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SUMMARY WITH CRITICAL APPRAISAL

Alpha$_2$-Adrenergic Agonists for the Reduction or Discontinuation of Opioids or Opioid Substitution Therapy: A Review of Clinical Effectiveness and Guidelines

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Context and Policy Issues

Opioids are powerful substances used to relieve severe pain. However, there is high potential for abuse due to the feelings of euphoria and relaxation that also occur.[1] In Canada, the number of people seeking treatment for opioid dependence has increased substantially in the last decade. For example, in Ontario, there were 29,000 people enrolled in methadone maintenance treatment in 2010 and just under 50,000 in 2014.[2]

Stopping using opioids is associated with severe withdrawal symptoms such as anxiety, restlessness, diarrhea, vomiting, profuse sweating, and tachycardia.[3] Medically supervised opioid withdrawal involves using medications to lessen the severity of these symptoms. Medications whose mechanism of action targets the opioid receptors, including methadone and buprenorphine, are commonly used; however, while they generate controversy because they are opioids themselves,[4] they may be more effective with other supportive interventions such as addiction treatment counselling.

Alpha$_2$-adrenergic agonists are an alternative and/or supportive medication to assist in opioid withdrawal. Rather than targeting the opioid receptors, these medications act by binding to the alpha-2 receptors located in the central nervous system.[5] This mechanism then involves reducing noradrenergic hyperactivity, which reduces the intensity of withdrawal symptoms. The potential of this class of drugs to aid in opioid withdrawal was observed by 1979.[6] There are three major drugs in this class used in opioid withdrawal: clonidine, lofexidine and guanfacine. Clonidine and guanfacine are not approved for opioid withdrawal in Canada, but it has been suggested that clonidine is widely used for this purpose.[7] Lofexidine is approved for opioid withdrawal only in the UK.[8]

Using alpha$_2$-adrenergic agonists may be effective in opioid reduction or discontinuation relative to other supportive interventions or opioid substitution therapies. Further, there may be differences in effectiveness between alpha$_2$-adrenergic agonists in themselves. This review considered the evidence and guidelines to this effect, to explore whether alpha$_2$-adrenergic agonists could assist in reducing the burden of opioid dependence.

Research Question

1. What is the clinical effectiveness of alpha$_2$-adrenergic agonists when used as a tool for the reduction or discontinuation of opioids or opioid substitution therapy?
2. What are the evidence-based guidelines regarding the use of alpha$_2$-adrenergic agonists for the treatment of patients who are reducing or discontinuing opioids or opioid substitution therapy?

Key Findings

Alpha$_2$-adrenergic agonists were found to be more effective than placebo for managing withdrawal, however less effective than buprenorphine and potentially similar to methadone. Hypotension was a common adverse effect with clonidine specifically. Evidence comparing alpha$_2$-adrenergic agonists to non-medicinal support therapies was not

identified. Overall the quality of studies was highest in comparisons of alpha$_2$-adrenergic agonists against buprenorphine and placebo, followed by alpha$_2$-adrenergic agonists against methadone, but the evidence was limited in quantity for comparing alpha$_2$-adrenergic agonists to each other. The identified guidelines do not recommend alpha$_2$-adrenergic agonists as a first-line medication when buprenorphine and methadone are an option.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, PsycINFO, PubMed, The Cochrane Library, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, guidelines, and safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and January 17, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults reducing or discontinuing opioids or opioid substitution therapies (e.g., methadone, buprenorphine)
Intervention	Alpha$_2$-adrenergic agonists (e.g., clonidine, lofexidine) alone or in combination with opioid substitution therapies or non-medicinal supportive methods
Comparator	Q1: Placebo, non-medicinal supportive methods, other alpha2-adrenergic agonists, opioid substitution therapies Q2: Not applicable
Outcomes	Q1: Detoxification, duration of opioid or opioid substitution taper, achieving opioid abstinence, relief of withdrawal symptoms, safety and harms including diversion or abuse Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008. Studies were also excluded where opioids were taken for post-operative pain. Due to the volume of higher level evidence identified in the literature search, non-randomized studies were not included.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR 2 checklist,[9] randomized studies were critically appraised using the Downs and Black checklist,[10] and guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 330 citations were identified in the literature search. Following screening of titles and abstracts, 304 citations were excluded and 26 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were additionally retrieved from the grey literature search. Of these potentially relevant articles, 21 publications were excluded for various reasons, while 15 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Detailed study characteristics by study design are presented in Appendix 2.

1. *What is the clinical effectiveness of alpha$_2$-adrenergic agonists when used as a tool for the reduction or discontinuation of opioids or opioid substitution therapy?*

Study Design

Six systematic reviews[12-17] and six randomized controlled trials (RCTs) were included.[18-23] One of the systematic reviews included an analysis of indirect comparisons between alpha$_2$-adrenergic agonists and control interventions, even if this was not the primary comparison of the individual studies.[10] One 2016[12] and one 2017[14] systematic review contained 22 and 14 RCTs, respectively. Another 2017 systematic review contained four cohort studies and five RCTs.[16] Three older systematic reviews published in 2010,[13] 2011,[15] and 2013[17] contained 12 RCTs, two systematic reviews and 11 RCTs, respectively.

Of the six included RCTs, four were double-blinded,[18-21] and the remaining two RCTs were open-label.[22,23] Two publications appeared to be based on an identical RCT; however, the studies did not reference each other, and the link between them was not explicit.[19,20]

Country of Origin

The systematic reviews did not have geographic restrictions for included studies, but the lead authors of all these reviews were based in the UK.[12-17]

Two RCTs were conducted in Iran,[19,20] two were conducted in the U.S.,[18,23] one in India[22] and one in Russia.[21]

Patient Population

Four systematic reviews included adults with opioid dependence undergoing managed withdrawal,[12,14,16,17] while one additionally included those on treatment for stabilization or relapse prevention.[15]

Five of six RCTs included subjects seeking treatment who fulfilled the Diagnostic and Statistical Manual of Mental Disorders IV criteria for opioid dependence,[18-22] while the remaining RCT did not specify diagnostic criteria but included those seeking treatment for opioid dependence.[23] The primary opioid of choice was heroin in three studies,[20,21,23] though three studies were unclear and/or did not specify the substance.[18-20] Finally four studies included inpatients only,[18-20,22] one study included outpatients only[21] and one included both.[23] The primary exclusion criteria were related to pregnancy,[18,21] abnormal liver function,[19-21] mental or psychotic illness,[18,20-22] renal disease[19-21] and cardiovascular disease.[18-21] One study specified only that patients needed to be in good general health.[23]

Interventions and Comparators

In two systematic reviews, alpha$_2$-adrenergic agonists were explicitly stated as the intervention as part of the protocol.[12,13] In one review, the intervention was any treatment used for opioid withdrawal, stabilization or relapse prevention including alpha$_2$-adrenergic agonists.[15] In three systematic reviews, the specified intervention was buprenorphine,[14] methadone taper,[17] or opioid antagonists;[16] however, they all included studies and conclusions comparing these to alpha$_2$-adrenergic agonists which are relevant to this report. Additional comparators included alternative alpha$_2$-adrenergic agonists regimens,[12,13] tapered methadone[12] or any other treatment for opioid withdrawal, stabilization or relapse prevention.[15]

