2024

UPDATE TO NATIONAL GUIDELINE

of the Canadian Research Initiative in Substance Matters

# for the Clinical Management of Opioid Use Disorder

CRISM
Canadian Research Initiative
in Substance Matters

# Territorial Acknowledgement

The guideline development committee would like to respectfully acknowledge that much of the development of this manuscript occurred in Tiohtià:ke, the ancestral and unceded territory of the Kanien'kehá:ka Nation, and Mi'kma'ki, the ancestral and unceded territory of the Mi'kmaq. Internal and external review committee members are located all across Turtle Island, the land also known as Canada, and we acknowledge that Indigenous peoples are the traditional guardians of this land.

It is recognized that the ongoing criminalization, institutionalization, and discrimination against people who use drugs disproportionately harm Indigenous peoples and that continuous efforts are needed to dismantle colonial systems of oppression.

Achieving reconciliation with Indigenous peoples requires making significant and ongoing changes to the health care system. We are committed to taking constructive steps toward this goal and ensuring that all individuals receive the care and support they need without any form of discrimination or bias.

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# Acknowledgements


## Funding

The production of this guideline was supported by a financial contribution from Health Canada (Substance Use and Addiction Program 2223-HQ-000151). The views expressed herein do not necessarily represent the views of Health Canada. Dr. Bruneau (Clinical Lead) is supported by the Canadian Institutes of Health Research (CIHR) grant: Quebec Node Canadian Research Initiative in Substance Matters (CRISM) Phase II (FRN 181678).

Santé Canada Health Canada

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

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The guideline development team gratefully acknowledges Noémie Harriet, Manuela Mbcafou and Aïssata Sako for their coordination of the development of this update of the guideline. The committee would like to thank Pacifique Bugingo for coordinating and facilitating the guideline review and Shirley Wong, Denise Adams, Farihah Ali, Aïssata Sako and Jennifer Swansburg for their tremendous help in the review process. The committee would like to thank Robin Parker for her expertise and for developing the systematic literature review search strategies. Additionally, the committee is also thankful for the involvement of all the external reviewers, with a particular mention to Karine Laroche, Katie Upham, Mille Schulz, Madelyn Gold and Jonny Mexico for the linguistic review of the guideline. The committee acknowledges Jill Fikowski for her contribution to the funding process. Finally, the committee also wishes to acknowledge Annie St Amand for the graphic design, Stevenson & Writers for the revision and translation of the guideline document and anyone who has helped or supported the development of this document in any way.

# Content Disclaimer

The recommendations in this guideline represent the view of the national guideline development committee, which produced at them after careful consideration of the available scientific evidence and external expert peer review.

## Population

General **adult** (aged 18 years and older) population living with opioid use disorder, regardless of severity.

## Content

**Inclusion**

This guideline includes **evidence-based recommendations** on:

- ✔ Oral opioid agonist therapies
- ✔ Withdrawal management strategies
- ✔ Psychosocial interventions
- ✔ Harm reduction approaches

This guideline also includes **specific considerations** for:

- ✔ Oral naltrexone
- ✔ Pregnant persons

**Exclusion**

The guideline **does not cover** the literature and, therefore, does not include recommendations on specific practices such as:

- ✘ Injectable opioid agonist therapies. For recommendations regarding injectable opioid agonist therapies such as hydromorphone or diacetylmorphine, please refer to the Injectable opioid agonist treatment for opioid use disorder: a national clinical guideline (1).
  - ✘ Extended-release agonist (i.e. Sublocade®): The guideline development committee acknowledges the growing use of this formulation; however, this guideline focuses solely on oral formulations
  - ✘ Extended-release antagonist (i.e.Vivitrol®): Despite the growing body of evidence regarding this medication, it is not available in Canada; therefore, it is not part of the scope of this national guideline

- ✘ Induction protocols
- ✘ Take-home doses
- ✘ Dosing schedule
- ✘ Urine Drug Testing

The guideline development committee recognizes the importance of addressing such practices; however, those require a review of specific literature that is meant to be assessed in separate projects and are consequently outside the scope of this clinical guideline.

# Disclaimer for Health Care Providers

This guideline is designed for decision-making in the general care of patients with OUD. The application of the recommendations in this guideline does not override the responsibility of health care professionals to make decisions that are appropriate to the needs, preferences, and values of an individual patient, in consultation with that patient and their family members or guardian(s), and, when appropriate, external experts (e.g., specialty consultation). When exercising clinical judgment in the treatment of opioid use disorder, health care professionals are expected to take this guideline fully into account while upholding their duty to adhere to the fundamental principles and values of the Canadian Medical Association Code of Ethics and the Code of Ethics of the Canadian Psychological Association, especially compassion, beneficence, non-maleficence, respect for persons, justice and accountability, as well as the required standards for good clinical practice defined by relevant governing bodies within regional or local jurisdictions. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

# Legal Disclaimer

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This guideline is intended to give an understanding of a clinical issue and outline one or more preferred approaches to the investigation and management of the issue. This guideline is not intended as a substitute for the advice or professional judgment of a health care professional, nor is it intended to be the only approach to the management of a clinical issue. We cannot respond to patients or patient advocates requesting advice on issues related to medical conditions. If you need medical advice, please contact a health care professional.

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# Abbreviations and Acronyms

| | |
|---|---|
| **ACOG** | American College of Obstetricians and Gynecologists |
| **aHR** | adjusted Hazard Ratio |
| **aOR** | adjusted Odds Ratio |
| **ASAM** | American Society of Addiction Medicine |
| **CBT** | Cognitive Behavioural Therapy |
| **CDSA** | Controlled Drugs and Substances Act |
| **CI** | Confidence Interval |
| **CIHR** | Canadian Institutes of Health Research |
| **CM** | Contingency Management |
| **CMR** | Crude Mortality Rate |
| **COVID-19** | Coronavirus Disease 2019 |
| **COWS** | Clinical Opiate Withdrawal Scale |
| **CRISM** | Canadian Research Initiative in Substance Matters |
| **DBT** | Dialectical Behavioural Therapy |
| **DSM-5** | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| **FDA** | Food and Drug Administration |
| **GRADE** | Grading of Recommendations, Assessments, Development and Evaluation |
| **HCV** | Hepatitis C Virus |
| **HIV** | Human Immunodeficiency Virus |
| **HRI** | Harm Reduction International |
| **iOAT** | injectable Opioid Agonist Therapy |
| **IPT** | InterPersonal Therapy |
| **MBRP** | Mindfulness-Based Relapse Prevention |
| **MD** | Mean Difference |
| **MET** | Motivational Enhancement Therapy |
| **META-PHI** | Mentoring, Education, and Clinical Tools for Addiction—Partners in Health Integration |
| **NAS** | Neonatal Abstinence Syndrome |
| **NOWS** | Neonatal Opioid Withdrawal Syndrome |
| **NPI** | Nominated Principal Investigator |
| **NSAID** | Non-Steroidal Anti-Inflammatory Drugs |
| **OAT** | Opioid Agonist Therapy |
| **OR** | Odds Ratio |
| **OUD** | Opioid Use Disorder |
| **PHAC** | Public Health Agency of Canada |
| **PICOS** | Population, Intervention, Comparison, Outcome, and Study design |
| **PrEP** | Pre-exposure Prophylaxis |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **PRISMA-ScR** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews |
| **PTSD** | Post-Traumatic Stress Disorder |
| **PWUD** | People Who Use Drugs |
| **RCT** | Randomized Controlled Trial |
| **RR** | Risk Ratio |
| **SAMHSA** | Substance Abuse and Mental Health Service Administration |
| **SD** | Standard Deviation |
| **SMD** | Standardized Mean Difference |
| **SOGC** | Society of Obstetricians and Gynecologists of Canada |
| **SROM** | Slow-Release Oral Morphine |
| **SUD** | Substance Use Disorder |
| **UK** | United Kingdom |
| **UNODC** | United Nations Office on Drugs and Crime |
| **USA** | United States of America |
| **WHO** | World Health Organization |

# Glossary

### Abstinence
Self-indulgence that restraints from—which means avoiding, or not engaging in—the compulsive pursuit of substances and behaviours for the purpose of obtaining reward, pleasure or relief. Abstinence can have any length of time and may, therefore, be temporary or permanent. The use of medications approved by Health Canada for the treatment of opioid use disorder is consistent with abstinence.

### Addiction care
Ongoing care for substance use disorder that is delivered by a trained care provider and offered as part of the continuum of care. This includes evidence-based interventions such as pharmacological long-term therapies, psychosocial treatments, withdrawal management services, and harm-reduction services. A patient may visit and revisit each service as needed.

### Addiction treatment
Treatment that refers to evidence-based pharmacological treatment (opioid agonist or antagonist treatment in case of opioid use disorder), evidence-based psychosocial treatments, residential treatment, or combinations of these treatment options. Addiction treatment may be provided in outpatient or inpatient settings. In isolation, withdrawal management, harm-reduction services, low-barrier housing and unstructured peer-based support would not be considered "addiction treatment".

### Alpha$_2$-adrenergic agonist
Non-opioid medication that acts centrally in the brain to moderate some symptoms and signs of noradrenergic hyperactivity. Clonidine is commonly used to treat withdrawal symptoms and is available in Canada as oral tablets.

### Basic Medical management
Medical management for opioid use disorder is medically focused, unstructured, informal counselling provided by the treating clinician in conjunction with pharmacological treatment. Basic medical management includes, but is not limited to: health and wellness checks, support and advice, assessing motivation and identifying barriers to change, creating a treatment plan, fostering medication adherence, optimizing dosing, supporting treatment adherence and relapse prevention, and providing referrals to appropriate health and social services.

### Clonidine (hydrochloride)
Medication that acts centrally as an alpha 2-adrenergic agonist that blocks chemicals triggering sympathetic responses associated with opioid withdrawal symptoms. Clonidine is commonly used to treat withdrawal symptoms and is available in Canada as oral tablets.

### Cognitive behavioural therapy
A structured, practical, goal-oriented, and problem-focused form of psychotherapy that is time-limited and usually involves efforts to change thinking and behavioural patterns. It helps individuals identify and cope with specific challenges.

### Contingency management
A type of behavioural therapy that involves encouraging positive behaviour change in patients by providing rewards or reinforcing consequences when patients meet their treatment goals. Conversely, punitive measures or withholding of reinforcers are used for undesired behaviour.

### Continuum of care
Concept that refers to the provision of continuous care to patients across various disciplines and over time, with the aim of meeting their evolving needs. This approach encompasses not only treatments but also ensuring that patients are able to transition safely between health care facilities and providers. The goal is to promote better health outcomes for patients and to improve the overall quality of care within the health care system.

### Diversion
Any non-intended or non-medical use of a prescribed opioid (including prescribed opioid agonist medication) or use by any individual other than the individual for whom it was prescribed.

### Drug poisoning
See Overdose

## Formulation
Term that refers to the form in which a medication is delivered (e.g., sublingual, sustained release, injectable, etc.).

## Harm reduction
Policies and programs that aim to minimize immediate health, social, and economic harms (e.g., transmission of infectious disease, overdose mortality, criminal activity) associated with the use of psychoactive substances without necessarily requiring a decrease in substance use or a goal of abstinence. Examples include needle and syringe exchange programs, take-home naloxone programs, supervised injection or consumption services, and outreach and education programs for high-risk populations.

## Health care provider/professional
Health professional or organization that provides healthcare services by advising on or applying preventive and curative measures and by promoting health with the goal of improving health outcomes. This includes, but is not restricted to, physicians, nurses, therapists, psychologists, pharmacists, dentists, paramedical practitioners, etc.

## Illicit/ illegal drug
Substance covered by the Controlled Drugs and Substances Act in Canada, which possession, use and/or sale is prohibited. Also see unregulated drug.

## Non-medical use
Use of a medication without a prescription or with a prescription but for reasons other than what the medication is intended for or in a manner or time period other than what was prescribed[i].

## Opioids
Substances commonly prescribed for pain management that bind and activate opioid receptors in the brain, suppressing the ability to feel pain. At high doses, opioids can cause euphoria, dysphoria, and respiratory depression. Opioids may be prescribed or obtained illegally and include synthetic (e.g., fentanyl, methadone, buprenorphine), semisynthetic (e.g., heroin, hydromorphone, oxycodone), and naturally derived (e.g., opium, morphine, codeine) classes. The term «opiate" refers to compounds naturally derived from the opium poppy. Depending on the opioid type, formulation and individual preference, opioids are consumed via ingestion, inhalation, transdermal delivery, or subcutaneous, intramuscular or intravenous injection.

## Opioid agonist
Any substance that binds to and activates mu (μ) opioid receptors, providing relief from withdrawal symptoms and cravings in people with opioid use disorder and pain relief if used for chronic pain management. Oral opioid agonists used for treating opioid use disorder include methadone, buprenorphine, and slow-release oral morphine.

### Buprenorphine
A long-acting synthetic opioid that acts as a partial mu (μ) opioid receptor agonist with a half-life of approximately 24 to 42 hours. Buprenorphine has a high affinity for the opioid receptor but, as a partial agonist, has a lower intrinsic activity or effect at the opioid receptor compared to full agonist opioids. These pharmacological properties create a «ceiling" on opioidergic effects—including respiratory depression—at higher doses. Buprenorphine's high affinity for the opioid receptor also confers an antagonistic effect on other opioids; it preferentially binds to the receptor and displaces other opioids if they are present, which can cause precipitated withdrawal (see below). In Canada, buprenorphine is available in a combined formulation with naloxone (see below).

### Buprenorphine/Naloxone
A 4:1 combined formulation of buprenorphine and naloxone, available as a sublingual tablet in Canada. Naloxone is an opioid antagonist with poor oral bioavailability when swallowed or administered sublingually and is included to deter non-medical injection and diversion. When buprenorphine/naloxone is taken as directed sublingually, the naloxone component has negligible effects, and the therapeutic effect of buprenorphine predominates. However, if diverted for injection use via subcutaneous, intramuscular, or intravenous routes, sufficient naloxone is absorbed to induce some withdrawal symptoms in physically dependent active opioid users. Buprenorphine/naloxone is generally taken once daily, but due to its favourable safety profile and pharmacological properties, it can also be prescribed at higher doses on alternate-day schedules.

### Methadone
A long-acting synthetic opioid that acts as a full mu (μ) opioid receptor agonist. It has a half-life of approximately 24 to 36 hours and is well absorbed. In Canada, it is most frequently administered as an oral solution, generally given as a single daily dose. Methadone tablets are also available in a limited context (e.g., for travel). Methadone is classified as a controlled substance in accordance with Section 56

i Borrowed from UNODC. The non-medical use of prescription drugs. Policy Direction Issues (Discussion Paper), 2011.

of the Controlled Drugs and Substances Act and the Narcotic Control Regulations. However, as of May 19, 2018, clinicians are no longer required to hold an exemption from Health Canada in order to prescribe, sell, provide or administer methadone for the treatment of opioid use disorder or pain.

**Slow-Release Oral Morphine (SROM)**
A 24-hour slow-release formulation of morphine, a full agonist at the mu (μ) opioid receptor, that is taken orally once per day. In Canada, slow-release oral morphine is available as a capsule containing polymer-coated pellets (to slow absorption and release) of morphine sulfate. Its elimination half-life is approximately 11 to 13 hours. It is currently approved for pain management in Canada, and its use for the treatment of opioid use disorder would be considered off-label.

## Opioid agonist therapy (or treatment) (OAT)
Opioid agonist medications prescribed for the treatment of opioid use disorder. OAT is typically provided in conjunction with provider-led counselling; long-term substance-use monitoring (e.g., regular assessment, follow-up, and urine drug tests); comprehensive preventive and primary care; and referrals to psychosocial treatment interventions, psychosocial supports, and specialist care as required. In this document, OAT refers to long-term (i.e., more than six months) treatment with an opioid agonist medication that has an evidence base for use in the treatment of opioid use disorder. "Opioid agonist therapy (OAT)" is the preferred terminology, representing an intentional shift from the use of "opioid substitution treatment" (OST), "opioid maintenance treatment" (OMT), and "opioid replacement therapy" (ORT).

## Opioid antagonist
Medication that works by blocking opioid receptors, preventing the body from responding to opioids. Opioid antagonist medications may be used to rapidly displace opioid agonist molecules from receptors in an overdose situation (e.g., naloxone), or to facilitate continued abstinence from using opioid drugs (e.g., naltrexone). In Canada, naloxone is available in the form of an intramuscular injection preparation (an intranasal formulation is available to a limited extent), while naltrexone is available as an oral tablet taken once per day.

## Opioid use disorder (OUD)
Problematic pattern of opioid use leading to clinically significant impairment or distress that meets the DSM-5 Diagnostic Criteria for Opioid Use Disorder. OUD includes the use of synthetic and/or naturally derived opioids, whether prescribed or illegally obtained. The DSM-5 terminology represents a deliberate shift away from DSM-IV terminology of "opioid abuse" or "opioid dependence", which may be considered pejorative and/or stigmatizing, to describe this condition.

## Overdose
Accidental or intentional use of a larger than usual or recommended amount of medicine, drug, or a combination of medicines or drugs resulting in a serious, toxic reaction (non-fatal) or death (fatal).

## Patient
A person who receives treatment for substance use disorder.

## Patient-centred approach
An approach that involves the treatment and care of patients with respect and dignity. It also requires involving the patient in any decision related to their health and being mindful of their unique circumstances and needs.

## Physical dependence
Physiological adaptation that a person experiences when taking a substance that has an effect on the central nervous system. Symptoms of physical dependence occur when the person stops or decreases the amount taken.

## Polydrug use
Use of more than one drug or type of drug at the same time or taking one drug under the influence of another.

## Precipitated withdrawal
A withdrawal syndrome that can occur when an opioid antagonist or partial agonist, such as buprenorphine, is administered to a patient who is physically dependent and has recently used a full opioid agonist. Due to buprenorphine's high affinity but low intrinsic activity at the mu (μ) receptor, the partial agonist displaces full agonist opioids from the mu (μ) receptors without activating the receptor to an equivalent degree, resulting in a net decrease in effect. Precipitated withdrawal is more intense and has a much faster onset than typical withdrawal from opioids.

### Psychosocial supports
Non-therapeutic social support services aim to improve overall individual and/or family stability and quality of life, which may include community services, social and family services, temporary and supported housing, income assistance programs, vocational training, life-skills education, and legal services.

### Psychosocial treatments /interventions
Structured and/or manualized treatments delivered by a trained care provider that incorporate principles of cognitive behavioural therapy, interpersonal therapy, motivational interviewing, dialectical behaviour therapy, contingency management, structured relapse prevention, biofeedback, and family and/or group counselling. Psychosocial interventions may include culturally specific approaches such as traditional healers, elder involvement, and Indigenous healing ceremonies.

### Recovery
A process of change through which a person achieves a most favourable state of well-being (physical, social and emotional), uniquely defined by each person.

### Recovery management
Support, interventions and services established by the patient, health care team, family and support group to accompany a person through their recovery, however they define it.

### Relapse/ Return to use
Refers to a return to drug use that the person has previously managed to control or quit completely. In the case of relapse, the use of drugs goes back to previous levels of use or close to it.

### Standard of care
A defined set of prerequisites that must be met for any treatment modality or intervention to be considered safe and effective, regardless of the underlying treatment philosophy or the treatment setting[ii].

### Substance use disorder (SUD)
A condition measured on a continuum from mild to severe that is characterized, according to the DSM-5-TR, by the uncontrolled and continued use of a substance or substances despite the negative and harmful consequences associated with such use. The DSM-5-TR recognizes substance-related disorders resulting from the use of 10 separate classes of drugs, including opioids. It also points out to criteria falling under four categories: impaired control, pharmacological criteria, social impairment and risky use.

### Tolerance
A person's reduced response to a substance following its repeated use and the body adapting to the substance's presence. As a result, the person needs higher doses to experience the drug's effects.

### Unregulated drug
A drug whose quality and composition are unknown, questionable and potentially dangerous. Usually, illegally manufactured, unregulated drugs are not subject to quality-control measures and are typically mixed (or "cut") with potentially harmful substances and contaminants to increase volume and profit in the illegal drug market. Common examples of unregulated opioids are street heroin, fentanyl, carfentanil, morphine, and oxycodone, as unregulated opioids may also be found in the form of counterfeit tablets pressed to look like pharmaceutical opioids.

### Withdrawal management (medically assisted)
Use of pharmacological treatment (e.g., opioid agonist tapers, alpha$_2$-adrenergic agonists) that aims to mitigate withdrawal symptoms and withdrawal-related adverse events when a person stops using opioids in pursuit of abstinence. This terminology represents a deliberate shift away from the use of "detox" or "detoxification" to refer to medically supervised withdrawal from substances.

ii Definition borrowed from International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing. Geneva: World Health Organization and United Nations Office on Drugs and Crime; 2020. License: CC BY-NC-SA 3.0 IGO.

# Preamble

### About the Canadian Research Initiative in Substance Matters

The Canadian Research Initiative in Substance Matters (CRISM) is a unique national research network anchored by five interdisciplinary regional teams (Nodes) representing British Columbia (Principal Investigators: Drs. Evan Wood & Eugenia Socias), the Prairies (Principal Investigator: Dr. David Hodgins), Ontario (Principal Investigator: Dr. Jürgen Rehm), Quebec (Principal Investigator: Dr. Julie Bruneau), and the Atlantic provinces (Principal Investigator: Dr. Sherry Stewart). Funded by the Canadian Institutes of Health Research (CIHR), CRISM's mission is to address issues of substance use in Canada by providing national leadership and coordinating scientific evidence-based actions. CRISM continuously seeks different ways to reduce harm and improve the quality of life for people with lived experience of substance use and substance use disorders, as well as their friends and families, thus enriching the health and well-being of Canadians.

### Rationale for the update

In March 2018, North America was facing a rising opioid-related death crisis initially driven by greater availability and use of prescription opioids, followed by a change in the drug market with the introduction of illicitly manufactured fentanyl. This posed a major threat to public health. In response, CRISM published the first Canadian national clinical practice guideline to assist clinicians in making informed decisions regarding the clinical management of opioid use disorder (OUD).[2,3] Recommendations were made in light of existing evidence on prioritizing available treatments and support for people with OUD.

Over the past six years, additional measures have been implemented to help reduce the epidemic. In May 2018, the Government of Canada made a significant advancement in improving accessibility to treatment options by lifting restrictions on methadone prescriptions. As a result, subsection 56[1] class exemptions of the Controlled Drugs and Substances Act (CDSA) are no longer required to prescribe, administer or provide methadone, allowing better access to OUD treatment options.

The COVID-19 pandemic from March 2020 then marked an increase in opioid-related harms nationwide as access to essential services and support was restricted during that time, and the drug supply became increasingly toxic and volatile. According to data from the Public Health Agency of Canada (PHAC) and various authorities across the country, opioid-related harms and deaths significantly rose, and the number of fatalities has continued to exceed pre-pandemic levels ever since.[4] To address these synergistic epidemics, additional measures and efforts, such as the expansion of telehealth services,[5] have been implemented to alleviate barriers and ensure continuous access to treatment and care for people with OUD.

In an ever-changing landscape of practices and policies, particularly following the COVID-19 pandemic, reviewing and incorporating the latest scientific and clinical evidence is crucial to ensuring optimal clinical management for individuals with OUD. As such, the current CRISM National Guideline for the Clinical Management of Opioid Use Disorder needs to be continuously updated to provide Canadian health care professionals with timely, comprehensive information and evidence-based recommendations on the most effective practices for the treatment of OUD.

In alignment with the Canadian government's objectives and CRISM's mission, the following are the 2024 updated national clinical recommendations. This practice guidance updates the 2018 version and incorporates peer-reviewed research published between January 2017 and August 2023. Clinical insights and values of persons with lived, and living experience (PWLLE) were also considered when developing these guidelines. This document aims to build consensus and support efforts to achieve the highest national standards of care for the clinical management of OUD.

# Executive Summary

## Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition – Text Revision (DSM-5-TR), opioid use disorder (OUD) is characterized by the continued use of opioids despite the negative social, interpersonal, physical and psychological consequences associated with it. Its severity can range from mild to severe.

The World Health Organization (WHO) stipulates that OUD, as a chronic condition, requires the highest standards of care similar to those applied to other chronic diseases such as diabetes or cardiovascular disorders. These include a patient-centred approach with respect for patients' rights and dignity. The treatment plan should be evidence-based and founded on the patient's needs, preferences, and experience. Patients should be offered a continuum of care with a set of integrated health services, including evidence-based harm reduction services, opioid agonist treatments (OAT), withdrawal management services, and psychosocial therapies. As OUD is a complex condition with a non-linear course for clinical management, the components of the continuum can be visited and revisited by a patient and their care team whenever needed. While treatment services should be accessible through multiple entry points, it is necessary to provide all patients with access to primary health care. Subgroups of people with OUD (i.e., pregnant persons, Black, Indigenous and People of Colour (BIPOC) populations, immigrants, sex workers, and people of diverse sexual orientations and gender identities) may need unique considerations. To address this, it is essential to integrate an anti-stigma, anti-racism and trauma-informed framework into the OUD treatment program to avoid discrimination and stigmatization. It is also suggested that complementary services such as housing, employment, or legal assistance be offered, if necessary.

The guideline development team of the Canadian Research Initiative on Substance Matters (CRISM) adheres to the standards of care mentioned above. Clinicians and healthcare professionals should incorporate these standards into their regular clinical practice when implementing clinical recommendations.

## Purpose and Scope

Emerging as a pressing global concern, the overdose crisis continues to be particularly challenging in Canada, where opioids account for over 69% of drug-related deaths. The increased opioid-related harms involving fentanyl or polydrug use further underpin the need for effective interventions and treatments to address non-medical opioid use, addiction and related harm. To this end, CRISM launched an update of the 2018 National Guideline for the Clinical Management of Opioid Use Disorder (hereinafter referred to as

the 2018 CRISM *National OUD Guideline*), aiming to integrate the latest scientific evidence published between 2017 and 2023.

This guideline is intended for use by health care providers, including physicians, nurse practitioners, pharmacists, clinical psychologists, social workers, medical educators, and clinical care case managers with or without specialized experience in addiction treatment. It informs the targeted audiences about the following:

(1) Recommended evidence-based OATs. The opioid agonists covered are the oral medications approved by Health Canada for the treatment of OUD, namely methadone and buprenorphine. Slow-release oral morphine (SROM), used off-label in Canada, is compared to Health Canada-approved oral medications.
(2) Recommended evidence-based approach for withdrawal management.
(3) Recommended complementary evidence-based interventions: psychosocial and harm reduction interventions.
(4) Special evidence-based considerations for oral naltrexone and special populations such as pregnant persons.
(5) Overview of other emerging issues in OUD management, including the prescription of short-acting opioids as stand-alone or as combined OAT (often referred to as safer supply).

## Methodology

The update followed standard norms for guideline development, including an exhaustive systematic review of the literature, management of conflicts of interest, and an external review committee. Moreover, health care practitioners and people with lived and living experience (PWLLE) were surveyed to learn more about emerging substance use issues.

A guideline development committee composed of experts in review methods, addiction medicine specialists, and librarians was created to conduct the systematic literature review. The MEDLINE, EMBASE, PsycINFO, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from January 1, 2017, to September 1, 2023, for studies limited to human subjects written in English. Meta-analyses, randomized controlled trials (RCTs), and quasi-experimental and observational cohort studies were included. Two independent reviewers performed study selection, data extraction, and quality assessment. Data were then synthesized to update the 2018 clinical recommendations according to the following GRADE (Grading of Recommendations, Assessments, Development, and Evaluation) criteria: quality of evidence, balance between benefits and harms, patients' values and preferences, and costs and resources. These determinants were also used to assess the strength of the new recommendations.

An external national committee made up of health care providers (e.g., physicians, nurses, pharmacists, clinical psychologists), policymakers, and PWLLE from across Canada reviewed the recommendations.

### Literature review

Two independent reviews were performed: pharmacotherapeutic and adjunctive interventions (psychosocial and harm reduction strategies). The reviews identified 32,825 new studies since 2017 (14,205 articles for the pharmacotherapeutic review and 18,746 articles for the adjunctive interventions review), which were screened using their title and abstracts. From these, 1,282 articles (573 articles for the pharmacotherapeutic review and 709 articles for the other review) were selected for a full-text review, resulting in the inclusion of 150 studies (105 studies for pharmacotherapeutic interventions and 45 for adjunctive psychosocial and harm reduction interventions).

## Pharmacotherapies

### Opioid agonists therapies

From the included studies, substantial new evidence comparing methadone to buprenorphine was identified. This highlighted the similar effectiveness of both treatments in reducing opioid use (four meta-analyses, two RCTs, eight cohort studies; high certainty of evidence) and adverse events (two meta-analyses, three RCTs, 11 cohort studies; high certainty of evidence). Findings favoured methadone for treatment retention (six meta-analyses, two RCTs, 20 cohort studies; high certainty). However, methadone, in comparison to buprenorphine, was associated with a higher risk of mortality during the first four weeks of treatment, which diminished to the lowest rate during the maintenance period (three meta-analyses, 11 cohort studies; moderate certainty). Few studies evaluated patient satisfaction and costs. One observational study found patients were more satisfied in the buprenorphine group, while one RCT did not find any difference between the two treatments. Three cohort studies examining costs and findings tended to favour methadone.

Based on solid evidence and considering a patient-centred approach, offering both methadone and buprenorphine as first-line treatment options would be beneficial to improve patient engagement. Thus, the following revisions were made to the existing recommendations.

**Recommendation 1** – Buprenorphine and methadone should both be considered as standard first-line treatment options for opioid agonist therapy (strong recommendation, high certainty of evidence).

- *For people who initiate opioid agonist therapy with buprenorphine, clinicians should be aware of the higher risk of attrition after the first month of initiation and offer alternative opioid agonist medications in these circumstances (high certainty of evidence).*
- *When considering methadone, clinicians should be aware of the higher risk of mortality during the first month compared to the remainder of the treatment period (moderate certainty of evidence).*

Evidence about the SROM, an off-label treatment, was scarce (two meta-analyses, five cohort studies). Little and low-certainty evidence suggests that treatment retention was similar in patients receiving SROM compared to patients receiving methadone or buprenorphine. Nevertheless, SROM was found to be less effective in reducing adverse events (low certainty) and was associated with a higher risk of mortality (low certainty). No new study compared SROM to methadone and buprenorphine in terms of opioid use, patient preference, and costs.

The new findings about SROM are too limited to make changes to the previous 2018 recommendation. Since methadone and buprenorphine have become equally first-line treatments, SROM is now recommended as a second-line treatment. Yet, precautions must be taken, including daily-witnessed doses and close monitoring initially; only experienced clinicians should prescribe SROM for OUD.

**Recommendation 2** – Opioid agonist therapy with slow-release oral morphine should be available and offered as a second-line treatment option (strong recommendation, moderate certainty of evidence).

## Withdrawal management

Opioid withdrawal involves a set of symptoms and signs experienced by people physically dependent on opioids following a decrease in or cessation of opioid use. As the physical and affective symptoms vary widely and can be distressing to these people, proper management of such symptoms beyond the initial acute phase is critical to prevent relapse and increased risks of OUD-related harms.

**Safety considerations for opioid withdrawal:** New evidence from three RCTs and one cohort study reported either less or no difference in substance use when comparing OAT maintenance to managed withdrawal. There was also no difference in adverse events between OAT and forced withdrawal. As in previous research, the need for long-term sup-

port was highlighted, particularly for populations who are incarcerated following release from custody.

**Opioid agonist taper and alpha$_2$-adrenergic agonists:** Previous literature suggests that if people wish to pursue withdrawal management over long-term treatment with OAT, they should be informed of the potential increased risks and be offered either buprenorphine or methadone as part of a slow taper strategy with a closely supervised, long-term follow-up allowing for OAT continuation if OUD symptoms or relapse re-emerge. Since 2018, one clinical trial emphasized the need for a slow taper approach to reduce opioid use and lessen withdrawal symptoms.

**Opioid agonist discontinuation:** In the past six years, two observational studies reported on the effectiveness of a slow taper approach for OAT discontinuation. Both suggested starting after at least one year of stable and sustained OAT with a slow taper rate.

The limited new evidence and their clinical judgment allowed the guideline development committee to reiterate the previous 2018 recommendations regarding opioid withdrawal management.

**Recommendation 3** – Patients with opioid use disorder should not be offered withdrawal management alone because of the increased rates of relapse, morbidity, and mortality. Concurrent long-term addiction treatment is recommended (Strong recommendation, moderate certainty of evidence).

**Recommendation 4** – When withdrawal management alone is pursued, a supervised slow opioid agonist taper (depending on the patient) should be provided, with close follow-up, and opioid agonist therapy should immediately be offered if the risk of relapse emerges. (Strong recommendation, moderate certainty of evidence).

**Recommendation 5** – For patients with a successful and sustained response to opioid agonist therapy who wish to discontinue opioid agonist therapy (i.e., desiring medication cessation), clinicians should consider a slow taper approach (depending on the patient). Ongoing addiction care should be considered upon cessation of opioid use. (Strong recommendation, moderate certainty of evidence).

# Psychosocial and harm reduction interventions

## Adjunctive psychosocial interventions

Psychosocial interventions for OUD are activities or strategies that target drug use-related behaviours and reasons (e.g., trauma), social and interpersonal relationships, and cognitive, emotional, and environmental factors. They aim to improve patient health, functioning, and well-being. The goal of the current update was to re-examine the impact of psychosocial interventions on selected OUD outcomes.

