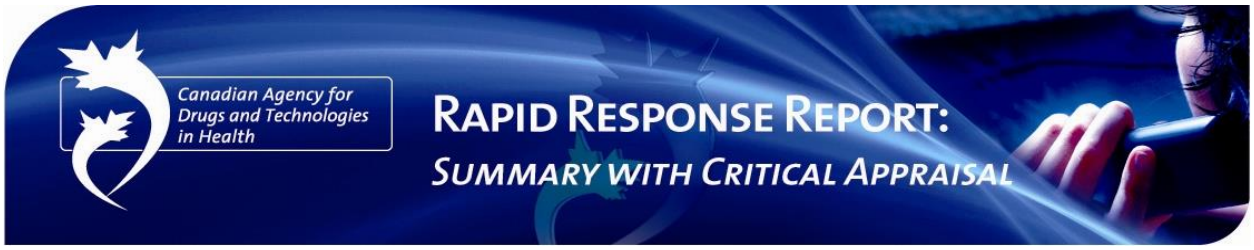

TITLE: Rapid and Ultra-Rapid Detoxification in Adults with Opioid Addiction: A Review of Clinical and Cost-Effectiveness, Safety, and Guidelines

DATE: 15 January 2016

CONTEXT AND POLICY ISSUES

Opioids are medicinally used to alleviate pain.[1] However, they can potentially cause euphoria[1] and are highly addictive.[2] It was estimated in 2012 that there were 15.6 million illicit opioid users worldwide, with 11 million who primarily used heroin,[3] which is the most commonly-abused opioid.[2] Other opioids include buprenorphine, codeine, methadone, and morphine.[2] Opioid abuse is associated with increased morbidity and mortality,[1] often caused by overdose and trauma.[4]

There are three stages to treating opioid dependence—namely, stabilization, withdrawal, and maintenance.[2] Stabilization aims to ensure that the opioid use becomes independent of the mental state (e.g., craving and mood) and circumstances (e.g., finance and physical location) and is usually achieved by substitution treatment.[2] Withdrawal aims to detoxify from opioids.[2] Traditional methods of detoxification include tapering with an opioid receptor agonist (e.g., buprenorphine or methadone[4]) or discontinuing opioids and administering an alpha-2 adrenergic receptor agonist (i.e., clonidine, dexmedetomidine, or lofexidine[4]).[5] Maintenance aims to prevent relapse.[2] After detoxification, maintenance treatment is of great importance for abstinence from opioids, and many clinicians recommend daily administration of an opioid receptor antagonist (e.g., naltrexone or naltrexone[4]).[5]

Even when pharmacologic agents are used in treating opioid dependence, there is often a significant amount of patient discomfort.[5] For example, opioid withdrawal may cause irritability, anxiety, apprehension, muscular and abdominal pains, chills, nausea, diarrhea, yawning, lacrimation, sweating, sneezing, rhinorrhea, general weakness, and insomnia,[6] and these withdrawal symptoms may last for days or weeks.[5] While opioid withdrawal is rarely life-threatening or associated with significant aberrations of mental state, the completion of withdrawal treatment is difficult for most people.[6]

Attempts have been made to shorten opioid withdrawal, with the use of sedation or anesthesia.[5,7] In rapid or ultra-rapid opioid detoxification (ROD or UROD), opioid receptor

antagonists are administered under heavy sedation or general anesthesia, with the intent of inducing withdrawal.[7] In theory, patients sleep through the most difficult period of having withdrawal symptoms,[7] thereby shortening the lag time between the patients' last dose of an opioid and the commencement of their maintenance treatment.[5] The distinction between ROD and UROD is made based on the duration of sedation or anesthesia, which is shorter for UROD than for ROD—although the exact length of time may vary (e.g., up to 30 minutes[8] or six hours[5] for UROD versus up to eight hours[8] or 72 hours[5] for ROD).

The purpose of this report is to identify and summarize the evidence for clinical and cost-effectiveness, and safety, as well as evidence-based clinical guidelines, on ROD and UROD in adults with opioid addiction.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of rapid and ultra-rapid opioid detoxification (ROD and UROD) in adults with opioid addiction?

2. What is the cost-effectiveness of ROD and UROD in adults with opioid addiction?

3. What are the evidence-based guidelines associated with the use of ROD and UROD in adults with opioid addiction?

KEY FINDINGS

There is some evidence suggesting earlier peaking of, and lower scores for, withdrawal symptoms and higher rates of the commencement and continuation of maintenance treatment in patients receiving UROD, compared to patients in control groups (e.g., conventional withdrawal treatment). However, no significant differences were identified between UROD and control groups in the commencement or duration of withdrawal treatment. Mixed results were identified between UROD and control groups in the completion of withdrawal treatment and the incidence of adverse events, depending on what pharmacologic agents were used. One guideline recommended against the use of UROD, due to high risk for adverse events. No evidence on ROD or on cost-effectiveness of ROD and UROD was identified.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources, including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Emergency Care Research Institute (ECRI), and Canadian and major international health technology agencies. A focused search was conducted on the Internet. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, published between January 1, 2010 and December 10, 2015.

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 (i.e., ≥ 18 years of age) with opioid addiction
Intervention	ROD or UROD
Comparator	Conventional detoxification programs (e.g., normal additions programs, administration of methadone for critical detoxification, or mental health sessions)
Outcomes	Q1: Clinical effectiveness and safety Q2: Cost-effectiveness Q3: Evidence-based guidelines
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized controlled studies, economic evaluations, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or if they were published prior to 2010.

