (days):** Mean 12
- **Setting:** Five rehabilitation centres in China
- **Notes:** RANDOMISATION: No details

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Drug</th>
<th>Duration (days)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1     | 100 | Opiate agonist: methadone | Mean 12 | Randomisation: No details
| 2     | 100 | Alpha2 adrenergic agonist: clonidine | Mean 12 | Randomisation: No details
| 3     | 100 | Opiate partial agonist: buprenorphine | Mean 12 | Randomisation: No details

**Baseline:**
- Mean duration of opiate dependence = 7.5 (3.6) years
- Duration in MMT = 3.4 (2.4) years

**Notes:**
- PRIMARY DRUG: 17/39 participants were using heroin on top of methadone
- Baseline: Mean duration of opiate dependence = 7.5 (3.6)
- 41% HIV+

**Data Used**
- Withdrawal severity
- Hamilton Anxiety Rating Scale
- Notes: Dropout outcomes were observer-rated; not extracted

**Study Quality:** 1+

---

### JOHNSON1992
**Study Type:** RCT (randomised controlled trial)

- **Blindness:** Double blind
- **Duration (days):** Mean 180
- **Setting:** US

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Drug</th>
<th>Duration (days)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1     | 54 | Opiate agonist: methadone with outpatient | Mean 180 | Randomisation: No details
| 2     | 53 | Opiate partial agonist: buprenorphine with outpatient | Mean 180 | Randomisation: No details
| 3     | 55 | Opiate agonist: methadone with outpatient | Mean 180 | Randomisation: No details

**Baseline:**
- GROUPS: Methadone / clonidine
- Using orally only: 80% / 67%

**Notes:**
- REFERRALS: Not all participants entered voluntarily

**Data Used**
- Completion
- Abstinence: endpoint
- Withdrawal assessed by total number of negative urine samples -- not used

**Study Quality:** 1+

---

### KAHN1997
**Study Type:** RCT (randomised controlled trial)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Drug</th>
<th>Duration (days)</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1     | 14 | Alpha2 adrenergic agonist: lofexidine | Mean 18 | Randomisation: No details

**Baseline:**
- GROUPS: Buprenorphine (8 mg / day)/ methadone (20 mg / day) / methadone (60 mg / day)
- Months of addiction: 31.0 (11.2) / 31.5 (10.8) / 30.2 (9.6)
- $ / day opioid use: 114.1 (91.7) / 115.3 (65.3) / 106.2 (49.9)

**Study Quality:** 1+
### KLEBER1985

**Study Type:** RCT (randomised controlled trial)  
**Study Description:** Double dummy design; binding of nurse who administered withdrawal rating scale, and physician who provided psychological support  
**Blindness:** Single blind  
**Duration (days):** Mean 30  
**Setting:** Component of multicentre study in USA  
**Notes:** RANDOMISATION: No details

<table>
<thead>
<tr>
<th>Group</th>
<th>N= 49</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiate agonist:</strong></td>
<td>Methadone with outpatient</td>
</tr>
<tr>
<td><strong>Alpha2 adrenergic agonist:</strong></td>
<td>Clonidine with outpatient</td>
</tr>
<tr>
<td><strong>Notes:</strong></td>
<td>PRIMARY DIAGNOSIS: by history and urine screen</td>
</tr>
</tbody>
</table>

#### Data Used

<table>
<thead>
<tr>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASI (Addiction Severity Index)</strong></td>
</tr>
<tr>
<td><strong>Withdrawal severity</strong></td>
</tr>
<tr>
<td><strong>BDI (Beck Depression Inventory)</strong></td>
</tr>
<tr>
<td><strong>Completion</strong></td>
</tr>
</tbody>
</table>

#### Diagnosis:

- 100% opiate dependence by eligibility for/receipt of MMT  
- Age outside range 21-50  
- Current use of MAO inhibitors, neuroleptics, sedatives or other antihypertensive drugs (except diuretics)  
- Current alcohol abuse  
- History of allergy to imidazolidone drugs  
- Any medical or psychiatric illness that would subject patient to unnecessary risk or compromise objective evaluation of the investigative drug (e.g. cardiac disorders, renal disorders, hypertension, schizophrenia, severe affective disorders)  
- Pregnancy

#### Exclusions:

- Age outside range 21-50  
- Current use of MAO inhibitors, neuroleptics, sedatives or other antihypertensive drugs (except diuretics)  
- Current alcohol abuse  
- History of allergy to imidazolidone drugs  
- Any medical or psychiatric illness that would subject patient to unnecessary risk or compromise objective evaluation of the investigative drug (e.g. cardiac disorders, renal disorders, hypertension, schizophrenia, severe affective disorders)  
- Pregnancy  

#### Notes:

- Primary Diagnosis: Receiving methadone ≤20 mg per day for ≥6 months  
- Ethnicity: 71% White  
- Baseline: Length of addiction: 10 years  
- Setting: Component of multicentre study in USA  
- Notes: RANDOMISATION: No details  

### KRABBEE2003

**Study Type:** Non-randomised controlled trial  
**Type of Analysis:** ITT (dropouts treated as nonabstinent)  
**Blindness:** Open  
**Duration (days):** Range 4-20  
**Follow-up:** 3 months  
**Setting:** Hospital in the Netherlands  
**Notes:** RANDOMISATION: Consecutive assignment (first 15 to ultrarapid group) - potential bias  
**Info on Screening Process:** 30 enrolled

<table>
<thead>
<tr>
<th>Group</th>
<th>N= 30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiate agonist:</strong></td>
<td>Methadone with outpatient</td>
</tr>
<tr>
<td><strong>Alpha2 adrenergic agonist:</strong></td>
<td>Clonidine with outpatient</td>
</tr>
<tr>
<td><strong>Notes:</strong></td>
<td>PRIMARY DIAGNOSIS: Receiving methadone ≤20 mg per day for ≥6 months</td>
</tr>
</tbody>
</table>

#### Data Used

<table>
<thead>
<tr>
<th>Data</th>
</tr>
</thead>
</table>
| **Withdrawal:** | OOWS (Objective Opiate Withdrawal)  
| **Subjective Opiate Withdrawal Scale** |  
| **Abstinence:** | 1 month  
| **Completion** |  

#### Diagnosis:

- 100% opiate dependence by DSM-IV  
- Age outside range 18-40  
- No documented failed efforts of standard methadone tapering  
- No definite desire for sustained abstinence  
- Dependent on other drugs  
- Severe physical illness contraindicating general anaesthesia  
- Pregnancy

#### Exclusions:

- Age outside range 18-40  
- No documented failed efforts of standard methadone tapering  
- No definite desire for sustained abstinence  
- Dependent on other drugs  
- Severe physical illness contraindicating general anaesthesia  
- Pregnancy  

#### Notes:

- Followups: Monthly for 3 months  
- Dropout: 60% methadone, 0% ultrarapid  
- Setting: Hospital in the Netherlands  
- Notes: RANDOMISATION: Consecutive assignment (first 15 to ultrarapid group) - potential bias  

### LIN1997

**Study Description:** Double dummy design; binding of nurse who administered withdrawal rating scale, and physician who provided psychological support  
**Blindness:** Single blind  
**Duration (days):** Mean 30  
**Setting:** Component of multicentre study in USA  
**Notes:** RANDOMISATION: No details

<table>
<thead>
<tr>
<th>Group</th>
<th>N= 14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiate agonist:</strong></td>
<td>Methadone with outpatient</td>
</tr>
<tr>
<td><strong>Alpha2 adrenergic agonist:</strong></td>
<td>Clonidine with outpatient</td>
</tr>
<tr>
<td><strong>Notes:</strong></td>
<td>PRIMARY DIAGNOSIS: by history and urine screen</td>
</tr>
</tbody>
</table>

#### Data Used

<table>
<thead>
<tr>
<th>Data</th>
</tr>
</thead>
</table>
| **Withdrawal:** | OOP (Objective Opiate Withdrawal)  
| **Subjective Opiate Withdrawal Scale** |  
| **Abstinence:** | 1 month  
| **Completion** |  

#### Diagnosis:

- 100% opiate dependence by eligibility for/receipt of MMT  
- Age outside range 21-50  
- Current use of MAO inhibitors, neuroleptics, sedatives or other antihypertensive drugs (except diuretics)  
- Current alcohol abuse  
- History of allergy to imidazolidone drugs  
- Any medical or psychiatric illness that would subject patient to unnecessary risk or compromise objective evaluation of the investigative drug (e.g. cardiac disorders, renal disorders, hypertension, schizophrenia, severe affective disorders)  
- Pregnancy  

#### Exclusions:

- Age outside range 21-50  
- Current use of MAO inhibitors, neuroleptics, sedatives or other antihypertensive drugs (except diuretics)  
- Current alcohol abuse  
- History of allergy to imidazolidone drugs  
- Any medical or psychiatric illness that would subject patient to unnecessary risk or compromise objective evaluation of the investigative drug (e.g. cardiac disorders, renal disorders, hypertension, schizophrenia, severe affective disorders)  
- Pregnancy  

#### Notes:

- Primary Diagnosis: Receiving methadone ≤20 mg per day for ≥6 months  
- Ethnicity: 71% White  
- Baseline: Length of addiction: 10 years  
- Setting: Component of multicentre study in USA  
- Notes: RANDOMISATION: Consecutive assignment (first 15 to ultrarapid group) - potential bias  