The RCTs' interventions included lofexidine,[18] clonidine[19,20,22,23] and guanfacine.[21] The comparators included placebo,[18,21] placebo combined with buprenorphine,[19,20] and buprenorphine-naloxone (Suboxone©).[22,23] Two studies administered the clonidine alongside a buprenorphine placebo, compared with buprenorphine and a clonidine placebo, and initiated naltrexone starting two days after first-line treatment was ceased in both groups.[19,20] One study administered guanfacine with naltrexone in one intervention arm, and guanfacine with naltrexone placebo in another intervention arm. Both arms also had individual drug counselling, and were compared to the complimentary placebo.[21]

Outcomes

All the systematic reviews assessed treatment completion or retention. Additional outcomes included the severity of withdrawal symptoms,[12,14-17] duration of treatment,[12,14,16] engagement in further treatment[12,14,16] and assessment of adverse effects.[12,14-17] One review also considered mortality and criminality,[15] while two considered abstinence.[15,17]

The outcomes assessed in the RCTs included duration of treatment, retention or time to dropout,[18-21,23] number of days remaining on subsequent maintenance treatment,[19,20] relapse (three consecutive positive urines),[21] negative urine toxicology,[21,23] and use of concomitant medications.[18] In addition, several scales were used. To assess withdrawal severity or cravings, these included the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop),[18] the Clinical Opiate Withdrawal Scale (COWS),[19,20,22,23] the Adjective Rating of Withdrawal Scale (ARWS)[19,20,23] and the visual analogue scale for craving.[19-22] Additional scales included the visual analogue scale for efficacy,[18] the Modified Clinical Global Impressions Scale (MCGI)[18] and the Perceived Stress Score.[21]

The identified studies did not report on diversion or abuse.

2. *What are the evidence-based guidelines regarding the use of alpha$_2$-adrenergic agonists for the treatment of patients who are reducing or discontinuing opioids or opioid substitution therapy?*

Study Design

Three guidelines met the inclusion criteria. They were developed by the World Health Organization,[24] the British Columbia Centre for Substance Use[25] and the World Federation of Societies of Biological Psychiatry.[26] Descriptions of the methods for the identification and evaluation of the literature, as well as for recommendation development and evaluation, are provided in Appendix 2, Table 4.

Intended Users

The three guidelines specified that the intended users were those involved in managing pharmacological treatment of opioid dependence, and two specifically targeted clinicians.[25,26] One guideline additionally targeted policy-makers focused on meeting addition needs.[25]

Interventions Considered

Two of the guidelines considered the use of methadone, buprenorphine, buprenorphine/naloxone, naltrexone, and alpha$_2$-adrenergic agonists for opioid withdrawal.[24,26] One of these additionally considered heroin for withdrawal.[26] The remaining guideline considered any medically-assisted detoxification.[25]

Outcomes

Two of three guidelines specified outcomes. These included treatment completion, severity of withdrawal and adverse effects,[24] opioid abstinence and decrease in opioid use.[26] The remaining guideline did not specify outcomes of interest, and in the end did not provide any recommendations pertaining to alpha$_2$-adrenergic agonists despite including this intervention at the outset.

Summary of Critical Appraisal

1. *What is the clinical effectiveness of alpha$_2$-adrenergic agonists when used as a tool for the reduction or discontinuation of opioids or opioid substitution therapy?*

The systematic reviews all included comprehensive database searches including multiple databases, risk of bias and quality assessment using the Scottish Intercollegiate Guidelines Network (SIGN) or Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The heterogeneity across studies was assessed in four reviews using I^2 and/or Chi-squared criterion.[12,14,16,17] Two studies combined results with significant heterogeneity according to the tests,[14,17] however random effects models were used as is appropriate in this situation. Failure to adequately account for this heterogeneity would result in underestimating the width of the confidence intervals around the final estimates.

The main limitation of the systematic reviews was that one reviewer screened abstracts and extracted the information. In two exceptions, two reviewers reviewed the abstracts, and three reviewers confirmed abstract screening.[14,15] In one study, though one reviewer screened abstracts, two reviewers assessed full texts and extracted information.[17] In two reviews, the Population, Intervention, Comparator and Outcome (PICO) criteria were not

clearly defined,[13,15] so the target population and specifically which treatments were targeted were unclear. One review did not report the degree of heterogeneity across studies or study quality despite stating it was assessed.[13] However, this study used the Markov Chain Monte Carlo method to combine results which, similar to random effects models, minimizes the possible effects of heterogeneity. Finally, none of the reviews referred to published protocols.

Four of the RCTs reported balanced baseline characteristics across control and treatment groups,[18,20-22] such that the observed differences are not likely to be due to confounding factors. Two trials reported adequate randomization procedures,[18,21] and two reported a power calculation suggesting sufficient power,[18,21] though the rest did not. Of these, the sample sizes included n=35,[19] n=49,[20] n=54,[22] and n=344.[23] The statistical methods employed were generally considered adequate, and included repeat-measures analysis of variance or other modelling techniques where sample sizes were sufficient (> 50),[18,20,21,23] or simple reporting of differences where sample sizes were small (n=35).[19] At the same time, there were several limitations across the trials. Primarily, studies did not report adequate details of allocation concealment and/or randomization procedures.[18-20,22,23] In addition, a table of baseline characteristics was not reported in two studies,[19,23] making it unclear whether randomization was successful and thus the findings may have been subject to confounding bias. One study did not provide a PRISMA flow chart,[19] and one study did not state exclusion criteria,[23] so the generalizability was unclear. Two studies were at risk of differential treatment of the intervention and comparator groups and biased outcomes assessment as they did not employ blinding.[22,23] Finally, there was a risk of selection bias in one study that required a stable home address and phone number because such a restriction may not represent the opioid user population.[21]

2. *What are the evidence-based guidelines regarding the use of alpha$_2$-adrenergic agonists for the treatment of patients who are reducing or discontinuing opioids or opioid substitution therapy?*

The guidelines had clear intended users and stated scope. Two of three guidelines outlined systematic evidence collection and synthesis methods.[24,26] These included reviewing the existing systematic reviews and other guidelines, and categorizing evidence according to risk of bias and quality using the GRADE system. One study additionally conducted its own systematic reviews and meta-analyses when they were unavailable in the published literature.[24] The remaining guideline lacked detail on the search methods despite stating that they conducted a structured literature review where studies were independently assessed for inclusion by staff.[25] All of the guideline developers formed committees who evaluated and discussed the evidence for inclusion and recommendations development. In one guideline, the committee mainly consisted of psychiatrists or psychologists,[26] while the other two were more multi-disciplinary.[24,25] None of the guidelines reported patient involvement at early stages or guideline validation processes.

A summary of the critical appraisal for each included study and guideline is provided in Appendix 3.

