Characteristics of reviewed studies: Efficacy of pharmacological interventions

Comparisons Included in this Clinical Question

(Opiate antagonist + anaesthesia) versus pharmacological with minimal sedation
ARNOLDREED2005
COLLINS2005
DEJONG2005
FAVRAT2006
KRABBE2003
MCGREGOR2002
SEOANE1997

Buprenorphine versus adrenergic agonist
CHESKIN1994
JANIRI1994
LING2005
LINTZERIS2002
MARSCH2005
NIGAM1993
OCONNOR1997
PONIZOVSKY2006
RAISTRICK2005
UMBRICHT2003

Buprenorphine versus dihydrocodeine
SHEARD2007
WRIGHT2007A

Buprenorphine versus methadone
JOHNSON1992
PETITJEAN2002
SEIFERT2002
UMBRICHT2003

Buprenorphine versus other pharmacological treatment
JANIRI1994
SCHNEIDER2000

Buprenorphine-naloxone versus adrenergic agonists
LING2005

Clonidine versus lofexidine
CARNWATH1998
GERRA2001
KAHN1997
LIN1997

Clonidine versus opiate antagonists
GERRA1995

Methadone versus (methadone + adrenergic agonist)
GHODSE1994
SAN1994

Methadone versus adrenergic agonist
BEARN1996
GERRA2000
HOWELLS2002
JIANG1993
KLEBER1985
SAN1990
UMBRICHT2003
WASHTON1980

Methadone versus other opiate agonist
SALEHI2006
SORENSEN1982
TENNANT1975
TENNANT1978

Methadone versus other pharmacological treatment
BEARN1996
DRUMMOND1989
HOWELLS2002
JOHNSON1992
KLEBER1985
TENNANT1975

Opiate antagonist versus no opiate antagonist
BESWICK2003A
GERRA1995
GERRA2000
OCONNOR1997
UMBRICHT1999

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ARNOLDREED2005 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Open Duration (days): Range 1-10	n= 80 Age: Mean 30 Range 16-50 Sex: 51 males 29 females Diagnosis: 100% opiate dependence by DSM-IV	**Data Used** Abstinence: 1 month Completion Withdrawal severity	**Group 1 N= 41** 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)	Study quality: 1+

Followup: 4 weeks Setting: Perth, Australia Notes: Randomisation: No details reported Info on Screening Process: Not mentioned	Exclusions: - Enrolled in any other opiate treatment research project - Pregnant - Unable to complete study protocol, for example due to pending incarceration - History of adverse reactions to study medications - Medical conditions potentially exacerbated by opiates - Major psychiatric condition that would preclude informed consent Notes: PRIMARY DRUG: Heroin. 6.2% also used other opioids in addition to heroin Baseline: 66% used heroin for >=5 years, 47% daily for >=5 years Past month other substance use: 64% cannabis, 51% alcohol, 45% tranqulisers, 26% amphetamines, 1% cocaine		Opiate antagonist: naltrexone - 20-30 min after IV protocol, oral doses of 4, 8, 15 and 23mg naltrexone at 30 min intervals Symptomatic - Subcutaneous octreotide (0.1mg) and IV ondansetron (2mg) premedication; also oral flunitrazepam depending level of opioid use prior to treatment Midazolam hydrocholride during IV detox protocol depending on level of arousal/discomfort experienced **Group 2 N= 39** Alpha2 adrenergic agonist: clonidine. Mean dose 75-150 micrograms - 75-150 micrograms oral clonidine (reviewed daily), over 5-7 days for inpatient setting or 10 days for outpatient setting Symptomatic - 10-20mg temazepam, additional medications (for example hyosine butylbromide, quinine bisulphate, metacloprimide hydrochloride) at doses indicated for symptomatic relief	
BEARN1996 Study Type: RCT (randomised controlled trial) Study Description: Double dummy design Blindness: Double blind Duration (days): Mean 20 Setting: London, UK Notes: Randomisation procedure not reported Info on Screening Process: 86 referred and enrolled	n= 86 Age: Mean 32 Range 18-62 Sex: 69 males 17 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - major psychiatric or physical illness - pregnant - taking neuroleptic or antidepressant medication Notes: 37/86 were using benzodiazepines at admission Baseline: Years of heroin misuse: 10.5	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 42** Alpha2 adrenergic agonist: lofexidine with inpatient - 0.6 mg per day until day 4, maintained at 2 mg per day for 3 days, then tapered over 3 days Benzodiazepine: diazepam with inpatient - For those also dependent on benzodiazepines: 3 days' stabilisation then tapered over 21 days Placebo - Placebo syrup **Group 2 N= 44** Opiate agonist: methadone with inpatient - Variable initial dose, tapered over 10 days at a linear rate Placebo - Placebo tablet Benzodiazepine: diazepam with inpatient - For those also dependent on benzodiazepines: 3 days' stabilisation then tapered over 21 days	Both groups underwent 3-day stabilisation period during which methadone dose was titrated to subjective and observed opiate withdrawal symptoms Study quality 1+
BESWICK2003A Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol for follow-up analyses Blindness: Double blind Duration (days): Mean 6 Followup: 6 months Setting: Specialist drug dependency units in London Info on Screening Process: 220 invited; 91 randomised and 46 assigned to methadone group	n= 91 Age: Mean 32 Range 18-56 Sex: 105 males 32 females Diagnosis: 100% opiate dependence by ICD-10 Exclusions: - on >100 mg MMT - history of epilepsy - severe liver disease - pregnancy - psychotropic medication - alcohol dependence Notes: ETHNICITY: 89% White Baseline: 'No differences between the randomised groups' - but did not make clear what differences there might have	**Data Used** Opiate use Relapse Abstinence: 1 month Completion Notes: DROPOUTS: 27% lofexidine + naloxone, 22% lofexidine + placebo	**Group 1 N= 45** Alpha2 adrenergic agonist: lofexidine with inpatient: drug dependence unit (DDU) - As described in Bearn (1996): 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 Opiate antagonist: naloxone. Mean dose 0.8 mg - 0.8 mg naloxone solution days 3 6	Patients who refused randomisation or met exclusion criteria were retained in a non-randomised methadone control group (not described here) Study quality: 1+

	been		**Group 2 N= 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	
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	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%	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Withdrawal severity Completion	**Group 1 N= 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 **Group 2 N= 24** Alpha2 adrenergic agonist: clonidine - As per lofexidine except with 0.1 mg clonidine capsules	Study quality 1+
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	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	**Data Used** Withdrawal severity Completion	**Group 1 N= 13** Alpha2 adrenergic agonist: clonidine with inpatient - Total 2.7 mg oral in divided doses, three times daily over 3 days Placebo - 1 ml sublingual solution three times daily for 18 days **Group 2 N= 12** 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	Additional symptomatic medications available for specific symptoms, but were not requested by any participant throughout study Study quality 1++
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	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	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Subjective Opiate Withdrawal Scale Completion Retention: duration in treatment	**Group 1 N= 37** Opiate partial agonist: buprenorphine with inpatient. Mean dose 8 mg - Single sublingual dose on evening of day 1 Symptomatic with inpatient - As needed	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/L - 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++