Mixed findings from the past six years suggest that psychosocial interventions might improve OAT treatment retention (two meta-analyses, 10 RCTs, one non-RCT, two cohort studies; low certainty). Most RCTs showed no difference, while meta-analyses displayed inconsistent results. In terms of opioid abstinence, findings within the individual studies (three meta-analyses, 14 RCTs, one cohort study; moderate certainty) are also conflicting. Some favour the psychosocial treatments and OAT, while others report no difference.

Research evaluating costs, mortality, and patient preference were minimal. A few cost studies (two RCTs and three cohort studies) reported inconclusive results. One cohort study assessed mortality and did not find any benefit to adding psychosocial intervention to OAT maintenance. There have been no studies on patient preference for psychosocial interventions.

Based on the evidence, the guideline development committee agrees that the combination of psychosocial interventions and OAT is not inferior to OAT maintenance alone. The following revisions were made to the existing recommendations.

**Recommendation 6** – Psychosocial treatments, interventions and supports can be offered as adjunct treatments to opioid agonist therapy to increase treatment retention (Strong recommendation, moderate certainty of evidence).

**Recommendation 7** – Psychosocial treatment should not be a mandatory component of standard treatment for opioid use disorder and should not prevent access to opioid agonist therapy (Strong recommendation, moderate certainty of evidence).

## Harm reduction

In Canada, several accessible, evidence-based harm reduction services (e.g., needle and syringe programs, take-home naloxone distribution, and supervised consumption services) can reduce the risk of HIV and HCV by 30% to 50%, are cost-effective, and prevent

opioid-related overdoses. The new evidence, although limited, reports similar results and allows the guideline committee to reaffirm the importance of offering harm reduction as part of the continuum of care for people with OUD.

**Recommendation 8** – Harm reduction strategies should be offered as part of the continuum of care for patients with opioid use disorder (Strong recommendation, moderate certainty of evidence).

- *Current evidence supports the use of the following harm reduction programs: provision of sterile consumption equipment, overdose prevention education, and access to take-home naloxone kits.*

## Special considerations

### Alternative options – Oral naltrexone

As a competitive antagonist with no potential for abuse or diversion, oral naltrexone has been considered as an OUD treatment option for people who are no longer using opioids. However, limited evidence has been reported on its benefits compared to other treatments or even placebos. Therefore, in the 2018 CRISM *National OUD Guideline*, it was recommended to offer it as an adjunct medication for OUD only under particular circumstances. This update of the guideline does not reiterate the recommendation due to minimal new evidence that further reports a higher risk of treatment discontinuation, no apparent benefits in adverse events or opioid use, and the scarcity of requests for this medication.

**Special consideration** – For patients who decline or are not on standard treatments for opioid use disorder and have withdrawn from opioids, oral naltrexone could be discussed as an adjunct pharmacological option.

### Special population – Pregnant people

The 2018 CRISM *National OUD Guideline* did not provide a recommendation for pregnant persons but suggested both methadone and buprenorphine as effective treatments for OUD. Evidence from the last six years continues to support that both first-line treatment options should be offered to pregnant people. While most studies favour buprenorphine, the absence of information on precise neonatal exposure duration prevents a recommendation for one medication over another. Similar to other patients with OUD, pregnant people should be offered first-line treatment options, psychosocial interventions, and harm

reduction, regardless of the stage of pregnancy. There was no evidence about the effect of SROM on pregnant persons and their fetuses.

**Special consideration** – Pregnant people with opioid use disorder who are not in treatment should be encouraged to start a first-line treatment as soon as possible during pregnancy.

### Emerging issues

As part of the update process, the guideline development committee sought input from health care providers (e.g., physicians, nurses, pharmacists, social workers). The largest concern among these providers was the provision of a safe supply of pharmacological products.

## Safer supply

Following the onset of the COVID-19 pandemic in March 2020, temporary prescribing guidelines were introduced, particularly in British Columbia, as a specific pandemic harm reduction strategy to mitigate the risks of overdose and withdrawal during periods of self-isolation. At present, prescribing practices within safer supply services depend on various factors and rules at the patient, health care provider, and regional and provincial levels. Given the scarcity of literature, developing and including clinical recommendations on this topic in this updated version of the CRISM *National OUD Guideline* was not possible. Instead, a scoping review methodology was adopted to map and structure the literature on the use and role of safer supply. A concept analysis of safer supply following Walker and Avant's model was also conducted to systematically explore and clarify the key attributes associated with the medical model of safer supply prescribing practices; this work by Do et al will be reported elsewhere.

## Others

### Fentanyl and analogues

Fentanyl is a synthetic opioid approved as a potent pain reliever. Due to its high potency, fentanyl and its analogues increase the risk of non-fatal and fatal overdose events. There is a lack of studies addressing fentanyl and its analogues in several components of OUD management and in reviewing the effectiveness or best practices of OUD medication in people dependent on fentanyl, which prevents the committee from including a recommendation.

## Co-medication

Few studies included in the literature review only assessed the effect of medications for psychiatric comorbidities on the outcomes of OUD treatment. The evidence of the impact of such co-medication with OUD outcomes was not captured; therefore, the guideline development committee could not make a recommendation in this guideline.

# Recommendations

## Opioid agonist therapies

| | Quality of evidence | Strength of recommendation | Evidence summary |
|---|---|---|---|
| **Recommendation 1 (UPDATED)**<br>Buprenorphine and methadone should both be considered as standard first-line treatment options for opioid agonist therapy. |  |  | Pages 54-59; 60-63 |

- *For people who initiate opioid agonist therapy with buprenorphine, clinicians should be aware of the higher risk of attrition after the first month of initiation and offer alternative opioid agonist medications in these circumstances (high certainty of evidence).*
- *When considering methadone, clinicians should be aware of the higher risk of mortality during the first month compared to the remainder of the treatment period (moderate certainty of evidence).*

| | | | |
|---|---|---|---|
| **Recommendation 2 (UPDATED)**<br>Opioid agonist therapy with slow-release oral morphine should be available and offered as a second-line treatment option. |  |  | Pages 59-64 |

## Withdrawal management strategies

| | Quality of evidence | Strength of recommendation | Evidence summary |
|---|---|---|---|
| **Recommendation 3 (NO CHANGE)**<br>Patients with opioid use disorder should not be offered withdrawal management alone because of the increased rates of relapse, morbidity, and mortality. Concurrent long-term addiction treatment is recommended. |  |  | Pages 64-70 |
| **Recommendation 4 (NO CHANGE)**<br>When withdrawal management alone is pursued, a supervised slow opioid agonist taper (depending on the patient) should be provided, with close follow-up, and opioid agonist therapy should immediately be offered if the risk of relapse emerges. |  |  | Pages 64-70 |

LEGEND:  STRONG/HIGH  MODERATE

## Withdrawal management strategies

| | Quality of evidence | Strength of recommendation | Evidence summary |
|---|---|---|---|
| **Recommendation 5 (NO CHANGE)**<br>For patients with a successful and sustained response to opioid agonist therapy who wish to discontinue opioid agonist therapy (i.e., medication cessation), clinicians should consider a slow taper approach (depending on the patient). Ongoing addiction care should be considered upon cessation of opioid use. |  |  | Pages 64-70 |

## Psychosocial and harm reduction interventions

| | Quality of evidence | Strength of recommendation | Evidence summary |
|---|---|---|---|
| **Recommendation 6 (UPDATED)**<br>Psychosocial treatments, interventions, and supports can be offered as adjunct treatments to opioid agonist therapy to increase treatment retention. |  |  | Pages 71-76 |
| **Recommendation 7 (UPDATED)**<br>Psychosocial treatment should not be a mandatory component of standard treatment for opioid use disorder and should not prevent access to opioid agonist therapy. |  |  | Pages 71-76 |
| **Recommendation 8 (UPDATED)**<br>Harm reduction strategies should be offered as part of the continuum of care for patients with opioid use disorder. |  |  | Pages 76-79 |

- *Current evidence supports the use of the following harm reduction programs: provision of sterile consumption equipment, overdose prevention education, and access to take-home naloxone kits.*

LEGEND:  STRONG/HIGH  MODERATE

## Special considerations (NEW)

| | Evidence summary |
|---|---|
| **Alternative options**<br>For patients who decline or are not on standard treatments for opioid use disorder and have withdrawn from opioids, oral naltrexone could be discussed as an adjunct pharmacological option. | Pages 79-83 |
| **Special populations**<br>Pregnant people with opioid use disorder who are not in treatment should be encouraged to start a first-line treatment as soon as possible during pregnancy. | Pages 83-87 |

# 1. Introduction

## 1.1.
# Overview of the standards of care

Opioid use disorder (OUD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision (DSM-5-TR)[6] as a problematic pattern of opioid use leading to clinically significant impairment or distress. According to the DSM-5-TR criteria, OUD may result from the non-medical use of prescription opioids like oxycodone or hydromorphone and/or unregulated substances such as heroin, fentanyl and its analogues (e.g., carfentanil, acetylfentanil), and can range from mild to severe. Chronic opioid use may lead to physical and psychological dependence, tolerance, and substance use disorder (SUD), and it is commonly associated with increased morbidity and mortality rates.[7,8] Managing OUD involves multiple approaches with the ultimate goal of improving patients' health and quality of life. All treatment approaches (pharmacological, psychosocial, and harm reduction) must meet ethical requirements and scientific criteria for clinical efficacy.[9]

The CRISM guideline development committee endorses international standards of care established by the World Health Organization (WHO) and other national and international bodies.[9–12] Here are selected principles for providing optimal care for patients with OUD. Professionals must follow and apply them to all clinical recommendations. Health care providers should also use their clinical experience to provide individualized care.

### 1.1.1.
## Adopting a patient-centred approach as a standard of care

OUD management should be based on a patient-centred approach, which includes respect for the patient's rights, preferences, and dignity.[9]

#### Patient's rights

Health care providers should involve patients in all decisions about their care whenever possible. Patient-informed consent is mandatory, and treatment should not be forced. Withdrawal management for patients unable to provide consent (i.e., unconscious) is an exception. In this case, health care providers should seek the patient-appointed decision maker or a family member to obtain consent and follow institutional and local policies. Then, the patient's consent should be obtained as soon as possible. Health care providers should inform patients of all treatment options and procedures available, the risks, benefits, and alternatives of each medication, and the risks of refusing treatment entirely.[9]

#### Patient preferences

The patient's goals and preferences should be respected.[9] Treatment choice and duration should be based on the patient's needs and circumstances while following best practices and using evidence-based strategies and treatments. Clinicians, in partnership with pa-

tients, should carefully weigh the use of off-label treatments, balancing the benefits and risks of a specific situation. Further, to uphold professional and ethical standards, health care providers should abstain from advocating their personal beliefs.

### Patient dignity

Health care providers should be committed to treating patients with dignity and respect. Each patient should be treated as a unique human being with respect to their individuality. There should be no discrimination or stigmatization, regardless of the chosen trajectory of care. Therefore, health care providers should be aware of their language and the environment when addressing patients. The patient's ability to make their own choices, as well as their capacities and goals, should be recognized.[9,12]

### Patient experience

The accessibility (i.e., geographical barriers), flexibility, and intensity of the therapy should be considered, as these factors can significantly impact patients' experiences, preferences, and retention in treatment. The patient's comorbidities and past experiences with OUD medications are important; they should not prevent access to treatment.[9,12]

## 1.1.2. Considering the continuity of care as a standard

The continuum of care refers to a set of health services that should be continually offered to patients throughout their trajectory, from assessment to recovery management . Essential OUD-related services include harm reduction programs, withdrawal management strategies, opioid agonist treatments (OAT), and psychosocial interventions.[9–11] All these services should be available at different levels, from primary to tertiary care. Patients might use some or all services as they see fit, while they may need to revisit some over others. Clinicians should consider intensifying or simplifying treatment to offer the appropriate intervention (e.g. the type of pharmacological drugs, outpatient vs. inpatient services).

Multiple studies indicate that maintaining a long-term relationship between patients and providers enhances the therapeutic relationship, ensures high-quality care, and leads to better patient outcomes.[13–15] This has led to a new concept of continuity of care where a patient with a chronic health condition should see the same provider or health care team over time. Accordingly, primary health care professionals, who are often the entry point into the health care system, should be trained in how to screen, diagnose, and treat OUD and different comorbidities.[9]

In the case of a multifaceted health problem like OUD, continuity of care also implies the connection and linkage to different services, facilities, and settings. When transitioning from one setting to another (e.g., inpatient to outpatient service), patients should be continually informed and involved in decision-making about their health care. They should have access to the same high standards of care from one geographic area to another.[9,12]

### 1.1.3.
## Implementing integrated services as a standard of care

An integrated health care system is crucial for an effective continuum of care when dealing with OUD. A multidisciplinary team, including family medicine, nursing, psychiatry, psychology, and social work, should be implemented at the treatment site. The management team should also include people with lived or living experience (PWLLE) as peer support.[9,12]

Social support and clinical management of comorbidities should be incorporated into OUD treatment programs. Interventions to prevent drug-related harms should also be integrated into treatment services. Naloxone, used to reverse opioid poisoning, should be available at treatment sites and distributed to all patients with OUD, their partners and their families. Education on safe drug use practices and blood-borne infection risks should be offered. Patients should also be linked to supportive community-based organizations, including peer support, and needle exchange or syringe distribution programs.[11,12]

Finally, OUD treatment services should be accessible to people living in both urban and rural areas, either in person or virtually through telehealth. Services should be available at a wide range of opening hours and be financially affordable.[9,12]

### 1.1.4.
## Acclimating the needs of special populations as a standard of care

Special considerations need to be addressed for subgroups of patients with particular needs. These include people experiencing homelessness, unemployment, incarceration, pregnant persons, Black, Indigenous, and people of colour (BIPOC) populations, immigrants, sex workers, and people of diverse sexual orientations and gender identities, who are often vulnerable and victims of stigma and discrimination. Moreover, women are more susceptible to facing sexual abuse and domestic violence; they may need adapted clinical management.[9–12]

**Discrimination, stigma, and racism**

Treatment teams should be aware of the ongoing possibility of unconscious bias and forms of discrimination, stigmatization, or personal beliefs as factors impeding optimal care. Training should be provided, and efforts should be made to identify individual vulnerabilities and protocols for referring patients to complementary services. It is important to integrate an anti-racism framework into OUD treatment programs.[16] Cultural, racial, and religious sensitivities and gender identity should be considered to reduce barriers and improve accessibility. This means offering cultural mediators and interpreters when necessary.[9,11,12]

### Sexual abuse and violence

Women (cis, trans and 2spirit) and sex workers are at a higher risk of sexual abuse and violence. Health care professionals involved with these subgroups should be in contact with appropriate social agencies, when permitted by the patient, to ensure that violence problems are followed up on. Treatment should be offered in a safe, single-sex setting whenever possible. It is also important to prioritize the reproductive health of people of childbearing potential by providing them with access to contraception and education. Pregnant persons should receive adapted OUD management, as discussed later in section 4.3.2 Special population: Pregnant persons (p.83).[9,11,12]

### Incarceration

Unregulated opioid possession is a criminal offence in Canada. Opioid use is associated with increased criminal offences, often in order to support drug purchases and to avoid craving and withdrawal.[17,18] Heroin possession offence rate has increased by 115% between 2011 and 2021[19] and over 40% of crimes committed by people admitted to Canadian federal institutions (excluding impaired driving or violations of the Controlled Drugs and Substances Act) are associated with substance use.[20] Interestingly, OAT reduces the risk of re-incarceration.[18,21–25]

People with OUD in jails and prisons should have access to evidence-based treatment and should benefit from standards of care similar to those offered in the community.[26]

- To respect patient rights and dignity, people in jails and prisons should not be forced to initiate OUD treatment.[9,18,27]
- Criminal justice settings should offer appropriate services for OUD management, including harm reduction (e.g., prevention of blood-borne infections), evidence-based OATs, psychosocial treatments, and the management of comorbidities. All staff (penitentiary system officers and court professionals) should receive appropriate training to recognize the specific needs of people with OUD.[9,18,27]
- The continuity of care must be applied. This implies that at any stage of custody (i.e., from arrest to detention at the police station, to prison, to court, to release), people with OUD should have access to their treatment or to treatments appropriate to their condition or needs at that time. After release, coordination between the criminal justice system and the community is essential to ensure the continuity of treatment and prevent poisoning death due to return to use and loss of tolerance.[9,18,27]

## 1.2.
# Overview of the drug poisoning crisis in Canada

As per the recent report by the United Nations Office on Drugs and Crime (UNODC), approximately 60 million individuals across the globe reported opioid use in the year 2022.[28] The high incidence of drug-related overdoses presents a significant challenge, particularly in North America. The drug overdose crisis has emerged as a pressing global concern with an alarming increase in opioid-related deaths involving prescription and illegal opioids, as opioids accounted for over 69% of drug-related deaths.[29] Opioid-related harms in Canada and the United States of America (USA) continue to be a significant public health concern, particularly with the use of fentanyl. Between January 2016 and March 2024, there were 47,162 apparent opioid toxicity deaths across Canada. In 2023, of all accidental apparent opioid toxicity deaths, at least 82% involved non-pharmaceutical opioids and 81% involved fentanyl, which represents a 42% increase since 2016.[4] Furthermore, over half of accidental apparent opioid toxicity deaths also involved a stimulant, highlighting a poly-drug toxicity issue. While the drug poisoning crisis has a nationwide impact, it is particularly severe in the provinces of British Columbia, Alberta and the Yukon territory, which have exhibited higher rates of apparent opioid toxicity deaths (per 100,000 population) than the national average for the past three years.[4] These national and provincial/territorial statistics highlight the urgent need for effective interventions and treatments to address the non-medical use of opioids, OUD, and related harm.

Due to the chronic, relapsing nature of OUD and the complexity and variability in individuals' needs and goals, there is no linear trajectory suited to the clinical management of OUD. While it is recognized that ceasing use would be the only option that would prevent all adverse events and consequences related to opioid use, health care professionals should acknowledge individuals' choices, goals and motivations[30] to ensure the person's safety and well-being. Several options, including effective treatments and harm reduction, offer the possibility to improve the health and quality of life of people with OUD. Effective treatments of OUD typically involve pharmacotherapy, potentially in conjunction with psychosocial interventions. Pharmacotherapy consists mainly of the use of OATs to prevent relapse and reduce drug-related harms. Psychosocial interventions in OUD treatment may include counselling, behavioural therapies, and support groups[31] to help individuals with pharmacological treatment retention.[32] While the effectiveness of such treatments has been studied and recognized, barriers such as insufficient accessibility and misinformation persist. Collaboration between health care providers and policymakers is essential to address the drug poisoning crisis and to ensure that people with OUD have access to consistent, adequate, evidence-based treatments and support.

# 2. Purpose and Scope

This guideline is an update to the 2018 CRISM *National OUD Guideline*, which aims to provide clinicians with a standardized and nationwide framework for OUD management. Based on a thorough review of the latest research literature, encompassing the six years since its original publication, the guideline includes revised recommendations on both clinical and psychosocial treatment options, an overview of the recent evidence on the clinical management of OUD in pregnant persons, and a brief overview of the latest emerging issues including the provision of alternative pharmacological products for reducing exposure to unsafe supply of unregulated opioids.

## 2.1. Scope of guideline

This document has been developed to help health care professionals provide patients with consistent and effective treatment tailored to their individual needs and circumstances. It is based on the most recent scientific evidence on pharmacological and psychosocial interventions for people with OUD, including pregnant persons, and harm reduction services. It is recommended to refer to provincial guidelines for specific regulations, treatment procedures, and dosing schedules, as those fall outside of the scope of this guideline. Clinicians are encouraged to use their professional judgment to determine the best course of treatment for their patients.

### Medications

#### Pharmacotherapies

This guideline includes oral medications approved by Health Canada for the treatment of OUD, such as methadone and buprenorphine (a term that includes the mono-product and the combination buprenorphine-naloxone). Several formulations are now available for buprenorphine, and this update will consider the medication itself without providing a comparison between formulations.

Off-label medication, specifically slow-release oral morphine (SROM), is included, as it was in the 2018 CRISM *National OUD Guideline*, given the growing body of evidence for its use as an OAT option at that time. Oral naltrexone is also part of this national guideline because, as stated in the previous version, there may be specific circumstances where this medication could be used as a treatment option for OUD.

While the guideline development committee recognizes and acknowledges the evidence surrounding extended-release naltrexone as a treatment option for OUD under specific circumstances, this formulation is not offered in Canada, and there is no plan for its approval and commercialization. Therefore, it was not included in this national guideline.

Injectable opioid agonist therapies (iOAT) are outside the scope of this guideline, and recommendations regarding these treatment options are available in the following CRISM guidance documents: National Injectable Opioid Agonist Treatment for Opioid Use Disorder Clinical Guideline and National Injectable Opioid Agonist Treatment for Opioid Use Disorder Operational Guidance.

### Withdrawal management

Since the guideline development committee does not recommend withdrawal management as a stand-alone treatment (as established in the 2018 CRISM *National OUD Guideline*), comparative studies about medication options in the context of withdrawal management were not included in the literature review. For further details regarding withdrawal management strategies, please refer to the following CRISM guidance document: Opioid Use Disorder—Related Withdrawal Management.

### Psychosocial interventions and harm reduction

Evidence surrounding non-pharmacological approaches, including psychosocial interventions and harm reduction services, was reviewed. All psychosocial interventions examined were included and were evaluated in conjunction with OAT, compared to OAT alone. Harm reduction services, including, but not limited to, supervised consumption or injection sites, take-home naloxone, and sterile injection or smoking supplies distribution programs, were reviewed based on OUD diagnosis and not necessarily in association with pharmacological treatment.

### Special populations

The scientific evidence gathered regarding the treatment of OUD focuses on the general adult population (aged 18 years and older). However, the guideline development committee acknowledges that specific populations, such as older adults (aged 65 years and older) and adolescents (aged 12 to 17 years), should be offered evidence-based treatments and support for OUD, as recommended by guidelines on OUD among older adults[32] and other instances, such as the American Academy of Child and Adolescent Psychiatry[33] and the Society for Adolescent Medicine.[34]

The guideline development committee reviewed the scientific evidence for managing OUD in pregnant persons. It is worth noting that pregnant persons with OUD require specialized treatment and care. Although evidence for pregnant persons has been included in this update of the 2018 CRISM *National OUD Guideline*, a formal recommendation cannot be made as the data only spans the last six years. The evidence gathered, albeit insufficient to offer a comprehensive overview, has allowed the guideline development committee to provide a special consideration. For further details and formal recommendations, it is essential to refer to the guidelines for pregnant persons with OUD based on experts' opinions, such as Opioid Use Throughout Women's Lifespan: Opioid Use in Pregnancy and Breastfee-

ding,[36] Opioid Use and Opioid Use Disorder in Pregnancy,[37,38] and Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants.[39]

The literature review did not capture specific evidence about populations and communities such as persons in custody, women, LGBTQIA/2S+, Black Indigenous and People Of Colour (BIPOC), and individuals living with comorbidities. Therefore, no specific recommendations were made regarding these communities. Nonetheless, it is important to note that evidence-based OUD treatment should be provided based on the patient's unique needs and considerations, and patient-centred, anti-racism, and trauma-informed approaches should be adopted.

## 2.2. Intended audience

This second iteration of the CRISM *National OUD Guideline* is intended for use by physicians and allied health care professionals, nurse practitioners, pharmacists, clinical psychologists, social workers, medical educators, or clinical care case managers with or without specialized experience in addiction treatment. This update may also be a useful tool for policymakers and health care administrators at the national and provincial levels when developing and adjusting evidence-based strategies and programs to address gaps in addiction care, addiction medicine, and treatment access policies nationwide.

# 3. Methodology

The development of this practice guideline was financially supported by Health Canada's Substance Use and Addictions Program (2223-HQ-000151) and conducted under the direction of the CRISM Regional Nodes (British Columbia, Ontario, the Prairies, Quebec, and the Atlantic). The update was carried out following the established standards of the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines,[40] which included a thorough declaration of conflicts of interest, transparent methodology, patient involvement, and the inclusion of an external review committee. Specifically, the recommendations were formulated using the validated GRADE (Grading of Recommendations, Assessments, Development and Evaluation) process.[41] The GRADE tool enables a systematic approach to formulating clinical recommendations based on scientific evidence and clinical judgment.

## 3.1. Selection of Guideline Committees

Three separate committees were formed for the development of this guideline: a guideline steering committee, a guideline development committee, and an external review committee.

The guideline steering committee comprised 5 principal investigators (i.e., node leads) from CRISM. The guideline development committee consisted of 20 members, including a 6-member scientific team with knowledge of systematic reviews and methodology, 1 guideline development manager, 2 guideline coordinators, and 5 addiction medicine experts (i.e., clinical leads).

Meanwhile, the external review committee comprised 63 national multidisciplinary members recruited from different provinces and territories through the CRISM national network. These members were clinicians, key facilitators, and persons with lived and living experiences, representing urban, rural, and ethnocultural diversity communities. The clinicians invited were primary care physicians, addiction medicine physicians and psychiatrists, psychologists, pharmacists, nurse practitioners, and registered nurses. Three international experts (clinicians and academics) were part of the external review committee and were also invited to give their input.

## 3.2. Conflict of interest policy

Standards for disclosing conflicts of interest have been followed under the Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts.[42] Members of the development committee and external reviewers disclosed any remuneration from industry for-profit enterprises and other entities that could introduce the risk of bias using a standardized and adapted form.[43] Indirect conflict of interest may include academic advancement, clinical revenue, and professional or public standing. Committee members were asked to report any indirect conflicts of interest that could influence the recommendations. Detailed disclosure of competing interests is available in Appendix 1.

## 3.3. Content development

The GRADE approach for developing recommendations consists of the following steps:[41]

- Selection of clinical questions and topics
- Review and synthesis of the literature;
- Development of recommendations and the evaluation process;
- Consultation of the external review committee.

### Selection of topics

Since this guideline was an update to an existing guideline rather than a stand-alone project, the 2018 clinical questions were explicitly used to determine priority topics. A systematic search of the literature on pregnant people was added to the 2018 topics. In addition, a focus group with 4 PWLLE was held, and 98 health care providers across Canada were surveyed to learn about emerging substance use issues. One issue raised was safe supply, which is considered separately from the guideline. A summary of the results of the focus group and survey is available in Appendix 2.

### Literature review

A systematic appraisal of peer-reviewed scientific literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness Research guidelines was conducted.[40,42,44] Grey literature was excluded from this review. The protocol was previously registered with PROSPERO (CRD42023398663).

### Search strategy

An expert librarian developed two distinct search strategies to update the clinical recommendations according to previous 2018 clinical questions and Population, Intervention, Comparison, Outcome, and Study (PICOS) design statements (see Appendix 3). These strategies were designed to address the two main topic areas covered by this practice guideline, namely the pharmacotherapeutic and the psychosocial and harm reduction areas. The MEDLINE, EMBASE, PsycINFO, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from January 2017 to August 2023 for studies limited to human subjects and written in English. In addition, the reference list of all relevant studies was searched. A comprehensive overview of the search strategies and keywords by database and search topic is presented in Appendix 4.

### Inclusion criteria

To be included, studies must have reported on data from adult participants (aged 18 years and older) with DSM-IV-confirmed or DSM-5-confirmed OUD of any severity (mild, moderate, or severe). Participants may have used either illegal or prescribed opioid drugs by any administration route (e.g., injection, inhalation, ingestion). Interventions of interest involved long-term OAT in comparison to long-term therapy with another OAT, placebo, treatment as usual, short-term taper, oral naltrexone, or no treatment. The studies included also involved the evaluation of withdrawal management as a stand-alone treatment compared to long-term OAT. Studies evaluating psychosocial interventions delivered in conjunction with long-term OAT or harm reduction services were also of interest. Interventions could have been carried out in inpatient or outpatient settings.

The eligible types of studies were meta-analyses, RCTs, quasi-experimental and observational cohort studies (prospective and retrospective). The updated guideline expanded the scope of the included studies to observational studies, reflecting a broader scope of evidence gathering. While observational studies lack the rigour of controlled trials, they nonetheless constitute meaningful evidence when carried out in large numbers and support consistent, replicated findings. Qualitative and single-case designs were excluded due to their emphasis on inductive, hypothesis-generating processes rather than quantitative, deductive generalizations that could be used to guide population-level interventions.

### Study selection

The study selection process was performed using the Covidence systematic review platform. Each search area was integrated separately into Covidence, where duplicates from the databases were automatically eliminated. In total, 32,825 studies were identified using the two literature searches. A data screening protocol was implemented, with inter-rater reliability evaluation occurring at each stage. Initial screening of titles and abstracts was carried out independently and in duplicate by scientific members of the development committee. Disagreements were resolved through discussion and resolved by consensus. Abstracts meeting the inclusion criteria (573 articles from the pharmacotherapeutic

search and 709 articles from the psychosocial and harm reduction search) were selected for full-text review. The full text was also independently reviewed by two scientific members, and consensus was required for the inclusion of a study. Overall, 105 studies about pharmacotherapeutic interventions and 45 about psychosocial and harm reduction interventions were included. The study selection process is illustrated by the PRISMA diagrams in Appendix 5.

### Outcomes of interest and data extraction

The six outcomes of interest included:

1. Retention in treatment;
2. Abstinence or reduction in opioid use;
3. Adverse events;
4. Morbidity and mortality;
5. Direct and indirect costs; and
6. Patient preference.

These outcomes were identified through a prior Delphi consensus study[45] and the perspectives of expert clinicians. The selection of outcomes consisted of two rounds. First, two scientific committee members identified predefined outcomes (retention in treatment, abstinence or reduction in opioid use, adverse events, and mortality) based on the Delphi consensus study.[45] The expert clinicians reviewed and approved the predefined outcomes. The two other outcomes (direct and indirect costs and patient preference) were added to the list based on expert consensus. Costs and patient preference are important GRADE criteria to take into account when formulating clinical recommendations. Patient satisfaction was also considered, as it may influence preferences and expectations. All the outcomes were chosen for their importance in effective OUD treatment. In addition, the guideline development committee agrees that it is important to consider internationally standardized outcomes for better reproductivity over time. Treatment retention and opioid abstinence were identified as critical outcomes and were considered most important when summarizing the quality of evidence of pharmacological and psychosocial studies.

As the ultimate goal of harm reduction consists of minimizing the adverse consequences associated with drug use, different outcomes were considered for studies evaluating harm reduction services. In the absence of an international Delphi consensus, the guideline development committee based its considerations on data from systematic reviews.[46,47] With consensus, the committee opted for the following outcomes: Human Immunodeficiency Virus (HIV) incidence or prevalence, Hepatitis C Virus (HCV) incidence or prevalence, non-fatal overdose, naloxone use, mortality, and direct and indirect costs. Non-fatal overdose and mortality were defined as the most important outcomes when summarizing the quality of evidence.

A template for data extraction was developed to ensure consistency. Two independent scientists carried out the extraction, and discordance was resolved through discussion.

The data extracted included study characteristics (design, country, year of publication), population (number of participants, mean age, sex), type of intervention (number of groups and follow-up duration), key findings of outcomes of interest, funding, and conflicts of interest. All types of measures within each domain of relevant outcomes and numerical results with effect sizes and p-values were extracted. Data summary tables are available in Appendix 6.

### Risk of bias assessment

The risk of bias was evaluated by two scientists using appropriate tools based on the study design. The potential bias across multiple domains was assessed for individual studies. These domains included confounding bias, sample selection, measurement of exposures and outcomes, selective reporting of outcomes, and analysis. For meta-analyses, relevant domains of bias included a review protocol, search strategy, study selection, risk of bias assessment, method of meta-analysis, and publication bias. The following tools were used to evaluate the risk of bias for each corresponding study design: AMSTAR-2 for meta-analyses,[48] the Cochrane RoB-2 tool for RCTs,[49] the Cochrane ROBINS-I for non-randomized controlled trials,[50] and the Newcastle Ottawa Scale (NOS) for cohort studies.[51] The tools were selected to reflect the gold standard measures for risk of bias assessment based on both a review of the psychometric literature as well as consultation with systematic review experts. These tools permitted a systematic approach to assessing the risk of bias as high, moderate, or low. While decision algorithms were used with RoB2 and ROBINS-I to generate objective judgment,[49,50] scores for AMSTAR-2 and NOS were manually generated. Critical items noted by developers were considered in AMSTAR-2, leading to an increase in the study's risk of bias where applicable.

### Certainty of evidence assessment

The GRADE system was used to determine evidence certainty in a systematic way.[52–57] The body of evidence was sorted based on clinical questions and outcomes, then the data was synthesized narratively according to the type of study. A meta-analysis was not performed due to the high heterogeneity of outcome definitions and measures. According to the GRADE methodology, a "starting classification" was used in descending order of strength. Meta-analyses and RCTs were considered as high-quality evidence, quasi-experimental studies as moderate-quality evidence, and observational studies as low-quality evidence.[52] The GRADE tool provided the option to lower the grading of quality by considering specific parameters, including the risk of bias of primary studies, inconsistency between study results, indirectness (when results cannot be generalized), and publication bias.[52] The imprecision criteria were not assessed since no quantitative meta-analyses were conducted. Instead, all measures of interest were analyzed for trends across the studies. To determine the quality of evidence for each outcome, only the highest certainty was considered when all types of design pointed in the same direction. When the quality differed across study designs, the lowest quality was considered. The overall quality of evidence for every recom-

mendation was assessed by using the lowest quality of evidence from outcomes defined as the most important or critical. The GRADE certainty tables are shown in Appendix 7.