### Study Quality

**Group 1 N= 25**  
Opiate agonist: methadone with outpatient - Initial dose 20 mg per day, single daily oral dose tapered by 1 mg per day; choral hydrate 0.5-1 g permitted as an adjunct for insomnia  
Placebo - Methadone placebo from days 21-30; clonidine placebo tablets throughout study

**Group 2 N= 24**  
Alpha2 adrenergic agonist: clonidine with outpatient - Initial dose 0.3 mg per day in three divided doses, gradual increase to max 1 mg per day by day 6; tapered by 20-25% per day from day 11. Choral hydrate 0.5-1 g permitted as an adjunct for insomnia  
Placebo - Clonidine placebo tablets from days 16-30; methadone placebo syrup throughout study

**Study quality 1+**
<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>Type of Analysis: Per protocol</th>
<th>Setting: Taiwan</th>
<th>Notes: RANDOMISATION: No details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Used</td>
<td>Withdrawal severity</td>
<td>Group 1</td>
<td>Alpha2 adrenergic agonist: lofexidine with inpatient. Mean dose 0.2 mg capsules - four times a day on day 1, then titrated dependent on withdrawal symptoms and blood pressure. Dose held steady for next 2 days, then tapered to 0 over the next 2-4 days. Max dose never exceeded 8 capsules per day</td>
</tr>
<tr>
<td></td>
<td>Retention: duration in treatment</td>
<td>Group 2</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 0.075 mg - 4 times a day on day 1, then titrated dependent on withdrawal symptoms and blood pressure. Dose held steady for next 2 days, then tapered to 0 over the next 2-4 days. Max dose never exceeded eight capsules per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 3</td>
<td>Alpha2 adrenergic agonist: clonidine with outpatient. Oral &amp; transdermal patch: 0.05-0.1mg every 6 hrs day 1 (not exceeding 0.6mg in total), if oral dose well tolerated clonidine transdermal patch given for 7 days, oral clonidine discontinued on day 7, new patch delivered on day 7 and discontinued on day 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 4</td>
<td>Alpha2 adrenergic agonist: clonidine with outpatient. Oral &amp; transdermal patch: 0.05 0.1mg every 6 hrs day 1 (not exceeding 0.6 mg in total), if oral dose well tolerated clonidine transdermal patch given for 7 days, oral clonidine discontinued on day 3, new patch delivered on day 7 and discontinued on day 13</td>
</tr>
</tbody>
</table>

**LING2005**

<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>Type of Analysis: ITT</th>
<th>Setting: Six inpatient and six outpatient community-based treatment programmes in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Used</td>
<td>Withdrawal: COWS (Clinical Opiate Withdrawal) Completion</td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 4</td>
</tr>
</tbody>
</table>

**LINTZERIS2002**

<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>Type of Analysis: ITT</th>
<th>Followup: 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Used</td>
<td>Entry to further treatment: naltrexone maintenance Withdrawal: Short Opiate Withdrawal Scale Opiate use Completion</td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 2</td>
</tr>
</tbody>
</table>

[APPENDIX 15(a)](DRUG-MISUSE-OPPIOID-DETOXIFICATION)
### MARSCH2005

**Study Type:** RCT (randomised controlled trial)  
**Blindness:** Double blind  
**Duration (days):** Mean 28  
**Setting:** Australia, two specialist outpatient centres  

**Notes:** RANDOMISATION: By an independent organisation  
Info on Screening Process: 272 screened; 85 excluded and 45 chose not to participate.  

**Exclusions:**  
- <18 years  
- opiate-negative urine at screening  
- MMT for last 8 weeks  
- significant medical or psychiatric conditions  
- concurrent alcohol, benzodiazepine, amphetamine, cocaine dependence  
- homeless  
- pregnant  

Baseline: GROUPS: Buprenorphine / clonidine  
No. days’ use in 28: 26.3 (2.9) / 25.3 (4.5)  
Average daily cost in $AUS 95.90 (71.80) / 100.60 (74.20)  

**Data Used**  
Entry to further treatment: naltrexone maintenance  
Hair analysis  
Opiate use  
Completion  
Retention: duration in treatment  

Notes: Abstinence measured as number of negative urine samples -- not used  
**Notes:** Dropout: Buprenorphine = 8/58, clonidine = 32/56  
**Group 1 N = 56**  
Alpha2 adrenergic agonist: clonidine with outpatient. Mean dose 500 mcg / day - 100-150 mcg four times a day as required, plus symptomatic medications  

### MCGREGOR2002

**Study Type:** RCT (randomised controlled trial)  
**Study Description:** 3 days’ inpatient detoxification procedure followed by 9 months’ naltrexone maintenance plus psychosocial intervention  
**Type of Analysis:** Per protocol  
**Blindness:** No mention  
**Duration (days):** Mean 270  
**Followup:** 3 months  
**Setting:** Two public substance misuse treatment facilities and one teaching hospital in Australia  

**Notes:** RANDOMISATION: In blocks of four by research team member blind to participants’ identity or history  
Info on Screening Process: 162 telephone interviewed, 119 screened and 107 enrolled. 6 in pilot group so 101 randomised.  

**Data Used**  
Entry to further treatment: naltrexone maintenance  
Hair analysis  
Opiate use  
Completion  
Retention: duration in treatment  

Notes: Completion defined as absence of withdrawal syndrome (Objective Opiate Withdrawal Scale [OOWS] <=4)  
**Notes:** PRIMARY DIAGNOSIS: Heroin  
**Group 1 N = 50**  
Psychosocial: individual therapy with outpatient - For 9 months following hospital discharge: monthly naltrexone dispensing and counselling (based on motivational enhancement therapy [MET] and CBT principles)  
Opiate antagonist: naltrexone with outpatient. Mean dose total 10 or 12 mg - Intravenous naltrexone administered in four or five bolus doses at 30-min intervals  
Symptomatic with outpatient - Octreotide for relieving gastrointestinal withdrawal  
Anaesthetic: propofol with outpatient - Maintained for 4 hours  
Opiate antagonist: naltrexone with outpatient. Mean dose 50 mg - When OOWS <=5 following anaesthesia and naltrexone challenge, 50 mg naltrexone given orally  

Study quality: 1++
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Data Used</th>
<th>Group</th>
<th>Data Used</th>
<th>Group</th>
<th>Data Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIGAM1993</td>
<td>44</td>
<td>Withdrawal: Subjective Opiate Withdrawal Scale Completion</td>
<td>1</td>
<td>22</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>OCONNOR1997</td>
<td>162</td>
<td>Withdrawal severity Completion</td>
<td>1</td>
<td>55</td>
<td>2</td>
<td>54</td>
</tr>
<tr>
<td>PETITJEAN2002</td>
<td></td>
<td></td>
<td>2</td>
<td>53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NIGAM1993

**Study Type:** RCT (randomised controlled trial)

**Blindness:** No mention

**Duration (days):** Mean 10

**Setting:** India

**Notes:** RANDOMISATION: Method not reported

<table>
<thead>
<tr>
<th>n</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Exclusions</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>Mean 29</td>
<td>all males</td>
<td>100% opiate dependence by DSM-III-R</td>
<td>Polydrug use</td>
<td>Duration of heroin use = 4-5 years</td>
</tr>
</tbody>
</table>

### OCONNOR1997

**Study Type:** RCT (randomised controlled trial)

**Study Description:** Triple dummy design

**Blindness:** Double blind

**Duration (days):** Mean 8

**Setting:** Primary care clinic, USA

**Info on Screening Process:** 202 screened, 177 eligible. 15 failed to attend on day 1, so 162 randomised

<table>
<thead>
<tr>
<th>n</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Exclusions</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>162</td>
<td>Range 18-50</td>
<td>165 males 51 females</td>
<td>100% opiate dependence</td>
<td>Polydrug use</td>
<td>Duration of heroin use = 4-5 years</td>
</tr>
</tbody>
</table>

### PETITJEAN2002

**Study Description:**

<table>
<thead>
<tr>
<th>n</th>
<th>Age at first heroin use</th>
<th>Bags of heroin used in past 30 days</th>
<th>Weekly cocaine use (g)</th>
<th>Withdrawal score</th>
<th>Craving score</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>21.9 / 23.0 / 22.1</td>
<td>3.8 / 4.0 / 3.3</td>
<td>0.38 / 0.39 / 0.96</td>
<td>15.7 / 17.3 / 15.3</td>
<td>72.9 / 79.4 / 77.6</td>
</tr>
</tbody>
</table>

**Baseline:**

- GROUPS: Clonidine / clonidine + naltrexone / buprenorphine
- Age at first heroin use: 21.9 / 23.0 / 22.1
- Years of heroin use: 5.9 / 7.7 / 8.5
- Bags of heroin used in past 30 days: 3.8 / 4.0 / 3.3
- Weekly cocaine use (g): 0.38 / 0.39 / 0.96
- Withdrawal score: 15.7 / 17.3 / 15.3
- Craving score: 72.9 / 79.4 / 77.6

**Notes:**

- **Randomisation:** Method not reported
- **Setting:** India
- **Duration:** Mean 10 days
- **Blindness:** No mention
- **Study Type:** RCT (randomised controlled trial)
- **Diagnosis:** 100% opiate dependence by DSM-III-R
- **Exclusions:** Polydrug use, duration of heroin use = 4-5 years