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	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 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	Opiate use Withdrawal: COWS (Clinical Opiate Withdrawal) Abstinence: 1 month	Psychosocial: CRA (community reinforcement apprch) with outpatient - As per ultrarapid group Opiate antagonist: naltrexone with inpatient - 12.5 mg on day 1, 25 mg on day 2, 50 mg on day 3 Alpha2 adrenergic agonist: clonidine with inpatient - As per ultrarapid group **Group 2 N= 135** Symptomatic with inpatient - All participants treated with same medications at same dosages: 8am: diclofenac, ondansetron, diazepam, transdermal nicotine (for smokers) Post-naltrexone: octreotride, 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 apprch) 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. Mean dose 0.3 mg - Administered at 9 am to prevent high blood pressure Post-naltrexone: 0.15 mg subcutaneously at five intervals over the day	
DRUMMOND1989 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 14 Setting: Inpatient detoxification at three Glasgow hospitals Notes: RANDOMISATION: Participants randomly assigned to one of two groups. Pharmacy department disguised preparations. Info on Screening Process: 33 screened, 9 excluded, 24 met inclusion criteria	n= 24 Age: Mean 25 Sex: 13 males 11 females Diagnosis: 85% opiate dependence by urinalysis Notes: Primary drug: heroin 3 participants took benzodiazepine on a regular basis 13 participants reported occasional use of cannabis Baseline: Mean duration of drug use: 4.7 years (SD = 2.2) Mean daily dose of heroin 0.8 g (SD = 0.6)	**Data Used** Urinalysis Withdrawal: Subjective Opiate Withdrawal Scale Withdrawal: OOWS (Objective Opiate Withdrawal)	**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 **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	Study quality 1+
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 retentior 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 naltrexon Alpha2 adrenergic agonist: clonidine with inpatient - During anaesthesia, clonidine or lidocaine used to deepen anaesthesia and control withdrawal signs	Study quality: 1++
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	n= 152 Age: Range 18-32 Sex: 125 males 27 females Diagnosis: 100% opiate misuse by DSM-III-R Exclusions: - cirrhosis - psychiatric symptoms (Minnesota Multiphasic Personality Inventory [MMPI]) - immune system depression Notes: PRIMARY DIAGNOSIS: Abused heroin for 24-48 months Baseline: None reported	**Data Used** Withdrawal severity Urinalysis Completion Notes: DROPOUTS: 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+

			Group 3 N= 58 Psychosocial: individual therapy - Psychotherapy -- no further details Opiate antagonist: naloxone with outpatient - 0.2 mg intravenous naloxone on day 2, 0.4 mg twice daily over next 2 days Placebo with outpatient - Orally from day Opiate antagonist: naltrexone with outpatient. Mean dose 50 mg - Maintained from day 2 for 3 months Alpha2 adrenergic agonist: clonidine with outpatient - As per clonidine group **Group 4 N= 19** Psychosocial: individual therapy - Psychotherapy -- no further details Placebo with outpatient - Intravenous saline for 4 days, and oral placebo from day 2 for 3 months	
GERRA2000 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: No mention Duration (days): Mean 10 Followup: 6 months Setting: Italy	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 11pm 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, adminstered once daily in syrup	Intravenous heroin administered to all participants until 12 hours before treatment All participants admitted to naltrexone maintenance post treatment Study quality 1+
GERRA2001 Study Type: RCT (randomised controlled trial) Blindness: Single blind Duration (days): Mean 3 Setting: Italy Info on Screening Process: All those asked gave consent and were randomised	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%, lofexidine 10%	**Group 1 N= 20** Alpha2 adrenergic agonist: lofexidine - 0.2 mg tablets three times in the morning and three times in the afternoon for 3 days. On day 2, additional tablet at 9pm and at 12pm. 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+

	- renal disease - other chronic medical disorders - recent significant weight loss or obesity - endocrinopathy - immunodeficiency Notes: PRIMARY DIAGNOSIS: Heroin Baseline: Heroin use: 3-6 years, 1.5-2.0 g street heroin daily		**Group 2 N= 20** 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.	
GHODSE1994 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 14 Followup: 4 weeks Setting: Drug dependency unit in UK	n= 86 Age: Range 18-47 Sex: 59 males 27 females Diagnosis: 100% opiate dependence by eligibility for/receipt of MMT Exclusions: Cardiovascular or other disorder which might contraindicate clonidine Notes: PRIMARY DIAGNOSIS: Receiving a stable regime of MMT	**Data Used** Withdrawal severity Completion Notes: DROPOUTS: 18/42 clonidine, 14/44 placebo failed to complete detoxification	**Group 1 N= 42** Opiate agonist: methadone - Initial dose 40 mg, reduced by 5 mg every other day down to 0 Alpha2 adrenergic agonist: clonidine with inpatient. Mean dose 0.1 mg tablets - Divided doses, initially 0.2 mg daily, increasing by 0.1 mg daily until maximum tolerated dose or 1.2 mg reached. Dose reduced by 0.1 mg if a blood pressure reading < 90/60 mm Hg recorded. **Group 2 N= 44** Opiate agonist: methadone - Initial dose 40 mg, reduced by 5 mg every other day down to 0 Placebo with inpatient - Administered identically to clonidine	Study quality 1+
HOWELLS2002 Study Type: RCT (randomised controlled trial) Study Description: Allocation by pharmacist, who oversaw blinding 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 Info on Screening Process: 76 eligible, 2 withdrew consent and so 74 randomised. 6 mistakenly entered for detoxification twice; 68 included in analysis.	n= 68 Age: Mean 31 Range 22-49 Sex: all males Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age >=55 - serious psychiatric (including psychotic depression and schizophrenia) or physical illness Notes: PRIMARY DIAGNOSIS: Opiate use confirmed by urinalysis Baseline: GROUPS: methadone / lofexidine Years from first use of heroin: 9.5 / 8.8 Use of other drugs in past month: benzodiazepines 68%, amphetamine 5%, non-prescribed methadone 5%, cocaine 1%, crack cocaine 2%	**Data Used** Withdrawal: WPS (Withdrawal Problems Scale) Withdrawal: Short Opiate Withdrawal Scale SDS (Severity of Dependence Scale) Withdrawal severity Completion	**Group 1 N= 36** 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 Placebo - Placebo peach coloured tablets, twice daily for 10 days **Group 2 N= 32** Alpha2 adrenergic agonist: lofexidine with prison - 0.6 mg day 1, increased by 0.4 mg per day until day 4, 2 mg per day for 3 days, next 3 days tapered by 0.4 mg per day Placebo - Placebo green syrup, twice daily for 10 days	Study quality 1++
JANIRI1994 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 6 Setting: Italy Notes: RANDOMISATION: not reported	n= 39 Age: Mean 26 Sex: 23 males 16 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - polydrug use	**Data Used** Completion	**Group 1 N= 13** Opiate partial agonist: buprenorphine with inpatient - Intramuscularly: 0.9 mg days 1 and 2, 0.45 mg day 3, 0.15 mg day 4 **Group 2 N= 13** Alpha2 adrenergic agonist: clonidine with inpatient - Intramuscularly: 0.3-0.9 mg per day for 6 days	Study quality 1+