Summary of Findings

1. *What is the clinical effectiveness of alpha$_2$-adrenergic agonists when used as a tool for the reduction or discontinuation of opioids or opioid substitution therapy?*

Relative to placebo, alpha$_2$-adrenergic agonists were found to result in less severe symptoms of opioid withdrawal, longer times in treatment, and higher rates of treatment completion in both an RCT and studies identified in a systematic review.[12,18] Two systematic reviews identified less evidence comparing alternative alpha$_2$-adrenergic agonist regimens, but the evidence collected suggested that they performed similarly with no significant differences in treatment completion,[13,15] withdrawal rates or symptom severity[15] between lofexidine and clonidine. One systematic review deemed that the data used by studies comparing lofexidine and clonidine was both, "limited and diverse," (pg 19)[12] precluding quantitative analysis; however, the evidence suggested similar effects of both drugs on withdrawal symptoms.[12] The one study that included guanfacine in combination with naltrexone found no significant difference in retention or relapse rates, relative to naltrexone alone.[21] However, the perceived stress score was significantly lower in groups receiving active guanfacine treatment.[21]

Three systematic reviews found the severity of withdrawal symptoms[12,15] and treatment completion[17] were similar between alpha$_2$-adrenergic agonists and methadone. For example, peak withdrawal scores and mean withdrawal severity were similar (Standardized Mean Difference (SMD) = 0.22 [95% confidence interval [CI] -0.02 to 0.46] and SMD = 0.13 [95% CI -0.24 to 0.49], respectively).[12] Another systematic review using indirect comparisons found methadone detoxification treatment resulted in a higher likelihood of treatment completion relative to clonidine, though the effect was imprecise and the confidence interval approached the null value of 1. (Odds Ratio (OR) = 2.42 [95% CI 1.07 to 5.37]) but not lofexidine (OR = 1.62 [95% CI 0.58 to 4.57]).[13]

Alpha$_2$-adrenergic agonists were generally found to perform worse than buprenorphine. One systematic review found lower withdrawal scores (SMD = -0.43 [95% CI -0.58 to -0.28]) and increased chance of treatment completion (Risk Ratio (RR) = 1.59 [95% CI 1.23, 2.06]) in the buprenorphine group.[14] Another systematic review also favoured buprenorphine for treatment completion compared with clonidine. (OR = 3.95 [95% CI 2.01 to 7.46]).[13] No significant difference was found compared with lofexidine (OR = 2.64 [0.90 to 7.50]).[13] Similarly, the remaining systematic review studying buprenorphine found less severe withdrawal symptoms and higher treatment retention relative to clonidine. The exception were two Iranian studies based on the same trial which found no significant differences in COWS, ARWS or craving stores between buprenorphine and clonidine.[19,20] The trial underlying these two studies also had a follow-up time of six months, though the intervention stopped on Day 5 and naltrexone was administered to both arms until study end.

Similarly, alpha$_2$-adrenergic agonists were less effective than buprenorphine-naloxone treatment in two studies. One reported that COWS and craving scores were significantly higher in with buprenorphine-naloxone relative to clonidine,[22] while the other reported significantly greater reductions of withdrawal symptoms measured through COWS and ARSW in the buprenorphine-naloxone group than in the clonidine group.[23] Further it reported a higher likelihood of abstinence and retention at the end of follow up. (OR = 9.503 [95% CI 4.604 to 19.614] and OR = 22 [95% CI 11 to 46], respectively).[23]

The most common adverse events associated with alpha$_2$-adrenergic agonists included hypotension (particularly with clonidine),[12,18-20,22] dizziness[12,18,20,22] and dry mouth.[12,18,22] In the largest study (n = 264), these occurred in 34 (25.4%) patients, 30 (22.4%) and 19 (4.2%) of patients, respectively.[18] Two systematic reviews reported that adverse effects appeared to be worse with clonidine than lofexidine.[12,15,21] Low blood pressure was reported to lead to discontinuation in the clonidine intervention group in three trials.[19,20,22]

2. *What are the evidence-based guidelines regarding the use of alpha$_2$-adrenergic agonists for the treatment of patients who are reducing or discontinuing opioids or opioid substitution therapy?*

Two guidelines do not recommend alpha$_2$-adrenergic agonists as a first-line medication, however they could be considered as a second-line medications if using other opioid substitution therapies is not possible.[24,26] One guideline further does not recommend using alpha$_2$-adrenergic agonists in combination with methadone and possibly buprenorphine except in cases with marked hypertension.[26] The remaining guideline[25] cited the conclusions of the systematic review by Gowing et al. 2016[12] in its literature review on alpha$_2$-adrenergic agonists for opioid withdrawal management. However, this guideline did not provide recommendations specifically pertaining to the use of alpha$_2$-adrenergic agonists.[25]

Detailed descriptions of study findings and guideline recommendations are provided in Appendix 4.

Limitations

The quality of evidence contained within the systematic reviews and guidelines varied depending on the comparison and outcome. Evidence was considered better quality for comparisons of buprenorphine to alpha$_2$-adrenergic agonists,[14,24] but less strong in comparisons of alpha$_2$-adrenergic agonists to methadone.[12] Comparisons of different alpha$_2$-adrenergic agonists regimens,[12,16] were based generally on low quality and heterogeneous studies which precluded meaningful meta-analysis. The main limitation of the clinical trials was that follow up times were relatively short. Three studies followed patients for six months or more,[19-21] however the rest were less than 14 days. It is thus difficult to interpret the evidence beyond this period, despite opioid discontinuation generally taking longer. Finally, evidence comparing alpha$_2$-adrenergic agonists to non-medicated regimens, such as behavioural therapy or peer-support, was not available, and most of the evidence pertained to clonidine specifically.

Conclusions and Implications for Decision or Policy Making

Alpha$_2$-adrenergic agonists were found to be more effective than placebo to assist with opioid reduction or discontinuation, however they appear less effective than buprenorphine and potentially similar to methadone and to drugs within the same class. Two studies based on the same trial were the exception, and found the effectiveness of clonidine and buprenorphine were similar,[19,20] though the study setting was Iran which may be contextually different. Hypotension was a common adverse effect with clonidine that led to discontinuation in three trials.[19,20,22] Overall the quality of studies was highest in comparisons of alpha$_2$-adrenergic agonists against buprenorphine and placebo, followed by alpha$_2$-adrenergic agonists against methadone, and the evidence was highly limited in quantity for comparing alpha$_2$-adrenergic agonists to each other.