---

**(Data Used: Withdrawal: Subjective Opiate Withdrawal Scale Completion)

**Group 1:**

- Alpha2 adrenergic agonist: clonidine
- Opiate antagonist: naltrexone - Full blocking dose of 50 mg on day 8
- Placebo - Placebos for buprenorphine

**Group 2:**

- Opiate antagonist: naltrexone - Full blocking dose of 50 mg on day 8
- Placebo - Placebos for buprenorphine

**Group 3:**

- Opiate partial agonist: buprenorphine - Sublingual tablet: initial dose 0.6 mg / day with maximum 1.2 mg / day in 3 divided doses. Nitracearn as adjunct medication

---

**Heroin users = 90%, opium users = 10%

Study quality 1+**
### Study Type: RCT (randomised controlled trial)

**Blindness:** Open  
**Duration (days):** Mean 15  
**Setting:** Inpatient unit, Switzerland  
**Notes:** RANDOMISATION: Method not reported

**Data Used**  
**Withdrawal:** Short Opiate Withdrawal Scale  
**Completion**

**Group 1 N= 19**  
**Opiate partial agonist:** buprenorphine with clonidine  
**Notes:** DROPOUTS: Buprenorphine = 10/100, clonidine = 50/100

**Group 2 N= 18**  
**Opiate partial agonist:** buprenorphine with clonidine

Limited reporting in conference abstract; some additional data obtained from Cochrane review (unpublished data)  
**Study quality:** 1+

---

### Study Type: RCT (randomised controlled trial)

**Study Description:** Cluster randomised  
**Setting:** Inpatient unit, Switzerland  
**Duration (days):** Mean 10  
**Setting:** Israel

**Data Used**  
**Completion**  
**Withdrawal:** Short Opiate Withdrawal Scale  
**Abstinence:** 1 month

**Group 1 N= 100**  
**Opiate partial agonist:** buprenorphine with clonidine

**Group 2 N= 100**  
**Alpha2 adrenergic agonist:** clonidine with naltrexone

**Notes:** DROPOUTS: Buprenorphine = 37/107, lofexidine = 56/103  
**Followup:** 1 month  
**Setting:** UK  
**Duration (days):** Mean 7  
**Blindness:** Double blind  
**Type of Analysis:** Per protocol  
**Study quality:** 1+

---

### Study Type: RCT (randomised controlled trial)

**Study Description:** No evidence of allocation concealment  
**Type of Analysis:** Per protocol  
**Blindness:** Double blind  
**Duration (days):** Mean 14  
**Followup:** None  
**Setting:** University hospital in Iran; unclear whether detox actually took place within hospital  
**Notes:** Randomisation procedure not reported  
**Info on Screening Process:** 617 screened, 136 excluded (repeat detoxifications [n=95], florid psychosis [n=1], researcher unavailability [n=2], unstable substance use [n=19], dihydrocodeine [n=19])

**Data Used**  
**Withdrawal:** Short Opiate Withdrawal Scale  
**Abstinence:** 1 month  
**Completion**

**Group 1 N= 107**  
**Opiate partial agonist:** buprenorphine with clonidine  
**Notes:** DROPOUTS: Buprenorphine =37/107, lofexidine = 56/103  
**Followup:** None  
**Setting:** University hospital in Iran; unclear whether detox actually took place within hospital  
**Duration (days):** Mean 14  
**Blindness:** Double blind  
**Type of Analysis:** Per protocol  
**Study quality:** 1+

---

### Study Type: RCT (randomised controlled trial)

**Study Description:** No evidence of allocation concealment  
**Type of Analysis:** Per protocol  
**Blindness:** Double blind  
**Duration (days):** Mean 14  
**Followup:** None  
**Setting:** University hospital in Iran; unclear whether detox actually took place within hospital  
**Notes:** Randomisation procedure not reported  
**Info on Screening Process:** 167 screened, 70 excluded (repeat detoxifications [n=95], florid psychosis [n=1], researcher unavailability [n=2], unstable substance use [n=19], dihydrocodeine [n=19])

**Data Used**  
**Withdrawal:** Short Opiate Withdrawal Scale  
**Completion**

**Group 1 N= 36**  
**Opiate agonist:** methadone - 15 mg per day methadone at entry, reduced by 15% per day to reach 0 at day 7. Placebo thereafter.  
**Symptomatic:** 0.3 mg / day clonidine, 10-30 mg / day oxazepam  
**Followup:** None  
**Setting:** University hospital in Iran; unclear whether detox actually took place within hospital  
**Duration (days):** Mean 14  
**Blindness:** Double blind  
**Type of Analysis:** Per protocol  
**Study quality:** 1+
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Description</th>
<th>Data</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAN1990</td>
<td>RCT (randomised controlled trial)</td>
<td>Per protocol</td>
<td>Withdrawal severity, Retention: duration in treatment</td>
<td>Primary Diagnosis: Daily opium use (equivalent to ≤15 mg methadone) Baseline: Methadone / tramadol Years of opiate dependence: 12.86 / 12.85 Short Opiate Withdrawal Scale (SOWS) score at entry: 11.97 / 10.28 Daily opium use: unknown</td>
</tr>
<tr>
<td>Group 1</td>
<td>N=30</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 1.05 mg / day - tapered over 11 days. Initial dose titrated on body weight and recent heroin use</td>
<td>Data Used: Withdrawal severity, Completion</td>
<td>Group 1</td>
</tr>
<tr>
<td>Group 2</td>
<td>N=30</td>
<td>Opiate agonist: methadone with inpatient. Mean dose 37.3 mg / day - tapered over 11 days. Initial dose titrated on body weight and recent heroin use Benzodiazepines as adjuncts as needed</td>
<td>Data Used: Withdrawal severity, Completion</td>
<td>Group 1</td>
</tr>
<tr>
<td>Group 3</td>
<td>N=30</td>
<td>Alpha2 adrenergic agonist: guanfacine with inpatient. Mean dose 3.58 mg / day - tapered over 11 days. Initial dose titrated on body weight and recent heroin use</td>
<td>Data Used: Withdrawal severity, Completion</td>
<td>Group 1</td>
</tr>
<tr>
<td>SAN1994</td>
<td>RCT (randomised controlled trial)</td>
<td>Allocation by pharmacy</td>
<td>Withdrawal: OWS (Opiate Withdrawal Syndrome), OWC (Opiate Withdrawal Checklist)</td>
<td>Data Used: Withdrawal severity, Completion</td>
</tr>
<tr>
<td>Group 2</td>
<td>N=26</td>
<td>Alpha2 adrenergic agonist: guanfacine with inpatient. Mean dose 4 mg - beginning on day 9</td>
<td>Data Used: Withdrawal severity, Completion</td>
<td>Group 1</td>
</tr>
<tr>
<td>Group 3</td>
<td>N=43</td>
<td>Alpha2 adrenergic agonist: guanfacine. Mean dose 3 mg - beginning from day 9</td>
<td>Data Used: Withdrawal severity, Completion</td>
<td>Group 1</td>
</tr>
<tr>
<td>SCHNEIDER2000</td>
<td>RCT (randomised controlled trial)</td>
<td>ITT</td>
<td>Completion</td>
<td>Data Used: Completion</td>
</tr>
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</table>

**Notes:** PRIMARY DIAGNOSIS: Heroin dependence Baseline: HIV+: 52%
<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>n= 26</th>
<th>Group 2 N= 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: ITT</td>
<td>Age: Mean 32</td>
<td>Opiate partial agonist: buprenorphine with inpatient - 3 mg per day for 7 days then tapered and ceased on day 11. Received 900 mg carbamazepine for 7 days then tapered and ceased on day 20.</td>
</tr>
<tr>
<td>Blindness: No mention</td>
<td>Sex: 22 males 4 females</td>
<td></td>
</tr>
<tr>
<td>Duration (days): Mean 13</td>
<td>Diagnosis: 100% opiate dependence by DSM-IV</td>
<td></td>
</tr>
<tr>
<td>Setting: Germany</td>
<td>Baseline: GROUPS: Buprenorphine / oxazepam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration opiate use: 11.9 (5.4) / 8.7 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Data Used</td>
<td>Withdrawal: Short Opiate Withdrawal Scale Completion</td>
<td></td>
</tr>
<tr>
<td>completion</td>
<td>Study quality 1+</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>n= 300</th>
<th>Group 1 N= 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Analysis: Per protocol</td>
<td>Age: Mean 30</td>
<td>Opiate partial agonist: buprenorphine with inpatient - 4 mg per day for 3 days then tapered to cease on day 10. Received 900 mg carbamazepine per day for 6 days then tapered to cease on day 14</td>
</tr>
<tr>
<td>Blindness: No mention</td>
<td>Sex: 210 males 90 females</td>
<td></td>
</tr>
<tr>
<td>Duration (days): Mean 1</td>
<td>Diagnosis: 100% opiate dependence by DSM-III-R</td>
<td></td>
</tr>
<tr>
<td>Followup: 1 month</td>
<td>Exclusions: - heroin consumption &lt; 100 mg / day - poor general health - lack of proof for high motivation - alcoholism with chronic consumption &gt; 100 g / day - probable or known pregnancy - acute infectious pathology - cachexia or terminal disease - probable or known allergy to study medications - bronchospasm that fails to respond to inhaled beta2 agonists - psychosis</td>
<td></td>
</tr>
<tr>
<td>Setting: Spain</td>
<td>Baseline: GROUPS: Methadone / buprenorphine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years of opiate misuse: 8.6 (6.8) / 10.5 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Data Used</td>
<td>Abstinence: 1 month Completion</td>
<td>Study quality 1++</td>
</tr>
<tr>
<td>withdrawal</td>
<td>Withdrawal: Wang Scale</td>
<td></td>
</tr>
<tr>
<td>Notes: No treatment comparisons given for completion and 1-month abstinence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DRUG MISUSE: OPIOID DETOXIFICATION