	- not been on MMT for >=1 year - severe complicating medical conditions, or psychiatric disorders impairing volition and reality testing - body weight abnormalities - not highly motivated toward abstinence Notes: PRIMARY DRUG: 17/39 participants were using heroin on top of methadone Baseline: Mean duration of opiate dependence = 7.5 (3.6) years, duration in MMT = 3.4 (2.4) years 41% HIV+		**Group 3 N= 13** Lefetamine with inpatient - Intramuscularly: 60-240 mg per day for 6 days	
JIANG1993 Study Type: RCT (randomised controlled trial) Blindness: No mention Duration (days): Mean 12 Setting: Five rehabilitation centres in China Notes: RANDOMISATION: No details	n= 200 Age: Mean 25 Sex: 155 males 45 females Diagnosis: opiate dependence by DSM-III-R Exclusions: Concurrent medical conditions, infectious diseases or mental illness Notes: REFERRALS: Not all participants entered voluntarily Baseline: GROUPS: Methadone / clonidine Using orally only: 80% / 67%	**Data Used** Withdrawal severity Hamilton Anxiety Rating Scale Notes: DROPOUTS: None reported Withdrawal outcomes were observer-rated; not extracted	**Group 1 N= 100** Opiate agonist: methadone with outpatient. Mean dose max 21.6 mg - Max dose on days 1-2, then tapered and ceased after day 12; dose titrated against withdrawal and side effects **Group 2 N= 100** Alpha2 adrenergic agonist: clonidine with inpatient - 'Sufficient' dose days 1-4, tapered days 5-8, ceased after day 11; dose titrated against withdrawal and side effects	Report in Chinese; data extracted by Ryan Li Study quality 1+
JOHNSON1992 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 180 Setting: US	n= 162 Age: Mean 33 Sex: 113 males 49 females Diagnosis: Exclusions: - <21 or >50 years of age - self-reported duration <4 months - <2 episodes of heroin use per day - self-reported daily value of use <$50 per day - <4 on self-reported level of withdrawal on a 9-point scale 12 hours after last heroin dose - <2/3 urine samples positive for opiates (not including methadone) - severe psychiatric condition 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)	**Data Used** Completion Abstinence: endpoint Notes: DROPOUTS: Buprenorphine = 70%, methadone 60 mg = 80%, methadone 20 mg = 94% Abstinence assessed by total number of negativ urine samples -- not used	**Group 1 N= 54** Opiate agonist: methadone with outpatient - Maintained on 60 mg methadone for 17 weeks followed by 10 weeks of detoxification. Gradual detoxification carried out by decreasing dosage by same percentage for a given week of the study **Group 2 N= 53** Opiate partial agonist: buprenorphine with outpatient - Maintained on 6 mg buprenorphine for 17 weeks followed by 10 weeks of detoxification. Gradual detoxification carried out by decreasing dosage by same percentage for a given week of the study **Group 3 N= 55** Opiate agonist: methadone with outpatient - Maintained on 20 mg methadone for 17 weeks followed by 10 weeks of detoxification. Gradual detoxification carried out by decreasing dosage by same percentage for a given week of the study	No discussion of whether opiate dependent Study quality 1+
KAHN1997 Study Type: RCT (randomised controlled trial) Study Description: Patients blind to methadone cessation on day 3 Blindness: Double blind Duration (days): Mean 18	n= 28 Age: No information Sex: 19 males 9 females Diagnosis: 100% opiate dependence Exclusions: - not stabilised on methadone 3-4 days prior to study	**Data Used** Withdrawal severity	**Group 1 N= 14** Alpha2 adrenergic agonist: lofexidine - 0.4 mg rising to max 1.8 mg per day, tapered over days 15-18; lorazepam as adjunct as appropriate Opiate agonist: methadone - Substituted with placebo on day 3; placebo stopped on day 14	Study quality 1+

	- alcohol dependence Notes: PRIMARY DIAGNOSIS: by history and urine screen		**Group 2 N= 14** Opiate agonist: methadone - Substituted with placebo on day 3; placebo stopped on day 14 Alpha2 adrenergic agonist: clonidine - 0.2 mg rising to max 0.9 mg per day, tapered over days 15-18; lorazepam as adjunct as appropriate	
KLEBER1985 Study Type: RCT (randomised controlled trial) Study Description: Double dummy design; blinding 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	n= 49 Age: Mean 29 Sex: 37 males 12 females Diagnosis: 100% opiate dependence by eligibility for/receipt of MMT 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	**Data Used** ASI (Addiction Severity Index) Withdrawal severity BDI (Beck Depression Inventory) Completion	**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+
KRABBE2003 Study Type: Non-randomised controlled trial Type of Analysis: ITT (dropouts treated as nonabstinent) Blindness: Open Duration (days): Range 4-20 Followup: 3 months Setting: Hospital in the Netherlands Notes: RANDOMISATION: Consecutive assignment (first 15 to ultrarapid group) - potential bias Info on Screening Process: 30 enrolled	n= 30 Age: Mean 33 Sex: 24 males 6 females Diagnosis: 100% opiate dependence by DSM-IV 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 Baseline: (GROUPS: Ultrarapid / Methadone) Years of heroin use: 11.1 / 6.3 Years of methadone use: 9.4 / 3.5 Methadone dose (mg/day): 58.4 / 38.5 Number of previous treatments: 9.6 / 6.9	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Subjective Opiate Withdrawal Scale Abstinence: 1 month Completion Abstinence: 3 months Notes: FOLLOWUPS: Monthly for 3 months DROPOUTS: 60% methadone, 0% ultrarapid	**Group 1 N= 15** Opiate agonist: methadone with inpatient - Tapered to 0 in 1-2 weeks Opiate antagonist: naltrexone with outpatient - Approx. 6 days after last dose of methadone, 50mg maintenance dose administered daily under supervision **Group 2 N= 15** Symptomatic - Range of adjunct medications after 2nd naltrexone dose (e.g. anti-emetics, anti-diuretics, clonidine Anaesthetic: propofol with inpatient - Naltrexone 100mg oral + 5mg tropisetron IV. Propofol anaesthesia induced when withdrawal evident. Mechanical ventilation. 0.8mg naloxone test every 20 min until no withdrawal, then 100mg naltrexone via nasogastric tube. Opiate antagonist: naltrexone with outpatient. Mean dose 50mg - After discharge, maintenance dose given for 3 months	
LIN1997				

Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 9 Setting: Taiwan Notes: RANDOMISATION: No details	n= 80 Age: Mean 32 Sex: 65 males 15 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: None specified Notes: PRIMARY DIAGNOSIS: Street heroin ETHNICITY: Chinese Baseline: Years of heroin use: 4.2 lofexidine / 4.6 clonidine Estimated pure heroin used daily, mg: 315 Administration route: 88% injection, 12% smoking Using methamphetamine: 14/80	**Data Used** Withdrawal severity Retention: duration in treatment	**Group 1 N= 40** 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 **Group 2 N= 40** 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	Study quality 1+
LING2005 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: Open Duration (days): Mean 13 Setting: Six inpatient and six outpatient community-based treatment programmes in US	n= 344 Age: Mean 38 Sex: 234 males 110 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - <18 years - serious medical or psychiatric condition - allergy or sensitivity to study medications - pregnancy Baseline: Years of use: inpatient sample = 9, outpatient sample = 7	**Data Used** Withdrawal: COWS (Clinical Opiate Withdrawal) Completion	**Group 1 N= 77** Opiate partial agonist: buprenorphine-naloxone with inpatient - Sublingually: 8 mg buprenorphine/2 mg naloxone day 1, increasing in stepwise manner to 16 mg buprenorphine/4 mg naloxone day 3, and tapering to 2 mg buprenorphine/0.05 mg naloxone by days 12/13 **Group 2 N= 157** Opiate partial agonist: buprenorphine-naloxone with outpatient - Sublingually: 8 mg buprenorphine/2 mg naloxone day 1, increasing in stepwise manner to 16 mg buprenorphine/4 mg naloxone day 3, and tapering to 2 mg buprenorphine/0.05 mg naloxone by days 12/13 **Group 3 N= 74** Alpha2 adrenergic agonist: clonidine with outpatient - Oral & 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 **Group 4 N= 36** Alpha2 adrenergic agonist: clonidine with inpatient - Oral & 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	Study quality 1+
LINTZERIS2002 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: Open Duration (days): Mean 8 Followup: 4 weeks	n= 114 Age: Mean 30 Sex: 74 males 40 females Diagnosis: 100% opiate dependence by DSM-IV	**Data Used** Entry to further treatment: naltrexone maintenance Withdrawal: Short Opiate Withdrawal Scale Opiate use Completion	**Group 1 N= 58** Opiate partial agonist: buprenorphine with outpatient. Mean dose 6 mg / day - Supervised single daily dose of sublingua tablet, adjusted to symptoms and ceased on day 5	Both groups received counselling during treatment, naltrexone or counselling offered as aftercare Study quality 1++