High-quality evidence denotes that the body of evidence included in our review has very few limitations and variations. Moderate quality indicates that only a few studies with no major limitations are included in our review. Low or very low quality means that the findings of the studies included in the review have major limitations and variations.[41,52]

## Development of recommendations

### Draft recommendations

The previous CRISM *National OUD Guideline* published in 2018 generated a list of 11 clinical recommendations.[58] To update these 11 recommendations, the committee utilized tables summarizing new evidence and the GRADE decision framework to move from evidence to recommendations. In the first round, scientific members drafted the recommendation statements based on the certainty of evidence and various factors, including the benefits and risks balance, patient preferences and values, costs, and the availability of resources. In the second round, the clinical leads were requested to make changes to the draft recommendations based on their clinical judgment. Scientists and clinical experts agreed on wording and which recommendations should be updated, removed, or unchanged. If new and higher-quality evidence was available, all necessary modifications were made to the original recommendation. Note that despite incorporating clinical expertise and consultation in updating the guidelines, the guideline committee prioritized the available research evidence when formulating the final recommendations, adhering to its evidence-based goals.

### Strength of recommendations

After reaching a consensus on wording, the guideline development committee determined the strength of the recommendations. Scientific members proceeded with the initial rating, followed by a discussion with clinical leads. The rating process was adopted from the GRADE methodology.[59,60] Accordingly, determinants used to formulate recommendations—the balance between benefits and harms, patients' values and preferences, and costs and resources—were also employed in this process. These determinants were applied as described in the table below.

**TABLE 1. GRADE CRITERIA FOR ASSESSMENT OF THE STRENGTH OF RECOMMENDATIONS**[59,60]

| GRADE criteria | Explanation |
|---|---|
| **Balance between benefits and harms** | The larger the differences between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation is warranted. |
| **Patients' values and preferences** | Patients' perspectives, beliefs, expectations, and goals for health and life. The greater the variability or uncertainty in values and preferences, the more likely a weak recommendation is warranted. |
| **Costs and resources** | The higher the costs of an intervention (the more resources consumed), the less likely a strong recommendation is warranted. |

Each recommendation was labelled as either "strong" or "weak." Different questions were used to guide the committee in making decisions, as shown in Table 2.

**TABLE 2. DECISION-MAKING FRAMEWORK: FROM EVIDENCE TO RECOMMENDATIONS**[59,60]

Question/recommendation:

| Decision domain | Subdomains influencing decision | Judgment |
|---|---|---|
| **Balance between desirable and undesirable outcomes**<br>• Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? | Baseline risk for desirable and undesirable outcomes<br>• Is the baseline risk similar across subgroups?<br>• Should there be separate recommendations for subgroups?<br>Relative risk for benefits and harms<br>• Are the relative benefits large?<br>• Are the relative harms large?<br>Requirement for modelling<br>• Is there a lot of extrapolation and modelling?<br>Typical values<br>• What are the typical values?<br>• Are there differences in the relative value of the critical outcomes? | ◯ Yes<br>◯ No |

## Question/recommendation:

| Decision domain | Subdomains influencing decision | Judgment |
|---|---|---|
| **Confidence in estimates of effect (quality of evidence)**<br>• Is there high or moderate-quality evidence? | Key reasons for rating evidence down or rating up | ◯ Yes<br>◯ No |
| **Values and preferences**<br>• Are you confident about the typical values and preferences, and are they similar across the target population? | Source of typical values (panel or representative patients)<br>Source of estimates of variability and extent of variability<br>Method for determining values satisfactory for this recommendation | ◯ Yes<br>◯ No |
| **Resource implications**<br>• Are the resources worth the expected net benefit from following the recommendation? | What are the costs per resource unit?<br>Feasibility<br>• Is this intervention generally available?<br>Opportunity cost<br>• Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?<br>Differences across settings<br>• Is there a lot of variability in resource requirements across settings? | ◯ Yes<br>◯ No |
| **Overall strength of recommendation** | A strong recommendation may be warranted despite the low quality of evidence when the evidence suggests a benefit in a life-threatening situation. | ◯ Strong<br>◯ Weak |

A ***strong recommendation*** in favour of an intervention supports that benefits undoubtedly outweigh the harm or that adverse effects prevail on benefits if the recommendation is against an intervention. This type of recommendation also suggests that it is in the best interest of the majority of patients. In the context of clinical practice, a strong recommendation means that it can be adopted as a policy and that variability between individuals and regions would be inappropriate.[59,60]

A ***weak recommendation*** implies that most informed people would choose the recommended action. However, a substantial number would not. Concretely, a weak recommendation in favour or against an intervention, respectively, suggests that there are few possible benefits compared to harms or that adverse effects may prevail over the benefits

of the intervention. It also indicates that different choices may be appropriate for different patients.[59,60]

Note that a weak recommendation does not imply "weak evidence," nor does a strong recommendation imply "strong evidence." A recommendation may be qualified as weak depending on available resources or patients' preferences.[59,60]

## External review

Following standards of trustworthy clinical practice guidelines, as established by the US Institute of Medicine Committee,[40] we sought feedback from stakeholders, including clinicians, key facilitators, and PWLLE. Reviewers (national and international) were requested to rate the appropriateness of the new recommendations and to give general comments on the whole guidance document (scope, rationale, etc). They were encouraged to use their clinical judgment as well as their personal experiences and values.

Each reviewer was given the following: a full-text guidance document and a list of included studies. Reviewers also received rating forms to help them with the review. One rating form was an adapted version of the Appraisal of Guidelines Research & Evaluation—Recommendation EXcellence (AGREE-REX) instrument.[61] The purpose is to assess the appropriateness of each recommendation based on four categories: clarity, relevance, values and preferences, as well as overall appropriateness. The adapted scale allows a score from 1 to 7 that reflects the opinion of the reviewer on each category. An overall score of 5 and above indicates that the recommendation is appropriate, while an overall score of 3 or 4 indicates that the recommendation is uncertain. An overall score of 2 or below means that the recommendation is inappropriate. Reviewers were asked to consider the feasibility and rationale of each recommendation. If evidence was questioned, reviewers were asked to provide new supporting evidence. They were also required to supply alternative phrasing for any questioned recommendation. The full-text document was assessed using an adapted instrument from the Institute of Medicine Committee on Clinical Practice Guidelines.[62] The assessment instrument has five sections evaluating clinical applicability (i.e., scope), clinical flexibility (i.e., exceptions and patient preferences), evidence validity, clarity of the guideline (i.e., headings, abstract, flowcharts), and multidisciplinary process. The percentage of satisfaction was provided. Each review domain with less than 50% satisfaction was revised.

The guideline development committee gathered all feedback and revised the guidance document. Recommendations judged appropriate (mean score of 5 or above) were automatically integrated into the final document. Recommendations judged uncertain or inappropriate were discussed and revised by the guideline development committee. Changes were applied to the recommendations in terms of either direction ("for" or "against") or strength only if new strong evidence or rationale had been raised from reviewers' comments.

# 4. Literature Review

# 4.1. Pharmacotherapies

## 4.1.1. Opioid agonist therapies

In Canada, the only medications approved for OUD are OATs. There are currently several options of opioid agonists permitted by Health Canada for treating OUD, including different types of buprenorphine (mono-product and in combination with naloxone) and methadone (Metadol-D, Methadose, Sandoz Methadone).[63] In the context of an urgent public health need and to address the overdose crisis, the Government of Canada reacted by increasing access to medications.[5] In 2019, Health Canada approved a new indication for injectable hydromorphone and diacetylmorphine as OATs for severe OUD in adults.[64] SROM in a 24-hour formulation (Kadian), approved for pain management, has also been used off-label in Canada to treat OUD since 2017.[63,65]

Buprenorphine and methadone are both synthetic opioids that activate the mu (μ) opioid receptor. Buprenorphine is a partial agonist, while methadone is a full agonist. The opioidergic agonist effect allows them to prevent withdrawal symptoms in patients with OUD. Moreover, when binding to the μ receptor, buprenorphine and methadone block the effects of other opioids and reduce cravings, which leads to a reduction in unregulated opioid use.[66] The high amount of evidence, including four meta-analyses, three systematic reviews, and eight individual studies, has previously shown that OAT is more effective than non-pharmacotherapy in managing patients with OUD,[67–70] and it has been found to reduce adverse outcomes such as mortality and opioid use.[71–81] For that matter, methadone and buprenorphine remain on the 2023 WHO Model List of Essential Medicines.[82] In our updated search, three cohort studies have reaffirmed the superiority of OAT over non-medication, reporting lower mortality rates. A cohort study from the United States that followed people with OUD for four years (2015-2019) reported a two-fold higher risk of mortality in patients who did not receive medications.[83] A second US study also found that there was a lower mortality rate among patients with OUD exposed to buprenorphine compared to no treatment.[84] Similarly, a recent study from Sweden followed 5,757 patients for 7.3 years and found that buprenorphine and methadone were significantly associated with a lower risk of mortality.[85] Regarding other outcomes, one large retrospective cohort study involving 40,885 participants supports that people receiving buprenorphine or methadone were less likely to experience an overdose compared to the no-treatment group.[86] Two meta-analyses[87,88] conducted in 2019 and 2022 compared buprenorphine to non-pharmacological treatment across different outcomes, including treatment retention, opioid abstinence, and adverse events. Both reviews concluded that buprenorphine was more effective than non-pharmacological treatments.

It is widely accepted that OAT is better than non-pharmacological treatment. However, there is still an ongoing debate about the best use of these medications in practice. The previous

national guidelines from 2018 recommended buprenorphine as the first-line treatment for OUD, followed by methadone as the second-line treatment, and SROM as an alternative third-line treatment. Yet, six years down the road, it is now time to reassess these previous guidelines. As a result, a review of new evidence comparing buprenorphine, methadone, and SROM has been conducted to answer the following clinical question: "What is the best evidence-based first-line option for opioid agonist treatment?"

## Buprenorphine vs. methadone

The 2018 CRISM *National OUD Guideline* suggested initiating OAT with buprenorphine whenever possible but at the same time suggested considering the transition to methadone if a patient is not responding. Methadone could be offered at initiation when buprenorphine is not a preferred option. These recommendations were justified at the time by the following:

- It was found that buprenorphine was less effective in retaining patients in treatment compared to methadone. However, both treatments were equally effective in suppressing unregulated opioid use.
- When transitioning from one to the other, studies suggested a gradual methadone taper or 36–72-hour interval before buprenorphine induction. In contrast, the transition from buprenorphine to methadone could be approached easily within 24 hours.
- The literature highlighted the superior safety profile of buprenorphine over methadone in terms of overdose potential and respiratory depression, enabling earlier provision of take-home buprenorphine doses.

In the following sections, the most recent evidence is presented and organized around OUD outcomes of interest.

### *Treatment retention*

Substantial new evidence comparing methadone to buprenorphine, measuring treatment retention as an outcome, has been published in the last six years. This includes six meta-analyses,[26,87–91] two RCTs,[92,93] and 20 observational studies.[73,94–112]

Consistent with the 2018 literature review, five of the reviewed meta-analyses support that treatment retention is higher in patients on methadone compared to buprenorphine.[26,87–90] For example, Lim *et al.* published a meta-analysis of RCTs in 2022 and reported that patients on methadone had a higher likelihood of retention compared to those on buprenorphine (risk ratio [RR] = 1.22; 95% CI: 1.06 – 1.40).[89] Nielsen *et al.* also published a meta-analysis of RCTs in the same year and found similar results in favour of methadone (RR = 1.21, 95% CI: 1.02 – 1.43).[88] Interestingly, a recent meta-analysis published in 2023 by Degenhardt and colleagues reported retention rates at different time points, including at one month, three months, six months, and 12 months.[90] The retention rate at one month did not differ significantly between the two treatment groups (22 RCTs, N = 41121; 19 observational stu-

dies, N = 140888). However, at three, six, and 12 months, the retention rate was significantly higher in the methadone group. The pooled risk ratio at three months for RCTs was 0.88 (95% CI: 0.82 – 0.95, 23 studies). At six and 12 months, the risk ratios in RCTs were RR = 0.76 and RR = 0.82, respectively. Thus, a gradual reduction in buprenorphine retention over time was observed, specifically after one month. This new data points to vigilance regarding a high risk of attrition for patients on buprenorphine after the first month of induction. Of the six meta-analyses we reviewed, only one reported similar retention rates beyond one month.[91] Klimas *et al.*'s meta-analysis included studies that measured retention at 12 weeks and up to 52 weeks. It is worth noting that this meta-analysis included studies (eight RCTs and three observational studies) published before 2014, therefore not reflecting the latest evidence regarding the two medications.[91]

The body of evidence from individual studies supports the same conclusions as the meta-analyses in favour of methadone. Ten of the 20 observational studies reported findings that favour methadone over buprenorphine,[95,97,99,100,102–106,113] three studies were in favour of buprenorphine,[98,107,108] and one study showed no difference between the two treatments.[112] Six observational studies reported only descriptive data, though results were mostly in favour of methadone.[94,96,101,109–111] Of the two RCTs, one supported that treatment retention was higher in patients on methadone,[93] whereas the other study found no difference between the treatment groups.[92]

This new evidence shows that treatment retention is better in patients who were treated with methadone versus buprenorphine. Note that the retention rates tend to be similar for the first month of treatment and become significantly different after the initiation period.

### *Opioid abstinence*

Four new meta-analyses,[26,87,88,90] two RCTs,[93,114] and eight observational studies[83,96,101,106,110,115–117] have been published, examining the effectiveness of methadone and buprenorphine in reducing opioid use in people with OUD. Out of the four meta-analyses, three found no significant difference between methadone and buprenorphine in opioid use measured by urine analysis.[87,88,90] One meta-analysis, which combined outcomes measured either by self-report or urine test, reported that patients using methadone were less likely to use other opioids. This meta-analysis may highlight the importance of considering the outcome measure when interpreting results.[26] For instance, when opioid use was self-reported, Nielsen *et al.* found that methadone was more effective than other treatments (RR = 0.49, 95% CI: 0.28 – 0.86; two RCTs, 165 participants). Yet, this study did not reveal any significant difference in urinalysis between methadone and buprenorphine (RR = 0.81, 95% CI: 0.57 – 1.17; three RCTs, 206 participants).[88]

The two newly published RCTs in 2021 and 2022[93,114] did not find any significant difference between buprenorphine and methadone in opioid use as measured by urinalysis. Findings from the OPTIMA trial conducted in Canada showed a significant adjusted mean difference (MD; MD = 8.70%; 95% CI: 3.00 – +∞; $p < 0.01$) in the proportion of opioid-free urine drug screens in the first 12 weeks. The mean difference decreased in the last 12 weeks of treat-

ment and became insignificant (MD = 2.40%, 95% CI: -3.30 – +∞; p = 0.24).[114] Opioid use evaluated at 12 months in a multisite RCT, driven in six Vietnamese HIV clinics, was similar in buprenorphine and methadone groups.[93] Among the observational studies reviewed, none favoured methadone. Four cohort studies did not find any significant difference,[101,106,115,116] while the remaining four studies were in favour of buprenorphine.[83,95,110,117]

Overall, in agreement with our previous research, this update supports that methadone and buprenorphine are equally effective in reducing opioid use.

### *Adverse events*

Opioid treatment's side effects or adverse events comprise a long list of symptoms such as constipation, excessive sweating, dry mouth, drowsiness, weight gain, sexual dysfunction, risk of cardiac arrhythmia, and risk of overdose.[118] Most of these side effects, including cardiac arrhythmia or sexual dysfunction, are commonly attributed to methadone. This update went beyond simply categorizing the negative effects of methadone and buprenorphine, further evaluating the occurrence rates of side effects associated with these drugs. This approach provides a more comprehensive understanding of the potential risks and benefits of using methadone versus buprenorphine as a treatment option.

Two meta-analyses,[86,88] three RCTs,[91,112,117] and 11 observational studies were reviewed to assess the occurrence of side effects among patients with OUD treated with methadone and buprenorphine.[94,96,101,102,106,115,116,119–121] The two meta-analyses reported similar results, indicating no significant difference in adverse events between the two treatment groups.[88,90]

Most individual studies reported similar conclusions: two RCTs[114,122] and six cohort studies.[94,106,115,116,120,123] However, two cohort studies suggested that people treated with buprenorphine experienced fewer side effects.[96,102] These two studies reported a higher risk of non-fatal overdose within the first 30 days after induction of methadone. Interestingly, a recent cohort study conducted in the UK with a large sample size (N = 20,898) aimed to evaluate the risk of non-fatal overdoses among patients who were prescribed OAT along with other medications such as benzodiazepines, antidepressants, antipsychotics, Z-drugs, gabapentinoids, and opioids. The study found that there was a high risk of overdose when methadone was co-prescribed with other opioids. Regarding buprenorphine, the risk of overdose was elevated when it was co-prescribed with non-opioid medications.[96] This highlights the potential protective effect of buprenorphine against opioid poisoning but not against other drug-related poisoning, especially during the induction period.

Altogether, the body of evidence suggests that methadone and buprenorphine do not differ regarding adverse events occurring after the induction period.

### *Mortality*

The literature search captured three meta-analyses[124–126] and 11 cohort studies that assessed mortality in patients on OATs.[83,96,101,104,126–132] No RCT was found.

All three meta-analyses consistently favour buprenorphine over methadone. A meta-analysis of 21 observational studies, published in 2019, found that the overdose-specific mortality rates were higher in patients on methadone than in the buprenorphine group (crude mortality rates [CMR] for methadone = 6 overdose deaths per 1000 person-years; 95% CI: 5–7; buprenorphine = 3 overdose deaths per 1000 person-years; 95% CI: 3–4). The all-cause mortality rates were also higher in the methadone group (CMR = 17 deaths per 1000 person-years: 95% CI: 15-20) than in buprenorphine (CMR = 7 deaths per 1000 person-years; 95% CI= 6-8)[124]. Consistent with this, a meta-analysis published the same year also estimated a higher all-cause mortality rate during methadone treatment (CMR= 1.05, 95% CI: 0.86–1.25, 14 observational studies) compared to buprenorphine (CMR = 0.38, 95% CI: 0.31–0.46, 2 observational studies).[125] The estimated mortality rate was higher at initiation relative to the remainder treatment period. The Santo *et al.* study published in 2021,[126] in particular, showed that the risk of mortality doubled during the first four weeks of methadone treatment (RR= 2.81; 95% CI: 1.55-5.09) but not for buprenorphine (RR= 0.58; 95% CI: 0.18-1.85). This was suggested to be related to the elevated risk of drug-related poisoning and respiratory depression during methadone induction.[126]

Eight of the 11 cohort studies reported a lower mortality risk in patients treated with buprenorphine.[83,96,104,127–130,132,133] In agreement with Santo's hypothesis, a prospective cohort study also demonstrated a lower drug-related poisoning risk for patients on buprenorphine than for those on methadone at treatment initiation.[127] A retrospective cohort study from Australia also highlighted buprenorphine's protective feature against fatal overdose in a specific population of patients with circulatory and respiratory diseases.[130] The remaining three cohort studies reported an equal risk between the two treatments. Of note, these cohort studies had a follow-up period ranging from two to seven years, suggesting that mortality risk in stabilized patients may not differ between the two treatments.[94,129,131]

The current literature review provides consistent evidence of a lower risk of mortality with buprenorphine compared to methadone, especially during the induction period. During that period, it is important to be cautious about the risk of methadone-related drug poisoning.

### *Patient satisfaction and costs*

The guideline development committee considered two additional outcomes, namely patient preference and costs, in addition to the key outcomes identified by the Delphi consensus.[45] Since there were no studies available on "patient preference," the committee evaluated studies that assessed "patient satisfaction" instead. Treatment retention can be influenced by patient satisfaction, while accessibility of treatment can be influenced by cost, and these factors are vital in implementing policies.

Limited evidence evaluating patient satisfaction with OAT was found. A meta-analysis[90] and an RCT[92] provided some insights. The meta-analysis included a unique observational study, and the data favoured buprenorphine over methadone. The RCT found no significant diffe-

rence in patient satisfaction between the two groups.[90] Note that both studies measured treatment satisfaction using a validated scale.

Only three cohort studies comparing methadone and buprenorphine examined costs.[112,134,135] A secondary analysis of a pragmatic Canadian trial compared the cost-effectiveness of buprenorphine to methadone. Flexible take-home buprenorphine was found to be less effective and costlier than methadone due to better retention rates in methadone treatment.[134] Another observational study from the United States evaluated the total costs of care between the two medications and found significant differences.[112] Buprenorphine increased pharmacy costs by $219, while those receiving methadone decreased pharmacy costs by $23 ($p = 0.01$). However, non-adherence was associated with a significant cost increase in methadone compared to buprenorphine[112] The final study conducted in Europe reported a significant difference in 12-month costs of three medications ($p < 0.01$), namely levomethadone (€8400; SD: €11,080), methadone (€7090; SD: €10,900), and buprenorphine (€6670; SD: €7430). Post-hoc comparisons revealed a significant difference only between buprenorphine and levomethadone. Thus, different formulations can explain the cost difference between the two medications.[135]

The very few studies did not allow for any conclusions to be drawn. However, it appears that patient satisfaction may favour buprenorphine, while costs tend to favour methadone.

### Slow-release oral morphine

In this section, the off-label opioid agonist SROM is discussed. It is compared to oral medications approved by Health Canada to determine its effectiveness.

SROM is a pure opioid agonist that binds to the μ receptor and is one of the most potent analgesics[66,136]. In Canada, it has been used off-label for OUD management, leading to the need for guidelines about its use as OAT medication. The 2018 CRISM *National OUD Guideline* recommended SROM as an alternative OAT whenever Health Canada-approved OATs, methadone and buprenorphine cannot be used.[58] SROM has been compared to the other OATs, and limited evidence concluded it was acceptable for use in OUD clinical management. A 2013 Cochrane review of three RCTs, by Ferri *et al.*, showed no difference in treatment retention and non-medical opioid use but reported more adverse events in the SROM group compared to methadone and buprenorphine groups.[137] However, single studies noted better improvements for SROM in withdrawal symptoms, sleep quality, and craving.[138–141]

New evidence has emerged from two meta-analyses[89,142] and five cohort studies.[99,105,143–145] One meta-analysis by Klimas *et al.* comparing SROM to methadone was conducted in 2019 and included four RCTs.[142] Three of the four trials included in that meta-analysis were already part of the 2013 Cochrane review;[137] the fourth was published in 2014 by Beck *et al.*[146] The most recent meta-analysis of RCTs by Lim *et al.*, published in 2022, also included the same four studies[89] Therefore, no new RCT comparing SROM to methadone or buprenorphine has been conducted in the last ten years. Consistent with the 2013 Cochrane

review, the new meta-analyses did not find significant differences between SROM and methadone in treatment retention.[89,142] Moreover, Klimas *et al.* reported no difference in effectiveness between SROM and methadone in reducing opioid use. However, they noted that SROM was more effective in reducing cravings than methadone.[142]

Five retrospective cohort studies have been conducted in the last six years to compare SROM to either methadone or buprenorphine. Among these studies, three were conducted in Canada,[99,105,144] and evaluated treatment retention, which was similar between the groups in two studies.[105,144] The other Canadian study, which analyzed 220,474 treatment initiation episodes, reported that SROM had lower odds of completing induction compared to methadone. The three-month retention rates for methadone and SROM were 36.70% and 25.90%, respectively. Retention rates decreased over time in both groups, with the 12-month retention rate being 18% for methadone and 8.90% for SROM.[99]

The remaining cohort studies were conducted in France in 2019 and 2022 by the same research team.[143,145] Bertin *et al.* compared morphine sulfate to buprenorphine and methadone across three outcomes: adverse events (overdose), mortality, and morbidity. Data from both studies support that the risk of overdose was higher in SROM compared to the other OATs. The 2019 study showed that the one-year overdose crude incidence per 100,000 patients-years was 3.8 points higher for SROM compared to buprenorphine and 2.0 points higher compared to methadone.[145] As for the other study, overdose risk was lower in patients on buprenorphine compared to SROM (adjusted odd ratio [aOR] = 0.50, 95% CI: 0.40 – 0.70), but it did not differ between SROM and methadone (aOR = 1.00, 95% CI: 0.70 – 1.40).[143] The authors also reported a higher mortality rate in the SROM group. The one-year all-cause mortality risk was 9.1 times greater in the morphine group compared to buprenorphine ($p < 0.01$) and 3.9 times higher compared to methadone ($p < 0.01$).[145] Additionally, the prevalence of HIV, hepatitis B virus (HBV), and HCV was higher in SROM users than in other OATs users.[143]

As previously mentioned, the retention of treatment and opioid use seems to be comparable between SROM and standard OATs. SROM is associated with a higher risk of overdose and mortality in some observational studies, but this may be in part because SROM has been reserved for patients with more severe OUD. Patients receiving SROM are those who have not sufficiently benefited from methadone or buprenorphine and would, therefore, be expected to have higher rates of opioid use-related health harm. In sum, it is important to bear in mind that the amount of evidence evaluating SROM is very limited, making it challenging to reach an objective conclusion. Further studies that assess the effectiveness of SROM are urgently needed, given its increasingly common use in clinical settings.

## From evidence to clinical recommendations

### *Recommended first-line treatment*

In the previous sections, the advantages and disadvantages of various OATs for OUD were discussed based on the exhaustive review of the body of evidence published to date. In summary, the new body of evidence shows that methadone and buprenorphine are simi-

larly effective in reducing opioid use (high certainty) and adverse events (high certainty). The body of evidence favours methadone in terms of treatment retention (high certainty) while favouring buprenorphine in terms of mortality as long as patients are maintained in treatment (moderate certainty). A low quality of evidence showed that methadone costs less than buprenorphine treatment. Lastly, there is not enough evidence to determine patient preference. The GRADE certainty tables are shown in Appendix 7.

The decision-making process used to move from evidence to recommendations followed the GRADE framework, which considers various factors such as the quality of evidence, balancing benefits and risks, patient preferences and values, costs, and availability of resources. The guideline development committee relied on the experience of health care providers and PWLLE to assess the availability of resources and patient values and preferences. The committee members were confident in their understanding of the typical values and preferences of patients. Furthermore, confidence in resource availability was based on recent governmental measures lifting restrictions on methadone prescriptions, as well as new treatment modalities driven by the COVID-19 pandemic, such as telehealth.[5] It was concluded that offering both methadone and buprenorphine would be beneficial by increasing patient engagement and that the available resources justified the expected net benefit. As a result, the guideline development committee stated that methadone is no longer considered a second-line treatment option. Methadone and buprenorphine are now considered equal first-line treatment options. However, it is important to note that different precautions should be taken with each medication. Methadone has been associated with a higher risk of mortality (especially during the induction period), while buprenorphine is associated with a lower retention rate.

While scientific evidence is a strong basis for establishing clinical recommendations, the guideline development committee highlights the importance of applying the standards of care in clinical practice. The clinician should work together with the patient to select the most appropriate OAT after presenting all available Health Canada-approved medications, namely buprenorphine and methadone. The patient's goals and preferences should be respected, and the patient's past experiences with OATs should be carefully noted, as well as any existing comorbidities and co-medications to avoid potential drug interactions.[147,148]

Special considerations for specific populations are also required. The American Society of Addiction Medicine (ASAM) recently released clinical considerations for patients who are on buprenorphine treatment and also exposed to fentanyl and stimulants.[149] These patients may be highly opioid-tolerant. ASAM experts highlighted some of the challenges associated with buprenorphine initiation. Experts recommend that clinicians should be aware of the barriers and discomforts caused by opioid withdrawal syndrome during the initiation phase. To prevent attrition, clinicians should consider different emerging initiation strategies such as "low-dose buprenorphine with opioid continuation" or "rapid high-dose buprenorphine initiation after opioid discontinuation." After initiation, clinicians should consider higher long-term buprenorphine doses for this specific population.[149]

In addition, clinicians should carefully monitor all patients prescribed methadone and buprenorphine for possible physical dependence, life-threatening breathing problems, diversion, and misuse, as well as an opportunity to revisit treatment goals and engagement.

### *Recommended second-line treatment*

The 2018 *National OUD Guideline* suggested SROM as a third-line treatment option based on moderate evidence.[58] The current update brought little new evidence and did not show that SROM is superior to methadone and buprenorphine (see GRADE table in Appendix 7). The evidence suggests that opioid use and retention rates in the SROM treatment group are similar to those of methadone and buprenorphine (low certainty). Still, SROM is less effective in reducing adverse events (low certainty) and may have a higher risk of mortality (low certainty). There is no new evidence comparing SROM to methadone and buprenorphine in terms of patient preference and/or satisfaction and costs. Overall, there is limited evidence to make changes to the previous 2018 recommendation. However, as methadone is no longer considered a second-line treatment, SROM automatically becomes the second-line treatment option.

As a reminder, SROM is used off-label to treat OUD.[150] The expert committee underscored the importance of generating new evidence. For patients who do not benefit from methadone or buprenorphine, SROM should be available everywhere when indicated.

The SROM dosages determined by the manufacturer are established for pain management.[150] Therefore, experienced clinicians should prescribe SROM for OUD. If an experienced prescriber is unavailable, consultation should be sought after thorough telementoring, teleconsultation, or other means for the patient to be offered equitable quality care. In all cases, precautions must be taken, including close monitoring of patients, attention to contraindications, and drug interactions.[150]

Overall, the present guideline development committee recommends that the selection of a specific OAT should be based on both evidence and an individualized approach driven by clinical judgment.

## Summary of recommendations—opioid agonist therapies

After reviewing new evidence and considering clinical judgment, the guideline development committee has made the following revisions to the existing recommendations:

### RECOMMENDATION 1

Key changes: Methadone becomes a first-line treatment option along with buprenorphine

**2018**

**Recommendation 1** – Initiate opioid agonist treatment (OAT) with buprenorphine/naloxone whenever feasible to reduce the risk of toxicity, morbidity, and mortality, as well as to facilitate safer take-home dosing.

**Recommendation 2** – For individuals responding poorly to buprenorphine/naloxone, consider transitioning to methadone treatment.

**Recommendation 3** – Initiate OAT with methadone when treatment with buprenorphine/naloxone is not the preferred option.

**Recommendation 4** – For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transitioning to buprenorphine/naloxone since its superior safety profile allows for more routine take-home dosing and less frequent medical appointments.

**2024**

**Recommendation 1** – Buprenorphine and methadone should both be considered as standard first-line treatment options for opioid agonist therapy.

- For people who initiate opioid agonist therapy with buprenorphine, clinicians should be aware of the higher risk of attrition after the first month of initiation and offer alternative opioid agonist medications in these circumstances (high certainty of evidence).
- When considering methadone, clinicians should be aware of the higher risk of mortality during the first month compared to the remainder of the treatment period (moderate certainty of evidence).

Quality of evidence:  HIGH

Strength of recommendation:  STRONG

**RECOMMENDATION 2**

Key changes: Slow-release oral morphine becomes a second-line treatment option

2018 **Recommendation 5** – In patients for whom first- and second-line treatment options are ineffective or contraindicated, OAT with slow-release oral morphine (ideally prescribed as once-daily witnessed doses) can be considered. Slow-release oral morphine treatment should only be prescribed by physicians with a Section 56 exemption to prescribe methadone or following consultation with an addiction practitioner experienced in OAT with slow-release oral morphine.

2024 **Recommendation 2** – Opioid agonist therapy with slow-release oral morphine should be available and offered as a second-line treatment option.

Quality of evidence: MODERATE

Strength of recommendation: STRONG

### 4.1.2. Opioid withdrawal management

Opioid withdrawal refers to a cluster of physical symptoms experienced by people dependent on opioids following a reduction or cessation of chronic opioid use. Opioid withdrawal signs and symptoms vary in intensity and time of onset, as well as differing from one person to another for various reasons, including previous experiences. However, those signs and symptoms are similar for all types of opioid use. The withdrawal symptoms include dysphoria, piloerection, yawning, fever, sweating, diarrhea and vomiting, among others. The duration and severity of opioid withdrawal symptoms vary widely and are dependent on the type of opioid, the duration of opioid use, the person's health status and the suddenness of discontinuation.[151,152] For short-acting opioids, such as heroin, fentanyl, hydrocodone, or oxycodone, individuals can experience severe opioid withdrawal symptoms within a few hours after last use, with a duration of up to seven to eight days. In contrast, cessation of long-acting opioids, like buprenorphine and methadone, leads to a delayed onset of symptoms (i.e., 24 hours or more since the last dose). However, the duration of symptoms varies and can last up to two weeks or more for methadone.[153]

The phenomenon of tolerance is complex and encompasses a variety of factors, but with respect to chronic opioid use, it may be broadly divided into physical and psychological tolerance. Physical (or pharmacological) tolerance involves the need for higher doses of opioids to obtain the same effect. Conversely, psychological tolerance may emerge from various behavioural adaptations developing from the apprehension of experiencing withdrawal symptoms and a depressed emotional state between opioid doses.[154] Repeated exposure to increasing doses of opioids causes the brain to adapt (i.e., neuroadaptation)

to the presence of opioids, resulting in altered functioning in their absence.[155,156] As a result, in the absence of opioids, and in addition to the physical symptoms, individuals may experience distressing psychological symptoms such as dysphoria (i.e., state of dissatisfaction), irritability, sleep disturbances, and hyperkatifeia (i.e., hypernegative emotional state).[157,158] Prolonged drug use can also lead to persistent changes in the brain, which may be responsible for cravings that cause compulsive drug-seeking behaviours and possible relapse even years after ceasing the use of opioids.[155]

To avoid these distressing symptoms, individuals tend to pursue or resume opioid use. Therefore, adequate management of such symptoms and opioid withdrawal as a whole, including long-term treatment and support, is critical to prevent relapse.[151,159]

### Safety considerations for opioid withdrawal

Based on previous research, the main reasons to avoid withdrawal management on its own, without transition to long-term maintenance therapy, are the increased associated risks, including relapse and overdoses. Previous data supporting safety considerations were drawn from a few key studies. One RCT reported that participants receiving withdrawal management without linkage to outpatient services and support were 10 times less likely to meet abstinence criteria across all follow-up assessments (2.50% vs. 25.90%; p<.001) than participants linked to intensive outpatient treatment programs.[160]

The reduction or cessation of opioid use experienced during incarceration can be likened to an involuntary or a forced withdrawal. A previous meta-analysis showed that individuals were three to eight times more likely to experience a drug-related death within the first two weeks following prison release compared to the following 10 weeks.[161] The authors suggested that this increased risk could be the result of a loss of tolerance to drugs during incarceration.[159] When withdrawal was managed in prison with a 20-day taper regimen with buprenorphine or methadone, participants still in prison at the time of assessment were 15 times more likely (95% CI: 4.19 - 55.28) to be abstinent at eight days post-detoxification, and they had seven times (95% CI: 2.22 - 22.25) the odds of still being abstinent at one-month post-detoxification.[162] This shows that linkage to support services following withdrawal management or prison release is paramount to avoid relapse. In light of this evidence, withdrawal management alone, without transition to long-term addiction treatment and support, was not considered a safe or effective treatment option for OUD and was not recommended for the treatment of OUD in the 2018 CRISM *National OUD Guideline*.