APPENDIX 15(a)
DRUG MISUSE: OPIOID DETOXIFICATION

**SHEARD2007**

| Study Type: RCT (randomised controlled trial) | n= 90
---|---
Blindness: Open | Age: Range 16-65
Duration (days): Mean 16 | Sex: no information
Followup: 6 months | Diagnosis: 100% opiate misuse
Setting: Prison in UK | Exclusions: - <18 years >65 years
Notes: RANDOMISATION: computer randomised | - negative urine for illicit opiates
CONCEALMENT OF ALLOCATION: opaque sealed envelopes | - remaining in custody for <28 days
| | - contraindications for buprenorphine or methadone
| | - co-existing acute medical conditions requiring emergency admission
| | - currently undergoing detox from other addictive drugs

**Data Used**
- Abstinence: 3 months
- Abstinence: endpoint

**Group 2 N= 150**
- Opiate antagonist: naloxone with inpatient
- Symptomatic with inpatient
- Anaesthetic: propofol with inpatient - As per light sedation group, but bolus infusion lasted only the time necessary to put the patient to sleep (usually 2-4min), maintenance sedation was started immediately thereafter
- Opiate antagonist: naltrexone with inpatient
- Alpha2 adrenergic agonist: clonidine with inpatient

**SORENSEN1982**

| Study Type: RCT (randomised controlled trial) | n= 61
---|---
Blindness: Double blind | Age: Mean 29
Duration (days): Mean 42 | Sex: all males
Setting: Outpatient detoxification clinic, San Francisco, US | Diagnosis: 100% opiate dependence by urinalysis
Notes: RANDOMISATION: Stratified by employment status | Exclusions: - age < 18
| | - no evidence of physical addiction to opiates
| | - life-threatening medical conditions
| | Notes: PRIMARY Diagnosis: Heroin dependence
| | ETHNICITY: 53% White, 38% Hispanic, 11% Other
| | Baseline: 33% employed, 57% arrested in past 2 years, 90% had previous treatment

**Data Used**
- Entry to further treatment: MMT
- Entry to further treatment Completion
- Abstinence: endpoint

**Data Not Used**
- Abstinence: 3 months

**Group 1 N= 42**
- Opiate partial agonist: buprenorphine with prison - reducing regimen of buprenorphine over a period less than 16 days at the discretion of the prescribing doctor

**Group 2 N= 48**
- Opiate agonist: dihydrocodeine with prison - reducing regimen of dihydrocodeine over a period less than 16 days at the discretion of the prescribing doctor

**Group 3 N= 13**
- Opiate agonist: LAAM - 3-week detox: 30mg on day 1; optional 10mg methadone on day 2 if showing withdrawal symptoms, 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling and referral

**Study quality 1+**
### TENNANT1975

**Study Type:** RCT (randomised controlled trial)

**Type of Analysis:** Per protocol

**Blindness:** Double blind

**Duration (days):** Mean 21

**Followup:** 1 month

**Setting:** Los Angeles, USA

**Notes:** RANDOMISATION: No details

<table>
<thead>
<tr>
<th>Group</th>
<th>N= 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiate agonist:</strong> methadone with outpatient</td>
<td>3-week detox: 30mg on day 1, raised to 40mg on day 2 if showing withdrawal symptoms; 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling, and referral</td>
</tr>
</tbody>
</table>

**Data Used**

- Entry to further treatment: MMT
- Opiate use
- Abstinence: 1 month
- Completion

**Notes:**
- Study quality 1+
- Data Used: Withdrawal severity
- Opiate use
- Retention: duration in treatment
- Completion
- Notes: 1-month and 6-month follow-ups

**Diagnosis:**

- Age: Mean 28
- Sex: 57 males 15 females
- 100% opiate dependence by clinical assessment

**Exclusions:**

- Age <18
- Notes: PRIMARY DIAGNOSIS: By history, needle marks, positive urine test and observation of withdrawal symptoms
- ETHNICITY: 53% White
- Baseline: GROUPS: Methadone / propoxyphene napsylate
- Years of heroin use: 7.8 / 9.1
- Months of daily heroin use: 8.8 / 7.0

### TENNANT1978

**Study Type:** RCT (randomised controlled trial)

**Study Description:** Double dummy - all participants received the same number of capsules

**Type of Analysis:** Per protocol

**Blindness:** Double blind

**Duration (days):** Mean 42

**Followup:** 6 months

**Setting:** California, USA

**Notes:** Randomisation procedures not reported

**Info on Screening Process:** 70 screened, 22 eligible and randomised

<table>
<thead>
<tr>
<th>Group</th>
<th>N= 36</th>
</tr>
</thead>
</table>
| **Opiate antagonist:** naltrexone - 0 mg day 1, 12 mg days 2-3, 25 mg day 4, 50 mg thereafter
| **Symptomatic:** Clonidine and other medications prescribed according to standard indications for opiate withdrawal when OOWS score >=5 |

**Data Used**

- Completion
- Withdrawal: OOWS (Objective Opiate Withdrawal)

**Notes:**
- Study quality 1+
- Study Type: RCT (randomised controlled trial)
- Type of Analysis: Per protocol
- Blindness: Double blind
- Duration (days): Range 4-8
- Setting: Residential research ward, Baltimore, USA
- Notes: Randomisation procedure not described

**Info on Screening Process:** 33 ineligible; 47 didn't complete screening evaluation so 60

<table>
<thead>
<tr>
<th>Group</th>
<th>N= 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiate agonist:</strong> methadone with outpatient</td>
<td>Mean dose tablet form - Starting dose 30 mg (15 mg in-clinic, 15 mg take-home) reduced by 5 mg every 5 days, down to 2.5 mg by day 35 through to day 42; tapered to 0 on day 43.</td>
</tr>
</tbody>
</table>

**Data Used**

- Withdrawal severity
- Opiate use
- Retention: duration in treatment
- Completion
- Notes: 1-month and 6-month follow-ups

**Diagnosis:**

- Age: Mean 37
- Sex: 15 males 7 females
- 100% opiate dependence by eligibility for/receipt of MMT

**Exclusions:**

- not on MMT for >=3 months, or not wishing to withdraw
- not declared 'above average' in psychosocial rehabilitation as judged by the referring MMT programme
- evidence of heroin or other drug misuse in past 30 days
- not stabilised on 30 mg methadone for at least 10 days
- any medical or psychiatric illness requiring psychoactive drug therapy

**Notes:** ETHNICITY: 82% White

**Baseline:** GROUPS: Methadone / propoxyphene napsylate

**Years of heroin use:** 16.0 / 13.6

**Months of methadone use:** 33.2 / 33.8

**Highest methadone dose (mg):** 78.3 / 86.0

### UMBRICH1999

**Study Type:** RCT (randomised controlled trial)

**Blindness:** Double blind

**Duration (days):** Range 4-8

**Setting:** Residential research ward, Baltimore, USA

**Notes:** Randomisation procedure not described

**Info on Screening Process:** 33 ineligible; 47 didn't complete screening evaluation so 60

<table>
<thead>
<tr>
<th>Group</th>
<th>N= 32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opiate antagonist:</strong> naltrexone - 0 mg day 1, 12 mg days 2-3, 25 mg day 4, 50 mg thereafter</td>
<td></td>
</tr>
</tbody>
</table>

**Data Used**

- Completion
- Withdrawal: OOWS (Objective Opiate Withdrawal)

**Notes:**
- Study quality 1+
- Study Type: RCT (randomised controlled trial)
- Type of Analysis: Per protocol
- Blindness: Double blind
- Duration (days): Range 4-8
- Setting: Residential research ward, Baltimore, USA
- Notes: Randomisation procedure not described

**Info on Screening Process:** 33 ineligible; 47 didn't complete screening evaluation so 60
### UMBRICHT2003

**Study Type:** RCT (randomised controlled trial)

**Study Description:** Double dummy design (all participants received oral and sublingual doses daily)

**Blindness:** Double blind

**Duration (days):** Mean 56

**Setting:** AIDS service US

**Notes:** RANDOMISATION: Method not reported

<table>
<thead>
<tr>
<th>N</th>
<th>Study Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Opiate antagonist: naltrexone - Placebo days 1-7, naltrexone 50 mg (maintenance dose) on day 8. Placebo contained 50 mg acetaminophen to mimic bitterness of naltrexone. Symptomatic - Clonidine and other medications prescribed according to standard indications for opiate withdrawal when OOWS score &gt;=5</td>
<td>Opiate partial agonist: buprenorphine - Sublingual solution. 12 mg day 1, 8 mg day 2, 4 mg day 3, 2 mg day 4. Placebo solution from days 5-8</td>
</tr>
<tr>
<td>26</td>
<td>Opiate agonist: methadone with inpatient - 3-day taper: 30 mg day 1, 20 mg day 2, 10 mg day 3</td>
<td>Opiate partial agonist: buprenorphine with inpatient - 3-day taper: 0.6 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3</td>
</tr>
<tr>
<td>16</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient - 3-day taper: 0.2 mg loading dose and 0.1 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient - 3-day taper: 0.2 mg loading dose and 0.1 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3</td>
</tr>
</tbody>
</table>