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)	Notes: DROPOUTS: Buprenorphine = 8/58, clonidine = 32/56	**Group 2 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	
MARSCH2005 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 28 Setting: US	n= 36 Age: Mean 17 Range 13-18 Sex: 14 males 22 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - pregnancy - active significant psychiatric disorder - significant medical illness (e.g. cardiovascular) Notes: Adolescent sample Baseline: GROUPS: Buprenorphine / clonidine Days' use in last 30: 27.7 (3.0) / 27.7 (4.8)	**Data Used** Completion Abstinence: endpoint Notes: Abstinence measured as number of negative urine samples -- not used	**Group 1 N= 18** Opiate partial agonist: buprenorphine with outpatient - Sublingually: <70 kg and 1-3 bags of heroin starting dose 6 mg, >=70 kg and >3 bags of heroin starting dose 8 mg day 1. Buprenorphine reduced by 2 mg every 7 days. All participants received four tablets daily. Placebo with outpatient - Placebo clonidine patches throughout the study which paralleled timeline administration of active clonidine patches in clonidine group **Group 2 N= 18** Placebo with outpatient - All received placebo buprenorphine tablets throughout study paralled timeline of administrationof active buprenorphine doses in the buprenorphine group Alpha2 adrenergic agonist: clonidine with outpatient - Transdermal patches: single patch 0.1 mg day 1, second patch of 0.1 mg added on day 2 worn for days 2-6, optional third patch added for days 4-6. All patches replaced with 0.2 mg dose, day 14 replaced with 0.1 mg, day 21 replaced with 0 mg (placebo patch)	All participants were offered CM and community reinforcement approach (CRA) Study quality: 1++
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.	n= 101 Age: Mean 31 Sex: 61 males 40 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - unable to provide details of contact person - currently enrolled in other research - MMT in past 3 months - pregnant, lactating or planning to become pregnant over next 12 months - contraindications to naltrexone - HIV+ - history of adverse events with study medications - medical conditions potentially exacerbated by heroin withdrawal Notes: PRIMARY DIAGNOSIS: Heroin Baseline: GROUPS: Clonidine / ultrarapid Mean severity of dependence: 11.5 / 11.7 Mean age at first heroin use: 21.2 / 21.3	**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)	**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: naloxone with inpatient. Mean dose total 10 or 12 mg - Intravenous naloxone administered in four or five bolus doses at 30-min intervals Symptomatic with inpatient - Octreotide for relieving gastrointestinal withdrawal Anaesthetic: propofol with inpatient - Maintained for 4 hours Opiate antagonist: naltrexone with inpatient. Mean dose 50 mg - When OOWS <=5 following anaesthesia and naloxone challenge, 50 mg naltrexone given orally	Study quality 1++

	Mean years of heroin use: 9.7 / 10.2 Mean frequency of heroin use in past month: 87.4 / 86.8		Alpha2 adrenergic agonist: clonidine with inpatient **Group 2 N= 50** Psychosocial: individual therapy with outpatient - For 9 months following hospital discharge: monthy naltrexone dispensing and counselling (based on METand CBT principles) Symptomatic with inpatient - Following standard clinical practice: included diazepam, orphenadrine, paracetamol, temazepam, naproxen, metoclopramide, buscopan and vitamins Alpha2 adrenergic agonist: clonidine with inpatient - Following standard clinical practice	
NIGAM1993 Study Type: RCT (randomised controlled trial) Blindness: No mention Duration (days): Mean 10 Setting: India Notes: RANDOMISATION: Method not reported	n= 44 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: Polydrug use Baseline: Duration of heroin use = 4-5 years	**Data Used** Withdrawal: Subjective Opiate Withdrawal Scale Completion	**Group 1 N= 22** Alpha2 adrenergic agonist: clonidine with inpatient - Oral: initial dose 0.3 mg / day with maximum of 0.9 mg / day in three divided doses. Nitrazepam as adjunct medication **Group 2 N= 22** Opiate partial agonist: buprenorphine with inpatient - Sublingual tablet: initial dose 0.6 mg / day with maximum 1.2 mg / day in 3 divided doses. Nitrazepam as adjunct medication	Heroin users = 90%, opium users = 10% Study quality 1+
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	n= 162 Age: Range 18-50 Sex: 115 males 51 females Diagnosis: 100% opiate dependence Exclusions: - age range outside 18-50 years - not enrolled in a drug treatment programme - lack of sufficient social support (e.g. transportation, residence) - pregnancy - reactions to study medications or contraindications to detoxification - contraindications to naltrexone (e.g. severe chronic hepatitis or pain) - psychiatric conditions necessitating intensive services (e.g. suicidal depression) Baseline: GROUPS: Clonidine / clonidine + naltrexone / buprenorphine Age at first heroin use: 21.9 / 23.0 / 22.1 Years of heroin use: 8.9 / 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	**Data Used** Withdrawal severity Completion	**Group 1 N= 55** Alpha2 adrenergic agonist: clonidine - 0.1 0.2 mg every 4 hours as needed to control withdrawal symptoms on days 1-7 Opiate antagonist: naltrexone - Full blocking dose of 50 mg on day 8 Placebo - Placebos for buprenorphine **Group 2 N= 54** Alpha2 adrenergic agonist: clonidine - As per clonidine group Opiate antagonist: naltrexone - 12.5 mg on day 1, 25 mg on day 2, 50 mg on day 3 Placebo - Placebos for buprenorphine **Group 3 N= 53** Opiate partial agonist: buprenorphine - 3 mg sublingual on days 1-3 Alpha2 adrenergic agonist: clonidine - As per clonidine group from day 4 Opiate antagonist: naltrexone - 25 mg on day 4, 50 mg on day 5	Study quality 1+
PETITJEAN2002				

Study Type: RCT (randomised controlled trial) Blindness: Open Duration (days): Mean 15 Setting: Inpatient unit, Switzerland Notes: RANDOMISATION: Method not reported	n= 37 Age: Mean 32 Sex: 28 males 9 females Diagnosis: 100% opiate dependence by ICD-10 Exclusions: Concurrent or benzodiazepine dependence -- these were treated prior to starting opiate detoxification Baseline: Not reported	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 19** Opiate partial agonist: buprenorphine with inpatient - Sublingual: 8 mg / 70 kg in 2 daily doses to max 16 mg / 70 kg reduced in 2 mg steps over average 12 days **Group 2 N= 18** Opiate agonist: methadone with inpatient - Oral: 40 mg / 70 kg in 2 daily doses to max 60 mg / 70kg reduced in 10 mg steps to 30 mg / 70 kg, then 5 mg steps over total of 15 days on average	Limited reporting in conference abstract; some additional data obtained from Cochrane review (unpublished data) Study quality: 1+
PONIZOVSKY2006 Study Type: RCT (randomised controlled trial) Study Description: Cluster randomised Blindness: Duration (days): Mean 10 Setting: Israel	n= 200 Age: Range 18-50 Sex: no information Diagnosis: 100% opiate dependence by ICD-10 Exclusions: - <18 years or >50 years - comorbid serious physical illness - suicide risk - acute psychosis - severe depression - organic brain syndrome - dependence on benzodiazepines or alcohol - pregnancy or breastfeeding	**Data Used** Completion General Health Questionnaire (GHQ) Notes: DROPOUTS: Buprenorphine = 10/100, clonidine = 50/100	**Group 1 N= 100** Opiate partial agonist: buprenorphine with inpatient - Sublingually: 6 mg at 9 am and 4 mg at 4 pm on day 1; 4 mg at 9 am and 4 mg at 4 pm on days 2-3; 4 mg at 9 am and 2 mg at 4 pm on day 4; 4 mg on day 5; 2 mg on days 6-7; 1 mg on days 8-9. **Group 2 N= 100** Alpha2 adrenergic agonist: clonidine with inpatient - Tablets: 0.15 mg four times per day (every 4 hours) on days 1-4; 0.15 mg three times per day on days 5-8; 0.075 mg three times per day on days 9-10. Adjuvant therapy with promethazine, dipyrone, trazodone, phenobarbital, antiemetics	Study quality: 1+
RAISTRICK2005 Study Type: RCT (randomised controlled trial) Blindness: Open Duration (days): Mean 7 Followup: 1 month Setting: UK 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])	n= 210 Age: Mean 28 Range 17-46 Sex: 157 males 53 females Diagnosis: 100% opiate dependence by ICD-10 Exclusions: - repeat detoxifications - florid psychosis - unstable substance use - electing dihydrocodeine	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Abstinence: 1 month Completion Notes: DROPOUTS: Buprenorphine =37/107, lofexidine = 56/103	**Group 1 N= 107** Opiate partial agonist: buprenorphine with outpatient - 7-day taper: 4 mg day 1, 6-8 mg day 2, 6 mg day 3, 4 mg day 4, 2 mg day 5, 0.8 mg day 6, 0.4 mg day 7. Naltrexone offered 2 days after last dose **Group 2 N= 103** Alpha2 adrenergic agonist: lofexidine with outpatient - 0.4mg 4 hourly days 1- 4; in addition adjunctive medications of co-phenotype prn max 8 tablets (diarrhoea), hyoscine butylbromide prn max 80mg (ab cramps), chlordiazepoxide max 60mg (muscle aches), chlorpromazine 25-50mg (insomnia); then Naltrexone 25mg	271 refused to be randomised and chose between the two treatments Study quality 1+
SALEHI2006 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	n= 70 Age: Mean 37 Sex: all males Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - age outside range 20-60 - contraindications for methadone or tramadol - taking 'extra medications' - polysubstance dependence - any major psychiatric disorder (bipolar, psychosis or major depressive disorder) - having objective signs of withdrawal when administered	**Data Used** Completion Withdrawal: Short Opiate Withdrawal Scale	**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	Study quality: 1+