Since 2018, only three RCTs and one cohort study (with an overall very low certainty) have examined the impact of withdrawal management on key OUD outcomes (i.e., treatment retention, opioid abstinence/reduction, adverse events, mortality, patient satisfaction, and costs), and their main findings are not consistent, depending on the medication or the treatment setting. An RCT comparing a five-day buprenorphine-managed withdrawal protocol to buprenorphine induction and transition to long-term buprenorphine in a short-term inpatient "detoxification" program reported that individuals linked to buprenorphine

maintenance treatment had five times fewer illicit opioid use days for every 30 days of follow-up at 95 days post-discharge (b=-4.95, 95% CI: -8.88 - (-1.03), p=0.013).[163]

The two other RCTs, which enrolled participants in prison, reported no difference between maintenance methadone treatment and withdrawal management.[164,165] When comparing opioid withdrawal treatment with methadone over seven days to OAT using methadone with or without patient navigation, there was no significant difference between conditions in the number of positive opioid urine tests over the course of the 24-month follow-up. The numbers of fatal and non-fatal overdoses were only reported descriptively (no statistical analyses), which prevents the drawing of clear conclusions. However, it is noteworthy that none of the fatal and very few (4.60%) of the non-fatal overdoses occurred during methadone treatment.[164] Another RCT comparing methadone maintenance treatment to forced withdrawal (i.e., tapered withdrawal from methadone after the first week of incarceration) did not find a difference in heroin use (continuous methadone: 28.10% versus forced withdrawal: 28.90%), prescription opioid use (continuous methadone: 12.50% versus forced withdrawal: 14.50%), or engagement in methadone maintenance treatment program (continuous methadone: 42.60% versus forced withdrawal: 38.80%).[164] When considering the data by methadone status at release (i.e., as-treated analysis), those who received methadone on the day before release were less likely to report using heroin and injecting drugs in the past 30 days and to have had a non-fatal overdose in the 12-month follow-up period (7% vs. 18%) than those who did not receive methadone the day before release.[165]

Lastly, a prospective cohort study in an inpatient psychiatric hospital revealed no difference in opioid withdrawal symptoms at baseline, week 1 and week 2 of treatment between individuals receiving methadone maintenance treatment and those receiving medications to reduce opioid withdrawal symptoms (i.e., acetaminophen codeine [acetaminophen=325 mg, and codeine phosphate=15 mg] plus clonidine [tablet=0.2 mg]).[166]

The new evidence reports no difference between long-term treatment and withdrawal management in OUD outcomes such as fatal or non-fatal overdoses or opioid use, especially for methadone. However, it should be noted that the majority of the new evidence comes from studies with people who are incarcerated. While this new evidence cannot be generalized to all people with OUD, it provides insights into the necessity of linking individuals to long-term treatment and support following withdrawal management to prevent relapse, particularly in the case of populations who are or have been incarcerated.

Abstinence can induce a loss of tolerance, possibly resulting in a higher risk of mortality following relapse.[132] This has been described in previous studies reporting an increased risk of fatal opioid overdose following withdrawal management alone, notably for individuals who lost tolerance to opioids[167] or within the first weeks following prison release.[161,168] Given the risks associated with withdrawal management alone and the lack of new evidence, if individuals wish to pursue withdrawal management as a stand-alone treatment, they should be informed of the increased risks and encouraged to consider integrating an addiction treatment (i.e., slow opioid agonist taper, transition to long-term OAT).

## Medications for opioid withdrawal

### *Opioid agonists taper and alpha$_2$-adrenergic agonists*

Different medications can be offered to alleviate withdrawal symptoms. Studies reported that opioid agonists taper (i.e., methadone, buprenorphine) and alpha$_2$-adrenergic agonists can reduce the severity of withdrawal symptoms compared to a placebo. As mentioned above, most patients will relapse to opioid use if the treatment strategy only involves opioid withdrawal management.[160,162,169–172]

When comparing opioid agonists (i.e., methadone or buprenorphine) taper to other medications (e.g., other opioid agonists or alpha$_2$-adrenergic agonists), no differences were found between treatment options in terms of adverse events reported, treatment completion, abstinence at follow-up, or withdrawal symptoms.[169] A 2017 meta-analysis reported no differences between buprenorphine and methadone tapers in treatment completion rates (RR = 1.04, 95% CI: 0.91 - 1.20; N = 457; 5 studies) and adverse events reported (no significant adverse events in both groups, three studies) during managed opioid withdrawal,[173] suggesting that both buprenorphine and methadone can be offered to a patient.

**Modalities for opioid agonist tapering during withdrawal:** Slow tapering doses of opioid agonists (i.e., buprenorphine or methadone), relative to rapid tapering, is the preferred option when available. A recent clinical trial examined the feasibility of a brief withdrawal management approach.[174] All groups were treated with buprenorphine for at least 40 days; then, buprenorphine was reduced by 2 mg every two weeks. Next, depending on the group to which they were randomized, buprenorphine treatment was suspended when the dose of 6, 4, or 2 mg per day was reached, or buprenorphine was progressively reduced (i.e., down to 1 mg per os[iii] once every two days until 34 days of treatment was reached). Their findings showed that the progressive and slow (over a month) reduction of buprenorphine resulted in a lower percentage of positive urine drug tests (18.50% vs. 41.40% and above) and less severe withdrawal symptoms measured by the Clinical Opiate Withdrawal Scale (COWS) during the study period.[174]

**Alternative medication for withdrawal:** Alpha$_2$-adrenergic agonists such as clonidine have been previously reported to be more effective at reducing withdrawal symptoms compared to a placebo.[170] However, results from the 2017 meta-analysis show that despite the lack of differences in the number of patients experiencing adverse events between alpha$_2$-adrenergic agonists and buprenorphine (RR = 0.93, 95% CI: 0.70 - 1.26; N = 493; four studies), buprenorphine was more effective than alpha$_2$-adrenergic agonists for the withdrawal treatment completion (RR = 1.59, 95% CI: 1.23 - 2.06; N=1,264; 12 studies), treatment retention (standardized mean differences SMD = 0.92, 95% CI: 0.57 - 1.27; N=558; five studies), and reduction in withdrawal symptoms scores (SMD = -0.43, 95% CI: -0.74 - (-0.13); N=521; six studies).[173] Therefore, alpha$_2$-adrenergic agonists should be offered only if patients cannot benefit from an OAT taper (i.e., hypersensitivity).

iii Note: At the beginning, sublingual buprenorphine was prescribed. Then for lower doses, the oral route was chosen due to the poor bioavailability of sublingual buprenorphine

### *Opioid agonist therapy discontinuation*

Because opioid withdrawal can occur upon reduction in regulated and unregulated opioid use, as recommended in the 2018 CRISM *National OUD Guideline*, an individual who wishes to discontinue their OAT medication should be offered the option of a long taper strategy. While insufficient evidence (i.e., two observational studies with low certainty) is available on the effectiveness of slower taper for OAT discontinuation, these studies seem in agreement about the strategy to avoid relapse and opioid overdose.[175,176]

The option to discontinue should be considered for individuals after at least one year under stable and sustained OAT. A recent retrospective study (N=5,774) showed that buprenorphine taper should be offered after at least one year of OAT to prevent the risk of opioid overdose (vs. <1 year: aHR = 0.69; 95% CI: 0.48 - 0.99), at a slower rate (mean rate ← 2 mg/month compared to mean rate > 4 mg/month: aHR = 0.83; 95% CI: 0.72 - 0.95) to lower the risk of medication for OUD re-entry within 182 days after treatment discontinuation or prescription opioid use.[175]

Similar to discontinuing OAT with buprenorphine, a retrospective study on methadone tapering (N=853) reported that individuals who started a methadone taper after at least 52 weeks of methadone maintenance (vs. <16 weeks: OR = 2.81, 95% CI: 1.48 - 5.34), with a start dose of less than 60 mg (vs. 60–120 mg: OR = 2.08, 95% CI: 1.44 - 3.00), a taper ratio inferior to the one proposed by guidelines (i.e., less than 5% per week vs. 5%–10% per week: OR = 2.08, 95% CI: 1.18–3.64), and doses reduced by 75% to 89% of tapering dose (vs. < 25%: OR = 3.07, 95% CI: 1.22–7.68) are more likely to be abstinent.[176]

## From evidence to clinical recommendations

The 2018 version of the CRISM *National OUD Guideline* recommended avoiding withdrawal management as a stand-alone treatment option and suggested a long-term taper approach for withdrawal in case it was pursued. These recommendations were based on evidence of moderate certainty. Very few recent studies (with overall very low to low certainty) investigated opioid withdrawal strategies.

Opioid withdrawal symptoms are distressing for individuals experiencing them. Therefore, immediate access to first-line treatment options to alleviate those symptoms should be offered. Once the acute opioid withdrawal has been managed, discussion about individuals' long-term treatment options, according to their goals and needs, should be engaged over withdrawal management as a stand-alone treatment option.

However, if withdrawal management is chosen over long-term treatment by the patient, after discussion regarding the potential risks, a slow taper strategy should be offered to prevent the high risk of relapse. The new evidence (low certainty) further adds to the existing body of evidence and shows that first-line treatment options (i.e., buprenorphine or methadone) can be provided as part of a taper treatment strategy in conjunction with close long-term follow-up and support and that the long-term taper approach should also be suggested for OAT discontinuation.

Despite the lack of strong new evidence regarding opioid withdrawal management, and according to their clinical judgment and experience, clinicians from the guideline development committee were confident that the benefits of a concurrent long-term addiction treatment outweigh the benefits of opioid withdrawal management alone. The known, distressing symptoms associated with withdrawal and the relapsing nature of OUD may require a long-term monitoring and treatment approach, which is in accordance with international standards of care. Moreover, the availability of resources for long-term addiction treatment in Canada, above the global average, allows the committee to endorse the long-term approach.

As a result, the guideline development committee decided not to change the core of the previous recommendations on withdrawal management.

### Summary of recommendations—opioid withdrawal management

As previously stated, no major changes were made to the existing recommendations regarding opioid withdrawal management.

#### RECOMMENDATION 3

No change (Minor rewording)

| | |
|---|---|
| 2018 | **Recommendation 6** – Offering withdrawal management alone (i.e., detoxification without immediate transition to long-term addiction treatment) should be avoided since this approach has been associated with increased rates of relapse. |
| 2024 | **Recommendation 3** – Patients with OUD should not be offered withdrawal management alone because of the increased rates of relapse, morbidity, and mortality. Concurrent long-term addiction treatment is recommended. |

Quality of evidence:  MODERATE

Strength of recommendation:  STRONG

### RECOMMENDATION 4

No change (Minor rewording)

**2018** **Recommendation 7** – When withdrawal management (without transition to OAT) is pursued, provide supervised slow (>1 month) opioid agonist taper (in an outpatient or residential treatment setting) rather than a rapid (<1 week) taper. During opioid-assisted withdrawal management, patients should be transitioned to long-term addiction treatment to help prevent relapse and associated health risks.

**2024** **Recommendation 4** – When withdrawal management alone is pursued, a supervised slow opioid agonist taper (depending on the patient) should be provided, with close follow-up, and opioid agonist therapy should immediately be offered if the risk of relapse emerges.

Quality of evidence:  MODERATE

Strength of recommendation:  STRONG

### RECOMMENDATION 5

No change (Minor rewording)

**2018** **Recommendation 8** – For patients with a successful and sustained response to OAT who wish to discontinue OAT (i.e., desiring medication cessation), consider a slow taper approach (over months to years, depending on the patient). Ongoing addiction care should be considered upon cessation of opioid use.

**2024** **Recommendation 5** – For patients with a successful and sustained response to OAT who wish to discontinue OAT (i.e., desiring medication cessation), clinicians should consider a slow taper approach (depending on the patient). Ongoing addiction care should be considered upon cessation of opioid use.

Quality of evidence:  MODERATE

Strength of recommendation:  STRONG

## 4.2.
# Psychosocial interventions and harm reduction

### 4.2.1.
### Adjunctive psychosocial interventions

Psychosocial interventions have been studied as a treatment for OUD for almost 40 years.[177] Defined as structured and/or manualized counselling that incorporates principles of psychotherapy, the most common such interventions are psychoanalytic therapy, cognitive behavioural therapy (CBT), interpersonal therapy (IPT), dialectic behavioural therapy (DBT), motivational enhancement therapy (MET), contingency management (CM), biofeedback, hypnotherapy/subliminal, twelve-step facilitation, and family/group counselling. The therapies span a variety of treatment targets, including thoughts, feelings, and behaviours related to opioid use, motivation to change, reinforcement of steps toward treatment goals, and social/interpersonal relationships (family therapy and twelve-step programs) with the aim of improving health, functioning, and well-being.[178] The expected changes in health include reductions in physical and mental health symptoms. Functioning outcomes include physical activity, employment, and family and peer relationships. Well-being refers to life satisfaction and quality of life.[178]

Psychosocial interventions are intended for patients with OUD in different phases of their treatment, including initiation, maintenance, and recovery[178,179] Although the 2018 CRISM *National OUD Guideline* recommended offering routine psychosocial treatment,[58] psychosocial interventions are used sparingly in Canada, with recent survey data of OUD treatment programs reporting that only one in three programs offer psychosocial interventions in addition to OAT.[180] It is also unclear whether the programs that do deliver psychosocial interventions for OUD tailor the therapy to the context of opioids or simply deliver a standard substance use disorder treatment protocol. One reason for the meagre implementation may be the modest effects of psychosocial interventions found in previous studies. A Cochrane review that included 35 RCTs reported that adding psychosocial treatment to standard OAT does not improve patient outcomes.[181] RCTs evaluating OAT with adjunct CBT did not find a difference compared to OAT alone,[182–185] whereas RCTs that studied CM reported benefits of this addition.[186–188] Results for ancillary counselling were mixed: one RCT found no difference,[189] while another reported benefits.[190]

In this section, the added value of psychosocial interventions to OUD medications was re-examined, taking new data into account. For the current work, psychosocial interventions were studied in combination with OATs, and the expected changes mentioned above were considered as mediators rather than outcomes. The main goal was to determine how much psychosocial activities impact the effectiveness of OATs. As such, the following

patient outcomes were chosen: treatment retention, opioid abstinence, mortality, patient satisfaction, and costs. The new findings are reported according to these outcomes.

### *Treatment retention*

In the past six years, numerous studies have compared treatment retention rates between OAT alone and OAT combined with psychosocial treatment. These comprise two meta-analyses,[178,190] 10 RCTs,[192–201] one quasi-experimental study,[202] and two cohort studies.[203,204]

Findings from the two meta-analyses were mixed.[179,191] A 2020 meta-analysis of 48 RCTs[179] revealed that psychosocial interventions in conjunction with OAT led to greater treatment retention as compared to OAT alone (counselling + CM + community reinforcement approach + OAT: OR = 2.79, 95% CI: 1.09 – 7.23, and CM + OAT: OR = 2.01, 95% CI: 1.28 – 3.01). Treatment retention was defined as the number of participants still receiving treatment at the study's latest follow-up time. When adjusted for follow-up duration (number of weeks of follow-up per study), treatment retention still favoured the combination of psychosocial interventions and OAT.[179] The most recent meta-analysis was published in 2023 and included 24 RCTs (N = 3599).[191] Unlike the 2020 meta-analysis, it demonstrated different results depending on the duration of follow-up. The majority of the included studies measured the retention at post-treatment (i.e., immediately after the delivery of the intervention; studies: N = 19) and found that the combination of psychosocial intervention and methadone treatment was better than methadone alone. Yet, the effect size was small (RR = 1.18, 95% CI: 1.11 – 1.25), and the heterogeneity between studies was significant. Interestingly, when these results were stratified by doses of methadone, there was no significant difference between groups for the < 60 mg/day dose group. In the → 60 mg/day dose group, retention was significantly better in the group receiving psychosocial intervention and methadone. Six studies measured retention at follow-up (i.e., 12 to 36 weeks after the intervention had been delivered) and reported that the two treatment modalities were equivalent in retention (RR = 1.01, 95% CI: 0.95 – 1.22, no significant heterogeneity).[191]

Nine of the 10 individual RCTs consistently indicated that patients exposed to a combination of psychosocial treatment and OAT had the same treatment retention rate as those who received OAT alone. Various psychosocial interventions (alone or a mix of interventions) were evaluated in these studies, which can be grouped into two categories: psychotherapies[192–198] and CM.[198–200] Most of the studies measured the treatment retention at 12 weeks and over (follow-up time ranging from three to 48 weeks). One RCT contrasted with the others, reporting better treatment attendance (days of participants taking methadone treatment during the 16 weeks of trial) for patients who received OAT along with psychosocial treatment.[201] The authors of this RCT highlighted the fact that they did not conduct a follow-up investigation which may limit the interpretation of their findings, as retention was only measured during the trial.

Evidence from quasi-experimental and observational studies yielded coherent conclusions in favour of the addition of psychosocial treatment. A non-blind quasi-experimental study conducted in Chinese methadone clinics assessed a six-month psychosocial service

based on behavioural maintenance theory.[202] Data about attrition rate was collected at one, six, and 12 months, showing a decrease in methadone use over time. Patients getting both psychosocial services and methadone had significantly lower attrition rates over time in comparison to those in the methadone group.[202] Two retrospective cohort studies evaluated the efficacy of psychotherapy treatment in buprenorphine patients, and both showed that this was associated with a lower risk of treatment discontinuation.[203,204] Note that the two studies used the same American insurance data, the MarketScan Commercial Claims and Encounters Database, and included practically the same number of participants (61,447 and 61,976, respectively)[203,204] with a follow-up period spanning from three to five years.

Considered together, mixed evidence suggests that the addition of psychosocial treatment to OAT could increase treatment retention. The type of psychosocial treatment and the short- versus long-term effect of the treatment may explain conflicting results. Further research is needed to make a decisive conclusion.

### *Opioid abstinence/reduction*

The outcome of interest "opioid abstinence/reduction" has been evaluated in three meta-analyses, 14 RCTs, and one cohort study. The results have been mainly conflicting with some aggregate findings reporting greater opioid use reduction from a combination of OAT and psychosocial intervention versus OAT alone (RR = 0.62, 95% CI: 0.48 - 0.78, Z = 3.91, p<0.001),[191] while other meta-analytic data reported no difference. When examining the effect of interventions that use regular rewards to positively reinforce substance use reduction or abstinence in patients receiving treatment for opioid addiction (i.e., CM), CM with OAT was not better than OAT alone for the longest duration of abstinence (d = -0.10, 95% CI: -0.61- 0.41, p=0.70) or the percentage of negative urine samples (d = 0.18, 95% CI: -0.11 - 0.46, p=0.22). This was the case when the intervention targeted opiate use specifically.[205]

The individual RCTs also reported mixed findings. Seven of the 14 RCTs included showed that patients receiving a combination of psychosocial interventions and OAT had a significant reduction in opioid use compared to those only receiving OAT. These RCTs evaluated the effectiveness of incentivized medication adherence and abstinence monitoring protocol (I-AAM) in combination with buprenorphine maintenance,[206] CBT either in conjunction with methadone[207] or with buprenorphine,[197] mindfulness-based relapse prevention (MBRP) with methadone,[208] cognitive remediation or cognitive rehabilitation with methadone[195] or with buprenorphine-naloxone,[192] and a case-formulation approach to personalized psychosocial interventions (e.g., CBT, CM, 12-step group facilitation).[198] All psychosocial interventions were for up to 13 weeks. Opioid abstinence was sometimes measured during the treatment period with, for example, an RCT reporting that individuals receiving personalized psychosocial interventions for 12 weeks were two times (95% CI: 0.62–4.00, p=0.007) more likely to be treatment responders (i.e., report of abstinence from opioids and cocaine in the last 28 days confirmed by urine tests) than those only receiving buprenorphine or methadone.[198] The effects of the combination of psychosocial interventions with OAT seem to last as other RCTs reported that opioid use was reduced and remained low at the two-month

follow-up (p=.010)[208] and at the three-month follow-up (z=2.23, p=0.01, d=0.83)[207] compared to those receiving methadone maintenance only. In one RCT, the effect of the combination of psychosocial intervention and OAT lasted for up to six months as the urine tests collected between the three- and six-month follow-up confirmed that individuals who received cognitive remediation had lower rates of opioid use compared to the control group (t=-4.28, p=.001, mean difference=-2.43, 95% CI: -3.50, -1.20).[195]

Conversely, findings from five RCTs showed no difference in opioid abstinence between the combination of psychosocial intervention with OAT and OAT alone. In one RCT, OAT alone was compared to OAT with either CM abstinence (i.e., positive reinforcement for both attendance to weekly meetings and abstinence) or CM attendance (i.e., positive reinforcement for on-time weekly meeting attendance only) in conjunction with OAT. At the 12-week follow-up, there was a significant reduction in opioid use for CM attendance with OAT compared to OAT alone (mean difference=0.20, SE=0.09, 95% CI: 0.002–0.40, p=.048) but not at the 24-week follow-up, when the incentives were withdrawn. There was no difference between OAT with CM abstinence and OAT alone at 12 or 24 weeks for opioid use.[209] In another RCT, the percentage of negative urine screens also did not differ from those receiving only OAT—t (80) = 0.02, p=.98—following a 12-week treatment with interactive voice response providing CBT-based modules.[196] The same conclusion was drawn from studies examining the effect of education and behavioural counselling with methadone for 16 weeks,[201] brief social behaviour and network therapy with OST,[193] or reinforcement-based therapy with methadone treatment induction for 13 weeks.[199]

One cohort study also reported no difference in opioid use between OAT with psychosocial intervention and OAT alone.210 However, it should be noted that in the study, the association between the treatment conditions and outcomes was based on a diagnosis of post-traumatic stress disorder (PTSD). There was no difference between opioid drug counselling with buprenorphine compared to buprenorphine alone in participants without a diagnosis of PTSD (OR = 0.99, 95% CI: 0.62 - 1.60, p=.99).[210]

In summary, the results from the included studies do not offer a straightforward verdict on the effectiveness of psychosocial intervention in addition to pharmacological treatment for opioid abstinence. Nonetheless, they provide further evidence that the combination is not inferior to OAT, regardless of the psychosocial intervention or the OAT chosen for the outcome of "opioid use."

### *Mortality, patient satisfaction, and costs*

Minimal research has been carried out in this area on the outcomes of mortality, patient satisfaction, and direct/indirect costs.

Two RCTs evaluated the direct and indirect costs of combined treatment with psychosocial interventions alongside OAT versus OAT alone.[198,209] These typically represent outcomes such as health service costs, societal costs, and treatment cost-effectiveness. One of the trials reported mixed findings, with cost-effectiveness favouring combined treatment and

societal costs favouring OAT alone, while other outcomes were equivalent.[209] The other trial had similarly mixed findings, with direct and indirect costs being better in the combined treatment of psychosocial with OAT, while other outcomes were equivalent.[198] Effect sizes were small for those studies favouring combined intervention across the board. Three cohort studies assessing costs were published,[200,211,212] of which two evaluated health service costs that favoured the combination of psychosocial with OAT.[211,212] The third cohort study reported cost benefits in favour of combined treatment.[200]

Only one cohort study evaluated the impact of psychosocial treatment after accounting for OAT treatment, reporting no effect on mortality.[213] No studies included in the literature review evaluated patient preference for OAT combined with psychosocial interventions compared to OAT alone.

### From evidence to recommendations

Although a moderate number of studies have investigated the role of psychosocial treatment for OUD as an adjunct to OAT during the six years reviewed, the state of the findings and methodology is mixed. There was no consistent agreement on the benefit of psychosocial interventions, with many studies demonstrating no adjunct benefit over OAT alone. Furthermore, the majority of the published studies had a serious risk of bias, with certainty in published findings being low to moderate. Lastly, the scope of the research is focused mainly on opioid abstinence and treatment retention, ignoring other relevant outcomes such as costs, patient preference, and mortality almost entirely.

Based on these trends, the guidelines committee sought to best reflect them by providing two recommendations instead of one on this topic: a recommendation capturing some potential benefit of psychosocial intervention as an adjunct and a recommendation highlighting that it should not be a barrier to OAT access given the weak evidence. This is a change from the previous version of the guidelines, which recommended offering psychosocial intervention and support routinely. The updated evidence of moderate size over the last six years suggests that clinicians can offer psychosocial support in the proper context. Still, the patients' decision about psychosocial treatment should not interfere with their access to pharmacological treatment.

### Summary of recommendations—psychosocial interventions

Given the evidence above, it is recommended that psychosocial treatments and supports be offered as an adjunct to OAT, particularly if the goal is to increase treatment retention where stronger effects have been reported.

**RECOMMENDATION 6**

Key changes: Rewording – recommendation separated into two

2018 **Recommendation 8** – Psychosocial treatment interventions and supports should be routinely offered but should not be viewed as a mandatory requirement for accessing OAT.

2024 **Recommendation 6** – Psychosocial treatments, interventions, and supports can be offered as adjunct treatments to opioid agonist therapy to increase treatment retention.

Quality of evidence: MODERATE

Strength of recommendation: STRONG

**RECOMMENDATION 7**

Key changes: New

2024 **Recommendation 7** – Psychosocial treatment should not be a mandatory component of standard treatment for opioid use disorder and should not prevent access to opioid agonist therapy.

Quality of evidence: MODERATE

Strength of recommendation: STRONG

### 4.2.2. Harm reduction interventions

According to Harm Reduction International (HRI), harm reduction is a set of "policies, programs, and practices that primarily aim to minimize the adverse health, social, and economic consequences of legal and illegal drug use, without necessarily reducing drug consumption. This approach benefits people who use drugs, their families, and the community."[214] While the concept of harm reduction lacks a clear and universally accepted definition, it is widely recognized that its ultimate goal is to minimize the adverse consequences associated with drug use. Harm reduction strategies and interventions focus on reducing harm while acknowledging that abstinence might not be a goal for some people who use drugs.[215–217] Therefore, harm reduction interventions are based on several principles that emphasize the aim to minimize harm but not necessarily drug use. These principles were defined by Hawk *et al.* and include humanism, pragmatism, individualism, autonomy,

incrementalism, and accountability, which should be considered in the development of harm-reduction services.[215]

In Canada, there are several accessible harm reduction services, including needle syringe programs, supervised consumption sites, overdose prevention education, and access to take-home naloxone kits, among others.[218] It has been recognized that integrating harm reduction into primary care[219] and the continuum of care for patients with OUD and their family members[220] would be beneficial. Several previous studies have reported the efficacy of specific harm reduction approaches and strategies at the individual, community, and societal levels.[221–224] Needle and syringe programs have been shown to reduce the risk of HIV[225] and HCV transmission[81] by 30% to 50%. Access to naloxone, particularly take-home naloxone, is effective in preventing opioid-related fatal overdoses[226] and is cost-effective.[227,228] Furthermore, overdose prevention education can increase the ability to recognize the signs of an opioid overdose and increase a person's comfort in their ability to manage symptoms of opioid poisoning,[220] suggesting better overdose intervention.

Minimal new evidence has been published in the last six years. Although many new studies only report descriptive results, the global evidence tends to confirm previous findings that harm reduction interventions have added value to OUD care. For instance, the provision of sterile injecting equipment decreases the incidence of injecting risk behaviours (aOR = 0.52, 95% CI: 0.32 - 0.83), HIV (RR = 0.42, 95% CI: 0.22 - 0.81), and possibly HCV (RR = 0.77, 95% CI: 0.38 - 1.54).[46] When evaluating the effect of education and patient navigation on HIV and HCV testing and treatment for patients in opioid treatment programs, a cohort study reported that 72% of patients with evidence of active HCV infection received post-test counselling, and 41% completed HCV treatment. While the latter study was only descriptive, it illustrates the potential impact of identifying and linking individuals with viral infections to appropriate care.[229]

Several studies evaluating the effect of overdose education programs globally found a significant increase in opioid overdose knowledge and a significant decrease in risky behaviours, such as escalating opioid dosage, benzodiazepine co-use[230] or using opioids when alone.[231] Individuals with OUD receiving overdose education and naloxone kits reported high rates of overdose reversals using their kits with community members,[231–233] and a lower percentage of emergency department visits or admissions.[234]

A retrospective study evaluating a Canadian program with supervised injectable hydromorphone or oral opioid doses paired with assisted housing showed that seven out of eight patients living with HIV and six out of 24 patients with HCV began treatment for HIV/HCV. Additionally, 58% of the participants had no overdose events up to 12 months after enrolling in the program. The authors reported this as a significant decrease in overdose events, considering that the same individuals reported at least one overdose the year before entering the program.[235] Findings from recent studies also supported the cost-effectiveness of specific harm reduction strategies such as contraceptive services and incentives to individuals with OUD at a high risk of unintended pregnancy[236] or patient navigation for

arrested individuals being treated for opioid withdrawal[237] in conjunction with the usual OUD care.

When considering the overall reduction of opioid-related harms as the primary outcome, OAT is viewed as one of the most effective harm reduction interventions.[46] As demonstrated in the previous sections on OUD pharmacotherapy options, high-quality and recent scientific evidence showed that OAT has a significant impact on most of the negative consequences of drug consumption, including incidence of overdoses and mortality. There is also strong evidence that OAT can help reduce HCV transmission. A meta-analysis of 12 studies examining primary HCV infection among people undergoing OAT found a 50% reduction in the risk of HCV infection (RR = 0.50, p=0.889).[238] Another meta-analysis evaluating the risk of HCV reinfection among 22 studies found that OAT was associated with a 73% decrease in HCV reinfection risk.[239]

Although both harm reduction strategies and OAT have proven effective, no clear conclusions can be drawn on the additional benefits of combining them. Findings from a 2018 meta-analysis evaluating the combination of OAT with needle and syringe programs (NSPs) on HCV infection risk showed that the NSP and OAT combination was much more effective than single interventions, reducing the risk of HCV infection by 74% (RR = 0.26, I2=80%, p=0.007; three studies).[238] Similarly, it appears that incarcerated individuals receiving a combination of patient navigation and methadone treatment experienced fewer non-fatal overdose events 24 months after release (15 overdose events for patient navigation + interim methadone vs. 40 overdose events for methadone alone, no p-value provided).[164] However, other studies have found nonsignificant results. Adding addiction support services such as interaction with peers or trained counselors or education information to OAT did not change the number of individuals tested for HCV nor the number of individuals at any stage of the HCV care continuum compared to people who only received OAT.[240] A recent overview of the evidence on the combination of harm reduction and OAT also reported varying levels of evidence depending on the outcomes. There was strong evidence regarding the benefit of adding NSP to OAT to prevent HCV transmission but insufficient new evidence to draw firm conclusions regarding other harm reduction strategies.[241]

### From evidence to clinical recommendations

The previous literature review (moderate certainty) supported the importance of offering a variety of harm reduction interventions. The updated review provides additional studies supporting this conclusion without raising the level of certainty. As such, the guideline development committee reaffirms the need to integrate harm reduction strategies as part of the patient-centred approach.

It is crucial to provide education and information about the potential adverse effects of opioid use while being mindful of individuals' goals and needs. Harm reduction interventions aim to reduce drug-related harms but not necessarily drug use. It is important for health care providers to keep in mind the relapsing nature of OUD and to consistently offer evidence-based harm reduction interventions regardless of the addiction treatment plan.

### Summary of recommendation—harm reduction interventions

Given the evidence provided above, and as recommended in the 2018 CRISM *National OUD Guideline*, harm reduction strategies should be offered as a part of the continuum of care for OUD patients.

**RECOMMENDATION 8**

Key changes: Rewording and addition of a list of evidence-based harm reduction programs

2018

**Recommendation 11** – Information and referrals to take-home naloxone programs and other harm reduction services (e.g., sterile injection supplies), as well as other general health care services, should be routinely offered as part of standard care for opioid use disorders.

2024

**Recommendation 8** – Harm reduction strategies should be offered as part of the continuum of care for patients with opioid use disorder.

- Current evidence supports the use of the following harm reduction programs: provision of sterile consumption equipment, overdose prevention education and access to take-home naloxone kits.