Two high quality guidelines[24,26] do not recommend alpha$_2$-adrenergic agonists as a first-line medication, however they could be considered as a second-line medications if using other opioid substitution therapies is not possible. One guideline further does not recommend using alpha$_2$-adrenergic agonists in combination with methadone and possibly buprenorphine except in cases with marked hypertension.[26]

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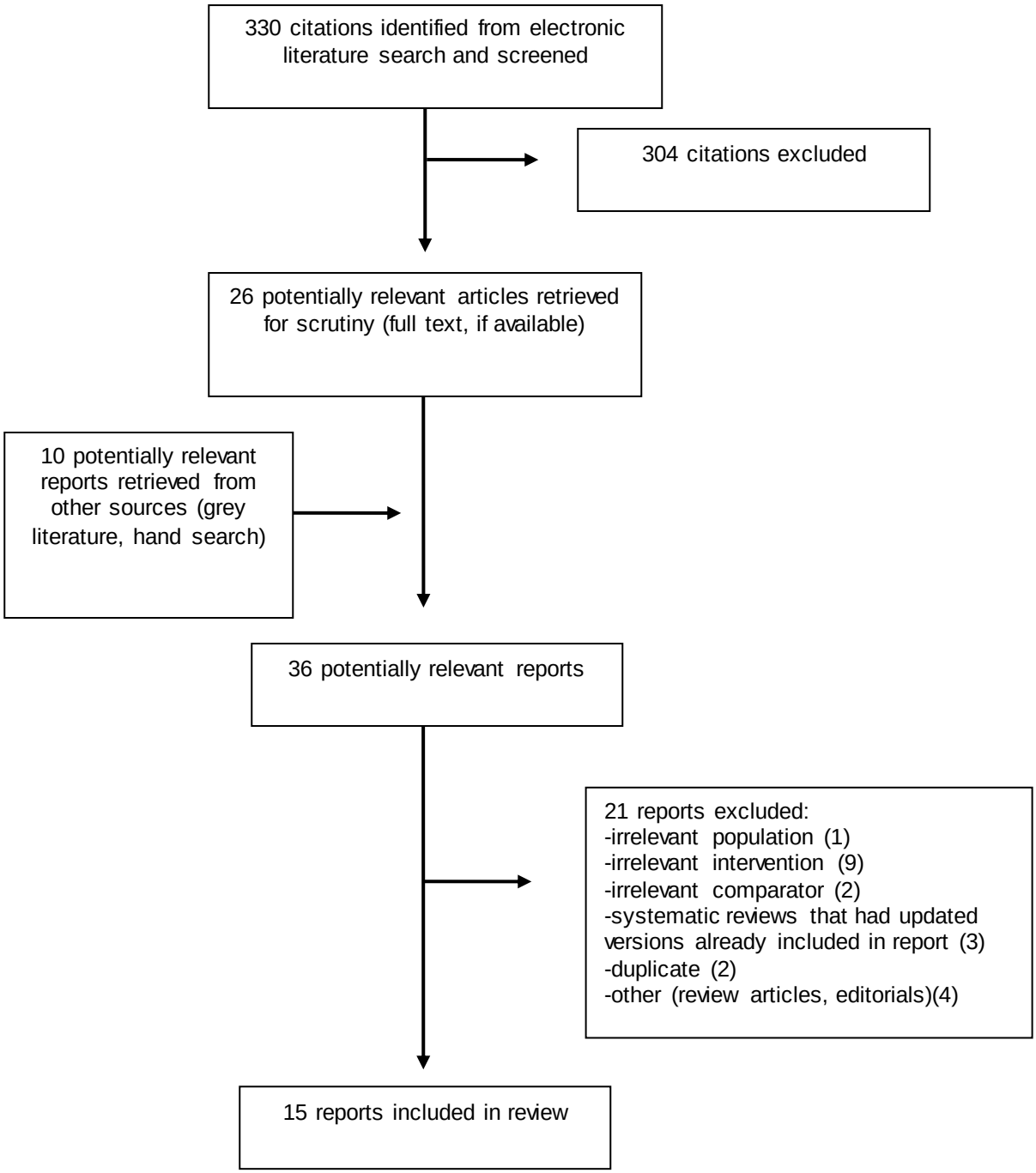
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
Amato, 2013[17]	11 RCTs with relevant comparisons (adrenergic agonists versus methadone)	Opioid users in tapered methadone treatment to manage withdrawal from heroin, methadone or buprenorphine	Adrenergic agonists	Methadone	-Treatment completion -Severity of withdrawal -Abstinence at follow up -Adverse effects
Gowing, 2017[16]	Nine studies (5 RCT and 4 prospective cohort) with relevant comparisons (treatment primarily based on clonidine or lofexidine versus clonidine or lofexidine plus opioid antagonist [naltrexone or naloxone])	Participants who were primarily opioid dependent and undergoing managed withdrawal.	Adrenergic agonists (including clonidine or lofexidine)	Placebo, methadone, buprenorphine, different adrenergic agonist, adrenergic agonists plus opioid antagonists (naltrexone or naloxone)	-Severity of withdrawal symptoms -Duration of treatment -Nature and incidence of adverse effects -Completion of treatment -Engagement in further treatment
Gowing, 2017[14]	14 RCTs with relevant comparisons (clonidine or lofexidine versus buprenorphine)	People with opioid dependence undergoing managed withdrawal.	Alpha$_2$-adrenergic agonists (clonidine or lofexidine)	Buprenorphine	-Intensity of withdrawal -Duration of withdrawal treatment -Nature and incidence of adverse events -Treatment completion -Engagement in further treatment
Gowing, 2016[12]	22 RCTs with relevant comparisons (including six with placebo comparator, 11 with reducing doses of methadone, four comparing different alpha$_2$-adrenergic agonists, and one comparing clonidine, methadone and guanfacine)	Participants who were primarily opioid dependent and underwent managed withdrawal.	Administration of an alpha$_2$-adrenergic agonist to ameliorate opioid withdrawal symptoms.	Reducing doses of methadone, placebo, or a different alpha$_2$-adrenergic agonist	-Withdrawal syndrome -Treatment duration -Completion of treatment -Adverse events -Seeking further treatment

First Author, Publication Year	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes
Meader, 2010[13]	12 RCTs with relevant comparisons (seven compared methadone and clonidine or lofexidine, one compared buprenorphine and lofexidine and four compared clonidine and lofexidine).	Opioid users	Clonidine or lofexidine	Opioid substitution medication (methadone or buprenorphine), or a different alpha$_2$-adrenergic agonist (clonidine or lofexidine)	Completion of treatment
Praveen, 2011[15]	Two systematic reviews with relevant comparisons (buprenorphine vs clonidine)	People with opioid dependence undergoing treatment for withdrawal, stabilization or relapse prevention	Any treatment used for opioid withdrawal, stabilisation or relapse prevention (including clonidine)	Any treatment used for opioid withdrawal, stabilisation or relapse prevention (including buprenorphine)	-Mortality -Opioid misuse -Treatment retention -Criminality -Adverse effects -Severity of withdrawal symptoms

RCT = randomized controlled trial.