eligible and randomised	methadone 15 mg for one day Notes: PRIMARY DIAGNOSIS: Daily opium use (equivalent to <=15 mg methadone) Baseline: Methadone / tramadol Years of opiate dependence: 12.86 / 12.85 Short Opiate Withrawal Scale (SOWS) score at entry: 11.97 / 10.28 Daily opium use: unknown		**Group 2 N= 34** Opiate agonist: tramadol - 450 mg per day (equivalent to 15 mg methadone) at entry, reduced by 15% per day to reach 0 at day 7. Placebo thereafter. Symptomatic - 0.3 mg per day clonidine, 10-30 mg per day oxazepam	
SAN1990 Study Type: RCT (randomised controlled trial) Study Description: Per protocol Type of Analysis: Per protocol (completed >=12 days of treatment) Blindness: Double blind Duration (days): Mean 12 Setting: Inpatient, Spain Info on Screening Process: 170 enrolled, 80 failed to complete >=12 days of treatment. Data presented for completers only	n= 90 Age: Mean 24 Range 18-36 Sex: 72 males 18 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - psychopathological antecedents before opiate addiction - signs of cardiovascular diseases - previous participation in clinical trial Baseline: GROUPS: Clonidine / methadone / guanfacine Years of opiate use: 5.4 / 5.5 / 4.6 Previously attempted treatment: 24/30, 20/30, 20/30	**Data Used** Withdrawal severity Completion Retention: duration in treatment	**Group 1 N= 30** 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 **Group 2 N= 30** 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 **Group 3 N= 30** 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	Study quality 1+
SAN1994 Study Type: RCT (randomised controlled trial) Study Description: Allocation by pharmacy Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 18	n= 144 Age: Mean 27 Sex: 102 males 42 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - history of psychiatric disorders - liver dysfunction - cardiovascular diseases - other addiction - pregnancy Notes: PRIMARY DIAGNOSIS: Heroin dependence Baseline: HIV+: 52%	**Data Used** Withdrawal: OWS (Opiate Withdrawal Syndrome) Withdrawal: OWC (Opiate Withdrawal Checklist) Completion	**Group 1 N= 75** Opiate agonist: methadone - Initial dose based on body weight and heroin consumption, tapered over 8 days to 10% of initial dose. Benzodiazepines/hypnotics as adjuncts as appropriate **Group 2 N= 26** Alpha2 adrenergic agonist: guanfacine with inpatient. Mean dose 4 mg - Beginning on day 9 Opiate agonist: methadone with inpatient - Initial dose based on body weight and heroin consumption, tapered over 8 days to 50% of initial dose and discontinued on day 9 **Group 3 N= 43** Alpha2 adrenergic agonist: guanfacine. Mean dose 3 mg - Beginning from day 9 Opiate agonist: methadone with inpatient - Initial dose based on body weight and heroin consumption, tapered over 8 days to 50% of initial dose and discontinued on day 9	Study quality 1++
SCHNEIDER2000 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: Open Duration (days): Mean 21 Setting: Germany Notes: RANDOMISATION: Method not reported	n= 27 Age: Mean 31 Sex: 24 males 3 females Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - participated in a structured drug trial in last 6	**Data Used** Completion	**Group 1 N= 12** Benzodiazepine: oxazepam with inpatient - 900 mg per day for 7 days then tapered and ceased on day 15. Received 900 mg carbamazepine per day for 7 days then tapered and ceased on day 20	Study quality 1+

	months - schizophrenia - bipolar disorder - hepatic disorder - cardiovascular disorder - abnormal ECG - chronic obstructive pulmonary disorder - pregnant Baseline: GROUPS: Buprenorphine / oxazepam Duration opiate use: 11.9 (5.4) / 8.7 (5.8)		**Group 2 N= 15** 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.	
SEIFERT2002 Study Type: RCT (randomised controlled trial) Type of Analysis: ITT Blindness: No mention Duration (days): Mean 14 Setting: Germany	n= 26 Age: Mean 32 Sex: 22 males 4 females Diagnosis: 100% opiate dependence by DSM-IV Baseline: GROUPS: Methadone / buprenorphine Years of opiate misuse: 8.6 (6.8) / 10.5 (7.5)	**Data Used** Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 14** 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 **Group 2 N= 12** Opiate agonist: methadone with inpatient - 20 mg on day 1 tapered to cease on day 10. Received 900 mg carbamazepine for 6 days then tapered to cease on day 14	Study quality 1+
SEOANE1997 Study Type: RCT (randomised controlled trial) Study Description: Envelope-concealed allocation Type of Analysis: Per protocol Blindness: No mention Duration (days): Mean 1 Followup: 1 month Setting: Spain Notes: RANDOMISATION: Computer-generated random number table Info on Screening Process: 359 screened, 47 met exclusion criteria and 312 gave consent. 12 dropped out or were excluded prior to treatment, so 300 randomised.	n= 300 Age: Mean 30 Sex: 210 males 90 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - heroin consumption <100 mg / day - poor general health - lack of proof for high motivation - alcoholism with chronic consumption > 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 Baseline: (GROUPS: Light / heavy sedation) Daily heroin use (mg): 735.3 / 747.2 Route: Intravenous: 39% / 46%; nasal: 19% / 20%; smoked: 17% / 19%; two or more: 25% / 15% Previous detoxification attempts: 4.6 / 4.4	**Data Used** Abstinence: 1 month Completion Withdrawal: Wang Scale Notes: No treatment comparisons given for completion and 1-month abstinence	**Group 1 N= 150** Opiate antagonist: naloxone with inpatient - After sedation, 0.06-0.08 mg / kg intravenous infusion for 5-10 min Symptomatic with inpatient. Mean dose 0.7 mg / kg - Metoclopramide to increase gastric emptying after sedation has begun 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	Study quality: 1++