**Notes:** 95-100% African American

**Baseline:** Years of drug use = 18

**Data Used**

- Withdrawal: OOWS (Objective Opiate Withdrawal)
- Withdrawal: Short Opiate Withdrawal Scale Completion

**Type of Analysis:** ITT

**Study quality:** 1+

**Diagnosis:**

- Age: Mean 40
- Sex: 30 males 25 females
- Opiate dependence by urinalysis
- 100% HIV positive
- Exclusions: - not HIV seropositive - age <18 - no hospitalisation for an acute medical illness - alcohol dependence - acute psychosis or AIDS dementia - hypotension, bradycardia or coagulopathy - thrombocytopenia precluding intramuscular injections - undergoing MMT
- Notes: 95-100% African American
- Baseline: Years of drug use = 18

**WASHTON1980**

**Study Type:** RCT (randomised controlled trial)

**Study Description:** Double dummy design

**Blindness:** Double blind

**Duration (days):** Mean 10

**Setting:** USA

**Notes:** RANDOMISATION: Method not reported

<table>
<thead>
<tr>
<th>N</th>
<th>Study Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>Opiate agonist: methadone - 15-30 mg starting maintenance dose, reduced by 1 mg / day until 0 reached</td>
<td>Opiate agonist: methadone - 15-30 mg starting maintenance dose, reduced by 1 mg / day until 0 reached</td>
</tr>
<tr>
<td>13</td>
<td>Alpha2 adrenergic agonist: clonidine - Abrupt substitution of clonidine for methadone</td>
<td>Alpha2 adrenergic agonist: clonidine - Abrupt substitution of clonidine for methadone</td>
</tr>
</tbody>
</table>

**Notes:** RANDOMISATION: Method not reported

<table>
<thead>
<tr>
<th>N</th>
<th>Study Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>Opiate agonist: methadone with inpatient - 3-day taper: 30 mg day 1, 20 mg day 2, 10 mg day 3</td>
<td>Opiate partial agonist: buprenorphine with inpatient - 3-day taper: 0.6 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3</td>
</tr>
<tr>
<td>13</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient - 3-day taper: 0.2 mg loading dose and 0.1 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient - 3-day taper: 0.2 mg loading dose and 0.1 mg every 4 hours day 1, every 6 hours day 2, every 8 hours day 3</td>
</tr>
</tbody>
</table>

**Notes:** 100% opiate misuse by urinalysis

**Baseline:** Mean years of heroin use: 10

**Data Used**

- Completion

**Type of Analysis:** ITT

**Study quality:** 1+

**Diagnosis:**

- Age: Mean 31
- Sex: 22 males 4 females
- Opiate dependence
- Exclusions: Evidence of serious medical or psychiatric illness
- Baseline: Mean years of heroin use: 10

**WRIGHT2007A**

**Study Type:** RCT (randomised controlled trial)

**Study Description:** Allocation centrally performed and concealed in opaque sealed envelopes

**Type of Analysis:** ITT

<table>
<thead>
<tr>
<th>N</th>
<th>Study Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>Opiate partial agonist: buprenorphine with outpatient. Mean dose max 8 mg - Dispensed as either 8 mg, 2 mg or 0.4 mg sublingual tablet under daily supervision. Within standard regimen (max 8 mg/day; on days 2-3), but at discretion of prescribing doctors, who</td>
<td>Opiate partial agonist: buprenorphine - Sublingual solution. 12 mg day 1, 8 mg day 2, 4 mg day 3, 2 mg day 4. Placebo solution from days 5-8</td>
</tr>
<tr>
<td>28</td>
<td>Opiate partial agonist: buprenorphine - Sublingual solution. 12 mg day 1, 8 mg day 2, 4 mg day 3, 2 mg day 4. Placebo solution from days 5-8</td>
<td>Opiate partial agonist: buprenorphine - Sublingual solution. 12 mg day 1, 8 mg day 2, 4 mg day 3, 2 mg day 4. Placebo solution from days 5-8</td>
</tr>
</tbody>
</table>

**Notes:** Use of adjuncts and reasons for leaving study were reported; no follow-up outcomes

**Dropouts:** 24% placebo, 44% naltrexone

**Baseline:** Placebo / naltrexone

- Years of heroin use: 6.5 / 8.3
- Days of heroin use in past 30: 29 / 29
- Years of cocaine use: 3.6 / 4.7
- Days of cocaine use (past 30): 12 / 10
- $ on drugs past 30 days: 1180 / 930
- Injection drug use: 29% / 31%
- Previous treatment attempts: 1.0 / 0.8

**Data Used**

- Mortality
- Abstinence: 3 months
- Abstinence: endpoint

**Type of Analysis:** ITT

**Study quality:** 1+
Blindness: Open
Duration (days): Mean 15

Setting: 10 general practices in Leeds, UK
Notes: Randomisation by random block size, stratified by practice and concealed in sealed opaque envelopes. Used Excel RAND function.

Info on Screening Process: 60 randomised

**References of Included Studies**

<table>
<thead>
<tr>
<th>Reference ID</th>
<th>Reason for Exclusion</th>
</tr>
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<tbody>
<tr>
<td>AHMADI2004A</td>
<td>Maintenance study</td>
</tr>
<tr>
<td>AMASS1994</td>
<td>n &lt;10 per group</td>
</tr>
<tr>
<td>AMASS2004</td>
<td>Only data for treatment group provided</td>
</tr>
<tr>
<td>BEARN1998</td>
<td>Assignment not random - patient preference</td>
</tr>
<tr>
<td>BICKE1988</td>
<td>Not required outcomes</td>
</tr>
<tr>
<td>CAMI1985</td>
<td>Does not adequately address question</td>
</tr>
<tr>
<td>CAMI1992</td>
<td>Not assessing efficacy of detoxification treatments</td>
</tr>
<tr>
<td>DAWE1995</td>
<td>Small sample size</td>
</tr>
<tr>
<td>FINGERHOOD2001</td>
<td>Not RCT</td>
</tr>
<tr>
<td>HAMEED1997</td>
<td>n=20</td>
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<tr>
<td>HARTMANN1991</td>
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<tr>
<td>KOSTEN1984</td>
<td>No extractable outcomes</td>
</tr>
<tr>
<td>KOSTEN1985</td>
<td>No extractable data</td>
</tr>
<tr>
<td>KOSTEN1992A</td>
<td>No treatment comparison for withdrawal phase</td>
</tr>
<tr>
<td>KOURI1996</td>
<td>No relevant outcomes; n&lt;10 per group</td>
</tr>
<tr>
<td>KRABBE2003</td>
<td>Not randomised</td>
</tr>
<tr>
<td>ORESKOVICH2005</td>
<td>n&lt;10 per group</td>
</tr>
<tr>
<td>PINI1991</td>
<td>Small sample size</td>
</tr>
<tr>
<td>SEES2000A</td>
<td>Compares detoxification with maintenance - not relevant</td>
</tr>
<tr>
<td>SIGMON2004</td>
<td>n&lt;10 per group</td>
</tr>
<tr>
<td>WILSON1993</td>
<td>Not an RCT</td>
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</table>

**References of Excluded Studies**

<table>
<thead>
<tr>
<th>Reference ID</th>
<th>Reason for Exclusion</th>
</tr>
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<tbody>
<tr>
<td>AHMADI2004A</td>
<td>Maintenance study</td>
</tr>
<tr>
<td>AMASS1994</td>
<td>n &lt;10 per group</td>
</tr>
<tr>
<td>AMASS2004</td>
<td>Only data for treatment group provided</td>
</tr>
<tr>
<td>BEARN1998</td>
<td>Assignment not random - patient preference</td>
</tr>
<tr>
<td>BICKE1988</td>
<td>Not required outcomes</td>
</tr>
<tr>
<td>CAMI1985</td>
<td>Does not adequately address question</td>
</tr>
<tr>
<td>CAMI1992</td>
<td>Not assessing efficacy of detoxification treatments</td>
</tr>
<tr>
<td>DAWE1995</td>
<td>Small sample size</td>
</tr>
<tr>
<td>FINGERHOOD2001</td>
<td>Not RCT</td>
</tr>
<tr>
<td>HAMEED1997</td>
<td>n=20</td>
</tr>
<tr>
<td>HARTMANN1991</td>
<td>n=20</td>
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<tr>
<td>KOSTEN1984</td>
<td>No extractable outcomes</td>
</tr>
<tr>
<td>KOSTEN1985</td>
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<td>WILSON1993</td>
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**Characteristics of Excluded Studies**

<table>
<thead>
<tr>
<th>Reference ID</th>
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<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNOLDREED2005</td>
<td>(Published Data Only)</td>
<td>A comparison of rapid (opioid) detoxification with clonidine-assisted detoxification for heroin-dependent persons. Journal of Opioid Management, 1, 17-23.</td>
</tr>
</tbody>
</table>
CARNWATH1998 (Published Data Only)