Critical Appraisal of Individual Studies

The included SRs were critically appraised, using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[9] The included RCT was critically appraised, using the Downs and Black instrument.[10] The included evidence-based guideline was critically appraised, using the Appraisal of Guidelines for Research and Evaluation (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.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 358 citations were identified in the literature search. Following screening of titles and abstracts, 338 citations were excluded, and 20 potentially-relevant reports from the electronic search were retrieved for full-text review. Five potentially-relevant publications were retrieved from the grey literature search and hand searches. Of these 25 potentially-relevant articles, 21 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

The four publications comprised two SRs,[2,6] one RCT,[12] and one evidence-based guideline.[4] One SR[6] had been included in the other SR[2] but was included in this report, as additional

outcomes were reported in the original SR.[6] Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

A summary of the characteristics of the included SRs, RCT, and evidence-based guideline is presented in Appendix 2.

Clinical Effectiveness and Safety of ROD and UROD in Adults with Opioid Addiction

Two SRs[2,6] and one RCT[12] on clinical effectiveness and safety of UROD in adults with opioid addiction were identified. The two SRs,[2,6] compared to this report, were broader in scope; relevant findings are presented in this report.

Study Design

One SR[2] was conducted in 2011 and included SRs of RCTs, as well as RCTs and non-randomized controlled studies, and grey literature, such as Do-Not-Do Recommendations from the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK); findings on two SRs of RCTs and the Do-Not-Do Recommendations that were included in the SR[2] were relevant and presented in this report.

One SR[6] by the Cochrane Collaboration was conducted in 2010 and included RCTs and quasi-randomized controlled studies; findings on three RCTs and one quasi-randomized controlled study that were included in the SR[6] were relevant and presented in this report. The SR[6] conducted MAs, where possible.

One RCT[12] was conducted in 2011. No details on blinding, allocation methods used, or the number of sites involved were provided.

Country of Origin

Two SRs were conducted in the UK[2] and Australia.[6] One RCT[12] was conducted in Egypt.

Patient Population

Two SRs[2,6] included adults (i.e., aged 16 years or older)[2] or all ages,[6] with opioid dependence. The evidence from the two SRs[2,6] presented in this report was based on studies, in which the mean age of the study participants ranged between 30 and 36 years. One RCT[12] included male adults (i.e., aged 25 to 45 years), with opioid addiction.

Interventions and Comparators

Two SRs[2,6] compared UROD, using opioid receptor antagonists (i.e., naloxone, naltrexone, or nalmefene) during heavy sedation[2,6] or anesthesia,[6] versus conventional withdrawal treatment, using buprenorphine, clonidine, or tapered methadone. One RCT[12] compared UROD, using dexmedetomidine during general anesthesia, versus lofexidine administered after general anesthesia. No studies on ROD were identified.

Outcomes

One SR[6] and one RCT[12] reported on withdrawal symptoms. One SR[2] reported on the completion of withdrawal treatment, continuation of maintenance treatment or abstinence from opioids at 12 weeks, and Do-Not-Do Recommendations; except for the Do-Not-Do Recommendations, all outcomes reported in the SR[2] were findings of another SR[6] that was also included in this report. One SR[6] also reported on the commencement and duration of withdrawal treatment, the commencement of maintenance treatment, and the incidence of adverse events. The RCT[12] also reported on hemodynamic changes.

Cost-Effectiveness of ROD and UROD in Adults with Opioid Addiction

No studies on cost-effectiveness of ROD and UROD in adults with opioid addiction were identified.

Evidence-Based Guidelines Associated with the Use of ROD and UROD in Adults with Opioid Addiction

One evidence-based guideline[4] associated with the use of UROD in adults with opioid addiction was identified. The guideline,[4] compared to this report, was broader in scope; relevant findings are presented in this report.

Study Design

One evidence-based guideline[4] was developed by the American Society of Addiction Medicine (ASAM) in 2015.

Country of Origin

The ASAM guideline[4] was developed in the US.

Patient Population

The ASAM guideline[4] included all patients with opioid use disorder but provided separate recommendations for adolescents (i.e., aged between 11 and 21 years old).

Interventions and Comparators

The ASAM guideline[4] assessed all available options for the evaluation and treatment of opioid use disorder and management of opioid overdose.

Outcomes

The ASAM guideline[4] provided recommendations on UROD.

Summary of Critical Appraisal

A summary of the critical appraisal of the included SRs, RCT, and evidence-based guideline is presented in Appendix 3.

Clinical Effectiveness and Safety of ROD and UROD in Adults with Opioid Addiction

Two SRs[2,6] were of mixed quality. Both SRs[2,6] provided a list of the included studies and their characteristics, evaluated the scientific quality of the included studies and used it appropriately in formulating conclusions, and employed appropriate methods to combine the findings of the included studies. However, in both SRs,[2,6] it is unclear whether an "a priori" design was used, and the likelihood of publication bias was not assessed. In one SR,[2] it was unclear whether there was duplicate study selection and data extraction and whether a comprehensive literature search, including grey literature, was conducted. In the other SR,[6] there was no duplicate study selection and data extraction, and the literature search did not include grey literature. While one SR[2] provided a list of the excluded studies, the other SR[6] did not. Some of the authors of both SRs[2,6] declared conflicts of interest.