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Gorodetzky, 2017, U.S.A[18]	Double-blinded RCT	In-patients aged 18 and over, seeking treatment for opioid dependence (DSM-IV), without serious medical or psychiatric illness	lofexidine 0.8 mg four times daily	Matching placebo	SOWS-Gossop, SOWS-Gossop AUC, OOWS, MCGI,VAS-efficacy -Time to dropout -Concomitant medications -Adverse events
Hussain, 2015, India[22]	Open-label RCT	Inpatients aged 15-50 fulfilling DSM-IV criteria for opiate dependence who were inpatients at a hospital, without serious psychiatric or medical illness	Clonidine administered orally for 10 d in the dose range of 50-200 µg/day in divided doses (50 twice daily for Day 1, then 50 every six hours day 2-4, then reduced back to 50 twice daily for day 5-7, then once daily until day 10)	Sublingual buprenorphine and naloxone combination (4.0/1.0 mg for day 1, 8.0/2.0 mg/day day 2 to day 4, and reduced to 4.0/1.0 mg for day 5 to day 7, and continued at 2.0/0.5 mg/day from day 8 till the end of study at day 10)	COWS, adverse events

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Krupitsky, 2013, Russia[21]	Double-blinded RCT	People aged 18-50 fulfill DSM-IV criteria for opioid dependence with education at the high school level or above and a stable address within the St. Petersburg, home telephone number, without series mental or physical illness	-Naltrexone 50 mg/day and guanfacine 1 mg/day -Naltrexone placebo and guanfacine 1 mg/day -Individual drug counseling	-Naltrexone 50 mg/day and guanfacine placebo -Naltrexone placebo and guanfacine placebo -Individual drug counseling	-Early termination -Relapse -Cumulative percentages of opiate negative urines -Adverse events
Ziaaddini, 2010, Iran[20]	Double-blinded RCT	Opioid-dependent inpatient males aged 18-40 who could read and write, without major mental or physical illness.	0.2 mg oral clonidine tablets and buprenorphine placebo. Naltrexone at 25 mg/day started 2 days after treatment end, for 6 months.	Oral clonidine placebo and 2 mg/day buprenorphine sublingual. Naltrexone at 25 mg/day started 2 days after treatment end, for 6 months.	-COWS, ARWS, VAS-craving -Success rate of detoxification phase -Retention -Positive urine samples
Ziaaddini, 2012, Iran[19]	Double-blinded RCT	Opioid-dependent inpatient males aged 18-40 who could read and write, without major mental or physical illness.	0.2 mg oral clonidine tablets and buprenorphine placebo. Naltrexone at 25 mg/day started 2 days after treatment end, for 6 months.	Oral clonidine placebo and 2 mg/day buprenorphine sublingual. Naltrexone at 25 mg/day started 2 days after treatment end, for 6 months.	-COWS, ARWS, VAS-craving -Success rate of detoxification phase -Retention -Positive urine samples
Ziedonis, 2009, USA[23]	Open-label RCT	Those 15 years of age and older, in general good health and seeking treatment for heroin dependence	Clonidine	Buprenorphine-naloxone	-Retention -Abstinence at end of treatment -COWS, ARSW

DSM-IV = Diagnostics and Statistical Manual for Mental Disorders; SOWS-Gossop = Short Opiate Withdrawal Scale-Gossop;OOWS = Objective Opiate Withdrawal Scale; AUC = Area Under the Curve; COWS=the Clinical Opiate Withdrawal Scale; ARWS=Adjective Rating of Withdrawal Scale; VAS = Visual Analogue Scale; MCGI = Modified Clinical Global Impressions Scale.

Table 4: Characteristics of Included Guidelines

	Intended users/Target pop	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, selection and synthesis	Evidence Quality and Strength	Recommendations development and Evaluation
WHO, 2009[24]	Those involved in providing psychosocially assisted pharmacological treatment of opioid dependence at any level	Use of methadone, buprenorphine, naltrexone and alpha$_2$-adrenergic agonists (clonidine, lofexidine and guanfacine) for opioid dependence and withdrawal.	Treatment completion, severity of withdrawal, side effects	-Reviewed literature for Cochrane reviews and other systematic reviews -Where no review existed, conducted an additional systematic review, or conducted additional meta-analyses	-Using the GRADE system, evidence is classified as "high", "moderate", "low", or "very low". -Strength of recommendations classified as "strong" or "standard".	-Technical experts considered the evidence and other sources of considerations to develop recommendations -Draft of guidelines sent to select organizations and WHO offices before finalization
Soyka, 2011[26]	Clinicians who diagnose or treat patients with opioid use disorders	Use of methadone, buprenorphine, buprenorphine/naloxone, heroin, naltrexone, clonidine for withdrawal	Abstinence from opioids, decrease in use of opioids	-Reviewed literature in MEDLINE and Cochrane Database -Reviewed other national and international guidelines -Categorized evidence according to bias risk	-Evidence graded from A (full evidence from controlled studies) to F (lack of or inadequate evidence). -Recommendations graded from 1 (Category A evidence and good risk-benefit ratio) to 5 (Category D evidence)	-Task force of 22 experts evaluated and discussed the evidence to develop recommendations
British Columbia Centre on Substance Abuse, 2017[25]	Physicians, nursing and allied healthcare professionals, and those forming policy to address addiction needs	Medically-assisted detoxification, residential treatment, long-term agonist therapy, antagonist medications, psychosocial treatment and harm reduction	Not specified	-Structured literature review, giving the most weight according to the evidence hierarchy -Staff independently selected studies and summarized evidence	-GRADE used to evaluate the literature and determine strength of recommendations	-Sought consensus between committee -Draft guidelines circulated and finalized within the committee, and then external experts and stakeholders

GRADE = Grading of Recommendations Assessment, Development and Evaluation; WHO = World Health Organization.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[9]

Strengths	Limitations
Amato, 2013[17]	
-Comprehensive database search -Clear PICO Question -Risk of bias assessment and quality summary using GRADE -Assessed heterogeneity using I^2 and Chi^2 test -Provided characteristics of excluded studies -Two reviewers assessed full texts for inclusion -Two reviewers extracted information -Evidence quality considered when interpreting results and formulating conclusions	-One reviewer scanned titles and abstracts -Did not report adverse effects identified by studies
Gowing, 2017[16]	
-Comprehensive database search -Clear PICO Question -Risk of bias assessment -Assessed heterogeneity using I^2 and Chi^2 test, and with forest plots, however studies too diverse to meta-analyze -Provided characteristics of excluded studies -Evidence quality considered when interpreting results and formulating conclusions	-One reviewer screened and extracted abstracts
Gowing, 2016[12]	
-Clear PICO question -Searched multiple databases -Assessment of risk of bias -Assessment of study heterogeneity using forest plots and I^2 -Appropriate meta-analysis -Provided list of excluded studies -Evidence quality considered when interpreting results and formulating conclusions	-One reviewer screened and extracted abstracts -Small number of studies precluded assessing publication bias
Gowing, 2017[14]	
-Clear PICO question -Search of multiple databases -Abstract screening confirmed by 3 reviewers -Assessment of risk of bias -Heterogeneity between studies assessed using I^2 and Chi^2 test -Appropriate meta-analysis -Evidence quality considered when interpreting results and formulating conclusions	-One reviewer assessed abstracts and extracted information, which was confirmed by other reviewers
Meader, 2010[13]	
-Comprehensive search of databases, journals and forward citations -Data extraction completed by the author and research assistant -Strong statistical analysis using MCMC method for direct and indirect comparisons	-PICO question not clearly defined -Double screening of abstracts not stated -No description of heterogeneity across studies, the model fit was assessed -No reporting of studies' quality