Quality of evidence:  MODERATE

Strength of recommendation:  STRONG

## 4.3. Special considerations

### 4.3.1. Alternative option: Oral naltrexone

Naltrexone is a competitive opioid antagonist that displaces opioid drugs from their receptors and reverses or blocks their reinforcing effects.[242,243] In the case of OUD, naltrexone could be used to prevent relapse in individuals who are no longer using opioids. Even after regular, long-term use, individuals do not develop tolerance,[244] and there is no potential for non-medical use or diversion with naltrexone.

Several formulations exist for naltrexone (e.g., oral and extended-release injectable). For this guideline, only oral naltrexone was reviewed, as this is the only formulation available in Canada. In addition, extended-release injectable naltrexone formulations are not to be reviewed in Canada in the near future for approval. A previous meta-analysis, dated 2011,

revealed that oral naltrexone does not provide consistent benefits compared to other treatments or even to a placebo.[245] There was no significant difference in treatment retention, abstinence or side effects between oral naltrexone, with or without psychotherapy, and placebo or no pharmacological treatment. Further, a study comparing mortality associated with oral naltrexone and other opioid dependence treatments showed a relative risk of death up to seven times higher for individuals treated with oral naltrexone compared to patients treated with methadone.[246] The limited evidence of the efficacy of oral naltrexone available at the time of the 2018 CRISM *National OUD Guideline*, as well as the known safety risks, led the previous guideline development committee to suggest oral naltrexone as a treatment option for OUD only under particular circumstances and as an adjunct medication.

In recent years, a few meta-analyses and cohort studies have compared the efficacy of oral naltrexone with other medications used for OUD, placebo, or no treatment. The most recent evidence (with very low to low certainty) on the effectiveness of oral naltrexone, summarized below, agrees with previous findings for the outcomes of interest (i.e., treatment retention, opioid abstinence, side effects and mortality; no recent studies reported the impact of oral naltrexone on patient satisfaction or costs) and suggests that oral naltrexone does not offer clear benefits over other treatments or placebo.

### *Treatment retention*

The 2019 meta-analysis, including one systematic review and four RCTs, showed that oral naltrexone is not better than placebo or usual care (26% vs. 19%; RR = 1.32, 95% CI: 0.97-1.79) for retention in treatment.[247] The same conclusion was drawn in another meta-analysis comparing naltrexone (oral naltrexone: n=164) to other interventions for OUD treatment (i.e., other active treatments [methadone or buprenorphine] and psychotherapy) or placebo. There was no significant improvement in treatment retention for oral naltrexone (RR = 1.32, 95% CI: 0.85–2.05; four studies).[248] When compared to buprenorphine or methadone specifically, the average percentage of retention rate for oral naltrexone, across all studies included in a 2022 meta-analysis, was lower (methadone: 64.10%, buprenorphine: 54.30%, naltrexone: 41%). Even when the retention rates were assessed by race/ethnicity, they were significantly lower for naltrexone, particularly for African American individuals.[249] Overall, oral naltrexone is associated with a higher risk of treatment discontinuation than OAT.

All recent cohort studies included in the literature review were in favour of buprenorphine or methadone or did not find a significant difference in terms of the treatment retention outcome. When compared to methadone, naltrexone is associated with a higher risk of treatment discontinuation, a risk that increases over time (at day 1, naltrexone/methadone: aHR = 2.49, 95% CI: 2.30 - 2.65 vs. at 12 months, naltrexone/methadone: aHR = 3.85, 95% CI: 3.63 - 4.09).[250] Naltrexone is also associated with a shorter treatment duration (methadone: mean number of days 206.92, SD: 122.05 vs. oral naltrexone: mean days 45.75, SD: 60.81).[110] In comparison to sublingual buprenorphine, oral naltrexone is also associated with a significantly higher hazard of discontinuation (HR = 2.54, 95% CI: 2.25 - 2.64)[251] or significantly higher drop-out rates at three months (naltrexone: 69.80% vs. buprenorphine: 30.20%,

p<0.001) and six months (naltrexone: 60.80% vs. buprenorphine: 39.20%, p<0.001).[252] Finally, when compared to psychosocial treatment alone, there was no difference between treatments in the likelihood of still being in treatment at six months, regardless of the individuals' classification ("opioid abuse" group: oral naltrexone aOR = 1.10, 95% CI: 1.00- 1.30 and "opioid dependence" group: oral naltrexone aOR = 1.10, 95% CI: 1.00- 1.20).[253]

### *Opioid abstinence*

Recent evidence reported no difference in opioid abstinence for individuals treated with oral naltrexone compared to other treatments. Oral naltrexone significantly reduced relapse rates (RR = 0.47, 95% CI: 0.27 - 0.81; four studies) but did not improve opioid abstinence (RR = 1.38, 95% CI: 0.92 - 2.08; three studies).[248] However, another meta-analysis stated that naltrexone significantly increased abstinence from opioids compared to controls (39% vs. 27% for controls, RR = 1.48, 95% CI: 1.11 - 1.98). Yet, these results included both oral and extended-release injectable naltrexone. When examining the individual studies included in this meta-analysis, the ones comparing oral naltrexone to another treatment (placebo, usual care, or buprenorphine) reported no significant difference between groups in opioid abstinence. In some cases, patients treated with oral naltrexone have a significant decrease in opioid use within 30 days (56% at baseline vs. 28.4% at three months)[254] or may even not use opioids during the study (although in this particular study, only three participants were included).[83]

### *Adverse events and mortality*

While a 2019 meta-analysis comparing naltrexone (oral and extended-release) to controls (i.e., treatment as usual, placebo, methadone, or buprenorphine) reported a significantly greater burden of adverse events in the naltrexone groups (RR = 1.49, 95% CI:1.13–1.95, six studies) but no difference in the number of serious adverse events (RR = 0.57, 95% CI: 0.23–1.46; eight studies),[248] another meta-analysis stated that, overall, there was no significant difference in adverse events between oral naltrexone and placebo or buprenorphine.[87] It is worth noting that naltrexone has been associated with a higher rate of arrhythmia (9.57%) compared to methadone (5.71%) and buprenorphine (3.81%), and the risk of arrhythmia is two times higher with naltrexone than methadone (aOR = 2.43; 95% CI: 1.61 - 3.65).[120] Overall, oral naltrexone does not provide clear benefits over other pharmacological treatments, placebo, or no treatment in terms of adverse events.

Recent studies draw mixed results regarding non-fatal and fatal overdoses. During periods of medication-assisted treatments, the all-cause mortality rate was the lowest for naltrexone (crude mortality rate (CMR = 0.26, 95% CI: -0.06 - 0.59) compared to methadone (CMR = 1.05, 95% CI: 0.86 - 1.25) and buprenorphine (CMR = 0.38, 95% CI: 0.31 - 0.46). However, after terminating the treatment, all-cause mortality rates were the highest for naltrexone (CMR = 2.03, 95% CI: 1.67 - 2.39).[125] Alternatively, a cohort study reported that during the months in which medication for OUD was received, there was a significant reduction in all-cause mortality with methadone and buprenorphine but not naltrexone (aHR = 0.34, 95% CI: 0.08 - 1.34).[255] When compared to no treatment, it seems that oral naltrexone is not more

effective. Oral naltrexone does not reduce or prevent overdose events as there is no difference in controls not receiving treatment (RR = 0.52, 95% CI: 0.09 - 2.91; four studies),[248] nor is oral naltrexone associated with non-fatal overdoses compared to no treatment at three months (aHR = 0.59; 95% CI: 0.29 - 1.20) or 12 months (aHR = 0.73; 95% CI: 0.48 - 1.11).[86] Recent discontinuation (within the past four weeks) of oral naltrexone does not appear to have a significant effect on overdose risk (HR = 1.15, 95% CI: 0.84 - 1.57), and it is not significantly protective against overdose compared to those not on treatment (HR = 0.93, 95% CI: 0.71 - 1.22).[256]

### From evidence to special considerations

The evidence on oral naltrexone gathered for the first iteration of the CRISM *National OUD Guideline* was limited and of low overall quality. A recommendation was formulated for specific circumstances where patients would prefer or request it.

In light of the previous and recent mixed results regarding the safety and efficacy of oral naltrexone and based on clinical observations, the guideline development committee decided not to reiterate the previous recommendation or formulate a new one but to consider including a special consideration. Oral naltrexone should only be offered after careful consideration and under very particular circumstances, and individuals should be informed about the potential safety risks associated with the use of naltrexone (i.e., loss of opioid tolerance). A close follow-up is also advised.

Naltrexone use can lead to immediate withdrawal. Therefore, if given to an individual still using opioids, naltrexone can induce precipitated withdrawal. It is strongly advised to ensure that patients interested in pursuing treatment with oral naltrexone are fully aware of the necessity to stop opioid use before initiating treatment. Naltrexone initiation is usually five to seven days after the last use of short-acting opioids or seven to 10 days after the last dose of long-acting opioids (i.e., methadone).[257]

As for any treatment, individual history and comorbidities should be assessed. Due to opioid receptor blockage, opioid drugs, including those used for pain management, will no longer be effective. This blockage should be taken into account when treating patients with OUD and living with chronic pain, and non-steroidal anti-inflammatory drugs (NSAIDs) should be offered when possible.[257]

**SPECIAL CONSIDERATION**

Key changes: No action is recommended for oral naltrexone as a treatment option unless under very specific circumstances. The recommendation has been changed to a key consideration.

| | |
|---|---|
| 2018 | **Recommendation 10** – Oral naltrexone can also be considered as an adjunct medication if cessation of opioid use is achieved. |
| 2024 | **Special consideration** – For patients who decline or are not on standard treatments for opioid use disorder and have withdrawn from opioids, oral naltrexone could be discussed as an adjunct pharmacological option. |

### 4.3.2. Special population: Pregnant people

In addition to the risks and adverse events associated with OUD that can occur in both pregnant and nonpregnant persons, opioid use during pregnancy can have obstetrical and neonatal negative consequences, such as increased risks of maternal death, preterm birth, low birth weight, and neonatal intensive care unit admission.[258] Opioid use during pregnancy is also associated with neonatal abstinence syndrome (NAS, now known as neonatal opioid withdrawal syndrome or NOWS), which refers to the spectrum of withdrawal symptoms observed in neonates following intrauterine opioid exposure. Concurrent with the accidental drug poisoning crisis that has been raging in Canada for several years, the number of newborns diagnosed with NAS has increased from 3.5 per 1,000 live births in 2010 to 6.3 per 1,000 live births in 2020, which represents an increase of 80%.[259,260]

While the 2018 CRISM *National OUD Guideline* did not provide a recommendation regarding the clinical management of OUD in pregnant persons, it offered an overview of the literature that suggested both methadone and buprenorphine as effective treatment options for OUD in pregnant persons, with buprenorphine presenting a safer profile in terms of neonatal outcomes.[261,262] Even though methadone, like other opioids, can cause NAS in exposed neonates, patients treated with methadone during pregnancy have better maternal and neonatal outcomes compared to untreated or medically supervised withdrawal management patients.[38] Due to less severe NAS symptoms,[263] lower risk of preterm birth, and better morphological outcomes for neonates,[264] buprenorphine was considered a potential first-line option in particular cases. Very few studies investigated the effect of buprenorphine/naloxone on obstetrical and neonatal outcomes. However, all reported no significant difference between buprenorphine (monoproduct or in combination with naloxone) and methadone, suggesting that buprenorphine/naloxone may be safe to use during pregnancy.

For this iteration, the same outcomes of interest (i.e., retention in treatment, abstinence or reduction in opioid use, adverse events, morbidity and mortality, direct and indirect costs, and patient preference) as for the general population with OUD were reviewed for pregnant people. Neonatal outcomes were considered and reported as part of the "adverse events." They included morphological findings (i.e., head circumference, birth weight), fetal (i.e., gestational age, rate of preterm births), and opioid-related outcomes (i.e., rate of NAS/NOWS, treatment for NAS/NOWS). Twenty-five studies were identified, including three meta-analyses and 22 cohort studies.

Evidence from the past six years suggests that buprenorphine may be offered as a first-line treatment for pregnant persons. Only a few studies (one meta-analysis and three cohort studies of the 25 studies included) reported on maternal OUD outcomes, such as treatment retention or opioid abstinence. A 2020 meta-analysis reported no difference between methadone and buprenorphine for treatment retention (RR = 0.66, 95% CI: 0.37 - 1.20, N=223, three studies, moderate quality evidence) and opioid abstinence (RR = 1.81, 95% CI: 0.70 - 4.68, 2 RCTs, low-quality evidence).[265] However, results from three cohort studies showed that pregnant persons treated with buprenorphine use significantly less heroin at the time of birth compared to methadone (methadone: 30.40% vs. buprenorphine:14.90%, p=0.033),[266] but a difference in opioid abstinence was found when compared to buprenorphine-naloxone (at least one return to opioid use during pregnancy: buprenorphine-naloxone: 36% vs. buprenorphine=23%, aOR = 1.93, 95% CI: 0.78- 4.76)[267] or naltrexone (buprenorphine: 23% vs. naltrexone: 0%; p=.52).[268]

Regarding neonatal outcomes, five out of 25 studies (two meta-analyses, three cohort studies[265,267,269–271]) found no difference between buprenorphine and the other OUD treatments. A meta-analysis showed no difference between buprenorphine and methadone in the number of neonates treated for NAS (RR = 1.19, 95% CI: 0.87 - 1.66, 2 RCTs, low-quality evidence).[265] Further findings from the RCTs included in a 2022 meta-analysis showed no difference between neonates from buprenorphine- or methadone-treated parents in head circumference, gestational age or relative risk of requiring NAS treatment. However, it should be noted that differences were observed for the cohort studies included in that meta-analysis.[269]

The vast majority of the reviewed studies (14 out of 25, 2 meta-analyses and 12 cohort studies) comparing OUD treatment during pregnancy favour buprenorphine. Results reported overall higher birth weight, higher gestational age, lower numbers of preterm births, and lower rates of risk of NAS for neonates exposed in utero to buprenorphine.[265,266,269,271–281]

When comparing buprenorphine-naloxone to other OUD treatments, results from seven studies (one meta-analysis and six cohort studies) are mixed depending on the neonatal outcomes. A meta-analysis from 2020 showed that the NAS treatment requirement was lower in the buprenorphine-naloxone group compared to the other OUD maintenance treatment (OR = 0.52, 95% CI:0.36-0.75) but did not find differences in other pregnancy outcomes.[282] In a study where patients received the same opioid maintenance therapy throughout the pregnancy, buprenorphine (mono-product or in combination with na-

loxone) and methadone did not differ for any of the neonatal outcomes measured (i.e., gestational age, preterm birth, morphology, and NOWS).[270] No difference was observed in another study comparing buprenorphine to buprenorphine-naloxone for any of the prenatal and neonatal outcomes measured.[267] Conversely, another cohort study with pregnant persons prescribed either buprenorphine or buprenorphine-naloxone during pregnancy showed that the proportion of neonates diagnosed with NAS and requiring treatment was significantly higher for buprenorphine (54.6% [n=59 infants] compared to buprenorphine-naloxone: 35.3% [n=30 infants], p=0.007).[283] A cohort study reported no difference in preterm birth and neonates' morphology outcomes between buprenorphine-naloxone and methadone but a higher prevalence of NOWS for neonates exposed to methadone (aOR = 3.46, 95% CI: 2.31 - 5.20, p<.01).[284] Other studies showed that neonates exposed to buprenorphine-naloxone were born at a later gestational age—buprenorphine-naloxone 38.20 weeks (1.78) vs. methadone 37.05 weeks (3.80); p<0.005—and had a lower NOWS incidence: buprenorphine-naloxone =70.10% vs. methadone =78.80% (p=0.06)[285] or had lower odds of preterm delivery (aOR=0.6, 95% CI: 0.3-0.9) and of NAS (aOR=0.6, 95% CI: 0.4-0.9).[286]

Of the 25 reviewed studies, only two studies reviewed the effect of naltrexone on pregnant people. One cohort study involving pregnant persons treated with naltrexone after complete detoxification showed that the rate of NAS was significantly lower compared to pregnant persons who chose OAT (i.e., methadone or buprenorphine; NAS rate: naltrexone 10/119 [8.40%] vs. buprenorphine or methadone: 79/105 [75.20%]; p<.0001).[287] The other cohort study stated that none of the infants in the naltrexone group met the criteria for a NAS diagnostic compared with 12 infants in the buprenorphine group (p<0.001). Still, there was no difference in the mean gestational age at birth or the birth weight.[268]

It is worth mentioning that while most studies favour buprenorphine, very few reported the length of treatment. Being in treatment was often self-reported or assessed at the time of delivery, so the duration of fetal exposure to the medication was often unclear. Therefore, clear conclusions regarding the efficacy of one treatment over another cannot be drawn.

No studies evaluating the impact of psychosocial interventions in conjunction with OAT were captured in the literature review, suggesting a potential gap in the literature about the psychosocial needs or options available for pregnant persons living with OUD. However, it is important to offer and refer to, if possible, psychosocial interventions based on each patient's needs and at any stage of the pregnancy or postpartum period. As per Recommendations 6 and 7 of this guidance document, the potential refusal to receive psychosocial treatment should not prevent pregnant persons from accessing pharmacological treatment for OUD.

Only one cohort study evaluating the added value of harm reduction for pregnant persons was included in the literature review. Pregnant persons in a pregnancy recovery centre received women-centred OUD treatment, including, but not limited to, pregnancy-specific dosing, family planning, prenatal and postpartum care, and testing and treatment for infectious diseases. Women who were part of the pregnancy recovery centre were more likely

to have a higher buprenorphine dosage, adapted to their changes in metabolism during pregnancy (16 mg vs. 14.1 mg; p=.02) and to attend postpartum visits (67.90% vs. 52.60%; p=.05) compared to women in a regular OUD treatment centre.[288] This study highlights the need for services that improve outcomes specific to certain populations, such as pregnant persons, to reduce stigma and barriers to access to care.

### From evidence to special considerations

The growing body of recent evidence comparing buprenorphine to methadone in pregnant persons showed that neonates exposed in utero to buprenorphine had a lower risk of being diagnosed with or treated for NAS than those exposed to methadone.[271–275,277,280] Buprenorphine also seems associated with a lower risk of preterm birth, small birth weight, and gestational age,[266,271–281] suggesting that buprenorphine could be offered as a first option. However, due to insufficient knowledge regarding treatment duration and neonatal exposure to medication in most studies, recommendations for a specific medication cannot be made. Health care providers should discuss the risks and benefits with their patients and offer both first-line treatment options.

Although buprenorphine-naloxone is no longer contraindicated in pregnancy, there is still limited evidence about its safety and efficacy in pregnant persons and neonates. However, as those findings agree on its non-inferiority compared to buprenorphine mono-product, there is a consensus that it could be offered as a treatment option during pregnancy.

As the metabolism changes during pregnancy, particularly during the third trimester, dosage adjustments might be required for pregnant persons treated with methadone.[289] It is worth noting that the risks and severity of NAS are not associated with the treatment dosage;[275] consequently, it should not interfere with appropriate dosage adjustment if required.

There is no evidence of the effect of transitioning from one OUD pharmacological treatment to another on obstetrical or neonatal outcomes. So, the decision to transition during pregnancy should be carefully considered by the patient and their health care provider and supervised by an addiction specialist.

While a recent systematic review revealed no increased risk of poor fetal and neonatal outcomes from tapering or rapid opioid withdrawal during pregnancy,[290] opioid withdrawal management alone is not recommended during pregnancy due to the increased risk of relapse and the negative consequences associated with it.

Despite the lack of evidence surrounding psychosocial interventions and harm reduction for pregnant persons, the recommendations made for the general population can apply, regardless of the stage of the pregnancy. As such, psychosocial intervention can be offered but should not be mandatory. Evidence-based harm reduction intervention should be offered as part of the continuum of care. Access to adequate psychosocial interventions, education services, and support should be made available.

### SPECIAL CONSIDERATION

Following the 2018 CRISM *National OUD Guideline* and the recommendations from the American College of Obstetricians and Gynecologists,[37] the Society of Obstetricians and Gynecologists of Canada,[36,38] WHO,291 and SAMSHA,[39] the guideline development committee reaffirms that pregnant persons with OUD who are not in treatment should be encouraged to start OUD treatments with buprenorphine (mono-product or in combination with naloxone) or methadone as soon as possible during pregnancy.

In all circumstances, it is recommended that health care providers seek specialist consultation if needed and refer to available guidelines for pregnant persons for detailed recommendations.

| | |
|---|---|
| 2024 | **Special consideration** – Pregnant people with opioid use disorder who are not in treatment should be encouraged to start first-line OAT treatment as soon as possible during pregnancy. |

# 5. Emerging Issues

## 5.1.
# Safer supply

As part of updating the 2018 CRISM *National OUD Guideline* and learning more about the reality and challenges of the health care landscape in the clinical management of OUD, the guideline development committee sought input from PWLLE and health care providers (e.g., physicians, nurses, pharmacists, social workers). The provision of a safer supply of pharmacological products was the most cited matter of concern.

Following the onset of the COVID-19 pandemic in March 2020, the surge in opioid-related harms nationwide due to the presence of illegal fentanyl in drug supplies prompted a paradigm shift in harm reduction strategies.[292,293] In British Columbia, where opioid-related risks and harms were pronounced, temporary prescribing guidelines were introduced as a specific pandemic harm reduction strategy to mitigate the risks of overdose and withdrawal during periods of self-isolation.[294,295] Risk mitigation prescribing practices marked a pivotal development within the multifaceted harm reduction initiatives, where an emerging focus on safer supply interventions gained prominence.[296] Proponents of safer supply programs contend that these initiatives can reduce fatal and non-fatal harm among those prescribed these alternatives.[297,298] However, concerns have been raised about certain safer supply models, especially those involving relatively low potency analgesic opioids for take-home dosing, resulting in high rates of diversion with implications for use by high-risk populations (e.g. street-involved youth) and iatrogenic opioid use disorder cases. [299–301]

At present, prescribing practices within safer supply services largely depend on individual health care practitioners' professional judgment, the unique needs of each patient, and regional and provincial rules and regulations on prescribing these medications.[297] Currently, the scientific literature defining the concept of safer supply and addressing safer supply as an alternative to toxic unregulated drug supply is still sparse and heterogeneous, thereby limiting robust conclusions. Given the scarcity of the literature, developing and including clinical recommendations on this topic in this updated version of our guideline for OUD was not possible. Hence, there is an urgent need to establish the current state of knowledge and to provide guidance for future research in order to generate evidence and guidelines for the safe provision of pharmaceutical-grade alternatives for people who are at risk of unregulated drug toxicity events and death in Canada.

As a first step to advance the knowledge and inform the generation of evidence needed on alternative prescribing, a scoping review methodology was adopted to map and structure the literature on the use and role of safer supply. The overarching aim of the scoping review is to summarize the extent, range, and nature of the literature on safer supply for people with OUD or substance use disorder (SUD) or people actively using illicit substances who are at high risk of illicit drug toxicity death or other drug-related harms due to toxic drug supply. A concept analysis of safer supply following Walker and Avant's model was used to systematically explore and clarify the key attributes associated with the medical model of

safer supply prescribing practices.[302] The protocol and search strategy were preregistered on Open Science Framework and Dataverse, respectively.[303,304] Results will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) statement.[305]

The insights derived from this scoping review have the potential to inform the safe integration of prescribed alternatives into future evidence-based research strategies, guidelines and policy decisions on substance use management. Additionally, the conceptual analysis involved in this process facilitates a nuanced understanding of the various dimensions and implications surrounding the philosophy of care and delivery of safer supply interventions, including consideration of unintended consequences, thereby offering a framework that can contribute to the ongoing discourse on this emergent issue in the nation. In summary, the scoping review is a crucial initial step toward generating evidence and developing effective strategies to combat the complexities of the drug toxicity public health emergency in Canada while ensuring interventions for people who use drugs are safe and do not contribute to increased risks of opioid addiction among vulnerable populations in the community.

## 5.2. Others

Clinicians and PWLLE mentioned other emerging challenges that they encountered during their practice, such as dealing with co-medication and highly opioid-tolerant patients due to fentanyl. A brief overview of the literature was conducted to address these topics.

### Fentanyl and analogues

Fentanyl is a synthetic opioid approved by the Food and Drug Administration (FDA) in the United States and by Health Canada as a potent opioid pain reliever.[306] Fentanyl is up to 100 times more potent than morphine,[307] but some of its analogues, like carfentanil, can be even more potent and, therefore, more dangerous.[308,309] The high potency of fentanyl and its analogues is driving an increase in the risk of non-fatal and fatal overdose events. Given the increase in illicit drug supply contaminated with fentanyl and its potential involvement in most of the apparent opioid-related deaths in the past years in Canada, it is important to address the impact of fentanyl on the clinical management of OUD.

While most studies report dependence on prescription or unregulated opioids such as heroin, very few studies mention the use of fentanyl by participants. There is an apparent lack of studies addressing fentanyl and its analogues in several components of OUD management, such as opioid withdrawal,[309] overdose reversal with naloxone,[310] or even reviewing the effectiveness of OUD medication in fentanyl-dependent individuals. A recent secondary analysis of a pragmatic RCT reported that both buprenorphine and methadone

could be considered first-line treatment options regardless of the use of or exposure to fentanyl.[310] It is worth noting that treatment with buprenorphine and methadone has a protective effect on the risk of mortality, even in the fentanyl era.[308]

Clinical judgment and experience should be used to address the potential individual impact of fentanyl use on each type of care for patients with OUD, and patient circumstances should be taken into consideration (i.e., polysubstance use, severity of OUD, and socio-economic factors). For recommendations and guidance regarding the initiation of OUD medication for patients using fentanyl, please refer to ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids[313] from the American Society of Addiction Medicine (ASAM) or the Methadone Treatment for People Who Use Fentanyl: Recommendations[314] from Mentoring, Education, and Clinical Tools for Addiction: Partners in Health Integration (META-PHI, Ontario).

## Co-prescribed medications

It is recognized that people with OUD are at a higher risk of comorbid psychiatric[311] and viral infectious conditions.[316,317] Only a few studies included in the literature review assessed the effect of medications for comorbidities on outcomes of OUD treatment. It is worth mentioning that none of the studies reported on the treatment of viral infectious diseases; instead, they assessed the impact of treatment for psychiatric comorbidities on OUD outcomes.

As a recent study highlighted a possible lack of knowledge regarding the impact of some medications given or taken with an OUD treatment,[318] it is essential to recognize potential drug interactions and to take appropriate measures to prevent them. The risk of adverse events resulting from the concurrent use of multiple medications should not be understated. For example, a few recent studies reported an elevated risk of overdose or drug-related deaths during co-prescription of OAT (i.e., buprenorphine or methadone) with benzodiazepines,[84,119,127,143] antipsychotics,[119] gabapentinoids,[119,143] or Z-drugs.[119,127] Therefore, it is crucial to be mindful of the potential for interactions between medications and to take measures to mitigate the risk to ensure patient safety and well-being.

As evidence surrounding the impact of co-medication with OUD treatments was not captured, the guideline development committee could not formulate a recommendation. However, to ensure optimal patient safety and improve clinical outcomes, it is recommended that health care providers adopt a comprehensive approach to managing potential drug interactions, which involves a thorough review of the patient's individual history of medications and comorbidities.

# 6. Limitations

The guideline development committee acknowledges some limitations due to the available scientific data:

- Very few quantitative studies evaluated patient preference and costs. Thus, the committee relied on its members' clinical experience and PWLLE to assess those factors.
- High-quality studies on special populations were very rare.
- For the majority of the studies included, the types of opioids used (e.g., fentanyl use or other high-potency opioids) by the participants were not specified.
- It was not possible to synthesize and conduct a meta-analysis due to the high heterogeneity of outcome definitions and measures.

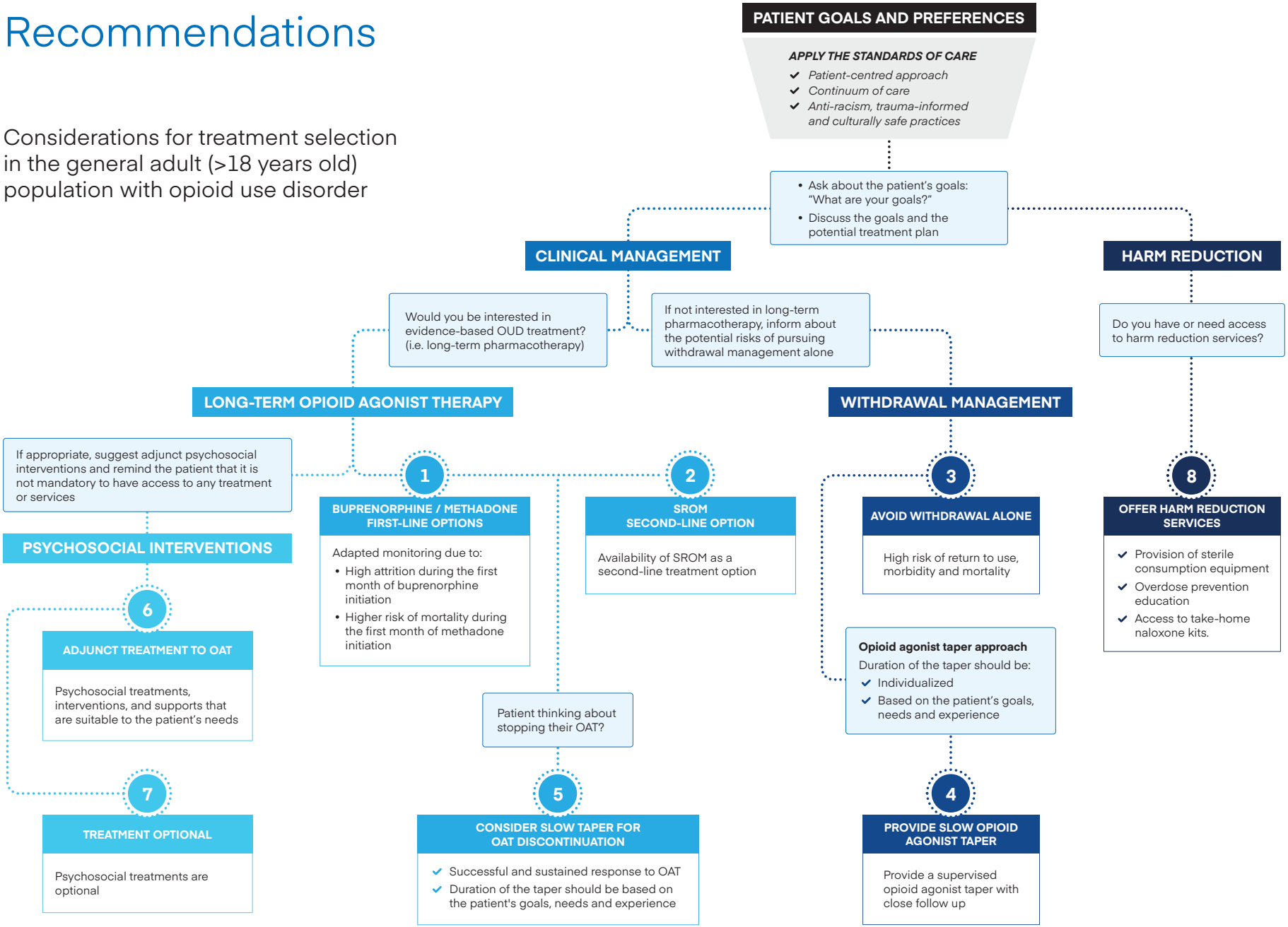
It is important to highlight the ethical limitations of research on pregnant individuals. Considered "scientifically complex,"[319] caring for and treating pregnant persons when scientific evidence is lacking can be a challenge. This is especially the case for non-pregnancy-related medications and interventions where the benefits for the health of pregnant persons should be consequential enough to outweigh the potential harms to fetuses.[320] As an example, it is well known that non-treated people with OUD are at greater risk of overdose and mortality. Therefore, the benefit of offering OUD treatment to pregnant persons and, as a result, potentially improving both (i.e., parent and neonate) their health outcomes should prevail on the risk of NAS for fetuses. However, despite these ethical considerations, the biological complexity of pregnancy has prevented researchers from including pregnant persons in clinical research. As a result, existing studies are mostly observational and include further limitations, such as the unspecified duration of medication use.

Other important limitations in drug addiction research concern the criminalization of drug use. Punitive approaches are imposed for illegally manufactured opioids rather than for the non-medical use of prescribed opioids. As a consequence, limited information is available on the type of illicit opioids used by participants due to the fear of facing legal issues. Thus, highly opioid-tolerant patients, namely people who use illegal fentanyl, who may need specific strategies and interventions to improve treatment retention are understudied.

# 7. Conclusion: Overview of 2024 Recommendations

# Overview of 2024 Recommendations

Considerations for treatment selection in the general adult (>18 years old) population with opioid use disorder



# Appendices

# APPENDIX 1

# Disclosure of competing interests

Standards established by the US Institute of Medicine for Developing Trustworthy Clinical Practice Guidelines[I] were used throughout the development and revision phases to ensure this updated guideline met international standards for transparency, high quality, and methodological rigour.

## Funding

The development activities for the guidelines were entirely supported by internal funding from Health Canada (Substance Use and Addiction Program) and the Canadian Institutes of Health Research (CIHR) Canadian Research Initiative in Substance Matters (CRISM) Quebec Node, without support from the pharmaceutical industry or associated stakeholders.