One RCT[12] was of low quality. The RCT[12] described its objective, outcomes measured, interventions, and findings, with estimates of random variability in the data; used appropriate statistical tests to assess the valid and reliable main outcomes; and randomized study participants who were recruited from the same population over the same period of time into intervention and control groups. However, it is unclear whether patients asked to participate or included in the study were representative of the entire population of interest, whether the trial design was representative of the care setting, and whether an attempt was made to blind study participants to the intervention they received or blind staff measuring the main outcomes. Further, the RCT provided limited descriptions of their characteristics, such as demographic and clinical factors; therefore, the distributions of potential confounders (e.g., baseline health status) between intervention and control groups were incompletely described, and it is unclear whether adjustment for confounding was needed in the analysis for the main findings. It is also unclear whether any study participants were lost to follow-up; compliance with the interventions was not described; other than withdrawal symptoms, no adverse events were reported; and, instead of actual probability values, the RCT reported statistical significance if the *p*-value was less than 0.05. No power calculations were provided, and it is unclear whether the study had sufficient power to detect a clinically-important effect.

Evidence-Based Guidelines Associated with the Use of ROD and UROD in Adults with Opioid Addiction

One evidence-based guideline[4] was of low quality. The guideline[4] described objectives, health questions, and target users; involved all relevant stakeholders in guideline development; outlined the methods for formulating recommendations, which considered benefits and harms and were explicitly linked to supporting evidence; was externally reviewed by experts prior to its publication; and described a procedure for updating the recommendations. However, the guideline[4] did not explicitly describe target populations; did not seek direct input from patients and caregivers; provided no search strategies, limited evidence selection criteria, and no evidence tables; did not critically appraise the quality of included evidence; and identified no facilitators or barriers, tools or resources, or resource constraints, for implementation or auditing criteria. Funding sources were partially disclosed, and seven of the eleven members of the Guideline Committee declared conflicts of interest.

Summary of Findings

A summary of the findings of the included SRs, RCT, and evidence-based guideline is presented in Appendix 4.

What is the Clinical Effectiveness and Safety of ROD and UROD in Adults with Opioid Addiction?

Withdrawal Symptoms

One SR[6] reported that a 2003 study found earlier peaking of an increase in withdrawal symptoms in patients receiving UROD (i.e., naltrexone during heavy sedation or anesthesia), compared to patients receiving tapered methadone. The SR[6] also reported that a 2005 study found no significant differences in withdrawal symptoms among patients receiving UROD (i.e., nalmefene followed by naltrexone during heavy sedation or anesthesia), buprenorphine, or clonidine. However, one RCT[12] reported higher scores for withdrawal symptoms in patients receiving lofexidine administered after general anesthesia, compared to patients receiving UROD (i.e, dexmedetomidine during general anesthesia).

Commencement of Withdrawal Treatment

One SR[6] conducted a MA of three studies and reported no significant differences in the number of patients who refused group allocation or failed to attend treatment between UROD (i.e., naloxone, naltrexone, or nalmefene during heavy sedation or anesthesia) and conventional withdrawal treatment (i.e., buprenorphine, clonidine, or tapered methadone) groups.

Duration of Withdrawal Treatment

One SR[6] reported that a 2005 study found no significant differences in the mean number of weeks in withdrawal treatment among patients receiving UROD (i.e., nalmefene followed by naltrexone during heavy sedation or anesthesia), buprenorphine, or clonidine.

Completion of Withdrawal Treatment

One SR[2] reported that it is unclear whether UROD (i.e., naloxone or naltrexone during heavy sedation) is more effective than conventional withdrawal treatment (i.e., buprenorphine, clonidine, or tapered methadone) at increasing the proportion of patients who complete detoxification treatment. The SR[2] rated the evidence associated with this outcome as low quality. Specifically, the Cochrane SR,[6] which informed the above SR,[2] reported that a 2003 study found higher rates of the completion of withdrawal treatment with UROD (i.e., naltrexone during heavy sedation or anesthesia), compared to clonidine, but that a 2006 study found no significant differences between UROD (i.e., naloxone and naltrexone during heavy sedation or anesthesia) and clonidine.

Commencement of Maintenance Treatment

One SR[6] conducted a MA of three studies and reported that the commencement of maintenance treatment with naltrexone was significantly more likely with patients receiving UROD (i.e., naloxone, naltrexone, or nalmefene during heavy sedation or anesthesia), compared to patients receiving clonidine. The SR[6] also reported that a 2005 study found that

the commencement of maintenance treatment with naltrexone was significantly more likely with patients receiving UROD (i.e., nalmefene followed by naltrexone during heavy sedation or anesthesia), compared to patients receiving buprenorphine.

Continuation of Maintenance Treatment or Abstinence from Opioids at 12 Weeks

One SR[2] reported that UROD (i.e., naloxone or naltrexone during heavy sedation) seems as effective as conventional withdrawal treatment (i.e., buprenorphine, clonidine, or tapered methadone) at increasing the proportion of people who are retained in naltrexone maintenance or abstinence from opioids at 12 weeks. The SR[2] rated the evidence associated with this outcome as moderate quality. Specifically, the Cochrane SR,[6] which informed the above SR[2] conducted a MA of three studies and reported that the continuation of maintenance treatment was significantly more likely with patients receiving UROD (i.e., naloxone, naltrexone, or nalmefene during heavy sedation or anesthesia), compared to patients receiving clonidine. The Cochrane SR[6] also reported that a 2003 study found no significant differences in the abstinence from opioids between UROD (i.e., naltrexone during heavy sedation or anesthesia) and conventional withdrawal treatment (i.e., buprenorphine, clonidine, or tapered methadone) groups.