			Group 2 N= 150 Opiate antagonist: naloxone with inpatien 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	
SHEARD2007 Study Type: RCT (randomised controlled trial) Blindness: Open Duration (days): Mean 16 Followup: 6 months Setting: Prison in UK Notes: RANDOMISATION: computer randomised CONCEALMENT OF ALLOCATION: opaque sealed envelopes	n= 90 Age: Range 16-65 Sex: no information Diagnosis: 100% opiate misuse Exclusions: - <18 years >65 years - negative urine for illicit opiates - 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 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	Study quality 1+
SORENSEN1982 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatient detoxification clinic, San Francisco, US Notes: RANDOMISATION: Stratified by employment status	n= 61 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence by urinalysis Exclusions: - age < 18 - no evidence of physical addiction to opiates - life-threatening medical conditions 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	**Data Used** Entry to further treatment: MMT Entry to further treatment Completion Abstinence: endpoint **Data Not Used** Abstinence: 3 months	**Group 1 N= 18** Opiate agonist: methadone with outpatient - 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 **Group 2 N= 15** Opiate agonist: LAAM with outpatient - 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 **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+

			Group 4 N= 15 Opiate agonist: methadone with outpatient - 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 referra	
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	n= 72 Age: Mean 28 Sex: 57 males 15 females Diagnosis: 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	**Data Used** Entry to further treatment: MMT Opiate use Abstinence: 1 month Completion	**Group 1 N= 36** Opiate agonist: propoxyphene napsylate with outpatient - Initial dose 800 mg, tapered daily **Group 2 N= 36** Opiate agonist: methadone with outpatient - Initial dose 24 mg, tapered daily	Study quality 1+
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	n= 22 Age: Mean 37 Sex: 15 males 7 females Diagnosis: 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 Years of heroin use: 16.0 / 13.6 Months of methadone use: 33.2 / 33.8 Highest methadone dose (mg): 78.3 / 86.0	**Data Used** Withdrawal severity Opiate use Retention: duration in treatment Completion Notes: 1-month and 6-month follow-ups	**Group 1 N= 12** Placebo - Placebo capsules Opiate agonist: methadone with outpatient. 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. **Group 2 N= 10** Opiate agonist: propoxyphene napsylate with outpatient - 100 mg in-clinic and 300 mg take-home dose from day 5; raised to 1100 mg total (600 mg in-clinic plus 500 mg take-home) by day 25; tapered to 0 by day 43. Placebo - Placebo capsules Opiate agonist: methadone - Administered in clinic. Starting dose 30 mg, reduced by 5 mg every 5 days down to 0 mg by day 25.	Study quality 1+
UMBRICHT1999 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	n= 60 Age: Mean 31 Sex: 29 males 31 females Diagnosis: opiate dependence by DSM-IV Exclusions: - not aged 18-40 - prior seizure disorders - cardiac ischaemia - hypertension	**Data Used** Completion Withdrawal: OOWS (Objective Opiate Withdrawal)	**Group 1 N= 32** 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	Study quality: 1+

randomised.	- diabetes mellitus - AIDS (CD4 T-cell count <200 / ml) - psychosis or suicidal ideation - current asthma - liver transaminases - acute need for medical care - pregnancy or lactation 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	Notes: Use of adjuncts and reasons for leaving study were reported; no follow-up outcomes DROPOUTS: 24% placebo, 44% naltrexone	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 **Group 2 N= 28** 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 >=5 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	
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 Info on Screening Process: 63 enrolled, 8 excluded from analysis (3 dropped out prior to receiving any study medication, 5 due to medication errors)	n= 55 Age: Mean 40 Sex: 30 males 25 females Diagnosis: 100% 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	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 18** Opiate agonist: methadone with inpatient - 3-day taper: 30 mg day 1, 20 mg day 2, 10 mg day 3 **Group 2 N= 21** 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. **Group 3 N= 16** 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	6-month study consisted of 4-month induction/maintenance phase followed by 2-month detoxification phase Study quality 1+
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	n= 26 Age: Mean 31 Sex: 22 males 4 females Diagnosis: 100% opiate dependence Exclusions: Evidence of serious medical or psychiatric illness Baseline: Mean years of heroin use: 10	**Data Used** Completion	**Group 1 N= 13** Opiate agonist: methadone - 15-30 mg starting maintenance dose, reduced by 1 mg / day until 0 reached **Group 2 N= 13** Alpha2 adrenergic agonist: clonidine - Abrupt substitution of clonidine for methadone	Study quality: 1+
WRIGHT2007A Study Type: RCT (randomised controlled trial) Study Description: Allocation centrally performed and concealed in opaque sealed envelopes Type of Analysis: ITT	n= 60 Age: Mean 29 Sex: 42 males 18 females Diagnosis: 100% opiate misuse by urinalysis Exclusions: - age <18	**Data Used** Mortality Abstinence: 3 months Abstinence: endpoint Completion	**Group 1 N= 28** 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	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	- not using street opiates as confirmed by urinalysis - contraindications to study medications - had been randomised into trial previously Notes: PRIMARY DIAGNOSIS: Using street opiates - 63% intravenous, 35% smoked, 2% both Baseline: (Buprenorphine / dihydrocodeine) Years of opiate use: 8.8 (4.9) / 7.0 (3.7) Daily opiate use £: min 17.1 (8.1) / 15.6 (7.2), max 23.2 (12.1) / 18.1 (9.0) Illicit opiates in initial urine: 82% / 84% Other drugs in initial urine: 64% / 37% 'Severely dependent': 28% / 31%		were free to titrate dose against symptoms. **Group 2 N= 32** Opiate agonist: dihydrocodeine with outpatient - Dispensed as 30 mg rapid-release tablets in take-home instalments; each instalment for min 3 and max 4 daily doses	

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
AHMADI2004A	Maintenance study
AMASS1994	n <10 per group
AMASS2004	Only data for treatment group provided
BEARN1998	Assignment not random - patient preference
BICKEL1988	Not required outcomes
CAMI1985	Does not adequately address question
CAMI1992	Not assessing efficacy of detoxification treatments
DAWE1995	Small sample size
FINGERHOOD2001	Not RCT
HAMEEDI1997	n<20
HARTMANN1991	n<20
KOSTEN1984	No extractable outcomes
KOSTEN1985	No extractable data
KOSTEN1992A	No treatment comparison for withdrawal phase
KOURI1996	No relevant outcomes; n<10 per group
KRABBE2003	Not randomised
ORESKOVICH2005	n<10 per group
PINI1991	Small sample size
SEES2000A	Compares detoxification with maintenance - not relevant
SIGMON2004	n<10 per group
WILSON1993	Not an RCT

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Characteristics of reviewed studies: Dosage of opioid detoxification

Comparisons Included in this Clinical Question

Exponential Versus Linear Dose Reduction	Full Information Versus Standard Information	High Versus Moderate Starting Dose	Variable Versus Fixed Dosage
STRANG1990	GREEN1988	BANYS1994 STRAIN1999	DAWE1991