Strengths	Limitations
-Risk of bias assessed using SIGN criteria	
Praveen, 2011[15]	
-Searched multiple databases -Two reviewers reviewed abstracts -Quality assessment using GRADE -Evidence quality considered when interpreting results and formulating conclusions	-Unclear PICO question - intervention/comparator, specific population of interest not pre-specified

PICO = Population, Intervention, Comparators, Outcome; GRADE = Grading of Recommendation, Assessment, Development and Evaluation; MCMC = Markov chain Monte Carlo; SIGN = Scottish Intercollegiate Guidelines Network

Table 6: Strengths and Limitations of Randomized Controlled Trials using Downs & Black[10]

Strengths	Limitations
Gorodetzky, 2017[18]	
-Power calculation demonstrates sufficient power -15 sites, double blind, matching placebo -Use of validated scale for outcome -Appropriate statistical analysis including using multiple imputation for missing data, and analysis of covariance to compare groups with adjustment for opioid dependence severity score -Balanced baseline characteristics between treatment and control groups -'Adaptive' randomization that favoured treatment using biased coin procedure, based on previous assignments	-No information on allocation concealment -50/135 (37%) in treated and 35/130 (27%) in placebo completed treatment -Present p-values for treatment outcomes rather than full confidence intervals
Hussain, 2015[22]	
-Balanced baseline characteristics across intervention and comparator groups -Use of validated scale for outcome	-Unclear allocation concealment and randomization process -Not blinded and open-label -Statistical analysis for small sample size with multiple testing, despite having large enough sample size (n=56) for more appropriate modelling and presenting confidence intervals
Krupitsky, 2013[21]	
-Identical placebos -Recruitment through hospital as well as district psychiatrists -Generated allocation sequence and randomization by biostatistician, and description of adequate procedures to ensure these -Appropriate analysis including ITT or group differences using repeat measures ANOVA where too many values were missing -Power calculation suggested adequate sample size -Balanced baseline characteristics	-Potentially non-representative due to requirement of a stable address and phone number -Primary and secondary outcome measures unclear in methods section -Results unclear, precluding understanding which outcome odds ratios refer to -Results not reported for all comparisons and stated outcomes
Ziaddini, 2010[20]	
-Matching placebo tablets -Appropriate statistical analysis including repeat measures ANOVA -Use of validated scale for outcome -Balanced patient characteristics, except higher proportion of single men in clonidine group	-No description of randomization or allocation concealment process -Urine screen outcome not analysed as stated -No flow chart -No source of funding stated

Strengths	Limitations
Ziaddini, 2012[19]	
-Matching placebo tablets -Appropriate statistical analysis given small sample size -No dropouts reported -Use of validated scale for outcome	-Small sample size, no power calculation -No description of randomization or allocation concealment process -No table of baseline characteristics of participants -Urine screen outcome not analysed as stated -No flow chart -No source of funding stated
Ziedonis, 2009[23]	
-Appropriate use of logistic regression models and ANOVA -Use of validated outcome scales	-Not randomized by setting, included both inpatients and outpatients -No information on randomization, allocation concealment or blinding (if any) -Did not state exclusion criteria -No population characteristics stratified by treatment group provided -No detail on intervention or comparator

Table 7: Strengths and Limitations of Guidelines using AGREE II[11]

Strengths	Limitations
World Health Organization, 2009[24]	
-Evaluated evidence using GRADE system -Population and objectives clearly described -Guideline development group included range of people and groups -Evidence limitations and evaluation criteria were clear -Systematic searching and meta-analysis where necessary	-No apparent patient involvement or public consultation, other than pre-selected groups
Soyka, 2011[26]	
-Clear intended user -Systematic assessment of study quality and risk of bias	-Mainly developed only by psychiatrists or psychologists -Lack of detail reported on developing the recommendations -Literature searching details not reported in detail
British Columbia Centre on Substance Abuse, 2017[25]	
-Interdisciplinary team with 28 members for the guideline committee -Followed AGREE-II instrument for development -Clear statement of interventions considered -Used of GRADE to evaluate literature -Draft guidelines reviewed by external stakeholders	-No apparent patient involvement or public consultation, other than pre-selected groups -Did not specify specific outcomes -Lack of detail on literature review methods

AGREE-II = Appraisal of Guidelines for Research & Evaluation Instrument-II; GRADE = Grading of Recommendation, Assessment, Development and Evaluation.

Appendix 4: Main Study Findings and Author's Conclusions

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Systematic Reviews	
Amato, 2013[17]	
Tapered methadone vs adrenergic agonists Completion of treatment: 7 studies; RR = 1.1 [0.91;1.32] (Note heterogeneity test suggested studies significant differences across studies, but 5/7 had null funding regardless) Abstinence at end-follow up: 1 study; No significant difference	"Comparing methadone with adrenergic agonists, studies showed no substantial clinical difference between the treatments in terms of completion of treatment...early withdrawal symptoms were less adequately controlled with lofexidine than methadone" (pg 16)
Gowing, 2016[12]	
Alpha$_2$-adrenergic agonist vs methadone (All low quality except withdrawal symptoms which was moderate quality) Participants with severe withdrawal: 5 studies; RR = 1.18 [95% CI 0.81; 1.73] Peak withdrawal score: 2 studies; SMD = 0.22 SD [95% CI -0.02; 0.46] Mean overall withdrawal severity: 3 studies; SMD = 0.13 [95% CI -0.24; 0.49] Duration of treatment: 3 studies; SMD -1.07 [-95% CI 1.31; -0.83] Hypotensive or other adverse effects: 6 studies; RR = 1.92 [95% CI 1.19; 3.10] Drop-out due to adverse effects: 4 studies; RR= 3.62 [95% CI 0.77; 16.94] Completion of treatment: 9 studies; RR = 0.85 [95% CI 0.69; 1.05] ***Alpha2-adrenergic agonist vs placebo (Moderate quality)*** Participants with severe withdrawal: 3 studies; RR = 0.32 [95% CI 0.18; 0.57] Completion of treatment: 3 studies; 3 studies; RR = 1.95 [95% CI 1.34; 2.84] ***Clonidine vs lofexidine/guanfacine*** No meta-analysis possible due to diverse studies Similar effectiveness on withdrawal syndrome based on limited studies Less hypotension with lofexidine compared with clonidine	"Compared to placebo, clonidine and lofexidine are associated with less severe withdrawal, longer time in treatment, and significantly higher rates of completion of treatment." (pg 26) "In comparison with reducing doses of methadone, the overall intensity of withdrawal associated with alpha2-adrenergic agonist treatment appears similar to, or perhaps marginally greater than, that that associated with reducing doses of methadone." (pg 26) "Data are limited, but it appears that clonidine and lofexidine have similar capacity to ameliorate the signs and symptoms of opioid withdrawal" (pg 7)
Gowing, 2017[14]	
Buprenorphine vs clonidine *Moderate quality* Mean overall withdrawal score: 7 studies; SMD = -0.43 [95% CI -0.58; -0.28] Number completing withdrawal treatment: 11 studies; RR = 1.59 [95% CI 1.23; 2.06]; significant heterogeneity Mean days in treatment: 3 studies; SMD = 0.92 [95% CI 0.57; 1.27]; significant heterogeneity *Very Low or Low Quality*	"The withdrawal scores and descriptive reporting of the withdrawal syndrome experienced by participants support a conclusion that buprenorphine is more effective than alpha2-adrenergic agonists in ameliorating the signs and symptoms of opioid withdrawal, both in terms of the peak average withdrawal score and the average daily withdrawal score over the withdrawal episode. We assessed the quality of evidence as low to moderate" (pg 28)