Hemodynamic Changes

One RCT[12] reported that the heart rate and systolic blood pressure, but not respiratory rate, during anesthesia were significantly higher in patients receiving lofexidine administered after general anesthesia, compared to patients receiving UROD (i.e, dexmedetomidine during general anesthesia), two and four, but not six, hours under anesthesia.

Adverse Events and Harms

One SR[6] reported that, while a 2002 study found no serious adverse events associated with UROD (i.e., naloxone during heavy sedation or anesthesia), a 2005 study reported three potentially life-threatening adverse events associated with UROD (i.e., nalmefene followed by naltrexone during heavy sedation or anesthesia)—namely, pulmonary edema 14 hours after extubation, mixed bipolar state with suicidal ideation five days after anesthesia, and diabetic ketoacidosis two days after discharge. One SR[2] reported Do-Not-Do Recommendations issued by NICE in the UK, stating that UROD under heavy sedation or general anesthesia must not be offered because of the risk of serious adverse events.

<u>What are the Evidence-Based Guidelines Associated with the Use of ROD and UROD in Adults with Opioid Addiction?</u>

The ASAM guideline[4] reported that UROD is not recommended due to high risk for adverse events or death and that naltrexone-facilitated opioid withdrawal management can be a safe and effective approach but should be used only by clinicians experienced with this clinical method and in cases in which anesthesia or conscious sedation are not being employed.

Limitations

Although the evidence from the two SRs[2,6] was based on studies, in which the mean age of the study participants ranged between 30 and 36 years, one SR[2] defined adults as those aged 16 years or older, and the other SR[6] was not specific to adults. One evidence-based guideline[4] was not specific to adults, although it provided separate recommendations for adolescents (i.e., aged between 11 and 21 years old). One RCT[12] included only male patients. Therefore, the findings of the included studies and guideline in this report may not be completely generalizable to adults defined in Table 1 as those aged 18 years or older.

One RCT,[12] conducted in Egypt, included lofexidine administered after general anesthesia, as the comparator. Therefore, the findings of the RCT[12] may not be generalizable to Canadian care settings.

No evidence on ROD was identified. However, the distinction between ROD and UROD, based on the duration of anesthesia or sedation, appears varied,[5,8] suggesting that there may not be a valid and reliable distinction in the field.

Although the included studies[2,6] and guideline[4] generally suggested against UROD because of the risk of serious adverse events, there was no unequivocal evidence to support the notion that UROD was significantly associated with adverse events. For example, while the included guideline[4] reported that an SR of five RCTs concluded a lack of potential serious harms, in fact, that SR,[6] included in this report, found one RCT, which identified three potentially life-threatening adverse events associated with UROD. Therefore, some of the interpretations in the literature of the data of the included studies may not be accurate.

Overall, the evidence on clinical effectiveness and safety of UROD and evidence-based guidelines associated with the use of UROD in adults with opioid addiction were limited and of low quality. No evidence on ROD or on cost-effectiveness of ROD and UROD in adults with opioid addiction was identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The findings of the three included studies and one evidence-based guideline were mixed. There is some evidence suggesting earlier peaking of, and lower scores for, withdrawal symptoms and higher rates of the commencement and continuation of maintenance treatment in patients receiving UROD, compared to patients in control groups (i.e., conventional withdrawal treatment). However, no significant differences were identified between UROD and control groups in the commencement or duration of withdrawal treatment. Mixed results were identified between UROD and control groups in the completion of withdrawal treatment and the incidence of adverse events, depending on what pharmacologic agents were used. The included guideline recommended against the use of UROD, due to high risk for adverse events. No evidence on ROD or on cost-effectiveness of ROD and UROD was identified.