## Selection of external reviewers

The clinical leads, node managers from each CRISM Node, and the coordinating team identified and contacted from seven to 15 expert candidates from each region to form a regional revision committee. An interdisciplinary group of 77 individuals, including primary care physicians, addiction-medicine physicians and psychiatrists, nurse practitioners and registered nurses, pharmacists, clinical psychologists, social workers, policymakers, people with lived/living experience, and First Nations representatives were invited to participate in the external revision process. Of these 77 external reviewers invited, 62 completed the external revision (discussed in the Methodology – External review section p. 52 of this document) and the approval process.

## Conflict of Interest Policy

The *Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts*[II] provided a framework for the development of this updated guideline. All members of the Guideline Development Committee (GDC), as well as external and international reviewers, were asked to report all direct and indirect sources and amounts received from businesses, pharmaceutical industries, universities, not-for-profit organizations and other organizations that may be perceived as biases and/or affect the interpretation of the evidence, the formulation of recommendations, and the revision of the guideline document. Using an adapted version of the Declaration of Interests for WHO Experts form,[III] each member involved in the guideline development and revision was required to report their professional position as well as their intellectual and financial interests in the past five years. In addition, with respect to indirect conflicts of interest, each member was also required to report university promotions, clinical income, and professional or public reputation.

Before the draft full-text guideline was distributed for review, a project manager independently reviewed and managed all disclosure forms to assess the nature and significance of each disclosed conflict.

In accordance with the US Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines,[I] clear exclusion criteria were established. Reviewers who, within the past five years, were employed by or received remuneration exceeding $1,000 from any commercial entity or organization with interests related to the guideline's subject were excluded. This includes those who received honoraria or fees for participation in speaker panels, lectures, training sessions, consulting services, or serving as technical advisors. Additionally, reviewers whose research programs received support exceeding $5,000 from any related commercial entity or organization, including grants, collaborations, sponsorships, and non-monetary support, such as equipment and travel expenses, were excluded. Reviewers holding intellectual property rights that could be influenced by the guideline's recommendations were also excluded to prevent conflicts of interest and maintain the integrity of the review process. No reviewers were excluded during the first screening as none met these exclusion criteria.

## Summary of disclosure

The following summary includes the disclosure of interest of any individuals who participated in the development, review and/or approval of the guideline (i.e., members of the GDC and external reviewers).

Of all the individuals involved in the guideline development process, 12 disclosed receiving remuneration as employees from a commercial entity that could theoretically benefit from the guideline recommendations. A total of 10 individuals received remuneration as consultants, and 17 received one-time-only honoraria for delivering or attending an industry-sponsored training seminar (funds ranged from $200 to $2500 CAD and were received prior to their involvement in the guideline development process). Several individuals also disclosed the receipt of grants-in-aid of research from for-profit corporations; however, none of these commercial entities have been or are currently involved in the development, manufacture, or marketing of pharmaceutical products reviewed, recommended, or otherwise impacted by this guideline. Receipt of research or program funding support from non-profit agencies or institutions was not considered a direct conflict of interest. A total of 24 individuals disclosed potential indirect sources of bias (e.g., specialization in addiction medicine, advisory board and committee membership, involvement with provincial opioid agonist treatment programs, previous guideline development, or research interests).

On review, none of the disclosed direct conflicts of interest were deemed of sufficient weight or relevance to warrant exclusion from this guideline development process.

## Risk mitigation

Upon reviewing the disclosures, it was determined that none of the potential conflicts of interest disclosed warranted exclusion from the guideline development or revision process. This decision was influenced by the historical nature of the remuneration and the fact that none of the conflicts were active at the time of participation.

In order to mitigate the risk of bias while maximizing the contributions of members in their respective areas of expertise, committee members were reminded to consider any influential factors or sources of bias during the review process.

All authors and contributors involved in the guideline development and revision process reviewed and granted final approval for the guideline contents and clinical recommendations.

### References


I. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust [Internet]. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, editors. Washington (DC): National Academies Press (US); 2011 [cited 2024 Jan 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK209539

II. Schünemann HJ, Al-Ansary LA, Forland F, Kersten S, Komulainen J, Kopp IB, *et al.* Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines. *Ann Intern Med.* 2015 Oct 6;163(7):548–53.

III. Compliance and Risk Management and Ethics (CRE). Declaration of interests for WHO experts [Internet]. World Health Organization; 2014. Available from: https://www.who.int/publications/m/item/declaration-of-interests-for-who-experts

# APPENDIX 2

# Summary of a focus group with people with lived or living experience (PWLLE) with opioid use disorder and health care providers about emerging issues and the scope of the update to CRISM National Guideline for the Clinical Management of Opioid Use Disorder

## A.2.1. CRISM PWLLE Working Group, Focus Group Summary

### Context

The focus group was conducted on Tuesday June 21st, 2022 from 4:00 to 6:00 pm EST.

Four people were attending, all coming from different organizations in harm reduction and fighting for people who use drugs rights.

### Objective

Consult people with a living or lived experiment on opioid use about updates of the CRISM national guidelines for clinical management of OUD.

### Summary of discussion

**Abstinence should not be considered as the main goal of every intervention with patients using opioids. Every patient should determine his/her own objectives with his/her physician, depending on his/her path and reality, in a pragmatic way.**

- Improve the quality of life of patients has to be considered: avoid the torture of looking for drugs through the street market, and stay away from felonies.
- Psychosocial intervention should be part of any intervention: patients are whole people with families, housing, work and personal stuff to deal with. They could use help in different areas.
- Withdrawal is hard, and patients have to be willing and supported. Imposing abstinence does not work.
- When it comes to addiction and opioid use, doctors dictate what is good for patients. They should stay open to questions and options.
- Considering opioid use as a disorder is a bias. Different types of opioid use coexist.

**Interventions should be focused on patients, not on molecules. Patients should have the opportunity to choose where they want to go as long as it improves their quality of life.**

- The title of the guidelines does not include patients. It should be "clinical management of patients with OUD".
- Doctors should know their patients, not only diseases and treatments.
- Consultations should be a safe space where partnership between patient and physician is built.
- Avoid offering predetermined services without talking to patients. It strengthens self-stigmatization and keeps patients away from health care services.
- Family doctors are important and a key link in clinical management. They do full check-ups during consultations and know their patients. They can adapt prescription, proximity gets things easier now they can prescribe methadone.

- Physicians should measure risks and take accountability for what they prescribe. Overprescribing is as dangerous as underprescribing, except the risks are not the same. Overprescribing engages doctors' responsibility when underprescribing affects patients' lives (withdrawal, risks of getting drugs from the black market, risks of OD mixing drugs, etc.)
  - N.B.: "overprescribing" is a perspective. Prescription should always be considered depending on the tolerance of patients and their way of using opioids.
- Prescriptions have to be adapted to patients need. During pandemics, benzos were prescribed with OAT. Anxiety and OUD could be treated at once.

**In the clinical management of opioid use disorder, punitive approaches should be avoided. Trust should be at the center of the relationship between patients and physicians. OUD management should be based on community models.**

- Going to the pharmacy every day to take methadone in front of everybody is humiliating. It reflects the lack of trust in patients. Patients understand doctors have to see how serious and involved they are, but they are not children or criminals.
- Empowerment of patients should be one of the objectives of clinical management. Patients evolving with their life should have options and not to still go to the pharmacy every day, treatments should be adapted to patients' realities.
- Patients have to be involved in their clinical management. It is dangerous not to trust or give them options; it forces them to lie and to take risks where they should have support and care.
- Carries should be developed and not considered as privileges.
- Treatment should not be cut off when a patient misses three doses. It should be possible to discuss and explain how to find a different strategy of treatment.

**All physicians and care providers should be educated and trained about addiction. They should adopt a pragmatic and humanist way to treat patients and avoid moral judgments.**

- Doctors who want to work with patients using opioids should be paired with physicians already practicing. They should learn on the ground.
- Physicians should get information and training from communities and PWLLE to know the population they are working with and understand how to treat them. They have to understand what it means to be a patient in the current context.
- It changes the lives of people using drugs to receive relevant services. Clinicians and academics have knowledge and work on solutions. The community should be involved in the process. Different perspectives must be confronted to build relevant strategies.
- Stigma on people using drugs keeps them away from health care services. In the current opioid crisis, they risk their lives. Moral judgements are considered before human rights; it has to change by considering expertise from PWLLE and people using drugs as humans with rights.

**Prescribing safer supplies should be considered as an option in the treatment of OUD.**

- Safer supplies are political. Even doctors finding it relevant do not want to support it. They seem afraid of consequences. Moral judgements seem stronger than patients' lives.
- With the opioid crisis, letting people use drugs bought on the street is letting them risk their lives.
- Physicians have been blamed for the opioid crisis. They are afraid of overprescribing or being permissive.
- Policymakers have to take accountabilities for people dying from drugs on the street.
- All options should be considered in managing OUD, not only politically or morally correct ones.

**Services should be organized and adapted for people they have to welcome.**

- Confidentiality has to be guaranteed. When patients come to get health care they should be respected and treated as anyone else. Their conditions should be discussed privately, in a confidential local.
- There should be options for people wanting to go into withdrawal at home.
- Telemedicine has been working well during the pandemic. It is possible, it should be facilitated in more places.

- Carries have been more accessible during the pandemic because of difficulties in accessing pharmacies. It has to be more developed and possible for more people.
- Methadone prescription should be adapted and discussed with patients. Change to Methadose had complex and dramatic consequences on patients because it has not been adapted to patients.

**Pandemic proved the system can operate quickly when facing an emergency, depending on what are the priorities.**

- Drug policy and clinical management should be oriented toward the rights and life quality improvement of people using drugs.
- Looking at policy in other countries proves the importance of values and objectives behind decisions.

**During pandemics, pharmacists had more responsibilities over treatments. They could renew, refill, extend, transfer prescriptions and even deliver narcotics. Everything got simpler because of the emergency.**

- Pharmacists see patients every day if they take methadone. Physicians meet patients monthly. Who is going to have a better clinical read on patients? Even if it is punctual, pharmacists should have the possibility to adapt prescriptions when it is not working for patients.
- Pharmacists are proximity care providers. With reduced access to health care services and drug supply realities, they could be a key link in clinical management.
- Pharmacists can also represent barriers according to their beliefs and interests. Naloxone should be distributed for free and anonymously in some provinces, but it can be hard to get some depending on the pharmacist. It is not always possible to choose your pharmacy if you do not live in a big city. This has to be considered.

**Specific guidelines have to be developed for the clinical management of OUD in prisons.**

- Even with a prescription, patients can go a few days without any OAT when they arrive at prison. People go through withdrawal or get drugs from detention, with all the consequences.
- When leaving prison, if the patient is on OAT, a few doses should be given to him/her to prevent OD from using street drugs.
- It can take up to six months to meet a doctor in prison. Most of the time, it depends on the nurse and even on the guards and how they want to help.
- Prison is about physical and emotional abuse, putting people in vulnerable places. Addiction and drug use increase the potential traumas, with multiple and brutal searches.

**Physicians and care providers from hospitals have to be educated about addiction, OAT and clinical management of OUD.**

- Nurses have to be informed about OAT to understand prescriptions and facilitate access to treatment for people hospitalized.
- Nurses should respect prescription and not only deliver it depending on their perception. There have to be protocols to confirm prescriptions and guarantee quick access to treatment for in-patients.
- Forced withdrawal does not encourage people who use drugs to go to the hospital even when it is needed.

**Chronic pain has to be considered for real, keeping in mind the risks related to opioid use.**

- Physical pain, if not treated correctly, can provoke mental pain and draw patients into vicious circles.
- Opioids can be addictive, and there is a risk of overdose. Acute and chronic pain has to be managed, and there are not a lot of options. Prescribers have to be vigilant and make decisions for patient well-being.

**Naltrexone injection does not seem relevant to be included in the OUD clinical management toolkit.**

- Injection as a mode of administration can be risky.
  - Example of a psychotic episode with an injection of Suboxone.
- Naltrexone injection seems to be driven by profit for pharmaceutical companies.
- Naltrexone is a monthly injection supposed to prevent people from using drugs but also from getting high. The risk of overdose is increased with tolerance to opioids decreasing.
- What happens if the patient keeps using opioids with Naltrexone injection?

# A2.2. Consultations of health care providers on changes, discussion points and/or clinical practices that could be considered in the update

## Organization of the consultations

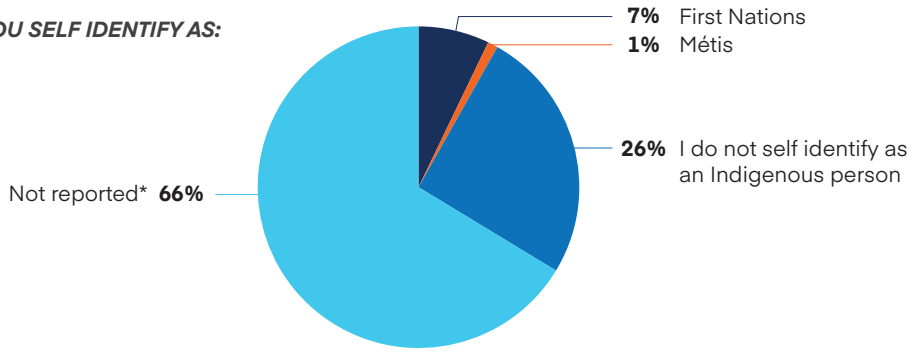
A survey has been disseminated to healthcare providers by several means:

- Newsletters for:
  - BC ECHO
  - CPMD (Quebec)
  - CSAM
  - Pharmaciens GMF
- Online platform:
  - Listserv for META:PHI (Ontario)
  - Facebook for Indigenous Physicians Association of Canada (National)
- Emails:
  - National Safer Supply Community of Practice (NSS-CoP)
  - Healthcare professionals connected to the Atlantic and Prairies Nodes
  - Health directors, physicians, harm reduction workers of several First Nations communities
  - Healthcare professionals invited to be part of the revision committees

Surveys were sent out from August 2022 until March 7th, 2023. Some questions were added on October 3rd, 2022 to further learn about the respondents.

## Summary of the results

### About the respondents (N=98)

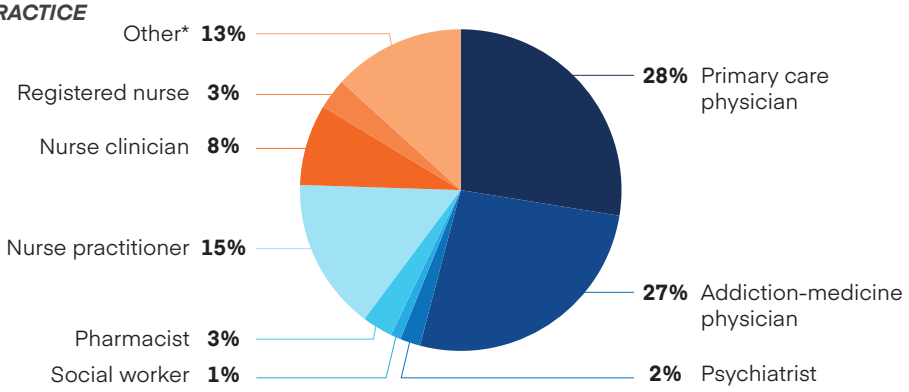



*Data not reported as the question was added on the survey as of October 3rd, 2022.

For those identifying as being part of a First Nation community:

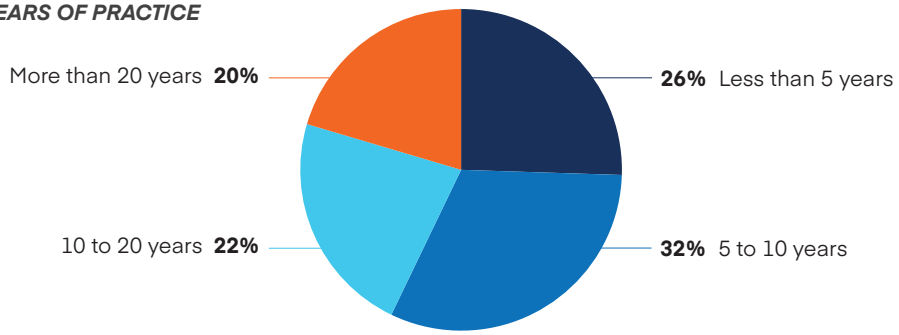
- 75% are located in Alberta
- 12.5% are located in British Columbia
- 12.5% are located in Saskatchewan

***PRACTICE***

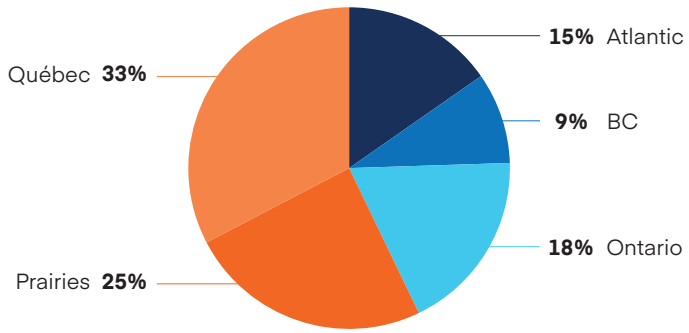



*Other includes:
- Primary care manager
- Harm reduction workers/advocates
- OAT consultants
- Health directors of Indigenous communities
- NNADAP workers
- Researchers...

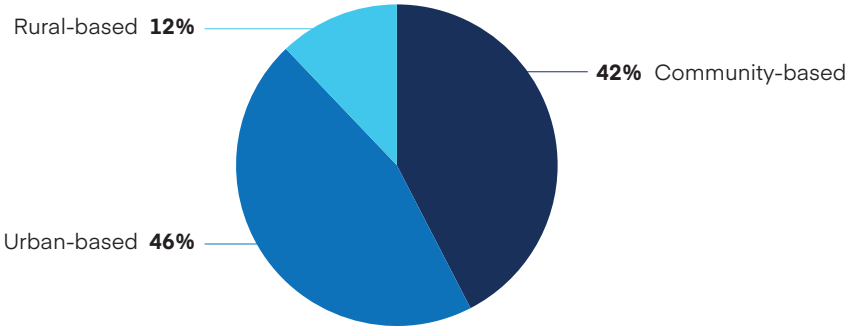
***YEARS OF PRACTICE***




***LOCATION***

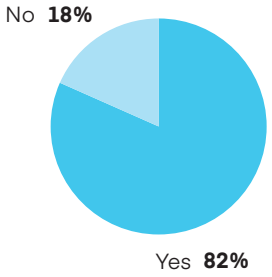



As of October 3rd, 2022, it was asked where the practice was predominantly based:



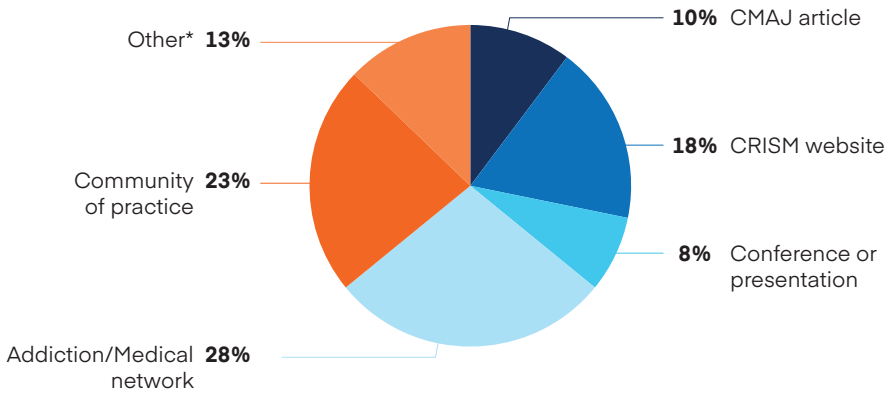
## Knowledge of the guidelines

***Have you heard of CRISM National Guidelines for the clinical management of opioid use disorder released in 2018?***



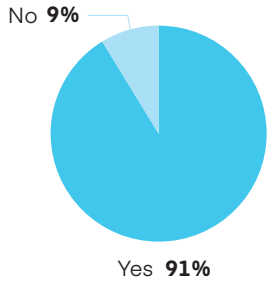

For those who answered **YES**, three additional questions were asked:

***1. How did you hear about them?***

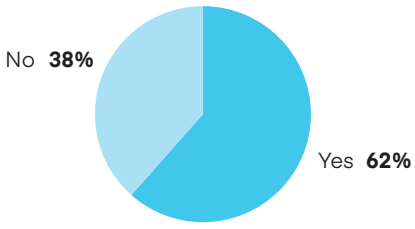



*Other includes:
- Education
- Contribution as a reviewer
- Colleagues/coworkers...

***2. Have you read them?***




***3. Do you use them in your practice?*** (question added on October 3rd, 2023)

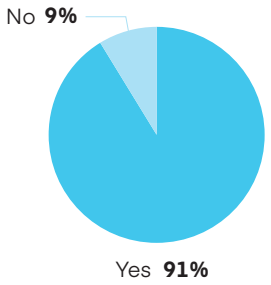


## Comments on the guidelines released in 2018

- ✓ Update needed
  - To represent all regions of Canada
  - To include mention of diversified options available in other jurisdictions
  - To reflect current trends and evidence
  - No longer applicable to current population who is seeking help for fentanyl use
- ✓ Helpful particularly to support initiation and prescription on buprenorphine in emergency department
- ✓ Need for harm reduction approaches to be included
- ✓ Missed opportunity to advocate for iOAT
- ✓ Very generalized, low on specific treatment recommendations
- ✓ Useful framework for prescribing practice
  - Excellent resource for the timeframe in 2018
  - Usable resource for providers where none existed before

## About the COVID-19 pandemic

***Has the pandemic had an impact on your practice, especially in the clinical management of opioid use disorder?***




## About the update of CRISM National Guideline for the clinical management of opioid use disorder

***What are the changes, discussion points and/or clinical practices you would like the CRISM team to consider or you would like to see included in the update?***

- ✓ **Safe supply (42%) Open discussion about safe supply as an option of treatment**
  - Consider the role of safer supply in OUD clinical management
  - Discuss community concerns about safer supply
  - Information on harm reduction strategies specifically safe supply (i.e Dilaudid or Ritalin for OUD and SUD respectively)
  - Guidelines around initiating, escalating and discontinuing safe supply. Transition from safe supply to OAT
- ✓ **Medication titration (29%) Consideration for people who use fentanyl, increase treatment dosage**
  - Higher titration, faster titration
  - Micro- or macro induction of buprenorphine-naloxone
  - More focused guidance on initiating OAT in fentanyl-dependent patients
  - Optimized dosing for known patients at risk of overdose
  - Guidance on omitted doses
- ✓ **Treatment options (25%) Consider all treatments with all their characteristics**

- Broaden the variety and consider the new treatment options
- Consider SROM as a legitimate treatment and include in update as well as iOAT
- Consider evidence of injectable depot buprenorphine and availability across provinces
- Consider methadone as first line for people who use fentanyl
- Update including best evidence or experts' opinion on MMT+SROM induction

✓ **Take-home doses (23%) Accessibility of "Carries"**

- increase possibilities, make them more accessible
- easing of non-supervised doses (e.g. 14-day methadone)
- guidance to reflect new evidence supporting safety of loosening methadone carries
- flexibility with carries

✓ **Telemedicine (20%) Consider telemedicine as a way of inducing OAT**

- Phone induction and virtual care
- Guidance around use of virtual care
- Telemedicine: when and for who?
- Recommendations for safe and reliable telemedicine

✓ **Patients (15%) Respect of patients' choices to develop trust**

- Avoid automatic urine drug screen (limited evidence supporting UDS)
  - UDS to be used for specific clinical decision points
- Consider patients' choice, be flexible
- Approach must be person-centred
- Discuss the possibility that abstinence might not be the patient's goal
- Treatment approach should be inclusive

✓ **Pharmacy and nursing (11%) Guidelines need to parallel with pharmacist and nurse practitioners' guidelines**

- Possibility of pharmacy transfer without a new prescription
- Oral prescription at community pharmacy
- Necessary partnership with pharmacy for collaborative care
- Partnership with pharmacy and nursing to titrate

✓ **Management of benzodiazepines (BZ) (8%)**

- Management of BZ withdrawal in the context of BZ-contaminated fentanyl or other illicit opioid supply
- Cautious BZ prescribing

✓ **Other (less than 5%)**

- **Patients' follow up**
  - Short term follow-up risks/ responsibilities
  - Withdrawal: when and how to address it to stable patients?
  - What type of long term follow up?
  - Consider a follow-up visit 3 months after OAT induction
- **OAT in emergency department: Withdrawal management in ER**
  - Continuity of care for patients admitted
  - Include buprenorphine-naloxone in withdrawal management in ER
  - Clinical management of withdrawal and OAT in ER
- **Management of pain in OUD patients**
  - Combined OUD/pain treatment clarification needed
  - Suggestions on how to manage people on OAT with acute pain

- **Harm reduction**
  - Information on harm reduction strategies
  - Use of harm reduction approaches with OAT
- **Polysubstance use**
  - How to manage concurrent substance use disorder
  - Information related to polysubstance use needed
- **Related issues**
  - Decrease in testosterone
  - Pregnancy
  - Women
  - Risk of transfer to another substance (e.g. alcohol with OAT)
  - Youth, adolescents
- **References to other guidelines:** References for in depth discussions on subpopulations when appropriate (i.e. women, pregnancy and OUD, youth…)
  - CAMH
  - BCCSU

## Suggestions to ensure the outreach of the updated guidelines

✓ **Dissemination**

- Colleges of Nurses and Nurses Practitioners Associations
- College of Family Physicians of Canada
- Colleges of Physicians and Surgeons

✓ **Training**

- Include in residents and care providers' training
- Include in OUD training of INSPQ

✓ **Publication**

- Scientific journal
- Newsletters
- Listserv
- Webinars
- Provincial Addiction Networks
- Conferences (CSAM, META:PHI, …)

✓ **Greater outreach:** *extending the outreach of the Guidelines by*

- Involving emergency rooms via strategic clinical networks
- Considering the remote nature of most First Nations and the barriers to access specialized services
- Involving people with lived and living experience supporting treatment and recovery

# APPENDIX 3

## Suggested revisions and updates to Population, Intervention, Comparator, Outcome, Study (PICOS) design statements

The following is a description of the PICOS statements used in the *2018 National Opioid Use Disorder Guidelines*, as well as suggested revisions and/or updates (if applicable) to each item within these statements. The recommendations are colour-coded based on suggested search groupings. Recommendations with the same colour are proposed to be captured by a single search strategy with data synthesis being separated to address the recommendations rather than carrying out independent searches.

# A3.1. Pharmacotherapies

## Opioid agonist therapies

**Research question:** ***Should individuals with opioid use disorder be offered buprenorphine/naloxone as the preferred first-line option for opioid agonist treatment?***

| | 2018 | 2024<br>Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed opioid use disorder (OUD) of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment (OAT) at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Long-term (i.e., "maintenance") therapy with buprenorphine or buprenorphine/naloxone. | |
| **Comparison** | Long-term (i.e., "maintenance") therapy with placebo, methadone, treatment as usual, or no treatment or short-term buprenorphine taper. | |
| **Outcome** | Primary outcomes: retention in treatment, abstinence from or reduction in illicit opioid use.<br>Secondary outcomes: side effects, adverse events, morbidity and mortality.<br>Other: direct and indirect costs, health service utilization. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

**Research question:** ***Should individuals with opioid use disorder who are not benefiting from buprenorphine/naloxone be offered the option of transitioning to methadone?***

| | 2018 | 2024 Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | A: Long-term (i.e., "maintenance") therapy with placebo, methadone, treatment as usual, or no treatment.<br>B: Transition from long-term therapy with buprenorphine or buprenorphine/naloxone to methadone. | |
| **Comparison** | A: Long-term (i.e., "maintenance") therapy with placebo, methadone, treatment as usual, or no treatment.<br>B: Treatment as usual. | |
| **Outcome** | Primary outcomes: retention in treatment, abstinence from or reduction in illicit opioid use.<br>Secondary outcomes: side effects, adverse events, morbidity and mortality.<br>Other: direct and indirect costs, health service utilization. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

**Research question:** ***Should individuals with opioid use disorder be offered methadone as a first-line treatment option when buprenorphine/naloxone is not preferred?***

| | 2018 | 2024<br>Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Long term (i.e., "maintenance") therapy with methadone. | |
| **Comparison** | Long-term (i.e., "maintenance") therapy with placebo, buprenorphine or buprenorphine/naloxone, treatment as usual, or no treatment. | |
| **Outcome** | Primary outcomes: retention in treatment, abstinence from or reduction in opioid use.<br>Secondary outcomes: side effects, adverse events, morbidity and mortality.<br>Other: direct and indirect costs, health service utilization. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

**Research question:** ***Should individuals with opioid use disorder who have achieved sustained clinical and social stability on methadone, and who express a desire for lower-intensity treatment or treatment simplification, be offered the option of transitioning to buprenorphine/naloxone?***

| | 2018 | 2024<br>Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | A: Long-term (i.e., "maintenance") therapy with methadone.<br>B: Transition from long-term (i.e., "maintenance") therapy with methadone to buprenorphine or buprenorphine/naloxone. | |
| **Comparison** | A: Long-term (i.e., "maintenance") therapy with placebo, buprenorphine, buprenorphine/naloxone, treatment as usual, or no treatment.<br>B: Treatment as usual. | |
| **Outcome** | Primary outcomes: retention in treatment, abstinence from or reduction in opioid use.<br>Secondary outcomes: side effects, adverse events, morbidity and mortality.<br>Other: direct and indirect costs, health service utilization. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

**Research question:** ***Should individuals with opioid use disorder who have not benefited from treatment with first- and second-line treatment options (buprenorphine/naloxone and/or methadone), be offered the option of opioid agonist treatment with slow-release oral morphine?***

| | 2018 | 2024<br>Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Long-term (i.e., "maintenance") therapy with slow-release oral morphine. | |
| **Comparison** | Long-term (i.e., "maintenance") therapy with placebo, methadone, buprenorphine or buprenorphine/naloxone, treatment as usual, or no treatment. | |
| **Outcome** | Primary outcomes: retention in treatment, abstinence from or reduction in opioid use.<br>Secondary outcomes: side effects, adverse events.<br>Other: quality of life, patient preference, physical and mental health, social functioning, other substance use, cravings. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

## Opioid withdrawal management

**Research question:** ***Should individuals with opioid use disorder be offered the option of withdrawal management as a stand-alone treatment?***

| | 2018 | 2024 Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Tapered dose regimens of opioid agonist treatments (buprenorphine, buprenorphine/naloxone, or methadone) or alpha$_2$-adrenergic agonists (clonidine). | |
| **Comparison** | Long-term (i.e., "maintenance") opioid agonist treatment. | |
| **Outcome** | Primary outcomes: completion of or retention in treatment, sustained abstinence from or reduction in opioid use.<br>Secondary outcomes: side effects, adverse events, morbidity and mortality. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

**Research question:** ***Should individuals with opioid use disorder who wish to pursue withdrawal management be offered the option of an extended opioid agonist taper (i.e., gradual dose reduction over a period of one month or more) in an outpatient or residential setting?***

| | 2018 | 2024 Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Buprenorphine, buprenorphine/naloxone or methadone taper regimens administered at variable amounts, duration, or rates. Alpha2-adrenergic agonist taper regimens were excluded. | |
| **Comparison** | Where applicable, treatment as usual (for within-class comparisons of opioid agonist tapers) or long-term (i.e., "maintenance") opioid agonist treatment. | |
| **Outcome** | Primary outcomes: completion of or retention in treatment, sustained abstinence from or reduction in opioid use.<br>Secondary outcomes: side effects, adverse events, morbidity and mortality. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

**Research question:** ***Should individuals with opioid use disorder who have sustained clinical stability on but wish to discontinue opioid agonist treatment be offered the option of a long-term stepped-tapering schedule (i.e., individually tailored, alternating schedule of gradual dose reduction and stabilization periods with a total duration of months to years)?***

| | 2018 | 2024 Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Buprenorphine, buprenorphine/naloxone or methadone taper regimens administered at variable duration, rates, and schedules. | |
| **Comparison** | Not applicable. | |
| **Outcome** | Primary outcomes: completion of or retention in treatment, sustained abstinence from or reduction in opioid use. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

## A3.2. Psychosocial Intervention And Harm Reduction Strategies

**Research question:** ***Should individuals with opioid use disorder who are engaged in opioid agonist treatment be offered the option to access or participate in psychosocial treatment interventions?***

| | 2018 | 2024 Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Psychosocial treatment interventions were defined as structured and/or manualized counselling that incorporates principles of psychoanalytic therapy, cognitive behavioural therapy, interpersonal therapy, dialectic behavioural therapy, contingency management, biofeedback, hypnotherapy/ subliminal, twelve-step facilitation, family/group counselling delivered in conjunction with long-term opioid agonist treatment.<br><br>Studies of psychosocial treatment interventions or supports delivered in conjunction with withdrawal management—short-term opioid agonist or alpha$_2$-adrenergic agonist tapers—were excluded. | |
| **Comparison** | Treatment as usual: long-term opioid agonist treatment with methadone, buprenorphine, or buprenorphine/naloxone. | |
| **Outcome** | Primary outcomes: retention in treatment, abstinence from or reduction in opioid use.<br><br>Secondary outcomes: side effects, adverse events, morbidity and mortality.<br><br>Other: direct and indirect costs, health service utilization, quality of life, mental health, social functioning, risk behaviours, HIV and hepatitis C infection, and criminality. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

**Research question:** ***Should individuals with opioid use disorder be offered harm reduction services?***

| | 2018 | 2024 Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Direct and indirect (information, referral and/or linkage with services) provision of harm reduction services (e.g., supervised consumption sites, take-home naloxone, overdose prevention education, safer injection education, HIV and hepatitis C prevention education, sterile injection or smoking supplies distribution). | |
| **Comparison** | Not applicable (omitted by design and/or study specific ethical reasons). | |
| **Outcome** | Primary Outcomes: Morbidity and mortality, fatal and non-fatal overdose events, HIV and hepatitis C infection.<br>Other: direct and indirect costs, health service utilization, risk behaviours, and criminality. | Suggest the addition of naloxone use as a secondary outcome. |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

# A3.3. Special Considerations

## Alternative options

**Research question:** ***Should individuals with opioid use disorder who have achieved cessation of opioid use be offered the option of treatment with oral naltrexone to prevent lapse or relapse to illicit opioid use?***

| | 2018 | 2024 Suggested Revisions/Updates |
|---|---|---|
| **Population** | Male and female adults with DSM-IV- or DSM-5-confirmed OUD of any severity (mild, moderate, or severe) with primary use of illegal heroin, prescribed or street-obtained pharmaceutical opioid drugs by any route of administration (e.g., injection, inhalation, ingestion). Studies that enrolled individuals with DSM-IV- or DSM-5-confirmed OUD who were engaged in opioid agonist treatment at study entry were included. Studies that enrolled pregnant women were excluded. | Suggest including pregnant persons with brief narrative description of considerations for the treatment of this population. Alternatively, if no data on the population are available, clarify that insufficient research data exist to guide the treatment of pregnant persons in this area. |
| **Intervention** | Long term (i.e., "maintenance") therapy with oral naltrexone.<br>Injectable naltrexone was excluded. | Injectable naltrexone still excluded. |
| **Comparison** | Long-term (i.e., "maintenance") therapy with placebo, methadone, buprenorphine, buprenorphine/naloxone, treatment as usual, or no treatment. | |
| **Outcome** | Primary outcomes: retention in treatment, abstinence from or reduction in opioid use.<br>Secondary outcomes: side effects, adverse events, morbidity and mortality. | |
| **Study Design** | Meta-analyses, systematic reviews, randomized controlled trials, quasi-experimental studies, or observational cohort studies (prospective and retrospective). | |

# APPENDIX 4

# Search Strategies

## A4.1. OUD Pharmacology Search Documentation

Searches ran as listed below by Robin Parker, from original searches saved in each database; results were uploaded to Covidence on 11 August 2023 for automated duplicate removal (number of duplicates removed noted below).