Main Study Findings	Author's Conclusion
Mean peak withdrawal score: 6 studies; SMD = -0.43 [95% CI -0.74;-0.13]; significant heterogeneity Number with adverse events: 3 studies; RR = 0.93 [95% CI 0.70; 1.26] Number discontinued due to AE: 3 studies; RR = 0.20 [95% CI 0.04; 1.15]	
Gowing, 2017[10]	
Antagonist-adrenergic agonist combination versus adrenergic agonist -Severity of withdrawal: Too much variability, low quality and small number of studies to conclude, but some suggestion that antagonist-induced withdrawal is similar or at best less severe, when combined with an alpha$_2$-adrenergic agonist -Adverse events: Adverse effects of alpha$_2$-adrenergic agonists (dizziness, sedation, dry mouth) are likely to be experienced in the first few days of treatment, but hypotension resulting in discontinuation may be rare when administered alongside an antagonist, and less likely with lofexidine then clonidine -Duration of treatment: Too little reported to conclude -Completion of treatment: Antagonist-induced withdrawal may result in significantly higher rates compared to regimens based mainly on an adrenergic agonist in some situations, but evidence inconsistent and uncertain	"The evidence is insufficient to establish a detailed picture of the nature of the opioid withdrawal syndrome induced by opioid antagonist treatment compared to that managed with an adrenergic agonist alone." (pg 20)
Meader, 2010[13]	
Direct Comparisons from study data (Treatment Completion [95% Credible Interval]) Lofexidine vs Clonidine: OR = 1.74 [95% CI 0.28; 10.82] Methadone vs Clonidine: OR = 1.98 [95% CI 0.47;6.99] Buprenorphine vs Clonidine: OR = 2.22 [95% CI 1.1; 4.26] Methadone vs Lofexidine: OR = 2.01 [95% CI 0.39; 10.17] Buprenorphine vs Lofexidine: OR = 1.40 [95% CI 0.009; 193.3] ***Indirect Comparisons (Treatment Completion)*** Lofexidine vs Clonidine: OR = 1.50 [95% CI 0.53;4.11] Methadone vs Clonidine: OR = 2.42 [95% CI 1.07; 5.37] Buprenorphine vs Clonidine: OR = 3.95 [95% CI 2.01;7.46] Methadone vs Lofexidine: OR = 1.62 [95% CI 0.58;4.57] Buprenorphine vs Lofexidine: OR = 2.64 [95% CI 0.90;7.50]	"In conclusion, buprenorphine and methadone appear to be the most effective detoxification treatments. Lofexidine and clonidine were very unlikely to be the most effective" (pg 113)
Praveen, 2011[15]	
Buprenorphine vs clonidine -Retention in treatment (high quality): Two systematic reviews favour buprenorphine for increasing the length of time people stay in outpatient treatment and at increasing the proportion of people who complete treatment -Severity of withdrawal symptoms (moderate-high quality): Two systematic reviews favour buprenorphine to reduce withdrawal scores -Two systematic reviews suggest no significant difference in adverse effects ***Alpha2-adrenoceptor agonists vs placebo***	"Methadone, buprenorphine, and alpha2-adrenoceptor agonists (lofexidine, clonidine) can all help people to withdraw from dependence on illicit opioids. Lofexidine and clonidine may be less effective than methadone and buprenorphine in withdrawal, although evidence is weak." (pg 1-2)

Main Study Findings	Author's Conclusion
-Retention in treatment (moderate quality): One systematic review favours alpha2-adrenoceptor agonists -Adverse effects: alpha2-adrenoceptor agonists associated with more adverse effects ***Alpha2-adrenoceptor agonists v methadone*** -Withdrawal rate (low quality): One systematic review found no significant difference -Retention in treatment (low quality): Based on three systematic reviews, alpha2-adrenoceptor agonists maybe less effective than tapered methadone at increasing time in treatment -Adverse effects: One systematic review found significantly more adverse effects with alpha2-adrenoceptor agonists, the other found lower mean blood pressure but insignificant ***Lofexidine versus clonidine*** -Withdrawal rate (moderate quality): One systematic review found no significant difference -Retention in treatment (low quality): One systematic review found no significant difference -Severity of withdrawal symptoms (very low quality): One RCT found no significant difference -Adverse effects: Two studies favoured lofexidine ***Lofexidine vs buprenorphine*** Retention in treatment (low quality): No significant difference	
Randomized Controlled Trials	
Gorodetzky, 2017[18]	
SOWS-Gossop scores -Mean = 6.32 (SD = 4.71) in lofexidine vs 8.67 (SD = 5.54) in placebo (p=0.0212) -Mean time to dropout time quadrant = 6.9 vs 6.4 (p=0.0034) -Area under withdrawal symptoms-times curve ITT Analysis: 26.04 (SD=21.28) vs 29.63 (SD = 20.64) (p=0.0979) ***Completer Analysis*** -OOWS: ITT, Completer: p < 0.0001 -MCGI Severity Subjects: ITT p = 0.0119, Completer p = 0.2777 -MCGI Severity Rater: ITT p = 0.1123, Completer p = 0.2444 -Visual Analogue Scale for Efficacy (VAS-E): ITT p = 0.0016, Completer p = 0.0118 -Concomitant medications given: ITT p = 0.0855 -Concomitant medications used daily: ITT p = 0.0003-0.0007 for days 1,2 and 3, p = 0.0730 for day 4, p = 0.0221 for day 5 ***Safety*** -Intervention group had significantly more hypotension (34 (SD=25.4) vs 1 (SD=0.8)), dizziness (30 (SD=22.4) vs 9 (SD=6.9)), dry mouth (19 (SD=14.2) vs 2 (SD=1.5)), bradycardia (13 (SD=9.7) 2 (SD=1.5)), sedation (11(SD=8.2) vs 2 (SD=1.5)), and significantly less lacrimation (7 (SD=5.2) vs 20 (SD=15.4)) and vomiting (7 (SD=5.2) vs 27 (SD=20.8)).	"In the present study, lofexidine significantly alleviated symptoms of opioid withdrawal, resulted in longer patient retention in treatment, a higher rate of completing the active treatment period, and demonstrated a favorable safety profile" (pg 87)