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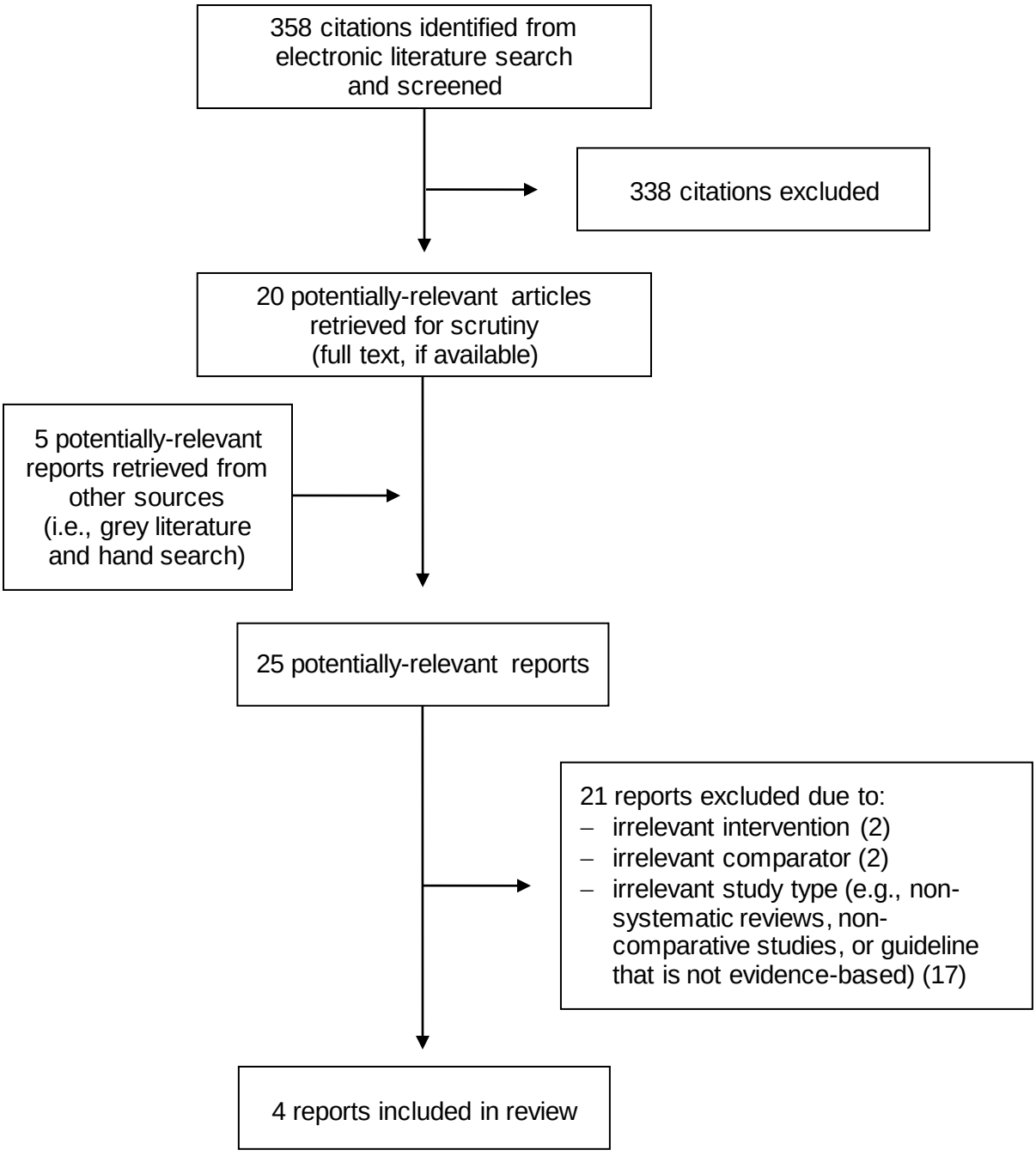
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews

First Author, Publication Year, and Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes and Length of Follow-Up
Praveen[2] 2011 UK	SR of 2 SRs of RCTs, published in 1998 and 2010, and grey literature, such as "Do Not Do Recommendations" from UK's NICE	Adults (i.e., aged 16 years or older), with opioid dependence	UROD[a] [a]Using opioid receptor antagonists (i.e., naloxone or naltrexone) during heavy sedation	Conventional withdrawal treatment[b] [b]Using buprenorphine, clonidine, or tapered methadone	Outcomes: Completion of withdrawal treatment; continuation of maintenance treatment or abstinence from opioids at 12 weeks; and Do-Not-Do Recommendations" Length of Follow-Up: Up to 12 weeks
Gowing[6] 2010 Australia	SR of 3 RCTs and 1 quasi-randomized controlled study, published between 2002 and 2006, and MA, where possible	All ages, with opioid dependence	UROD[a] [a]Using opioid receptor antagonists (i.e., naloxone, naltrexone, or nalmefene) during heavy sedation or anesthesia	Conventional withdrawal treatment[b] [b]Using buprenorphine, clonidine, or tapered methadone	Primary Outcomes: Withdrawal symptoms; commencement, duration, and completion of withdrawal treatment; and adverse events Secondary Outcomes: Commencement and continuation of maintenance treatment; and abstinence from opioids at 12 weeks Length of Follow-Up: Up to 12 weeks

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; MA = meta-analysis; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; UROD = ultra-rapid opioid detoxification

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, and Country	Study Design and Study Name (if reported)	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes and Length of Follow-Up
Nasr[12] 2011 Egypt	RCT, randomized using sealed assignment envelopes	60 male adults (i.e., aged 25 to 45 years), with opioid addiction[a] [a]Defined as continuous intake of opioids for a duration of 2 to 3 years	UROD[b] (n=30) [b]10 mg/(kg hour) propofol and 0.5 µg/(kg hour) dexmedetomidine were administered during general anesthesia. After anesthesia, dexmedetomidine was continued at 0.5 µg/(kg hour) on the second day and reduced to 0.2 µg/(kg hour) for the following 5 days. After discharge on the seventh day, patients were treated with 50 mg of naltrexone daily for 12 weeks.	Modified standard care[c] (n=30) [c]10 mg/(kg hour) propofol were administered during general anesthesia. After anesthesia, an oral dose of 0.2 mg of lofexidine was given three times daily. After discharge on the seventh day, patients were treated with 50 mg of naltrexone daily for 12 weeks.	Outcomes: Withdrawal symptoms[d] and hemodynamic changes[e] Length of Follow-Up: 6 hours (for hemodynamic changes) or 6 days (for withdrawal symptoms) [d]Assessed using OOWS (which provides scores on 13 symptoms that include yawning, rhinorrhea, piloerection, perspiration, lacrimation, hand tremors, mydriasis, hot and cold flushes, restlessness, vomiting, muscle twitches, abdominal cramps, and anxiety) and SOWS (which provides scores on 16 symptoms that include feeling anxious, restless, or nauseous; feeling like yawning or vomiting; perspiring; having teary eyes, a runny nose, goose bumps, hot or cold flushes, bone and muscle aches, muscle twitches, or stomach cramps; and shaking) [e]Including HR, SBP, and RER