Acknowledgements: Maddie Hare and Courtney Svab contributed to the development and translation of these searches in 2022. Kristy Hancock completed the PRESS (peer review of electronic search strategy) for this search prior to finalization in December 2022.

### MEDLINE ALL (via Ovid) – Date: Aug 10, 2023

Ovid MEDLINE® ALL <1946 to August 10, 2023>
Focus: 2017 to August 10, 2023

1129 citations exported to Covidence; 83 duplicates removed; 1016 records added to screen

| # | Query | Results |
|---|---|---|
| 1 | exp *Morphine Derivatives/ or exp *Fentanyl/ or exp *Narcotics/ or exp *Opiate Alkaloids/ | 110724 |
| 2 | (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or morphine or MS Contin or Nalbuphine or narcotic* or Norco or Nubain or Nucynta ER or Opana ER or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or Oxymorphone hydrochloride or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or Tuzistra XR or Vicodin or Vicoprofen or Vituz or Xartemis XR or Xodol or Xtampza ER or Zohydro ER or Zolvit or Zutripro or Zydone).ti,ab,kf. | 217422 |
| 3 | 1 or 2 | 239306 |
| 4 | exp *Opioid-Related Disorders/ | 27885 |
| 5 | (addict* or dependen* or abuse* or abusing).ti,ab,kf. | 2110690 |
| 6 | ((disorder* or addict* or dependen* or abuse* or abusing) adj3 (multiple drug* or polydrug* or street drug* or designer drug* or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or morphine or 'MS Contin' or Nalbuphine or narcotic* or Norco or Nubain or 'Nucynta ER' or 'Opana ER' or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or Oxymorphone hydrochloride or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or 'Targiniq ER' or Tramadol or TussiCaps or Tussionex or 'Tuzistra XR' or Vicodin or Vicoprofen or Vituz or 'Xartemis XR' or Xodol or 'Xtampza ER' or 'Zohydro ER' or Zolvit or Zutripro or Zydone)).ti,ab,kf. | 32846 |
| 7 | (PWUD or PWID or "people who use drugs" or (("use" or using or users) adj3 (illicit* or illegal* or inject*))).ti,ab,kf. | 45785 |
| 8 | 1 and (5 or 7) | 27267 |
| 9 | 4 or 6 or 8 | 56225 |
| 10 | 4 or 5 or 6 or 7 | 2160971 |
| 11 | animals/ or (mice or mouse or rat or rats or canine or dog? or rodent* or rabbit? or animal? or sheep or lamb? or monkey? or in vitro).ti,ab. | 8474948 |

| # | Query | Results |
|---|---|---|
| 12 | humans/ | 21405959 |
| 13 | 11 not (11 and 12) | 5710397 |
| 14 | 3 and 10 | 73085 |
| 15 | Clonidine/ or clonidine.ti,ab,kf. or exp Adrenergic alpha-2 Receptor Agonists/ or (adrenergic adj3 agonist*).ti,ab,kf. | 43293 |
| 16 | exp Narcotic Antagonists/ or exp Opiate Substitution Treatment/ or exp Methadone/ or exp Buprenorphine/ or exp Buprenorphine, Naloxone Drug Combination/ or exp Naloxone/ | 53510 |
| 17 | (Buprenorphine or naloxone or methadone or naltrexone).ti,ab,kf. | 51502 |
| 18 | agonist pharmacotherapy.mp. | 33 |
| 19 | ((opioid* or opiate* or narcotic* or benzodiazepine receptor) adj3 (agonist* or antagonist* or substitut* or replace* or stimula*)).ti,ab,kf. | 27459 |
| 20 | ("slow release oral morphine" or SROM).ti,ab,kf. | 157 |
| 21 | (oat or oar).ti,ab,kf. | 13663 |
| 22 | ((maintenance or long term) adj2 (therap* or pharmacotherap* or pharmaceutic*)).ti,ab,kw. | 42729 |
| 23 | or/15-22 | 175035 |
| 24 | 9 and 23 | 25956 |
| 25 | 24 not 13 | 19894 |
| 26 | 14 and 23 | 32138 |
| 27 | 26 not 13 | 22497 |
| 28 | (2017* or 2018* or 2019* or 202*).dp. | 9171158 |
| 29 | 27 and 28 | 8092 |
| 30 | 2017*.dp. | 1127422 |
| 31 | 27 and 30 | 836 |
| 32 | 2018*.dp. | 1173593 |
| 33 | 27 and 32 | 959 |
| 34 | 2019*.dp. | 1230100 |
| 35 | 27 and 34 | 1129 |
| 36 | 31 or 33 or 35 | 2924 |
| 37 | (2020* or 2021*).dp. | 2967938 |
| 38 | 27 and 37 | 2691 |
| 39 | 2022*.dp. | 1605518 |
| 40 | 27 and 39 | 1520 |
| 41 | 27 not 25 | 2940 |
| 42 | (202207* or 202208* or 202209* or 20221*).dt,ez,ed. | 961531 |
| 43 | 27 and 42 | 835 |
| 44 | 20221*.dt,ez,ed. | 518170 |
| 45 | 27 and 44 | 416 |
| 46 | (202212* or 2023*).dt,ez,ed. | 1281878 |
| 47 | 27 and 46 | 1099 |

## Embase (via Elsevier) – Date: 16 Dec 2022

2022-12-16: 3373 citation uploaded; 357 duplicates removed; 3016 records added to screen

| # | Query | Results | Comments |
|---|---|---|---|
| 25 | #24 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) | 3,373 | |
| 24 | #23 AND [01-01-2017]/sd NOT [17-12-2022]/sd | 8,590 | |
| 23 | #22 NOT #18 | 23,893 | |
| 22 | #15 AND #21 | 32,292 | OUD and Intervention |
| 21 | #1 OR #3 OR #20 | 71,165 | OUD |
| 20 | #5 AND #19 | 45,926 | Narcotics MeSH and addiction text terms |
| 19 | #2 OR #4 | 2,522,467 | |
| 18 | #16 NOT #17 | 7,246,646 | |
| 17 | 'human'/exp OR 'human' | 26,665,706 | |
| 16 | 'animal'/exp OR 'nonhuman'/exp OR mice:ti,ab OR mouse:ti,ab OR rat:ti,ab OR rats:ti,ab OR canine:ti,ab OR canines:ti,ab OR dog:ti,ab OR dogs:ti,ab OR rodent*:ti,ab OR rabbit:ti,ab OR rabbits:ti,ab OR animal:ti,ab OR animals:ti,ab OR sheep:ti,ab OR lamb:ti,ab OR monkey:ti,ab OR monkeys:ti,ab OR 'in vitro':ti,ab | 33,538,451 | |
| 15 | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 | 256,479 | |
| 14 | oat:ti,ab,kw OR oar:ti,ab,kw OR ost:ti,ab,kw | 22,973 | |
| 13 | ((maintenance OR 'long term') NEAR/2 (therap* OR pharmacotherap* OR pharmaceutic*)):ti,ab,kw | 67,282 | |
| 12 | 'slow release oral morphine':ti,ab,kw OR srom:ti,ab,kw | 382 | |
| 11 | 'agonist pharmacotherapy':ti,ab,kw | 49 | |
| 10 | ((opioid* OR opiate* OR narcotic* OR 'benzodiazepine receptor') NEAR/3 (agonist* OR antagonist* OR substitut* OR replace* OR stimula*)):ti,ab,kw | 33,867 | |
| 9 | buprenorphine:ti,ab,kw OR naloxone:ti,ab,kw OR methadone:ti,ab,kw OR naltrexone:ti,ab,kw | 65,679 | |
| 8 | clonidine:ti,ab,kw OR ((adrenergic NEAR/3 agonist*):ti,ab,kw) | 33,600 | |
| 7 | 'methadone'/exp/mj OR 'naltrexone'/exp/mj OR 'opiate substitution treatment'/exp OR 'narcotic antagonist'/exp/mj OR 'buprenorphine'/exp/mj OR 'buprenorphine plus naloxone'/exp/mj OR 'naloxone'/exp/mj | 54,973 | |
| 6 | 'alpha 2 adrenergic receptor stimulating agent'/exp/mj | 53,567 | |
| 5 | 'morphine derivative'/exp/mj OR 'narcotic analgesic agent'/exp/mj OR 'narcotic agent'/exp/mj | 191,567 | |
| 4 | pwud:ti,ab,kw OR pwid:ti,ab,kw OR 'people who use drugs':ti,ab,kw OR ((('use' OR using OR users) NEAR/3 (illicit* OR illegal* OR inject*)):ti,ab,kw) | 59,987 | |

| # | Query | Results | Comments |
|---|---|---|---|
| 3 | ((disorder* OR addict* OR dependen* OR abuse* OR abusing) NEAR/3 ('multiple drug*' OR 'polydrug*' OR 'street drug*' OR 'designer drug*' OR abstral OR actiq OR alfentanil OR anexsia OR astramorph OR avinza OR butrans OR carfentan* OR codeine OR 'co gesic' OR demerol OR diamorphine OR dilaudid OR dolophine OR duragesic OR embeda OR endocet OR exalgo OR fentanyl OR fentora OR heroin OR hycet OR hycodan OR hydrocodone OR hydromet OR hydromorphone OR hysingla OR ibudone OR kadian OR liquicet OR lorcet OR lortab OR maxidone OR meperidine OR morphabond OR 'ms contin' OR nalbuphine OR narcotic* OR norco OR nubain OR 'nucynta er' OR 'opana er' OR opiate* OR opioid* OR opium OR onsolis OR oramorph OR 'ora morph' OR oxaydo OR oxecta OR oxycet OR oxycodone OR oxycontin OR 'oxymorphone hydrochloride' OR palladone OR pentazocine OR percocet OR percodan OR pethidine OR reprexain OR rezira OR roxanol* OR roxicet OR roxicodone OR roxycodone OR sublimaze OR sufentanil OR tapentadol OR 'targiniq er' OR tramadol OR tussicaps OR tussionex OR 'tuzistra xr' OR vicodin OR vicoprofen OR vituz OR 'xartemis xr' OR xodol OR 'xtampza er' OR 'zohydro er' OR zolvit OR zutripro OR zydone)):ti,ab,kw | 39,415 | |
| 2 | abuse*:ti,ab,kw OR dependen*:ti,ab,kw OR addict*:ti,ab,kw OR abusing:ti,ab,kw | 2,473,315 | |
| 1 | 'narcotic dependence'/exp/mj | 21,967 | |

## Embase search update - Date: 11 Aug 2023

538 citations exported to Covidence; 177 duplicates removed; 361 records added to screen

| # | Query | Results |
|---|---|---|
| 96 | #92 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [01-12-2022]/sd NOT [12-08-2023]/sd | 538 |
| 95 | #92 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) | 8,212 |
| 94 | #93 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) | 3,337 |
| 93 | #92 AND [01-01-2017]/sd NOT [17-12-2022]/sd | 8,156 |
| 92 | #91 NOT #87 | 24,911 |
| 91 | #84 AND #90 | 33,370 |
| 90 | #70 OR #72 OR #89 | 73,770 |
| 89 | #74 AND #88 | 47,052 |
| 88 | #71 OR #73 | 2,595,676 |
| 87 | #85 NOT #86 | 7,400,220 |
| 86 | 'human'/exp OR 'human' | 27,621,108 |
| 85 | 'animal'/exp OR 'nonhuman'/exp OR mice:ti,ab OR mouse:ti,ab OR rat:ti,ab OR rats:ti,ab OR canine:ti,ab OR canines:ti,ab OR dog:ti,ab OR dogs:ti,ab OR rodent*:ti,ab OR rabbit:ti,ab OR rabbits:ti,ab OR animal:ti,ab OR animals:ti,ab OR sheep:ti,ab OR lamb:ti,ab OR monkey:ti,ab OR monkeys:ti,ab OR 'in vitro':ti,ab | 34,639,477 |
| 84 | #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 | 263,605 |
| 83 | oat:ti,ab,kw OR oar:ti,ab,kw OR ost:ti,ab,kw | 23,986 |
| 82 | ((maintenance OR 'long term') NEAR/2 (therap* ORpharmacotherap* OR pharmaceutic*)):ti,ab,kw | 69,700 |
| 81 | 'slow release oral morphine':ti,ab,kw OR srom:ti,ab,kw | 401 |
| 80 | 'agonist pharmacotherapy':ti,ab,kw | 49 |
| 79 | ((opioid* OR opiate* OR narcotic* OR 'benzodiazepine receptor') NEAR/3 (agonist* OR antagonist* OR substitut* OR replace* OR stimula*)):ti,ab,kw | 34,606 |
| 78 | buprenorphine:ti,ab,kw OR naloxone:ti,ab,kw OR methadone:ti,ab,kw OR naltrexone:ti,ab,kw | 67,408 |
| 77 | clonidine:ti,ab,kw OR ((adrenergic NEAR/3 agonist*):ti,ab,kw) | 34,056 |

| # | Query | Results |
|---|---|---|
| 76 | 'methadone'/exp/mj OR 'naltrexone'/exp/mj OR 'opiate substitution treatment'/exp OR 'narcotic antagonist'/exp/mj OR 'buprenorphine'/exp/mj OR 'buprenorphine plus naloxone'/exp/mj OR 'naloxone'/exp/mj | 55,978 |
| 75 | 'alpha 2 adrenergic receptor stimulating agent'/exp/mj | 54,836 |
| 74 | 'morphine derivative'/exp/mj OR 'narcotic analgesic agent'/exp/mj OR 'narcotic agent'/exp/mj | 195,946 |
| 73 | pwud:ti,ab,kw OR pwid:ti,ab,kw OR 'people who use drugs':ti,ab,kw OR ((('use' OR using OR users) NEAR/3 (illicit* OR illegal* OR inject*)):ti,ab,kw) | 62,141 |
| 72 | ((disorder* OR addict* OR dependen* OR abuse* OR abusing) NEAR/3 ('multiple drug*' OR 'polydrug*' OR 'street drug*' OR 'designer drug*' OR abstral OR actiq OR alfentanil OR anexsia OR astramorph OR avinza OR butrans OR carfentan* OR codeine OR 'co gesic' OR demerol OR diamorphine OR dilaudid OR dolophine OR duragesic OR embeda OR endocet OR exalgo OR fentanyl OR fentora OR heroin OR hycet OR hycodan OR hydrocodone OR hydromet OR hydromorphone OR hysingla OR ibudone OR kadian OR liquicet OR lorcet OR lortab OR maxidone OR meperidine OR morphabond OR 'ms contin' OR nalbuphine OR narcotic* OR norco OR nubain OR 'nucynta er' OR 'opana er' OR opiate* OR opioid* OR opium OR onsolis OR oramorph OR 'ora morph' OR oxaydo OR oxecta OR oxycet OR oxycodone OR oxycontin OR 'oxymorphone hydrochloride' OR palladone OR pentazocine OR percocet OR percodan OR pethidine OR reprexain OR rezira OR roxanol* OR roxicet OR roxicodone OR roxycodone OR sublimaze OR sufentanil OR tapentadol OR 'targiniq er' OR tramadol OR tussicaps OR tussionex OR 'tuzistra xr' OR vicodin OR vicoprofen OR vituz OR 'xartemis xr' OR xodol OR 'xtampza er' OR 'zohydro er' OR zolvit OR zutripro OR zydone)):ti,ab,kw | 41,389 |
| 71 | abuse*:ti,ab,kw OR dependen*:ti,ab,kw OR addict*:ti,ab,kw OR abusing:ti,ab,kw | 2,544,662 |
| 70 | 'narcotic dependence'/exp/mj | 22,911 |

## PsycINFO (via EBSCOhost) – Date: 19 Dec 2022

2022-12-19: **2239 results imported -> 1847 duplicates removed -> 391 records added to screening**
Monday, December 19, 2022 11:14:04 PM

| # | Query | Limiters/Expanders | Results |
|---|---|---|---|
| S22 | S14 AND S21 | Limiters - Publication Year: 2017-2022; Population Group: Human<br>Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 2,238 |
| S21 | S15 OR S16 OR S17 OR S18 OR S19 OR S20 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 34,675 |
| S20 | TI (((maintenance or long term or agonist) N2 (therap* or pharmacotherap* or pharmaceutic*))) OR AB (((maintenance or long term or agonist) N2 (therap* or pharmacotherap* or pharmaceutic*))) OR KW (((maintenance or long term or agonist) N2 (therap* or pharmacotherap* or pharmaceutic*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 6,239 |
| S19 | TI (Buprenorphine or naloxone or methadone or naltrexone or OAR or OAT or OST or "slow release oral morphine" or SROM) OR AB (Buprenorphine or naloxone or methadone or naltrexone or OAR or OAT or OST or "slow release oral morphine" or SROM) OR KW (Buprenorphine or naloxone or methadone or naltrexone or OAR or OAT or OST or "slow release oral morphine" or SROM) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 19,596 |
| S18 | TI (((opioid* or opiate* or narcotic* or "benzodiazepine receptor") N3 (agonist* or antagonist* or substitut* or replace* or stimula*))) OR AB (((opioid* or opiate* or narcotic* or "benzodiazepine receptor") N3 (agonist* or antagonist* or substitut* or replace* or stimula*))) OR KW (((opioid* or opiate* or narcotic* or "benzodiazepine receptor") N3 (agonist* or antagonist* or substitut* or replace* or stimula*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 9,002 |

| # | Query | Limiters/Expanders | Results |
|---|---|---|---|
| S17 | DE "Narcotic Antagonists" OR DE "Nalorphine" OR DE "Naloxone" OR DE "Naltrexone" OR DE "Buprenorphine" OR DE "Methadone" OR DE "Methadone Maintenance" | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 16,667 |
| S16 | TI (clonidine OR (adrenergic N3 agonist*)) OR AB (clonidine OR (adrenergic N3 agonist*)) OR KW (clonidine OR (adrenergic N3 agonist*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 2,838 |
| S15 | (DE "Adrenergic Blocking Drugs") OR (DE "Clonidine") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 3,275 |
| S14 | S6 OR S8 OR S13 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 25,180 |
| S13 | S1 AND S12 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 16,605 |
| S12 | S5 OR S11 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 408,961 |
| S11 | TI (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) OR AB (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) OR KW (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 16,728 |
| S10 | PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 16,843 |
| S9 | S1 AND S5 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 15,514 |
| S8 | DE "Opioid Use Disorder" OR DE "Heroin Use Disorder" OR DE "Morphine Dependence" | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 5,641 |
| S7 | S4 or S5 or S6 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 399,914 |

| # | Query | Limiters/Expanders | Results |
|---|---|---|---|
| S6 | TI ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) OR AB ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) OR KW ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 16,871 |
| S5 | TI (abuse* or dependen* or addict* or abusing) or AB (abuse* or dependen* or addict* or abusing) or KW (abuse* or dependen* or addict* or abusing) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 397,916 |
| S4 | MM "Heroin Addiction" | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 276 |
| S3 | S1 or S2 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 54,253 |

| # | Query | Limiters/Expanders | Results |
|---|---|---|---|
| S2 | TI (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or Opana ER or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or Xtampza ER or "Zohydro ER" or Zolvit or Zutripro or Zydone) or AB (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or Nucynta ER or Opana ER or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) or KW (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or Xtampza ER or "Zohydro ER" or Zolvit or Zutripro or Zydone) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 49,294 |
| S1 | (DE "Opiates" OR DE "Codeine" OR DE "Endogenous Opiates" OR DE "Heroin" OR DE "Morphine" OR DE "Papaverine") OR (DE "Opiates" OR DE "Narcotic Drugs" OR DE "Narcotic Agonists" OR DE "Narcotic Antagonists" OR DE "Opiates" OR DE "Opioid Analgesics") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | 31,386 |

## PsychINFO search update – Date - 11 August 2023

**222 records exported to Covidence; 152 duplicates removed; 70 records added to screen**

Friday, August 11, 2023 3:49:01 PM

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S23 | S14 AND S21 | Limiters - Published Date: 20221201-20230831<br>Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - APA PsycInfo | 222 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S22 | S14 AND S21 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 12,423 |
| S21 | S15 OR S16 OR S17 OR S18 OR S19 OR S20 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 35,350 |
| S20 | TI (((maintenance or long term or agonist) N2 (therap* or pharmacotherap* or pharmaceutic*))) OR AB (((maintenance or long term or agonist) N2 (therap* or pharmacotherap* or pharmaceutic*))) OR KW (((maintenance or long term or agonist) N2 (therap* or pharmacotherap* or pharmaceutic*))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 6,383 |
| S19 | TI (Buprenorphine or naloxone or methadone or naltrexone or OAR or OAT or OST or "slow release oral morphine" or SROM) OR AB (Buprenorphine or naloxone or methadone or naltrexone or OAR or OAT or OST or "slow release oral morphine" or SROM) OR KW (Buprenorphine or naloxone or methadone or naltrexone or OAR or OAT or OST or "slow release oral morphine" or SROM) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 20,047 |
| S18 | TI (((opioid* or opiate* or narcotic* or "benzodiazepine receptor") N3 (agonist* or antagonist* or substitut* or replace* or stimula*))) OR AB (((opioid* or opiate* or narcotic* or "benzodiazepine receptor") N3 (agonist* or antagonist* or substitut* or replace* or stimula*))) OR KW (((opioid* or opiate* or narcotic* or "benzodiazepine receptor") N3 (agonist* or antagonist* or substitut* or replace* or stimula*))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 9,201 |
| S17 | DE "Narcotic Antagonists" OR DE "Nalorphine" OR DE "Naloxone" OR DE "Naltrexone" OR DE "Buprenorphine" OR DE "Methadone" OR DE "Methadone Maintenance" | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 17,081 |
| S16 | TI (clonidine OR (adrenergic N3 agonist*)) OR AB (clonidine OR (adrenergic N3 agonist*)) OR KW (clonidine OR (adrenergic N3 agonist*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 2,861 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S15 | (DE "Adrenergic Blocking Drugs") OR (DE "Clonidine") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 3,288 |
| S14 | S6 OR S8 OR S13 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 26,028 |
| S13 | S1 AND S12 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 16,957 |
| S12 | S5 OR S11 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 417,834 |
| S11 | TI (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) OR AB (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) OR KW (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 17,179 |
| S10 | PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 17,298 |
| S9 | S1 AND S5 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 15,803 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S8 | DE "Opioid Use Disorder" OR DE "Heroin Use Disorder" OR DE "Morphine Dependence" | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 6,244 |
| S7 | S4 or S5 or S6 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 408,777 |
| S6 | TI ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) OR AB ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) OR KW ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 17,516 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S5 | TI (abuse* or dependen* or addict* or abusing) or AB (abuse* or dependen* or addict* or abusing) or KW (abuse* or dependen* or addict* or abusing) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 406,448 |
| S4 | MM "Heroin Addiction" | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 7,314 |
| S3 | S1 or S2 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 55,668 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S2 | TI (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or Opana ER or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or Xtampza ER or "Zohydro ER" or Zolvit or Zutripro or Zydone) or AB (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or Nucynta ER or Opana ER or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or Xtampza ER or "Zohydro ER" or Zolvit or Zutripro or Zydone) or KW (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or Xtampza ER or "Zohydro ER" or Zolvit or Zutripro or Zydone) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 50,670 |
| S1 | (DE "Opiates" OR DE "Codeine" OR DE "Endogenous Opiates" OR DE "Heroin" OR DE "Morphine" OR DE "Papaverine") OR (DE "Opiates" OR DE "Narcotic Drugs" OR DE "Narcotic Agonists" OR DE "Narcotic Antagonists" OR DE "Opiates" OR DE "Opioid Analgesics") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 32,176 |

## Cochrane Library – Date: 11 Aug 2023

Search Name: OUD Pharma
Date Run: 11/08/2023 23:16:22
Comment: 2022-12-23 Original Search date

| # | Query | Results |
|---|---|---|
| 1 | MeSH descriptor: [Narcotics] explode all trees | 10522 |
| 2 | MeSH descriptor: [Morphine Derivatives] explode all trees | 8053 |
| 3 | MeSH descriptor: [Opiate Alkaloids] explode all trees | 12576 |
| 4 | MeSH descriptor: [Fentanyl] explode all trees | 6221 |
| 5 | #1 OR #2 OR #3 OR #4 | 21994 |
| 6 | abuse*:ti,ab,kw OR dependen*:ti,ab,kw OR addict*:ti,ab,kw OR abusing:ti,ab,kw | 106316 |
| 7 | pwud:ti,ab,kw OR pwid:ti,ab,kw OR 'people who use drugs':ti,ab,kw OR ((('use' OR using OR users) NEAR/3 (illicit* OR illegal* OR inject*)):ti,ab,kw) | 8622 |
| 8 | #6 OR #7 | 112982 |
| 9 | #5 AND #8 | 3845 |
| 10 | MeSH descriptor: [Opioid-Related Disorders] explode all trees | 2719 |
| 11 | ((disorder* OR addict* OR dependen* OR abuse* OR abusing) NEAR/3 ('multiple drug*' OR 'polydrug*' OR 'street drug*' OR 'designer drug*' OR abstral OR actiq OR alfentanil OR anexsia OR astramorph OR avinza OR butrans OR carfentan* OR codeine OR 'co gesic' OR demerol OR diamorphine OR dilaudid OR dolophine OR duragesic OR embeda OR endocet OR exalgo OR fentanyl OR fentora OR heroin OR hycet OR hycodan OR hydrocodone OR hydromet OR hydromorphone OR hysingla OR ibudone OR kadian OR liquicet OR lorcet OR lortab OR maxidone OR meperidine OR morphabond OR 'ms contin' OR nalbuphine OR narcotic* OR norco OR nubain OR 'nucynta er' OR 'opana er' OR opiate* OR opioid* OR opium OR onsolis OR oramorph OR 'ora morph' OR oxaydo OR oxecta OR oxycet OR oxycodone OR oxycontin OR 'oxymorphone hydrochloride' OR palladone OR pentazocine OR percocet OR percodan OR pethidine OR reprexain OR rezira OR roxanol* OR roxicet OR roxicodone OR roxycodone OR sublimaze OR sufentanil OR tapentadol OR 'targiniq er' OR tramadol OR tussicaps OR tussionex OR 'tuzistra xr' OR vicodin OR vicoprofen OR vituz OR 'xartemis xr' OR xodol OR 'xtampza er' OR 'zohydro er' OR zolvit OR zutripro OR zydone)):ti,ab,kw | 42484 |
| 12 | #9 OR #10 OR #11 | 43728 |
| 13 | clonidine:ti,ab,kw OR ((adrenergic NEAR/3 agonist*):ti,ab,kw) | 7669 |
| 14 | MeSH descriptor: [Adrenergic alpha-2 Receptor Agonists] explode all trees | 326 |
| 15 | MeSH descriptor: [Clonidine] explode all trees | 2032 |
| 16 | buprenorphine:ti,ab,kw OR naloxone:ti,ab,kw OR methadone:ti,ab,kw OR naltrexone:ti,ab,kw | 10126 |
| 17 | ((opioid* OR opiate* OR narcotic* OR 'benzodiazepine receptor') NEAR/3 (agonist* OR antagonist* OR substitut* OR replace* OR stimula*)):ti,ab,kw | 31307 |
| 18 | agonist pharmacotherapy:ti,ab,kw | 247 |
| 19 | 'slow release oral morphine':ti,ab,kw OR srom:ti,ab,kw | 109 |
| 20 | ((maintenance OR 'long term') NEAR/2 (therap* OR pharmacotherap* OR pharmaceutic*)):ti,ab,kw | 17222 |
| 21 | oat:ti,ab,kw OR oar:ti,ab,kw OR ost:ti,ab,kw | 1707 |
| 22 | MeSH descriptor: [Narcotic Antagonists] explode all trees | 1486 |
| 23 | MeSH descriptor: [Buprenorphine] explode all trees | 1420 |
| 24 | MeSH descriptor: [Buprenorphine, Naloxone Drug Combination] explode all trees | 204 |
| 25 | MeSH descriptor: [Methadone] explode all trees | 1510 |
| 26 | MeSH descriptor: [Naloxone] explode all trees | 2918 |
| 27 | MeSH descriptor: [Opiate Substitution Treatment] explode all trees | 461 |

| # | Query | Results |
|---|---|---|
| 28 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 | 62940 |
| 29 | #12 AND #28 | 7399* |

*7399 = 7293 Trials + 100 Reviews + 1 Protocol + 1 Editorial
Limit to Date added to CENTRAL database 2022-12-01 to 2023-08-11 = 174 Trials exported to Covidence; 77 duplicates removed; 97 records added to screen

## A4.2. Psychosocial And Harm Reduction Interventions

Search strategies modified from Wild *et al.* (2021).

Wild TC, Hammal F, Hancock M, Bartlett NT, Gladwin KK, Adams D, Loverock A, Hodgins DC. Forty-eight years of research on psychosocial interventions in the treatment of opioid use disorder: a scoping review. Drug and alcohol dependence. 2021 Jan 1;218:108434.