CHESKIN1994 (Published Data Only)

COLLINS2005 (Published Data Only)

DE JONG2005 (Published Data Only)

DRUMMOND1989 (Published Data Only)

FAVRT2006 (Published Data Only)

GERRA1995 (Published Data Only)

GERRA2000 (Published Data Only)

GERRA2001 (Published Data Only)

GHODSE1994 (Published Data Only)

HOWELLS2002 (Published Data Only)

JANIRI1994 (Published Data Only)

JIANG1993 (Published Data Only)

JOHNSON1992 (Published Data Only)

KAHN1997 (Published Data Only)

KLEBER1985 (Published Data Only)

KRABBE2003 (Published Data Only)

LIN1997 (Published Data Only)
LING2005 (Published Data Only)

LINTZERIS2002 (Published Data Only)

MARSCH2005 (Published Data Only)

MCGREGOR2002 (Published Data Only)

NIGAM1993 (Published Data Only)

OCONNOR1997 (Published Data Only)

PETITJEAN2002 (Published Data Only)

PONIZOVSKY2006 (Published Data Only)

RAISTRICK2005 (Published Data Only)

SALEHI2006 (Published Data Only)

SAN1990 (Published Data Only)

SAN1994 (Published Data Only)

SCHNEIDER2000 (Published Data Only)

SEIFERT2002 (Published Data Only)


SEOANE1997 (Published Data Only)

SHEARD2007 (Unpublished and Published Data)
References of Excluded Studies

SORENSEN1982

TENNANT1975

TENNANT1978

UMBRICHT1999

UMBRICHT2003

WASHTON1980

WRIGHT2007A

References of Excluded Studies

AHMADI2004A

AMASS1994

AMASS2004

BEARN1998

BICKEL1988

CAMI1985

CAMI1992

DAWE1995

FINGERHOOD2001

HAMEEDI1997

HARTMANN1991
KOSTEN1984

KOSTEN1985

KOSTEN1992A

KOURI1996


ORESKOVICH2005

PINI1991

SEES2000A

SIGMON2004

WILSON1993

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## Characteristics of reviewed studies: Dosage of opioid detoxification

### Comparisons Included in this Clinical Question

<table>
<thead>
<tr>
<th>Exponential Versus Linear Dose Reduction</th>
<th>Full Information Versus Standard Information</th>
<th>High Versus Moderate Starting Dose</th>
<th>Variable Versus Fixed Dosage</th>
</tr>
</thead>
</table>

### Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Interventions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BANYS1994</strong></td>
<td>n= 38</td>
<td></td>
<td></td>
<td>Two patients from high-dose group could not tolerate full 80 mg dose and were analysed in low-dose group, and excluded from analysis subsequently Study quality 1+</td>
</tr>
<tr>
<td>Study Type: RCT (randomised controlled trial)</td>
<td>Age: Range 18-65</td>
<td>Data Used</td>
<td>Group 1 N= 19</td>
<td></td>
</tr>
<tr>
<td>Type of Analysis: Per protocol</td>
<td>Sex: 22 males 16 females</td>
<td>Urinalysis</td>
<td>Opiate agonist: methadone with outpatient - High-dose group: started on 30 mg, raised to 80 mg over 10 days, maintained until day 101, then tapered linearly during days 102-180</td>
<td></td>
</tr>
<tr>
<td>Blindness: Double blind</td>
<td>Diagnosis:</td>
<td>Withdrawal severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (days): Mean 180</td>
<td>- 100% opiate dependence by DSM-III-R</td>
<td>Retention: duration in treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: San Francisco, US</td>
<td>Exclusions: - age outside range 18-65</td>
<td>Notes: Twice weekly urine screens on random days; either test being positive marked as positive for that week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- no accessible veins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- pregnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- contraindications to high-dose methadone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- been on methadone in past 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- negative opiate or positive methadone urine screen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- &lt;3 objective signs of opiate withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline: Positive urinalysis for other drugs: 38% cocaine, 8% amphetamine, 11% benzodiazepine, 3% barbiturates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DAWE1991</strong></td>
<td>n= 39</td>
<td></td>
<td></td>
<td>Study quality 1+</td>
</tr>
<tr>
<td>Study Type: RCT (randomised controlled trial)</td>
<td>Age: Mean 26</td>
<td>Data Used</td>
<td>Group 1 N= 24</td>
<td></td>
</tr>
<tr>
<td>Study Description: Participants not told that they were being randomised to two withdrawal schedules</td>
<td>Sex: 28 males 11 females</td>
<td>Retention: duration in treatment</td>
<td>Opiate agonist: methadone with outpatient - Flexible dosage: Initial dose established as per fixed group, but thereafter participants could negotiate dose levels and rate of reduction. It was made clear that their aim was to reduce their dose to 0 within about 6 weeks. Otherwise as per fixed group</td>
<td></td>
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<tr>
<td>Blindness: Single blind</td>
<td>Diagnosis:</td>
<td>Completion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (days): Mean 70</td>
<td>- 100% opiate dependence by urinalysis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Setting: Outpatient detox in south London</td>
<td>Exclusions: - Pregnant</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Info on Screening Process: 82 eligible and randomised &gt; 39 attended first session</td>
<td>- Considered inappropriate on clinical grounds</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Baseline: Mean years of opiate use: 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age at first use: 19</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Administration: 38% IV, 53% inhaled, 9% IV and inhaled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sharing injecting equipment: 56% ever, 29% in past year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GREEN1988</strong></td>
<td>n= 30</td>
<td></td>
<td></td>
<td>Study Quality 1+</td>
</tr>
<tr>
<td>Study Type: RCT (randomised controlled trial)</td>
<td>Age: Mean 25 Range 19-35</td>
<td>Data Used</td>
<td>Group 1 N= 15</td>
<td></td>
</tr>
<tr>
<td>Study Description: No mention</td>
<td>Sex: 23 males 7 females</td>
<td>Completion</td>
<td>Opiate agonist: methadone with inpatient - 3 times daily oral methadone, linear reduction schedule. Given detailed withdrawal information which was not part of routine treatment, e.g. regarding length/intensity of symptoms they might experience; specific concerns or anxiety discussed and addressed</td>
<td></td>
</tr>
<tr>
<td>Blindness: Single blind</td>
<td>Diagnosis:</td>
<td>Withdrawal: OWS (Opiate Withdrawal Syndrome)</td>
<td></td>
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</tr>
<tr>
<td>Duration (days): Mean 21</td>
<td>- 100% opiate dependence by clinical assessment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Setting: Bethlem Royal Hospital, London</td>
<td>Exclusions: Not reported</td>
<td></td>
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<tr>
<td>Info on Screening Process: 35 admitted for detoxification - five excluded (three left study before start of detox, two failed to comply with form-filling) &gt; 30 randomised</td>
<td>Notes: PRIMARY DIAGNOSIS: 33/35 heroin, 2/35 prescribed methadone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Baseline: Mean years of opiate dependence: 6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References of Included Studies

BANYS1994  (Published Data Only)
DAWE1991

GREEN1988

STRAIN1999

STRANG1990

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### Characteristics of reviewed studies: Duration of opioid detoxification

#### Comparisons Included in this Clinical Question

<table>
<thead>
<tr>
<th>1 Week Versus 3 Weeks</th>
<th>Ultrarapid (&lt;=24 Hours) Versus Rapid (1-7 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENAY1981</td>
<td></td>
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<tr>
<td>SORENSEN1982</td>
<td></td>
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<tr>
<td>STITZER1984</td>
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#### Characteristics of Included Studies

<table>
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<tr>
<th>Methods</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Interventions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSADI2004</strong></td>
<td>n= 40</td>
<td>Data Used</td>
<td>Group 1 N= 20</td>
<td>Study quality 1++</td>
</tr>
<tr>
<td>Study Type: RCT (randomised controlled trial)</td>
<td>Age: Mean 32</td>
<td>Opiate partial agonist: buprenorphine with inpatient - 5 day taper: 2 x 1.5mg day 1, tapered to 2 x 0.3mg day 5.</td>
<td>Opiate partial agonist: buprenorphine with inpatient - Single sublingual dose on evening of day 1.</td>
<td></td>
</tr>
<tr>
<td>Type of Analysis: LOCF</td>
<td>Sex: 39 males 1 female</td>
<td>Withdrawal: OOWS (Objective Opiate Withdrawal)</td>
<td>Symptomatic with inpatient - As needed</td>
<td></td>
</tr>
<tr>
<td>Blindness: Double blind</td>
<td>Diagnosis: 100% opiate dependence by DSM-IV</td>
<td>Withdrawal: Short Opiate Withdrawal Scale Completion</td>
<td>Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed.</td>
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<tr>
<td>Duration (days): Mean 5</td>
<td>Exclusions: - &lt;18 years &gt;60 years</td>
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<td></td>
<td></td>
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<tr>
<td>Setting: Iran</td>
<td>- pregnancy or lactation</td>
<td>Alpha2 adrenergic agonist: clonidine with inpatient - As needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: RANDOMISATION: computer generated list of random numbers</td>
<td>- clinically unstable medical illness</td>
<td>Group 1 N= 37</td>
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</tr>
</tbody>
</table>