HR = heart rate; OOWS = Objective Opiate Withdrawal Scale; RCTs = randomized controlled trial; RER = respiratory rate; SBP = systolic blood pressure; SOWS = Subjective Opiate Withdrawal Scale; UROD = ultra-rapid opioid detoxification

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended Users, Target Population, and Development Country	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality and Strength**	**Recommendations Development and Evaluation**	**Guideline Validation**
ASAM, 2015[4] – US						
Intended Users: Physicians and other health care providers; medical educators and faculty for other health care professionals in training; and clinical care managers Target Population: All patients with opioid use disorders, including special populations (e.g., pregnant women, individuals with pain, and adolescents) Development Country: US	Evaluation and treatment of opioid use disorder and management of opioid overdose	Anesthesia-assisted opioid detoxification	Review of existing clinical guidelines and research literature Compilation of hypothetical statements, reflecting recommended medical or psychosocial treatment	Quality of evidence was not rated.	Recommendations were developed by a multidisciplinary Guideline Committee of experts from medical specialties and academic researchers, who rated hypothetical statements—compiled through a review of existing clinical guidelines and research literature—on their appropriateness and necessity, with considerations for benefits and harms, exclusive of costs.	A draft guideline was subject to one week of ASAM member (i.e., patient and caregiver groups, criminal justice system experts, government agencies, other professional societies, hospitals, and health care systems) and public consultation.

ASAM= American Society of Addiction Medicine; US = United States

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Included Systematic Reviews using AMSTAR[9] link to AMSTAR checklist

Strengths	Limitations
Praveen, 2011[2]	
• A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented, and the included studies were rated on their quality, using the GRADE checklist. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to combine the findings of the included studies were appropriate.	• It is unclear whether an "a priori" design was used. • It is unclear whether there was duplicate study selection and data extraction. • Although some grey literature was included, it is unclear whether a comprehensive literature search was performed since no detailed search strategy or flow diagram for the search results was provided. • A list of the excluded studies was not provided. • The likelihood of publication bias was not assessed. • Two of the four authors declared conflicts of interest, having received financial support from manufacturers of opioids.
Gowing, 2010[6]	
• Detailed search strategies and flow diagram for the search results were provided. • A list of the included studies and their characteristics were provided. • A list of the excluded studies was provided. • The scientific quality of the included studies was assessed and documented, using risk-of-bias criteria, and considered moderately strong. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to combine the findings of the included studies were appropriate.	• It is unclear whether an "a priori" design was used. • There was no duplicate study selection and data extraction. • The literature search did not include grey literature and was not comprehensive. • The likelihood of publication bias was not assessed. • Two of the three authors declared conflicts of interest, having authored one of the included studies.

AMSTAR = Assessment of Multiple Systematic Reviews; GRADE = Grading of Recommendations Assessment, Development, and Evaluation

Table A5: Strengths and Limitations of Included Clinical Studies using Downs and Black[10] link to Downs and Black

Strengths	Limitations
Nasr, 2011[12]	
Reporting • The hypothesis/aim/objective was described. • The outcomes were described. • The interventions were described. • The findings were described. • Estimates of the random variability in the data for the main outcomes were provided. Bias • The statistical tests used to assess the main outcomes were appropriate. • The main outcomes were valid and reliable. Confounding • Study participants in intervention and control groups were recruited from the same population over the same period of time. • Study participants were randomized to intervention and control groups.	Reporting • Aside from age, weight, height, addiction, and duration of procedure, no other characteristics of study participants were described. Therefore, the distributions of potential confounders between intervention and control groups were incompletely described. • It is unclear whether any study participants were lost to follow-up. • Other than withdrawal symptoms, no adverse events were reported. • Actual probability values were not reported; instead, statistical significance was reported if the *p*-value was less than 0.05. External Validity • It is unclear whether patients asked to participate or included in the study were representative of the entire population of interest. • It is unclear whether the trial design was representative of the care setting. Bias • It is unclear whether an attempt was made to blind study participants to the intervention they received or blind staff measuring the main outcomes. • Compliance with the interventions was not described. Confounding • It is unclear whether intervention assignment was concealed from both study participants and staff until recruitment was complete and irrevocable. • No adjustment for potential confounding was made in the analysis for the main findings. • Losses of study participants to follow-up were not taken into account. Power • No power calculations were provided, and it is unclear whether the study had sufficient power to detect a clinically-important effect.