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
BANYS1994 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 180 Setting: San Francisco, US	n= 38 Age: Range 18-65 Sex: 22 males 16 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - age outside range 18-65 - no accessible veins - pregnant - contraindications to high-dose methadone - been on methadone in past 30 days - negative opiate or positive methadone urine screen - <3 objective signs of opiate withdrawal Baseline: Positive urinalysis for other drugs: 38% cocaine, 8% amphetamine, 11% benzodiazepine, 3% barbiturates	**Data Used** Urinalysis Withdrawal severity Retention: duration in treatment Notes: Twice weekly urine screens on random days; either test being positive marked as positive for that week	**Group 1 N= 19** 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 **Group 2 N= 19** Opiate agonist: methadone with outpatient - Low-dose group: started on 30 mg, raised to 40 mg on day 2, maintained until day 101, then tapered linearly to 0 over days 102-180 (with 1 mg on days 178-180)	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+
DAWE1991 Study Type: RCT (randomised controlled trial) Study Description: Participants not told that they were being randomised to two withdrawal schedules Blindness: Single blind Duration (days): Mean 70 Setting: Outpatient detox in south London Info on Screening Process: 82 eligible and randomised > 39 attended first session	n= 39 Age: Mean 26 Sex: 28 males 11 females Diagnosis: 100% opiate dependence by urinalysis Exclusions: - Pregnant - Considered inappropriate on clinical grounds Baseline: Mean years of opiate use: 7 Mean age at first use: 19 Administration: 38% IV, 53% inhaled, 9% IV and inhaled Sharing injecting equipment: 56% ever, 29% in past year	**Data Used** Retention: duration in treatment Completion	**Group 1 N= 24** 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 **Group 2 N= 15** Opiate agonist: methadone with outpatient - Fixed dosage: Initial dose set according to DHSS guidelines, tapered over 6 weeks at a constant rate. Patient seen at least once a week by doctor and keyworker, and required to attend weekly support group and individual session	Study quality 1+
GREEN1988 Study Type: RCT (randomised controlled trial) Study Description: No mention Blindness: Single blind Duration (days): Mean 21 Setting: Bethlem Royal Hospital, London Info on Screening Process: 35 admitted for detoxification - five excluded (three left study before start of detox, two failed to comply with form-filling) > 30 randomised	n= 30 Age: Mean 25 Range 19-35 Sex: 23 males 7 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: Not reported Notes: PRIMARY DIAGNOSIS: 33/35 heroin, 2/35 prescribed methadone Baseline: Mean years of opiate dependence: 6	**Data Used** Completion Withdrawal: OWS (Opiate Withdrawal Syndrome)	**Group 1 N= 15** 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	Study Quality 1+

			Group 2 N= 15 Opiate agonist: methadone with inpatient - 3 times daily oral methadone, linear reduction schedule. Given standard information about admission and ward routine, and usual responses to any requests for information or reassurance.	
STRAIN1999 Study Type: RCT (randomised controlled trial) Study Description: Randomisation in sealed envelopes by pharmacy staff and RAs without any patient contact. Dosage always double-blinded; methadone administered in syrup Blindness: Double blind Duration (days): Mean 280 Setting: 40-week outpatient methadone programme, US Notes: RANDOMISATION: Stratified on cocaine-use status and level of opiate use Info on Screening Process: 192 randomised; 111 completed stabilisation phase and entered taper phase	n= 192 Age: Mean 38 Sex: 124 males 68 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - age < 18 - no documentation of >=2 previous methadone detoxification attempts, no opiate-positive urine sample or no physical evidence for needle use - any chronic medical illness - any major mental illness - positive pregnancy test result - treatment at this clinic in past month Notes: ETHNICITY: 94% White Baseline: GROUPS: Moderate dose / high dose Legally free: 66.0% / 77.9% Previous treatments: 4.0 / 4.2 Use in past week: opiates 25.8 / 24.7; cocaine 4.5 / 6.6; benzodiazepines 0.2 / 0.2	**Data Used** Completion Opiate use Urinalysis	**Group 1 N= 97** Opiate agonist: methadone with outpatient - Wk1: 30mg; Wks2-6: 2mg increase each week (up to 40mg/day) Wks8-30: If 2 of past 4 urines tested opiate +ve, 5mg dose increase given (up to max 50mg); dose decreased at patient's request, or if past 6 urines -ve Wks31-40: Tapered at rate of 10% per week Psychosocial: group therapy - Counsellor set treatment goals and developed individual treatment plan. Weekly individual and group therapy focusing on relapse prevention **Group 2 N= 95** Psychosocial: group therapy - As per moderate-dose group Opiate agonist: methadone - Wk 1: 30mg Wks 2-6: 2mg increase each wk (up to 80mg/day) Wks8-30: If 2 of past 4 urines tested opiate +ve, 10mg dose increase given (up to max 100mg); dose decreased at patient's request, or if past 6 urines -ve Wks31-40: Tapered at rate of 10% per wk	Study quality 1++
STRANG1990 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 10 Followup: 15 days Setting: Inpatient DDU, London	n= 87 Age: Mean 28 Sex: 64 males 23 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - Detoxification not required, or longer detoxification required (e.g. pregnancy) Notes: PRIMARY DIAGNOSIS: Heroin or methadone addicts Baseline: Almost all subjects used other drugs	**Data Used** Retention: duration in treatment Withdrawal: OWS (Opiate Withdrawal Syndrome) Completion	**Group 1 N= 43** Opiate agonist: methadone with inpatient - Linear: Dose initially titrated against withdrawal symptoms, reduced per day by 10% of starting dose. All doses delivered three times daily in 20ml fluid. No other drugs apart from tapered diazepam for BDZ codependence **Group 2 N= 44** Opiate agonist: methadone with inpatient - Exponential: Dose initially titrated against withdrawal symptoms, reduced each day by 20% of yesterday's dose. All doses delivered three times daily in 20ml fluid. No other drugs apart from tapered diazepam for BDZ codependence	Study Quality 1+

References of Included Studies

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Characteristics of reviewed studies: Duration of opioid detoxification

Comparisons Included in this Clinical Question

1 Week Versus 3 Weeks
SENAY1981
SORENSEN1982
STITZER1984

Ultrarapid (<=24 Hours) Versus Rapid (1-7 Days)
ASSADI2004
COLLINS2005
DEJONG2005
FAVRAT2006
SEOANE1997

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ASSADI2004 Study Type: RCT (randomised controlled trial) Type of Analysis: LOCF Blindness: Double blind Duration (days): Mean 5 Setting: Iran Notes: RANDOMISATION: computer generated list of random numbers	n= 40 Age: Mean 32 Sex: 39 males 1 female Diagnosis: 100% opiate dependence by DSM-IV Exclusions: - <18 years >60 years - pregnancy or lactation - clinically unstable medical illness - liver transaminases exceeding twice upper limit of normal - history of psychosis - mania or severe depression - concurrent dependency on alcohol - antisocial or borderline personality disorder Baseline: Mean duration of opioid use = 9 years	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Short Opiate Withdrawal Scale Completion	**Group 1 N= 20** Opiate partial agonist: buprenorphine with inpatient - 5 day taper: 2 x 1.5mg day 1, tapered to 2 x 0.3mg day 5. Indomethacin, trazadone, chlorpromazine, hyoscine adjunct medications as required. Relapse prevention using naltrexone **Group 2 N= 20** 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. Received indomethacin, trazadone, chlorpromazine, hyoscine, adjunct medications as required. Relapse prevention using naltrexone. Placebo saline remainder of study	Study quality 1++
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 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	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 - 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/L - history of food or drug allergy, sensitivity to study medication Notes: PRIMARY DIAGNOSIS: Opiate dependence >=6 months and seeking treatment ETHNICITY: 53% White	**Data Used** Withdrawal: OOWS (Objective Opiate Withdrawal) Withdrawal: Subjective Opiate Withdrawal Scale Completion Retention: duration in treatment	**Group 1 N= 37** Opiate partial agonist: buprenorphine with inpatient. Mean dose 8 mg - Single sublingual dose on evening of day 1 Symptomatic with inpatient - As needed 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	Study quality: 1++

	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		**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 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	**Group 1 N= 137** Symptomatic with inpatient - As per ultrarapid group Psychosocial: CRA (community reinforcement apprch) with outpatient - As per ultrarapid group Opiate antagonist: naltrexone with inpatient - 12.5 mg on day 1, 25 mg on day 2, 50 mg on day 3 Alpha2 adrenergic agonist: clonidine with inpatient - As per ultrarapid group	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		**Group 2 N= 135** Symptomatic with inpatient - All participants treated with same medications at same dosages: 8am: diclofenac, ondansetron, diazepam, transdermal nicotine (for smokers) Post-naltrexone: octreotride, 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 apprch) 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. Mean dose 0.3 mg - Administered at 9 am to prevent high blood pressure Post-naltrexone: 0.15 mg subcutaneously at five intervals over the day	
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	**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)	Study quality: 1++