| **COLLINS2005** | n= 106 | Data Used | Group 1 N= 37 | Study quality 1++ |
| Study Type: RCT (randomised controlled trial) | Age: Mean 36 Range 21-50 | Opiate partial agonist: buprenorphine with inpatient - 24 hour taper: 4 x 1.5mg between 12pm and 6pm day 1, 4 x 1.5mg between 6am and 12pm day 2. | Opiate partial agonist: buprenorphine with inpatient - Induced at 12.5 mg on day 2, 25 mg on day 3, then increased to maintenance dose of 50 mg on subsequent days | |
| Study Description: Patients not blinded | Sex: 76 males 30 females | Withdrawal: OOWS (Objective Opiate Withdrawal) | Symptomatic with inpatient - Induced at 12.5 mg on day 2, 25 mg on day 3, then increased to maintenance dose of 50 mg on subsequent days | |
| Type of Analysis: ITT | Diagnosis: 100% opiate dependence by DSM-IV | Withdrawal: Subjective Opiate Withdrawal Scale Completion | | |
| Blindness: Single blind | Exclusions: - age outside 21-50 range | Retention: duration in treatment | Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed | |
| Duration (days): Mean 84 | - poor general health or acute medical illness | | Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy | |
| Setting: US | - DSM-IV criteria for dependence on alcohol or non-opioid drugs | | Opiate antagonist: naltrexone with inpatient - Induced at 12.5 mg on day 2, 25 mg on day 3, then increased to maintenance dose of 50 mg on subsequent days | |
| 3 days' inpatient phase followed by 12 weeks' outpatient phase | - pregnancy or lactation or failure to use adequate birth control | | Alpha2 adrenergic agonist: clonidine with inpatient - As needed | |
| Notes: RANDOMISATION: Blocks of 12 with computer-generated assignments | | | |
| ALLOCATION: Staff remained unaware of randomisation sequence | Info on Screening Process: 169 screened; 35 | | |
| | met exclusion criteria and 28 lost to follow-up or refused consent; 106 enrolled and randomised | | |
Baseline: (GROUPS: ultrarapid / buprenorphine / clonidine)
Heroin use (days in past 30): 30 / 29 / 29
Lifetime heroin use disorder (years): 7.6 / 7.4 / 6.4
Previous inpatient detoxification attempts: 1.74 / 1.59 / 1.21
Previous outpatient detoxification attempts: 0.17 / 0.11 / 0.29
Previous MMT: 0.66 / 0.57 / 0.53

Group 1 N= 137
Symptomatic with inpatient - As per ultrarapid group
Psychosocial: CRA (community reinforcement approach) with outpatient - As per ultrarapid group
Other hypnotics: zolpidem with outpatient - 0.5 mg three times a day
Alpha2 adrenergic agonist: clonidine with outpatient - Up to 0.2 mg every 4 hours (max 1.2 mg/day)

Group 2 N= 34
Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed
Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy
Opiate antagonist: naltrexone with outpatient - Initial 12.5 mg dose on day 6, followed by 25 mg next day and 50 mg maintenance dose on subsequent days
Alpha2 adrenergic agonist: clonidine with outpatient - As needed

Group 3 N= 35
Symptomatic with inpatient - As required: clonazepam, up to 2 mg every 8 hours; ketorolac, 30 mg intramuscularly every 6 hours; ondansetron, 8 mg orally every 8 hours or prochlorperazine, 10 mg orally/intramuscularly every 8 hours; octreotide, 100 mcg every 8 hours; and so on
Other hypnotics: zolpidem with outpatient - For residual symptoms: clonidine up to 0.1 mg three times a day, 10 mg zolpidem and 50 mg trazodone, as needed
Psychosocial: RP (relapse prevention) with outpatient - Twice weekly manual-guided psychotherapy
Anaesthetic: propofol with inpatient - 25-150 mcg/kg per min; anaesthesia maintained for 2-4 hours
Opiate antagonist: naltrexone with inpatient. Mean dose 50 mg - Induced on 50 mg then maintained throughout outpatient phase
Alpha2 adrenergic agonist: clonidine with inpatient - As needed, up to 0.2 mg every 4 hours (max 1.2 mg/day)

Study Type: RCT (randomised controlled trial)
Study Description: 7 days' inpatient treatment followed by 10 months' outpatient community reinforcement approach
Type of Analysis: ITT
Blindness: Open
Duration (days): Mean 300
Setting: Four addiction treatment centres in the Netherlands
Notes: RANDOMISATION: Centralised and computerised, in blocks of two
Info on Screening Process: 296 screened, 24 met exclusion criteria or refused consent; 272 enrolled and randomised
n= 272
Age: Mean 36
Sex: 223 males 49 females
Diagnosis: opiate dependence by DSM-IV
Exclusions: age <18
- no previous unsuccessful detox attempts
- lack of a non-opiate user in social network
- severe somatic or psychiatric disorders
- pregnancy
- AIDS
- contraindications to general anaesthesia
- cocaine use in past 48 hours
Baseline: (GROUPS: ultrarapid / no anaesthesia)
Years of heroin use: 12.0 / 12.1
Age first heroin use: 20.9 / 20.8

Data Used
Withdrawal: Subjective Opiate Withdrawal Scale
Urinalysis
Opiate use
Withdrawal: COWS (Clinical Opiate Withdrawal)
Abstinence: 1 month

Study quality: 1++
Previous detoxification attempts: 7.4 / 8.4
Heroin use past 30 days: 18.0 / 18.8
Methadone use past 30 days: 22.0 / 23.6

<table>
<thead>
<tr>
<th>Group 2</th>
<th>N=135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic with inpatient - All participants treated with same medications at same dosages: 8am: diclofenac, ondansetron, diazepam, transdermal nicotine (for smokers) Post-naltrexone: octreotide, ondansetron, butylscopolamine, diazepam; haloperidol and midazolam as necessary Anaesthetic: propofol with inpatient. Mean dose 5000 ng/ml - Anaesthesia induced on first signs of opiate withdrawal, using target controlled infusion method, and maintained for 4 hours Psychosocial: CRA (community reinforcement approach) with outpatient - 23 sessions over 10 months: 10 monitoring naltrexone compliance, addictive behaviours and craving; 13 working on drug-refusal behaviour, relational issues, problem solving, social skills training and craving management with accompanying non drug user Opiate antagonist: naltrexone with inpatient - Administered at 9 am to precipitate withdrawal. At the end of anaesthesia, 100 mg administered through orogastric tube. Continued on maintenance dose (50 mg) for 10 months Alpha2 adrenergic agonist: clonidine with inpatient - Administered at 9 am to prevent high blood pressure Post-naltrexone: 0.15 mg subcutaneously at five intervals over the day</td>
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</table>

<table>
<thead>
<tr>
<th>Group 1</th>
<th>N=34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial: individual therapy with outpatient - As per ultrarapid group Symptomatic with inpatient - Limited to one drug at one dosage per indication: loperamide 4 mg, tolperisone 150 mg, ondansetron 4 mg, zolpidem 10 mg, olanzapine 5 mg, paracetamol 500 mg Alpha2 adrenergic agonist: clonidine with inpatient - 0.600 mg/day for first 3 days, 0.300 mg on day 4, 0.225 mg on day 5, 0.150 mg on day 6 and 0.075 mg on day 7 (in divided 0.075 mg doses)</td>
<td></td>
</tr>
</tbody>
</table>

FAVRAT2006

Study Type: RCT (randomised controlled trial)
Study Description: Randomisation by pharmacist
Type of Analysis: ITT
Blindness: No mention
Duration (days): Range 1-7
Setting: Switzerland
Notes: RANDOMISATION: Computer-generated numbers
Info on Screening Process: 113 eligible, 43 refused to participate but agreed to be followed up; 70 randomised

n=70
Age: Mean 30
Sex: 54 males 16 females
Diagnosis: 100% opiate dependence by DSM-IV
Exclusions: - age <18
- alcohol, cocaine or benzodiazepine dependence, or positive urinalysis prior to starting treatment
- pregnancy
- known idiosyncratic reactions
- severe psychiatric comorbidity
- other serious medical conditions
Baseline: (Ultra-rapid / clonidine)
ASI (drug): 0.34 / 0.35

Data Used
ASI (Addiction Severity Index)
Completion
Abstinence: 12 months
Abstinence: 3 months
Notes: Completion defined as 3 days of retention in treatment for anaesthesia without drug consumption and 7 days for clonidine FOLLOW-UPS: At 3, 6 and 12 months

Study quality: 1**
### SENAY1981

<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>Setting: Chicago, US</th>
<th>Duration (days): Mean 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 72</td>
<td>Mean starting methadone dose: 20.6mg Polydrug use: 82% / 81% Mean time to first treatment episode: 23 months Mean length of past 'run' of drug use: 11.6 months</td>
<td></td>
</tr>
<tr>
<td>Age: Mean 25</td>
<td>Diagnosis: 100% opiate dependence by clinical assessment</td>
<td></td>
</tr>
<tr>
<td>Sex: 40 males 32 females</td>
<td>Exclusions: - Age &lt;18 - Poor general health - Eligibility for MMT (with &gt;2 years addiction history) - &lt;6 months IV heroin use, or no period of daily use =&gt;3 months - No objective clinical evidence of IV use (e.g. needle marks) - No history of withdrawal symptoms</td>
<td></td>
</tr>
<tr>
<td>Notes: ETHNICITY: 53% Black, 14% White, 7% Other Baseline: (GROUPS: 3-week / 12-week)</td>
<td></td>
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</tbody>
</table>