Table A6: Strengths and Limitations of Included Guidelines using AGREE II[11] link to checklist

Strengths	Limitations
ASAM, 2015[4] – US	
Scope and Purpose • Objectives were described. • Health questions were described. Stakeholder Involvement • The guideline was developed by individuals from all relevant professional groups. • Targets users were described. Rigour of Development • Methods for formulating recommendations were described. • Recommendations considered benefits and harms, exclusive of costs, and their links to supporting evidence were explicit. • The guideline was externally reviewed by experts prior to its publication. • A procedure for updating the guideline was described. Clarity of Presentation • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable.	Scope and Purpose • Target populations were not explicitly described. Stakeholder Involvement • Although input was sought from patient and caregiver groups, direct input from patients and caregivers was not sought. Rigour of Development • Because search strategies for existing clinical guidelines and research literature were not provided, it is unclear whether systematic search methods were used. • Evidence selection criteria were not described in detail, and no evidence tables were provided. • The quality of included evidence was not critically appraised and not considered in recommendations. Applicability • Facilitators and barriers to implementing the guideline were not described. • Aside from a summary document, the guideline provided no links to tools or resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring or auditing criteria. Editorial Independence • Funding sources were partially disclosed (i.e., one organization was disclosed as having provided partial support). • Seven of the eleven members of the Guideline Committee declared conflicts of interest, having current relationships with industry and other entities.

AGREE = Appraisal of Guidelines for Research and Evaluation; ASAM = American Society of Addiction Medicine; US = United States

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusions
Praveen, 2011[2]	
Completion of Withdrawal Treatment • Compared with conventional withdrawal, it is unclear whether UROD is more effective at increasing the proportion of people who complete detoxification treatment (low-quality evidence). Continuation of Maintenance Treatment or Abstinence from Opioids at 12 Weeks • Compared with conventional withdrawal, UROD seems as effective at increasing the proportion of people who are retained in naltrexone maintenance or abstinent from opioids at 12 weeks (moderate-quality evidence). Do-Not-Do Recommendations • NICE states that UROD under general anesthesia or heavy sedation (where the airway needs to be supported) must not be offered. This is because of the risk of serious adverse events, including death. • When detoxification is given to people with opioid dependence, other approaches, such as clonidine, methadone, or buprenorphine, are likely to be at least as effective as anesthesia-assisted detoxification, and are also safer and far less costly. Because medical detoxification addresses only the very first steps of treatment, and many programs, being privately provided, do not provide ongoing treatment beyond detoxification, this approach can be fundamentally flawed for most people, especially those with chronic relapsing opioid dependence. Most data on this treatment are in the form of case series and non-randomized studies. Safety concerns have also been raised. Along with the risks inherent in general anesthesia, complications such as pulmonary and cardiac problems have been reported. However, despite the lack of evidence and important safety concerns, this form of treatment is still available. However, the effectiveness and safety of anesthesia-	• Ultra-rapid withdrawal can help in detoxification, although there are important safety risks in keeping people heavily sedated or under general anesthesia and outcomes are no better. • Serious adverse effects may occur in people undergoing detoxification under anesthesia.

Table A7: Summary of Findings of Included Systematic Reviews	
Main Study Findings	**Author's Conclusions**
assisted detoxification have been called into question. The additional risk, which should not be underestimated, is that the patient can see this as a "magic bullet", with no need to make any meaningful life changes.	
Gowing, 2010[6]	
Withdrawal Symptoms • A 2003 study reported that, based on OOWS and SOWS scores, an increase in withdrawal symptoms lasted four days in the UROD group and 20 days in the tapered methadone group. In the tapered methadone group, peak OOWS and SOWS scores occurred much later, compared to the UROD group. No statistical test results were provided. • A 2005 study reported, based on OOWS and SOWS scores and the Clinical Institute Narcotic Assessment, no significant differences in withdrawal symptoms on Days Two and Three, among the UROD, buprenorphine, and clonidine groups. Commencement of Withdrawal Treatment • In an MA of three studies, conducted in 2002, 2005, and 2006, the overall effect of UROD, compared to conventional withdrawal, on the number of patients refusing group allocation or failing to attend treatment was not significant. Duration of Withdrawal Treatment • A 2005 study reported no significant differences in the mean number of weeks in withdrawal treatment, combining detoxification and naltrexone aftercare, among the UROD, buprenorphine, and clonidine groups. Completion of Withdrawal Treatment • A 2003 study reported that the completion of withdrawal treatment was significantly more likely with the UROD group, compared to the tapered methadone group (RR 1.82, 95% CI 1.14 to 2.91, *p*-value = 0.01). • A 2006 study reported no significant differences between the UROD and clonidine groups in the completion of withdrawal treatment.	• Antagonist-induced withdrawal under heavy sedation or anesthesia is more intense but less prolonged than withdrawal managed by tapered methadone or clonidine plus symptomatic medications, and is associated with significant reductions in the time between opioid use and commencement of naltrexone treatment. However, given that the adverse events are potentially life-threatening, the value of antagonist-induced withdrawal under heavy sedation or anesthesia is not supported. The high cost of anesthesia-based approaches, both in monetary terms and use of scarce intensive care resources, suggest that this form of treatment should not be pursued.