			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 naltrexon Alpha2 adrenergic agonist: clonidine with inpatient - During anaesthesia, clonidine or lidocaine used to deepen anaesthesia and control withdrawal signs	
SENAY1981 Study Type: RCT (randomised controlled trial) Blindness: Double blind Duration (days): Mean 90 Setting: Chicago, US	n= 72 Age: Mean 25 Sex: 40 males 32 females Diagnosis: 100% opiate dependence by clinical assessment Exclusions: - Age <18 - Poor general health - Eligibility for MMT (with >2 years addiction history) - <6 months IV heroin use, or no period of daily use >=3 months - No objective clinical evidence of IV use (e.g. needle marks) - No history of withdrawal symptoms Notes: ETHNICITY: 53% Black, 14% White, 7% Other Baseline: (GROUPS: 3-week / 12-week) 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	**Data Used** Withdrawal severity Completion Abstinence: endpoint Retention: duration in treatment	**Group 1 N= 35** Psychosocial: group therapy - Intensive individual and group counselling Opiate agonist: methadone with outpatient - 3-week detox: Decreasing doses of methadone 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 **Group 2 N= 37** Psychosocial: group therapy - Intensive individual and group counselling Opiate agonist: methadone with outpatient - 12-week detox: Methadone taper for 84 days and placebo for final week. Dose adjustment allowed during 1st week if patient experienced moderate or marked discomfort	Study quality 1+
SEOANE1997 Study Type: RCT (randomised controlled trial) Study Description: Envelope-concealed allocation Type of Analysis: Per protocol Blindness: No mention Duration (days): Mean 1 Followup: 1 month Setting: Spain Notes: RANDOMISATION: Computer-generated random number table Info on Screening Process: 359 screened, 47	n= 300 Age: Mean 30 Sex: 210 males 90 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - heroin consumption <100 mg / day - poor general health - lack of proof for high motivation - alcoholism with chronic consumption > 100 g / day - probable or known pregnancy - acute infectious pathology - cachexia or terminal disease	**Data Used** Abstinence: 1 month Completion Withdrawal: Wang Scale Notes: No treatment comparisons given for completion and 1-month abstinence	**Group 1 N= 150** Opiate antagonist: naloxone with inpatient - After sedation, 0.06-0.08 mg / kg intravenous infusion for 5-10 min Symptomatic with inpatient. Mean dose 0.7 mg / kg - Metoclopramide to increase gastric emptying after sedation has begur	Study quality: 1++

met exclusion criteria and 312 gave consent. 12 dropped out or were excluded prior to treatment, so 300 randomised.	- probable or known allergy to study medications - bronchospasm that fails to respond to inhaled beta2 agonists - psychosis Baseline: (GROUPS: Light / heavy sedation) Daily heroin use (mg): 735.3 / 747.2 Route: Intravenous: 39% / 46%; nasal: 19% / 20%; smoked: 17% / 19%; two or more: 25% / 15% Previous detoxification attempts: 4.6 / 4.4		Anaesthetic: propofol with inpatient - Initiation with bolus at 0.3mg/kg combinec 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: naloxone with inpatien 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) Blindness: Double blind Duration (days): Mean 42 Setting: Outpatient detoxification clinic, San Francisco, US Notes: RANDOMISATION: Stratified by employment status	n= 61 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence by urinalysis Exclusions: - age < 18 - no evidence of physical addiction to opiates - life-threatening medical conditions 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	**Data Used** Entry to further treatment: MMT Entry to further treatment Completion Abstinence: endpoint **Data Not Used** Abstinence: 3 months	**Group 1 N= 18** Opiate agonist: methadone with outpatient - 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 **Group 2 N= 15** Opiate agonist: LAAM with outpatient - 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 **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 **Group 4 N= 15** Opiate agonist: methadone with outpatient - 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 referra	Study quality 1+

STITZER1984 Study Type: RCT (randomised controlled trial) Type of Analysis: Per protocol Blindness: Double blind Duration (days): Mean 70 Setting: Outpatient research unit, Baltimore, US Info on Screening Process: 104 admitted to outpatient detox > 26 had >=50% +ve urinalysis during 3 week enrolment phase and randomised	n= 26 Age: Mean 29 Sex: all males Diagnosis: 100% opiate dependence Baseline: Mean length of opiate addiction: about 8 years Previous MMT or methadone detox involvement: about half	**Data Used** Urinalysis Retention: duration in treatment	**Group 1 N= 13** Opiate agonist: methadone with outpatient. Mean dose 60mg - Dose raised from initial 30mg to 60mg over weeks 1-2, then lowered by 10mg steps at start of weeks 3, 5, 7, 8, 9, 10. Methadone delivered daily in cherry syrup supervised by nurse **Group 2 N= 13** Opiate agonist: methadone with outpatient. Mean dose 30mg - Dose maintained at 30mg through to end of week 7, then reduced in 10mg at start of weeks 8, 9 and 10. Methadone delivered in cherry syrup supervised by nurse	All participants stabilised on 30 or 40mg methadone during 3-week induction phase Study quality 1+

Characteristics of Excluded Studies

Reference ID	Reason for Exclusion
GOUREVITCH1999	Not detox

References of Included Studies

ASSADI2004 (Published Data Only)

Assadi, S. M., Hafezi, M., Mokri, A., et al. (2004) Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. Journal of Substance Abuse Treatment, 27, 75-82.

COLLINS2005 (Published Data Only)

Collins, E.D., Kleber, H.D., Whittington, R.A., et al. (2005) Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. The Journal of the American Medical Association, 294, 903-913.

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De Jong, C.A., Laheij, R.J. & Krabbe, P.F. (2005) General anaesthesia does not improve outcome in opioid antagonist detoxification treatment: a randomized controlled trial. Addiction, 100, 206-215.

FAVRAT2006 (Published Data Only)

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Senay, E. C., Dorus, W. & Showalter, C. V. (1981) Short-term detoxification with methadone. Annals of the New York Academy of Sciences, 362, 203-216.

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SORENSEN1982 (Published Data Only)

Sorensen, J.L., Hargreaves, W.A. & Weinberg, J.A. (1982) Withdrawal from heroin in three or six weeks. Comparison of methadyl acetate and methadone. Archives of General Psychiatry, 39, 167-171.

STITZER1984 (Published Data Only)

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References of Excluded Studies

GOUREVITCH1999 (Published Data Only)

Gourevitch, M. N., Hartel, D., Tenore, P., et al. (1999) Three oral formulations of methadone. A clinical and pharmacodynamic comparison. Journal of Substance Abuse Treatment, 17, 237-241.

Characteristics of reviewed studies: Efficacy of physical interventions

Comparisons Included in this Clinical Question

(Methadone + Acupuncture) Versus Methadone
ZENG2005

Characteristics of Included Studies

Methods	Participants	Outcomes	Interventions	Notes
ZENG2005 Study Type: RCT (randomised controlled trial) Blindness: No mention Duration (days): Mean 10 Setting: China, Drug Rehabilitation Centre Notes: RANDOMISATION: no mention of method used	n= 70 Age: Mean 34 Sex: 60 males 10 females Diagnosis: 100% opiate dependence by DSM-III-R Exclusions: - <18 >50 years of age - physical and psychiatric problems Baseline: Methadone + acupuncture/methadone Years of opiate use: 6.00(2.82)/6.23(2.93)	**Data Used** Withdrawal severity Completion Notes: DROPOUTS: Methadone + acupuncture 4/35 methadone = 9/35	**Group 1 N= 35** 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 Acupuncture with inpatient - Received acupuncture once a day. Needles were retained for 30 minutes, during which they were manipulated three times **Group 2 N= 35** 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	Study quality 1+

References of Included Studies

ZENG2005 (Published Data Only)

Zeng, X., Lei, L., Lu, Y., et al. (2005) Treatment of heroinism with acupuncture at points of the Du channel. Journal of Traditional Chinese Medicine, 25, 166-170