### SEOANE1997

<table>
<thead>
<tr>
<th>Study Type: RCT (randomised controlled trial)</th>
<th>Setting: Spain</th>
<th>Duration (days): Mean 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>n= 300</td>
<td>Diagnosis: 100% opiate dependence by DSM-III-R</td>
<td></td>
</tr>
<tr>
<td>Age: Mean 30</td>
<td>Exclusions: - heroin consumption &lt;100 mg / day - poor general health - lack of proof for high motivation - alcoholism with chronic consumption &gt; 100 g / day - probable or known pregnancy - acute infectious pathology - cachexia or terminal disease</td>
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</tr>
<tr>
<td>Sex: 210 males 90 females</td>
<td>Notes: RANDOMISATION: Computer-generated random number table Info on Screening Process: 359 screened, 47</td>
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</tbody>
</table>

### Data Used

#### SENAY1981
- Withdrawal severity
- Completion
- Abstinence: endpoint
- Retention: duration in treatment

#### SEOANE1997
- Abstinence: 1 month
- Completion
- Withdraw: Wang Scale
- Notes: No treatment comparisons given for completion and 1-month abstinence

### Group 1 (N= 35) & Group 2 (N= 37)
- Psychosocial: individual therapy - Intensive individual and group counselling
- Opiate antagonist: naltrexone with inpatient - Decreasing doses of naltrexone according to predetermined schedule for 21 days (with larger decrements at the beginning), followed by placebo for 69 days. Dose adjustment allowed during 1st week if experienced moderate or marked discomfort

### Study Quality
- 1++
- 1+
Anaesthetic: propofol with inpatient -
Initiation with bolus at 0.3mg/kg combined with bolus of midazolam at 0.04mg/kg.
Maintenance, for 6-8 hours, consisted of continuous infusion of propofol initially at 3mg/kg/hr, +/-10% previous dose as indicated, combined with midazolam at 0.10mg/kg/hr.

Opiate antagonist: naltrexone with inpatient.
Mean dose 50 mg - Administered via nasal-gastric probe after naloxone. Maintenance oral dose (50 mg) dispensed after discharge for 1 year.

Alpha2 adrenergic agonist: clonidine with inpatient.
Mean dose 3 mg / kg - Administered subcutaneously every four hours after sedation had begun.

Group 2 N= 150
Opiate antagonist: naltrexone with inpatient.
Symptomatic with inpatient.
Anaesthetic: propofol with inpatient - As per light sedation group, but bolus infusion lasted only the time necessary to put the patient to sleep (usually 2-4min); maintenance sedation was started immediately thereafter.

Opiate antagonist: naltrexone with inpatient.

Alpha2 adrenergic agonist: clonidine with inpatient.

---

<table>
<thead>
<tr>
<th>SORENSEN1982</th>
<th>Data Used</th>
<th>Data Not Used</th>
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<tbody>
<tr>
<td>Study Type: RCT (randomised controlled trial)</td>
<td>Entry to further treatment: MMT</td>
<td>Abstinence: 3 months</td>
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<tr>
<td>Blindness: Double blind</td>
<td>Entry to further treatment Completion</td>
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</tr>
<tr>
<td>Duration (days): Mean 42</td>
<td>Abstinence: endpoint</td>
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<tr>
<td>Setting: Outpatient detoxification clinic, San Francisco, US</td>
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<td></td>
</tr>
<tr>
<td>Notes: RANDOMISATION: Stratified by employment status</td>
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<td></td>
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<tr>
<td></td>
<td>n= 61</td>
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<tr>
<td></td>
<td>Age: Mean 29</td>
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<tr>
<td></td>
<td>Sex: all males</td>
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<td></td>
<td>Diagnosis:</td>
<td>100% opiate dependence by urinalysis</td>
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<td></td>
<td>Exclusions:</td>
<td>- age &lt; 18</td>
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<tr>
<td></td>
<td>- no evidence of physical addiction to opiates</td>
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<tr>
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<td>- life-threatening medical conditions</td>
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<tr>
<td>Notes: PRIMARY DIAGNOSIS: Heroin dependence</td>
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</tr>
<tr>
<td>ETHNICITY: 53% White, 36% Hispanic, 11% Other</td>
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<td></td>
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<tr>
<td>Baseline: 33% employed, 57% arrested in past 2 years, 90% had previous treatment</td>
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<table>
<thead>
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<th>Data Used</th>
<th>Data Not Used</th>
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<tr>
<td>Entry to further treatment: MMT</td>
<td>Abstinence: endpoint</td>
</tr>
<tr>
<td>Entry to further treatment Completion</td>
<td></td>
</tr>
<tr>
<td>Abstinence: endpoint</td>
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<table>
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<tr>
<th>Study quality 1+</th>
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</table>

Notes: PRIMARY DIAGNOSIS: Heroin dependence
ETHNICITY: 53% White, 36% Hispanic, 11% Other
Baseline: 33% employed, 57% arrested in past 2 years, 90% had previous treatment

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N=</th>
<th>Study</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>Opiate agonist: methadone with outpatient -</td>
<td>6-week detoxification: stabilisation at 40 mg for 3 weeks, weeks 4-6 gradually tapered to 0. Standard programme with health screening, limited counselling and referral</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>Opiate agonist: LAAM with outpatient -</td>
<td>6-week detoxification: stabilisation at 40 mg for 3 weeks, weeks 4-6 gradually tapered to 0. Standard programme with health screening, limited counselling and referral</td>
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<tr>
<td>3</td>
<td>13</td>
<td>Opiate agonist: LAAM - 3-week detox:</td>
<td>30mg on day 1; optional 10mg methadone on day 2 if showing withdrawal symptoms, 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling and referral</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>Opiate agonist: methadone with outpatient -</td>
<td>3-week detox: 30mg on day 1; raised to 40mg on day 2 if showing withdrawal symptoms; 40mg on days 3, 5 and 7, followed by gradual dose reduction to placebo on last 4 days. Standard programme with health screening, limited counselling, and referral</td>
</tr>
</tbody>
</table>

Notes: RANDOMISATION: Stratified by employment status
Setting: Outpatient detoxification clinic, San Francisco, US
Duration (days): Mean 42
Blindness: Double blind
Study Type: RCT (randomised controlled trial)

Notes: PRIMARY DIAGNOSIS: Heroin dependence
ETHNICITY: 53% White, 36% Hispanic, 11% Other
Baseline: 33% employed, 57% arrested in past 2 years, 90% had previous treatment

APPENDIX 15(a)
References of Included Studies

ASSAD12004 (Published Data Only)

COLLINS2005 (Published Data Only)

DEJONG2005 (Published Data Only)

FAVROT2006 (Published Data Only)

SENAY1981 (Published Data Only)

SEOVANE1997 (Published Data Only)

SOINES1982 (Published Data Only)

STITZER1984 (Published Data Only)

References of Excluded Studies

GOUREVITCH1999 (Published Data Only)

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Characteristics of reviewed studies: Efficacy of physical interventions

Comparisons Included in this Clinical Question
(Methadone + Acupuncture) Versus Methadone

ZENG2005

Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Interventions</th>
<th>Notes</th>
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<td>Study Type: RCT (randomised controlled trial)</td>
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<td>Data Used</td>
<td>Group 1 N= 35</td>
<td>Study quality 1+</td>
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<td>Blindness: No mention</td>
<td>Age: Mean 34</td>
<td>Withdrawal severity</td>
<td>Opiate agonist: methadone with inpatient - Received methadone once a day. Starting dose 1mg/kg then reduced daily by approx 20% until 1 mg on day 10 and zero dose on day 11</td>
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<td>Duration (days): Mean 10</td>
<td>Sex: 60 males 10 females</td>
<td>Completion</td>
<td>Acupuncture with inpatient - Received acupuncture once a day. Needles were retained for 30 minutes, during which they were manipulated three times</td>
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<tr>
<td>Setting: China, Drug Rehabilitation Centre</td>
<td>Diagnosis:</td>
<td>Notes: DROPOUTS: Methadone + acupuncture</td>
<td>Group 2 N= 35</td>
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<tr>
<td>Notes: RANDOMISATION: no mention of method used</td>
<td>100% opiate dependence by DSM-III-R</td>
<td>4/35 methadone = 9/35</td>
<td>Opiate agonist: methadone with inpatient - Received methadone once a day. Starting dose 1mg/kg then reduced daily by approx 20% until 1 mg on day 10 and zero dose on day 11</td>
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<tr>
<td>Exclusions: - &lt;18 &gt;50 years of age</td>
<td>Baseline: Methadone + acupuncture/methadone</td>
<td>Acupuncture with inpatient - Received acupuncture once a day. Needles were retained for 30 minutes, during which they were manipulated three times</td>
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<tr>
<td>- physical and psychiatric problems</td>
<td>Years of opiate use: 6.00(2.82)/6.23(2.93)</td>
<td>Years of opiate use: 6.00(2.82)/6.23(2.93)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References of Included Studies

ZENG2005

Published Data Only

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