Table A7: Summary of Findings of Included Systematic Reviews	
Main Study Findings	**Author's Conclusions**
<u>Commencement of Maintenance Treatment</u> • In an MA of three studies, conducted in 2002, 2005, and 2006, the commencement of maintenance treatment with naltrexone was significantly more likely with the UROD group, compared to the clonidine group (RR 4.28, 95% CI 2.91 to 6.30, *p*-value < 0.01). • A 2005 study reported that the commencement of maintenance treatment with naltrexone was significantly more likely with the UROD group, compared to the buprenorphine group (RR 1.29, 95% CI 1.04 to 1.60, *p*-value = 0.02). <u>Continuation of Maintenance Treatment</u> • 2003 and 2005 studies reported no significant differences between the UROD and tapered methadone or buprenorphine groups in the continuation of maintenance treatment. • In an MA of three studies, conducted in 2002, 2005, and 2006, the continuation of maintenance treatment was significantly more likely with the UROD group, compared to the clonidine group (RR 2.77, 95% CI 1.37 to 5.61, *p*-value=0.005). <u>Abstinence from Opioids at 12 Weeks</u> • A 2003 study reported no significant differences between the UROD and tapered methadone groups in the abstinence from opioids at 12 weeks. <u>Adverse Events</u> • A 2002 study reported no serious adverse events associated with UROD. • A 2005 study reported three potentially life-threatening adverse events, all in the UROD group, including pulmonary edema 14 hours after extubation, mixed bipolar state with suicidal ideation five days after anesthesia, and diabetic ketoacidosis two days after discharge.	

CI = confidence interval; MA = meta-analysis; NICE = National Institute for Health and Care Excellence; OOWS = Objective Opioid Withdrawal Scale; RER = respiratory rate; RR = risk ratio; SOWS = Subjective Opioid Withdrawal Scale; UROD = ultra-rapid opioid detoxification

Table A8: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
Nasr, 2011[12]	

<u>Withdrawal Symptoms</u>
• Scores for withdrawal symptoms after anesthesia, measured using both OOWS and SOWS, were, in general, significantly higher in the control group, compared to the UROD group, over six days following anesthesia. Specifically:
  ○ OOWS scores were significantly higher in the control group, compared to the UROD group, in all 13 symptoms on Day 1, nine symptoms on Day 2, six symptoms on Day 3, and one symptom on Days 5 and 6 following anesthesia.
  ○ SOWS scores were significantly higher in the control group, compared to the UROD group, in all 16 symptoms on Day 1, 13 symptoms on Day 2, ten symptoms on Day 3, seven symptoms on Day 4, and three symptoms on Day 5 following anesthesia.
<u>Hemodynamic Changes</u>
• Among adult male patients with opioid addiction, HR and SBP, but not RER, during anesthesia were significantly higher in the control group, compared to the UROD group, at two and four, but not six, hours under anesthesia. Specifically:
  ○ HR at two hours between the UROD and control groups was 75.9, with SD 4, versus 90.9, with SD 5 (p-value < 0.05).
  ○ HR at four hours between the UROD and control groups was 77.3, with SD 4, versus 91.2, with SD 5 (p-value < 0.05).
  ○ SBP at two hours between the UROD and control groups was 99.4, with SD 2, versus 141.2, with SD 3 (p-value < 0.05).
  ○ SBP at four hours between the UROD and control groups was 110.3, with SD 2, versus 165, with SD 4 (p-value < 0.05).
	• Among male patients with opioid addiction, admitted for detoxification, the UROD group had significantly fewer withdrawal symptoms, compared to the control group.

HR = heart rate; OOWS = Objective Opiate Withdrawal Scale; RER = respiratory rate; SBP = systolic blood pressure; SD = standard deviation; SOWS = Subjective Opiate Withdrawal Scale; UROD = ultra-rapid opioid detoxification

Table A9: Summary of Findings of Included Guidelines

Main Study Findings	Recommendations
ASAM, 2015[4] – US	
• Serious complications, including cardiac arrest and death, have been reported with anesthesia-assisted withdrawal management. The Centers for Disease Control issued a warning in 2013 about severe adverse events including death from anesthesia-assisted withdrawal management. Furthermore, an SR of five RCTs (included in this report[6]) concluded that the lack of benefit, potential serious harms, and costs of heavy sedation or anesthesia do not support its use.	• Opioid withdrawal management using anesthesia, UROD, is not recommended due to high risk for adverse events or death. Naltrexone-facilitated opioid withdrawal management can be a safe and effective approach but should be used only by clinicians experienced with this clinical method and in cases in which anesthesia or conscious sedation are not being employed.

ASAM = American Society of Addiction Medicine; RCT = randomized controlled trial; SR = systematic review; UROD = ultra-rapid opioid detoxification; US = United States

APPENDIX 5: Additional References of Potential Interest

Guidelines Associated with the Use of ROD and UROD in Adults with Opioid Addiction

The following guideline did not meet the selection criteria for an evidence-based guideline, with no reporting of the methodology used, but provided information on ROD procedures and protocols.

Mental Health and Drug Alcohol Office, NSW Health. Rapid opioid detoxification: guidelines [Internet]. North Sydney, NSW: NSW Department of Health; 2011 [cited 2015 Dec 15]. Available from: http://www0.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_009.pdf

The following guideline did not meet the selection criteria for an evidence-based guideline, with no systematic methodology used, but included the following recommendation on UROD: ultra-rapid detoxification is not recommended. Although the strength of the recommendation was rated high, the evidence, reported to have come from large representative population samples, could not be found in the guideline.

Lingford-Hughes AR, Welch S, Peters L, Nutt DJ, British Association for Psychopharmacology, Expert Reviewers Group. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol. 2012 Jul;26(7):899-952.