Main Study Findings	Author's Conclusion
Hussain, 2015[22]	
Clonidine vs Buprenorphine-naloxone COWS Score: 11.37± 3.00 to 2.56± 1.40 vs 11.41± 2.71 to 0.30±0.61; p = 0.001 at day 5 Craving (VAS): 87.41±9.84 to 7.78±6.41 vs 90.40±10.20 to 1.85±6.22; p = 0.001 at day 5 Adverse events: Significant hypotension [n=2/27 (7.4%)] resulting in discontinuation, dizziness (22%), dry mouth (11%) in clonidine group. Mild headache [n=10/27 (37%)], 29% constipation, 22% nausea in bup-nax group	"Buprenorphine was found to be more effective than clonidine in controlling the opioid withdrawal and craving for the abused substance, however it lost its superiority towards the end of the study." (pg 3)
Krupitsky, 2013[21]	
Naltrexone + guanfacine vs Naltrexone + placebo Retention without relapse at 6 months: n=20 (26.7%) vs 15 (19.7%); p = 0.258 Median retention: 6 weeks for both Relapse at 9 months: n= 29 (2/75 in remission) vs n=25 (8/76 in remission); p = 0.098 Relapse at 12 months: n = 26 (3/75 in remission) vs n= 20 (5/76 in remission); p = 0.719 ***Placebo + guanfacine vs placebo*** Retention without relapse at 6 months: n=5 (6.7%) vs 8 (10.7%); p = 0.002 Relapse at 9 months: n=27 vs n=20 (4/75 in remission) Relapse at 12 months: n=23 (3/75 in remission) vs n=16 (2/75 in remission) Median retention: 4 weeks versus 5 weeks Perceived Stress Score at 18 weeks: (16 [SD = 5] vs 26 [SD = 4]) (p = 0.01) in active guanfacine groups Craving scores were significantly lower for the guanfacine groups at week 18 (0.3 [SD = 0.9] vs 0.9 [SD = 0.9]) (p < 0.05) and week 24 (2.3 [SD = 0.8] vs 3.5 [SD = 0.8]) (p < 0.05). ***Adverse Events*** -No significant group differences were found - results not stratified by treatment group	"Guanfacine in this study reduced perceived stress at later time points in this study, but it did not also significantly improve retention in naltrexone treatment (though the retention in naltrexone with guanfacine group was slightly better than in naltrexone with placebo)" (pg 8)
Ziaddini, 2012[19]	
Clonidine vs Buprenorphine -COWS Score: MD= 12 to 3.5 vs 11.1 to 3.1; p = 0.615 -ARWS Score: MD= 53.1 to 24.1 vs 47.4 to 17.5; p = 0.18 -Craving: MD= 89.1 to 62 vs 72.1 to 92.1; p = 0.87 -No. days receiving naltrexone (6 months): MD= 30.7 ± 9.1 vs 38.4 ± 13.2; p = 0.743 -No. days in treatment (6 months): MD= 87.7 ± 14.9 vs 59.7 ± 19.6; p = 0.301 -Adverse events: low blood pressure resulting in discontinuation (n=1) and dysphoria (n=1) in clonidine group	"[C]omparing the effectiveness of [clonidine and buprenorphine] in terms of detoxification did not show statistically significant differences" (pg 82)
Ziaddini, 2010[20]	
Clonidine vs Buprenorphine -COWS Score: MD=12.6 to 5.7 vs 7.1 to 1.7; p = 0.615	"This investigation showed that administration of buprenorphine for a few days can not only be as effective as clonidine in

Main Study Findings	Author's Conclusion
-ARWS Score: MD=52.7 to 34.1 vs 43.4 to 24.1; p = 0.18 -Craving: MD=96.2 to 67.5 vs 89.2 to 55.1; p = 0.87 -No. days receiving naltrexone (6 months): MD=32.5 (SD=10.3) vs 31.6 (SD=10.9); p = 0.74 -No. days in treatment (6 months): MD=70.2 (SD=17.4) vs 66.7 (SD=17.9); p = 0.958 -Adverse events: low blood pressure resulting in discontinuation (n=2), dizziness (n=1) in clonidine group, euphoria (n=1) in buprenorphine group	controlling the signs and symptoms of withdrawal from heroine, it is significantly superior to clonidine in that respect." (pg 22)
Ziedonis, 2009[23]	
Buprenorphine-naloxone vs clonidine -Abstinence at end: OR = 9.503 [95% CI 4.604;19.614] -Retention at end: OR = 22 [95% CI 11;46] -ARSW score: F(1,235) = 8.979, p = .003 , favouring buprenorphine -COWS score: F(1,190) = 4.619, p = .033, favouring buprenorphine	"As expected, medication type (buprenorphine–naloxone versus clonidine) was the strongest predictor of treatment success. The ability of buprenorphine–naloxone to reduce symptoms and retain subjects in the early phase of treatment may be a critical factor in understanding the better outcomes compared to clonidine " (pg 33)
Guidelines	
World Health Organization, 2009[24]	
Buprenorphine vs alpha-2 agonists -Higher completion rates with buprenorphine (RR [1.53, 95% CI 1.18; 1.99], moderate-quality evidence) -Lower peak objective withdrawal scores (SMD –0.61, [95% CI –0.86;–0.36], moderate-quality evidence) -Lower overall self-reported levels of opioid withdrawal (SMD –0.59, [95% CI –0.79; –0.39], high-quality evidence). ***Tapered Methadone vs alpha-2 agonists*** -No significant difference between methadone and alpha-2 agonists in treatment completion (RR 1.09, [95% CI 0.90; 1.32], moderate-quality evidence). -There was no difference in rates of relapse at followup (intention-to-treat analysis) (RR 1.06: [95% CI 0.55; 2.02], low-quality evidence). ***Adverse effects*** Alpha-2 agonists can cause postural hypotension, which can lead to dizziness and fainting	Standard recommendation with moderate quality evidence: "[To manage opioid withdrawal], tapered doses of opioid agonists should generally be used, although alpha-2 adrenergic agonists may also be used" (pg xvii)
Soyka, 2011[26]	
Rapid detoxification using naltrexone in combination with clonidine "There is no convincing evidence for the use of the combination of opioid antagonists plus clonidine under heavy sedation. Given the lack of evidence for a substantial advantage of this approach, the associated risks and costs do not appear to be justified." (Grade of recommendation not reported, pg 175-6) ***Reducing withdrawal symptoms*** "Clonidine and lofexidine are less effective than methadone and buprenorphine in reducing the symptoms of opioid withdrawal. Clinical experience has shown that combining alpha2-	"[For detoxification], Clonidine and potentially lofexidine are second-line medications." (pg 178)

Main Study Findings	Author's Conclusion
adrenoreceptor agonists with methadone or possibly buprenorphine can be useful and practicable only in cases with marked hypertension or related symptoms." (Grade 3 recommendation, pg 175) -Recommendations based on evidence from controlled studies (grade B evidence)	
British Columbia Centre on Substance Abuse, 2017[25]	
No specific recommendations pertaining to alpha$_2$-adrenergic agonists	N/A

95% CI = 95% Confidence Interval; RR=Risk Ratio; OR = Odds Ratio; SD = Standard Deviation; MD = Mean Difference; SMD = Standardized Mean Difference.