### MEDLINE ALL (via Ovid) - Date: July 21, 2022

Ovid MEDLINE® ALL <1946 to July 21, 2022>

| # | Query | Results |
|---|---|---|
| 1 | exp *Morphine Derivatives/or exp *Fentanyl/or *Narcotics/or exp *Opiate Alkaloids/ | 75441 |
| 2 | (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or morphine or MS Contin or Nalbuphine or narcotic* or Norco or Nubain or Nucynta ER or Opana ER or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or Oxymorphone hydrochloride or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or Tuzistra XR or Vicodin or Vicoprofen or Vituz or Xartemis XR or Xodol or Xtampza ER or Zohydro ER or Zolvit or Zutripro or Zydone).ti,ab,kf. | 207192 |
| 3 | 1 or 2 | 221368 |
| 4 | exp *Opioid-Related Disorders/ | 26039 |
| 5 | (addict* or dependen* or abuse* or abusing).ti,ab,kf. | 2026381 |
| 6 | (('use' or using or disorder*) adj3 (multiple drug* or polydrug* or street drug* or designer drug* or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or morphine or 'MS Contin' or Nalbuphine or narcotic* or Norco or Nubain or 'Nucynta ER' or 'Opana ER' or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or Oxymorphone hydrochloride or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or 'Targiniq ER' or Tramadol or TussiCaps or Tussionex or 'Tuzistra XR' or Vicodin or Vicoprofen or Vituz or 'Xartemis XR' or Xodol or 'Xtampza ER' or 'Zohydro ER' or Zolvit or Zutripro or Zydone)). ti,ab,kf. | 35586 |
| 7 | 4 or 5 or 6 | 2057080 |
| 8 | exp *Psychotherapy/ or (psychotherap* or psycho-therap*).ti,ab,kf. | 173429 |
| 9 | ((cognitive adj2 therap*) or (behavio* adj2 therap*)).ti,ab,kf. | 36087 |
| 10 | (sociali?ation or (social adj2 adjust*) or (social adj2 support*)).ti,ab,kf. or exp *Socialization/ | 67306 |
| 11 | exp Cognitive Therapy/ or exp Behavior Therapy/ or (social adj2 skil*).ti,ab,kf. | 93474 |
| 12 | exp Adaptation, Psychological/ or exp Counseling/ | 183119 |

| # | Query | Results |
|---|---|---|
| 13 | (cope or (coping adj2 skill*) or 'self-control training' or 'structured counsel*').ti,ab,kf. | 46584 |
| 14 | ((marital or marriage or family or families or support* or group or couple* or interpersonal) adj2 therap*).ti,ab,kf. | 45417 |
| 15 | (commun* adj3 (service* or center* or centre* or network* or psychiatr* or psycholog* or reinforc*)).ti,ab,kf. | 55157 |
| 16 | ('community mental health' or 'community care' or 'assertive community treatment' or 'clubhouse*' or 'therapeutic communit*' or 'confrontational intervention*' or 'early intervention*').ti,ab,kf. | 39563 |
| 17 | exp *Mind-Body Therapies/ or ('relaxation therap*' or 'relaxation technique*' or 'talk therapy').ti,ab,kf. | 34771 |
| 18 | exp Complementary Therapies/ or ((traditional or complementary or holistic or natur* or alternative or native or mental*) adj2 (medicine* or therap*)).ti,ab,kf. | 317626 |
| 19 | ((traditional* or Native* or aboriginal* or indigenous or ceremon*) adj2 (heal* or medicine or medical*)).ti,ab,kf. or exp *Medicine, Traditional/ | 76440 |
| 20 | (((art or music or sound or colo?r) adj2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap* or 'psychedelic therapy')).ti,ab,kf. | 93482 |
| 21 | ('case management' or outreach or nonpharmacological or non-pharmacological or nonpharmaceutical or non-pharmaceutical).ti,ab,kf. | 47634 |
| 22 | ('street nurse*' or 'street outreach' or 'street clinic*' or 'safer inhalation' or 'crack kit*').ti,ab,kf. | 320 |
| 23 | ('12 step' or twelve-step).ti,ab,kf. or exp Self-Help Groups/ or (self-help or (support* adj2 group*)).ti,ab,kf. | 30123 |
| 24 | (((mutual or peer or recovery) adj support) or (stress adj2 manag*)).ti,ab,kf. | 15582 |
| 25 | ('problem solving' or operant* or 'discussion group*' or 'insight oriented' or 'client centered' or counsel* or insight* or paradox* or psychoanaly* or psychodynamic* or psychodrama* or psycho-drama* or 'role play*' or transactional or befriend* or mentor* or sponsor).ti,ab,kf. | 858833 |
| 26 | (psychological* adj2 debrief*).ti,ab,kf. | 171 |
| 27 | ((behavio* or psychosocial or psycho-social or psychoeducation* or psycho-education* or psychiatric or psychological or social) adj2 (treatment or therap* or program* or intervention* or service*)).ti,ab,kf. | 131196 |
| 28 | (((needle* or syringe*) adj3 exchang*) or (safe* adj1 injection*)).ti,ab,kf. | 2561 |
| 29 | (peerneedle* or 'peer needle*' or 'relapse prevention').ti,ab,kf. | 3603 |
| 30 | exp Needle-Exchange Programs/ | 1958 |
| 31 | exp Motivation/ or (incentive* or motivation*).ab. /freq=2 | 205691 |
| 32 | ('prevention program*' or supervis* consumption or 'formal intervention*' or 'motivate* or enhance*').ti,ab,kf. | 1678406 |
| 33 | (withdraw* or abst*).ti,ab,kf. | 455784 |
| 34 | ('Narcotics Anonymous' or 'Methadone Anonymous' or LifeRing or 'SMART Recovery').ti,ab,kf. | 161 |
| 35 | ('case care' or 'contingency management' or 'contingency therapy').ti,ab,kf. | 1340 |
| 36 | ('electrostimulation therap*' or electro-therap* or electrotherap* or 'electric* stimulation' or (stimulat* adj2 drug)).ti,ab,kf. or exp Electric Stimulation/ | 158731 |
| 37 | exp reinforcement psychology/ or (biofeedback or 'covert sensiti?ation' or 'aversi* stimulation').ti,ab,kf. | 68184 |
| 38 | (voucher* or reinforc* or 'reinforc* schedule*').ti,ab,kf. | 130700 |
| 39 | ((education* or literacy) adj2 (lecture* or program* or film* or intervention*)).ti,ab,kf. | 72525 |
| 40 | ('harm reduction' or 'reduc* harm').ti,ab,kf. or Harm Reduction/ | 9119 |
| 41 | Vocational Education/ or exp Rehabilitation, Vocational/ or Vocational Guidance/ or (((vocation* or 'individual placement) and support') or 'supported employment').ti,ab,kf. | 15776 |
| 42 | (housing or houses or volunteer* or 'voluntary worker*' or wraparound or 'wrap around' or 'occupation* guidance').ti,ab,kf. | 257960 |
| 43 | exp *Public Assistance/ or income-assistance.ti,ab,kf. | 46733 |
| 44 | exp *Housing/ or exp *Community Health Services/ or *Volunteers/ | 232478 |

| # | Query | Results |
|---|---|---|
| 45 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 | 4619342 |
| 46 | animals/ | 7156670 |
| 47 | humans/ | 20686057 |
| 48 | 46 not (46 and 47) | 5004793 |
| 49 | 3 and 7 and 45 | 29428 |
| 50 | 49 not 48 | 21103 |
| 51 | 202*.dp. | 4094609 |
| 52 | 50 and 51 | 5056 |
| 53 | (2021* or 2022*).dp. | 2688590 |
| 54 | 50 and 53 | 3418 |
| 55 | 2022*.dp. | 1088107 |
| 56 | 50 and 55 | 1468 |
| 57 | 2021*.dp. and 50 | 1950 |
| 58 | 2020*.dp. and 50 | 1638 |
| 59 | 2019*.dp. and 50 | 1401 |
| 60 | 2018*.dp. and 50 | 1114 |
| 61 | 2017*.dp. and 50 | 953 |
| 62 | (2015* or 2016*).dp. and 50 | 1581 |
| 63 | (2012* or 2013* or 2014*).dp. and 50 | 1962 |
| 64 | (2008* or 2009* or 2010* or 2011*).dp. and 50 | 1967 |

## MEDLINE search update – Date: September 14, 2023

Ovid MEDLINE® ALL <1946 to September 14, 2023>

| # | Query | Comments |
|---|---|---|
| 1 | exp *Morphine Derivatives/ or exp *Fentanyl/ or exp *Narcotics/ or exp *Opiate Alkaloids/ | |
| 2 | (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or morphine or MS Contin or Nalbuphine or narcotic* or Norco or Nubain or Nucynta ER or Opana ER or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or Oxymorphone hydrochloride or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or Tuzistra XR or Vicodin or Vicoprofen or Vituz or Xartemis XR or Xodol or Xtampza ER or Zohydro ER or Zolvit or Zutripro or Zydone).ti,ab,kf. | |
| 3 | 1 or 2 | |
| 4 | exp *Opioid-Related Disorders/ | |

| # | Query | Comments |
|---|---|---|
| 5 | ((disorder* or addict* or dependen* or abuse* or abusing) adj3 (multiple drug* or polydrug* or street drug* or designer drug* or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or morphine or 'MS Contin' or Nalbuphine or narcotic* or Norco or Nubain or 'Nucynta ER' or 'Opana ER' or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or Oxymorphone hydrochloride or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or 'Targiniq ER' or Tramadol or TussiCaps or Tussionex or 'Tuzistra XR' or Vicodin or Vicoprofen or Vituz or 'Xartemis XR' or Xodol or 'Xtampza ER' or 'Zohydro ER' or Zolvit or Zutripro or Zydone)).ti,ab,kf. | |
| 6 | (addict* or dependen* or abuse* or abusing).ti,ab,kf. | |
| 7 | (PWUD or PWID or "people who use drugs" or (("use" or using or users) adj3 (illicit* or illegal* or inject*))).ti,ab,kf. | |
| 8 | 3 and (6 or 7) | |
| 9 | 4 or 5 or 8 | Concept for Opioid use disorder |
| 10 | exp *Psychotherapy/ or (psychotherap* or psycho-therap*).ti,ab,kf. | |
| 11 | ((cognitive adj2 therap*) or (behavio* adj2 therap*)).ti,ab,kf. | |
| 12 | (sociali?ation or (social adj2 adjust*) or (social adj2 support*)).ti,ab,kf. or exp *Socialization/ | |
| 13 | exp Cognitive Therapy/ or exp Behavior Therapy/ or (social adj2 skil*).ti,ab,kf. | |
| 14 | exp Adaptation, Psychological/ or exp Counseling/ | |
| 15 | (cope or (coping adj2 skill*) or 'self-control training' or 'structured counsel*').ti,ab,kf. | |
| 16 | ((marital or marriage or family or families or support* or group or couple* or interpersonal) adj2 therap*).ti,ab,kf. | |
| 17 | (commun* adj3 (service* or center* or centre* or network* or psychiatr* or psycholog* or reinforc*)).ti,ab,kf. | |
| 18 | ('community mental health' or 'community care' or 'assertive community treatment' or 'clubhouse*' or 'therapeutic communit*' or 'confrontational intervention*' or 'early intervention*').ti,ab,kf. | |
| 19 | exp *Mind-Body Therapies/ or ('relaxation therap*' or 'relaxation technique*' or 'talk therapy').ti,ab,kf. | |
| 20 | exp Complementary Therapies/ or ((traditional or complementary or holistic or natur* or alternative or native or mental*) adj2 (medicine* or therap*)).ti,ab,kf. | |
| 21 | ((traditional* or Native* or aboriginal* or indigenous or ceremon*) adj2 (heal* or medicine or medical*)).ti,ab,kf. or exp *Medicine, Traditional/ | |
| 22 | (((art or music or sound or colo?r) adj2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap* or 'psychedelic therapy')).ti,ab,kf. | |
| 23 | ('case management' or outreach or nonpharmacological or non-pharmacological or nonpharmaceutical or non-pharmaceutical).ti,ab,kf. | |
| 24 | ('street nurse*' or 'street outreach' or 'street clinic*' or 'safer inhalation' or 'crack kit*').ti,ab,kf. | |
| 25 | ('12 step' or twelve-step).ti,ab,kf. or exp Self-Help Groups/ or (self-help or (support* adj2 group*)).ti,ab,kf. | |
| 26 | (((mutual or peer or recovery) adj support) or (stress adj2 manag*)).ti,ab,kf. | |
| 27 | ('problem solving' or operant* or 'discussion group*' or 'insight oriented' or 'client centered' or counsel* or insight* or paradox* or psychoanaly* or psychodynamic* or psychodrama* or psycho-drama* or 'role play*' or transactional or befriend* or mentor* or sponsor).ti,ab,kf. | |
| 28 | (psychological* adj2 debrief*).ti,ab,kf. | |
| 29 | ((behavio* or psychosocial or psycho-social or psychoeducation* or psycho-education* or psychiatric or psychological or social) adj2 (treatment or therap* or program* or intervention* or service*)).ti,ab,kf. | |
| 30 | (((needle* or syringe*) adj3 exchang*) or (safe* adj1 injection*)).ti,ab,kf. | |
| 31 | (peerneedle* or 'peer needle*' or 'relapse prevention').ti,ab,kf. | |

| # | Query | Comments |
|---|---|---|
| 32 | exp Needle-Exchange Programs/ | |
| 33 | exp Motivation/ or (incentive* or motivation*).ab. /freq=2 | |
| 34 | ('prevention program*' or supervis* consumption or 'formal intervention*' or 'motivate* or enhance*').ti,ab,kf. | |
| 35 | (withdraw* or abst*).ti,ab,kf. | |
| 36 | ('Narcotics Anonymous' or 'Methadone Anonymous' or LifeRing or 'SMART Recovery').ti,ab,kf. | |
| 37 | ('case care' or 'contingency management' or 'contingency therapy').ti,ab,kf. | |
| 38 | ('electrostimulation therap*' or electro-therap* or electrotherap* or 'electric* stimulation' or (stimulat* adj2 drug)).ti,ab,kf. or exp Electric Stimulation/ | |
| 39 | exp reinforcement psychology/ or (biofeedback or 'covert sensiti?ation' or 'aversi* stimulation').ti,ab,kf. | |
| 40 | (voucher* or reinforc* or 'reinforc* schedule*').ti,ab,kf. | |
| 41 | ((education* or literacy) adj2 (lecture* or program* or film* or intervention*)).ti,ab,kf. | |
| 42 | ('harm reduction' or 'reduc* harm').ti,ab,kf. or Harm Reduction/ | |
| 43 | Vocational Education/ or exp Rehabilitation, Vocational/ or Vocational Guidance/ or (((vocation* or 'individual placement) and support') or 'supported employment').ti,ab,kf. | |
| 44 | (housing or houses or volunteer* or 'voluntary worker*' or wraparound or 'wrap around' or 'occupation* guidance').ti,ab,kf. | |
| 45 | exp *Public Assistance/ or income-assistance.ti,ab,kf. | |
| 46 | exp *Housing/ or exp *Community Health Services/ or *Volunteers/ | |
| 47 | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 | Concept for psychosocial interventions |
| 48 | animals/ | |
| 49 | humans/ | |
| 50 | 48 not (48 and 49) | |
| 51 | 9 and 47 | |
| 52 | 51 not 50 | Complete search + reduce animal studies |
| 53 | 2023*.dt,ez,ed,dp. and 52 | Date limit to 2023 for export |
| 54 | 2022*.dt,ez,ed,dp. and 52 | Date limit to 2022 for export |
| 55 | 2021*.dt,ez,ed,dp. and 52 | Date limit to 2021 for export |
| 56 | 2020*.dt,ez,ed,dp. and 52 | Date limit to 2020 for export |
| 57 | 2019*.dt,ez,ed,dp. and 52 | Date limit to 2019 for export |
| 58 | (2017* or 2018*).dt,ez,ed,dp. and 52 | Date limit 2017-18 for export |

## CINAHL (via EbscoHost) – Date: August 12 2023

Friday, August 12, 2022 3:32:54 PM

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S51 | S49 | Limiters - Published Date: 20190101-20220831<br>Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 3,864 |
| S50 | S49 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 10,783 |
| S49 | S45 NOT S48 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 10,783 |
| S48 | S46 NOT (S46 AND S47) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 92,949 |
| S47 | (MH "Human") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 2,575,279 |
| S46 | (MH "Animals+") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 102,323 |
| S45 | S3 and S6 and S44 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 11,028 |
| S44 | S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 1,561,226 |
| S43 | (MH "Housing+") OR (MH "Community Health Services+") OR (MH "Volunteer Workers+") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 498,893 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S42 | (MH "Public Assistance+") OR (TI "income-assistance" OR AB "income-assistance) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 67,644 |
| S41 | TI (housing or houses or volunteer* or "voluntary worker*" or wraparound or "wrap around" or "occupation* guidance" or "vocation* guidance") OR AB (housing or houses or volunteer* or "voluntary worker*" or wraparound or "wrap around" or "occupation* guidance" or "vocation* guidance") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 64,520 |
| S40 | (MH "Vocational Education") OR (MH "Rehabilitation, Vocational+") OR (MH "Vocational Guidance+") OR (TI (vocation* or "individual placement and support" or "supported employment") OR AB (vocation* or "individual placement and support" or "supported employment")) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 13,898 |
| S39 | (TI ("harm reduction" or "reduc* harm") OR AB ("harm reduction" or "reduc* harm")) OR (MH "Harm Reduction") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 7,497 |
| S38 | TI ((education* or literacy) N2 (lecture* or program* or film* or intervention*)) OR AB ((education* or literacy) N2 (lecture* or program* or film* or intervention*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 54,122 |
| S37 | TI (voucher* or reinforc* or "reinforc* schedule*") OR AB (voucher* or reinforc* or "reinforc* schedule*") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 26,624 |
| S36 | (MH "Reinforcement (Psychology)+") OR (TI (biofeedback or "covert sensiti?ation" or "aversi* stimulation") OR AB (biofeedback or "covert sensiti?ation" or "aversi* stimulation")) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 13,612 |
| S35 | (TI ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* N2 drug)) OR AB ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* N2 drug))) OR (MH "Electric stimulation+") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 23,921 |
| S34 | TI ("case care" or "contingency management" or "contingency therapy") OR AB ("case care" or "contingency management" or "contingency therapy") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 720 |
| S33 | TI ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery") OR AB ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 160 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S32 | TI (withdraw* OR abstain* OR abstinence) OR AB (withdraw* OR abstain* OR abstinence) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 39,086 |
| S31 | (TI ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*") OR AB ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*")) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 14,745 |
| S30 | (MH "Motivation+") OR TI (incentive* or motivation*) OR AB(incentive* or motivation*) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 141,916 |
| S29 | (MH "Needle exchange programs+") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 1,444 |
| S28 | (TI(peerneedle* or "peer needle*" or "relapse prevention") OR AB (peerneedle* or "peer needle*" or "relapse prevention")) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 1,541 |
| S27 | TI ((((needle* or syringe*) N3 exchang*) or ((safe* OR supervis*) N1 injecti*))) OR AB ((((needle* or syringe*) N3 exchang*) or ((safe* OR supervis*) N1 injecti*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 1,745 |
| S26 | TI (((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social OR nonpharma* OR "non pharma*") N2 (treatment or therap* or program* or intervention* or service*))) OR AB (((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social OR nonpharma* OR "non pharma*") N2 (treatment or therap* or program* or intervention* or service*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 91,975 |
| S25 | TI (psychological* N2 debrief*) OR AB (psychological* N2 debrief*) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 80 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S24 | TI (("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanaly* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor)) OR AB (("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanaly* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 213,448 |
| S23 | TI ((((mutual or peer or recovery) N1 support) or (stress N2 manag*))) OR AB ((((mutual or peer or recovery) N1 support) or (stress N2 manag*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 13,218 |
| S22 | (TI ("12 step" or "twelve-step") OR AB ("12 step" or "twelve-step")) OR (MH "support groups+") OR (TI ("self-help" or (support* N2 group*)) OR AB("self-help" or (support* N2 group*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 24,188 |
| S21 | TI (("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*")) OR AB (("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*")) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 185 |
| S20 | TI (("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical")) OR AB (("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical")) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 26,933 |
| S19 | TI ((((art or music or sound or colo?r) adj2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap* or "psychedelic therapy"))) OR AB ((((art or music or sound or colo?r) adj2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap* or "psychedelic therapy"))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 47,161 |
| S18 | (MH "Medicine, Traditional+") or TI (traditional* or Native* or aboriginal* or indigenous or ceremon*) adj2 (heal* or medicine or medical*)) or AB (traditional* or Native* or aboriginal* or indigenous or ceremon*) adj2 (heal* or medicine or medical*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 55,730 |
| S17 | (MH "Alternative Therapies+") OR (TI ((traditional or complementary or holistic or natur* or alternative or native or mental*) N2 (medicine* or therap*)) OR AB ((traditional or complementary or holistic or natur* or alternative or native or mental*) N2 (medicine* or therap*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 284,576 |
| S16 | (MH "Mind Body Techniques+") OR ((TI("relaxation therap*" or "relaxation technique*" or "talk therapy")) OR (AB("relaxation therap*" or "relaxation technique*" or "talk therapy"))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 48,015 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S15 | TI (("community mental health" or "community care" or "assertive community treatment" or "clubhouse*" or "therapeutic communit*" or "confrontational intervention*" or "early intervention*")) OR AB (("community mental health" or "community care" or "assertive community treatment" or "clubhouse*" or "therapeutic communit*" or "confrontational intervention*" or "early intervention*")) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 21,194 |
| S14 | TI ((commun* N3 (service* or center* or centre* or network* or psychiatr* or psychology or reinforc*))) OR AB ((commun* N3 (service* or center* or centre* or network* or psychiatr* or psychology or reinforc*))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 35,735 |
| S13 | TI (((marital or marriage or family or families or support* or group or couple* or interpersonal) N2 therap*)) OR AB (((marital or marriage or family or families or support* or group or couple* or interpersonal) N2 therap*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 24,898 |
| S12 | TI ((cope or (coping N2 skill*) or "self-control training" or "structured counsel*") OR AB ((cope or (coping N2 skill*) or "self-control training" or "structured counsel*") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 19,936 |
| S11 | (MH "Adaptation, Psychological+") OR (MH "Counseling+") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 79,606 |
| S10 | (MH "Behavior Therapy+") OR (TI (social N2 skil*) OR AB (social N2 skil*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 44,879 |
| S9 | TI (sociali?ation or (social N2 adjust*) or (social N2 support*)) OR AB (sociali?ation or (social N2 adjust*) or (social N2 support*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 44,046 |
| S8 | TI ((cognitive N2 therap*) or (behavio* N2 therap*)) OR AB ((cognitive N2 therap*) or (behavio* N2 therap*)) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 18,932 |
| S7 | (MH "Psychotherapy+") OR ((TI(psychotherap* or "psycho-therap*")) OR (AB(psychotherap* or "psycho-therap*"))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 227,067 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S6 | S4 or S5 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 241,306 |
| S5 | (TI (("use" or using or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone))) OR (AB (("use" or using or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone))) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 18,538 |
| S4 | TI ((abuse* or addict* or abusing or dependen*)) OR AB ((abuse* or addict* or dependen* or abusing)) OR (MM "Substance Dependence") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 228,131 |
| S3 | S1 or S2 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search Database - CINAHL with Full Text | 82,881 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S2 | TI (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) OR AB (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or Ora-Morph or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 61,494 |
| S1 | (MH "Analgesics, Opioid+") OR (MH "Fentanyl+") OR (MH "Narcotics+") OR (MH "Opium+") | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/ Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL with Full Text | 59,313 |

## PsycINFO (via EbscoHost) – Date: Feb 9, 2023

2017 – 2023-03-09
Thursday, February 09, 2023 3:01:08 PM

| # | Query | Results |
|---|---|---|
| S48 | S47 NOT S46 | 2,799 |
| S47 | S41 AND S45 | 3,214 |
| S46 | S41 AND S45 | 415 |
| S45 | S2 OR S43 OR S44 | 25,786 |

| # | Query | Results |
|---|---|---|
| S44 | S1 AND S42 | 6,954 |
| S43 | TI (((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone))) OR AB ((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone)) OR KW ((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone))) | 24,127 |
| S42 | (DE “Addiction” OR DE “Drug Addiction” OR DE “Drug Abuse”) OR (DE “Substance Use Disorder” OR DE “Prescription Drug Misuse”) | 76,439 |
| S41 | S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 | 1,444,765 |
| S40 | (DE “Housing” OR DE “Assisted Living” OR DE “Dormitories” OR DE “Group Homes” OR DE “Retirement Communities” OR DE “Shelters”) or (DE “Mental Health Services” OR DE “Community Mental Health Services” OR DE “Psychological First Aid” OR DE “School Based Mental Health Services”) or (DE “Volunteers”) | 78,934 |
| S39 | (DE “Social Support”) or (DE “Psychosocial Rehabilitation” OR DE “Psychosocial Readjustment” OR DE “Therapeutic Social Clubs” OR DE “Vocational Rehabilitation”) or (DE “Social Programs” OR DE “Needle Exchange Programs” OR DE “Outreach Programs”) or (TI “income-assistance” OR AB “income-assistance” OR KW “income-assistance”) | 80,728 |
| S38 | TI ((housing or houses or volunteer* or “voluntary worker*” or wraparound or “wrap around” or “occupation* guidance”)) OR AB ((housing or houses or volunteer* or “voluntary worker*” or wraparound or “wrap around” or “occupation* guidance”) OR KW (housing or houses or volunteer* or “voluntary worker*” or wraparound or “wrap around” or “occupation* guidance”)) | 66,841 |
| S37 | (DE “Vocational Education”) or (DE “Occupational Guidance”) or (TI (vocation* or “individual placement and support” or “supported employment) OR AB (vocation* or “individual placement and support” or “supported employment) OR KW (vocation* or “individual placement and support” or “supported employment)) | 32,476 |
| S36 | (TI (“harm reduction” or “reduc* harm”) OR AB (“harm reduction” or “reduc* harm”) OR KW (“harm reduction” or “reduc* harm”)) or (DE “Harm Reduction”) | 7,640 |
| S35 | (TI ((education* OR literacy) near/2 (lecture* or program* or film* or intervention*)) OR AB ((education* OR literacy) near/2 (lecture* or program* or film* or intervention*)) OR KW ((education* OR literacy) near/2 (lecture* or program* or film* or intervention*))) | 30 |
| S34 | (TI (voucher* or reinforcement or “reinforc* schedule*”) OR AB (voucher* or reinforcement or “reinforc* schedule*”) OR KW (voucher* or reinforcement or “reinforc* schedule*”)) | 47,824 |

| # | Query | Results |
|---|---|---|
| S33 | (TI (biofeedback or "covert sensiti?ation" or "aversi* stimulation") OR AB (biofeedback or "covert sensiti?ation" or "aversi* stimulation") OR KW (biofeedback or "covert sensiti?ation" or "aversi* stimulation")) or (DE "Reinforcement" OR DE "Differential Reinforcement" OR DE "Negative Reinforcement" OR DE "Noncontingent Reinforcement" OR DE "Positive Reinforcement" OR DE "Primary Reinforcement" OR DE "Punishment" OR DE "Reinforcement Amounts" OR DE "Reinforcement Schedules" OR DE "Reward Learning" OR DE "Reward Sensitivity" OR DE "Rewards" OR DE "Secondary Reinforcement" OR DE "Self-Reinforcement" OR DE "Social Reinforcement") | 58,508 |
| S32 | (TI ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* near/2 drug)) OR AB ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* near/2 drug)) OR KW ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* near/2 drug)) or (DE "Electrical Stimulation" OR DE "Electrical Brain Stimulation" OR DE "Electroconvulsive Shock" OR DE "Nerve Stimulation") | 19,782 |
| S31 | (TI ("case care" or "contingency management" or "contingency therapy") OR AB ("case care" or "contingency management" or "contingency therapy") OR KW ("case care" or "contingency management" or "contingency therapy")) | 1,917 |
| S30 | (TI ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery") OR AB ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery") OR KW ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery")) | 10 |
| S29 | (TI (withdraw* or abstinen* or abstain*) OR AB (withdraw* or abstinen* or abstain*) OR KW (withdraw* or abstinen* or abstain*) | 65,181 |
| S28 | (TI ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*") OR AB ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*") OR KW ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*")) | 18,259 |
| S27 | (DE "Motivation" OR DE "Achievement Motivation" OR DE "Affiliation Motivation" OR DE "Agency" OR DE "Animal Motivation" OR DE "Aspirations" OR DE "Craving" OR DE "Drug Seeking" OR DE "Educational Incentives" OR DE "Employee Motivation" OR DE "Extrinsic Motivation" OR DE "Fear of Success" OR DE "Goals" OR DE "Hunger" OR DE "Incentives" OR DE "Intrinsic Motivation" OR DE "Monetary Incentives" OR DE "Needs" OR DE "Procrastination" OR DE "Self-Expansion" OR DE "Sex Drive" OR DE "Social Motivation" OR DE "Temptation" OR DE "Thirst" OR DE "Volition") or TI (incentive* or motivation*) or AB (incentive* or motivation*) or KW (incentive* or motivation*)/freq=2 | 245,557 |
| S26 | TI (peerneedle* or "peer needle*" or "relapse prevention") or AB (peerneedle* or "peer needle*" or "relapse prevention") or KW (peerneedle* or "peer needle*" or "relapse prevention") | 4,780 |
| S25 | TI (((needle* or syringe*) near/3 exchang*) or (safe* N1 injection*)) or AB (((needle* or syringe*) near/3 exchang*) or (safe* N1 injection*)) or KW (((needle* or syringe*) near/3 exchang*) or (safe* N1 injection*)) | 201 |
| S24 | ((MM "Relaxation Therapy") OR (DE "Rehabilitation" OR DE "Cognitive Rehabilitation" OR DE "Criminal Rehabilitation" OR DE "Neuropsychological Rehabilitation" OR DE "Neurorehabilitation" OR DE "Occupational Therapy" OR DE "Physical Therapy" OR DE "Psychosocial Rehabilitation" OR DE "Rehabilitation Centers" OR DE "Telerehabilitation")) OR (MM "Bibliotherapy") | 50,440 |
| S23 | DE "Support Groups" OR DE "Twelve Step Programs" or MM "Faith Healing" or (MM "Prayer") OR (MM "Meditation") | 11,929 |
| S22 | TI ((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social) near/2 (treatment or therap* or program* or intervention* or service*)) or AB((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social) near/2 (treatment or therap* or program* or intervention* or service*)) or KW ((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social) near/2 (treatment or therap* or program* or intervention* or service*)) | 18 |
| S21 | TI (psychological* near/2 debrief*) or AB (psychological* near/2 debrief*) or KW (psychological* near/2 debrief*) | 39 |
| S20 | TI ("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanalys* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor) or AB ("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanalys* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor) or KW ("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanalys* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor) | 479,231 |
| S19 | TI (((mutual or peer or recovery) near support) or (stress near/2 manag*)) or AB (((mutual or peer or recovery) adj support) or (stress near/2 manag*)) or KW (((mutual or peer or recovery) near support) or (stress near/2 manag*)) | 38 |
| S18 | TI ("12 step" or "twelve-step") or AB ("12 step" or "twelve-step") or KW ("12 step" or "twelve-step") or DE "Self-Help Techniques" OR DE "Self-Management" or TI ("self-help" or (support* adj2 group*)) or AB ("self-help" or (support* adj2 group*)) or KW ("self-help" or (support* adj2 group*)) | 19,110 |

| # | Query | Results |
|---|---|---|
| S17 | TI ("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*") or AB ("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*") or KW ("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*") or MM "Outreach Programs" | 1,211 |
| S16 | TI ("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical") or AB ("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical") or KW ("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical") | 19,869 |
| S15 | TI (((art or music or sound or colo?r) near/2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap*or "psychedelic therapy")) or AB (((art or music or sound or colo?r) near/2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap*or "psychedelic therapy")) or KW (((art or music or sound or colo?r) near/2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap*or "psychedelic therapy")) | 119,774 |
| S14 | DE "Alternative Medicine" OR DE "Acupuncture" OR DE "Aromatherapy" OR DE "Faith Healing" OR DE "Folk Medicine" OR DE "Shamanism" or TI ((traditional* or Native* or aboriginal* or indigenous or ceremon*) near/2 (heal* or medicine or medical*)) or AB ((traditional* or Native* or aboriginal* or indigenous or ceremon*) near/2 (heal* or medicine or medical*)) or KW ((traditional* or Native* or aboriginal* or indigenous or ceremon*) near/2 (heal* or medicine or medical*)) | 9,754 |
| S13 | MM "Mind Body Therapy" or TI ("relaxation therap*" or "relaxation technique*" or "talk therapy") or AB ("relaxation therap*" or "relaxation technique*" or "talk therapy") or KW ("relaxation therap*" or "relaxation technique*" or "talk therapy") | 2,520 |
| S12 | TI ("community mental health" or "community care" or "therapeutic communit*" or "confrontational intervention*" or "assertive community treatment" or "clubhouse*" or "early intervention*") or AB ("community mental health" or "community care" or "therapeutic communit*" or "confrontational intervention*" or "assertive community treatment" or "clubhouse*" or "early intervention*") or KW ("community mental health" or "community care" or "therapeutic communit*" or "confrontational intervention*" or "assertive community treatment" or "clubhouse*" or "early intervention*") | 36,424 |
| S11 | TI (commun* near/3 (service* or center* or centre* or network* or psychiatr* or psychology or reinforc*)) or AB (commun* near/3 (service* or center* or centre* or network* or psychiatr* or psychology or reinforc*)) or KW (commun* near/3 (service* or center* or centre* or network* or psychiatr* or psychology or reinforc*)) | 1 |
| S10 | MM "Couples Therapy" or (DE "Family Therapy" OR DE "Conjoint Therapy" OR DE "Strategic Family Therapy" OR DE "Structural Family Therapy") | 29,766 |
| S9 | TI ((marital or marriage or family or families or support* or group or couple* or interpersonal) near/2 therap*) or AB ((marital or marriage or family or families or support* or group or couple* or interpersonal) near/2 therap*) or KW ((marital or marriage or family or families or support* or group or couple* or interpersonal) near/2 therap*) | 267,637 |
| S8 | TI (cope or (coping near/2 skill*) or "self-control training" or "structured counsel*") or AB (cope or (coping near/2 skill*) or "self-control training" or "structured counsel*") or KW (cope or (coping near/2 skill*) or "self-control training" or "structured counsel*") | 32,340 |
| S7 | (MM "Cognitive Therapy" OR DE "Coping Behavior" OR DE "Coping Style") or (DE "Counseling" OR DE "Community Counseling" OR DE "Cross Cultural Counseling" OR DE "Educational Counseling" OR DE "Genetic Counseling" OR DE "Gerontological Counseling" OR DE "Grief Counseling" OR DE "Group Counseling" OR DE "Marriage Counseling" OR DE "Microcounseling" OR DE "Multicultural Counseling" OR DE "Occupational Guidance" OR DE "Pastoral Counseling" OR DE "Peer Counseling" OR DE "Premarital Counseling" OR DE "Psychotherapeutic Counseling" OR DE "Rehabilitation Counseling" OR DE "School Counseling") | 132,019 |
| S6 | MM "Cognitive Therapy" or TI (social near/2 skil*) or AB (social near/2 skil*) or KW (social near/2 skil*) | 4 |
| S5 | TI (sociali?ation or (social near/2 adjust*) or (social near/2 support*)) or AB (sociali?ation or (social near/2 adjust*) or (social near/2 support*)) or KW (sociali?ation or (social near/2 adjust*) or (social near/2 support*)) or (DE "Socialization" OR DE "Political Socialization" OR DE "Professional Socialization" OR DE "Reintegration") | 32,885 |
| S4 | (TI (cognitive near/2 therap*) or (behavio* near/2 therap*))) or (AB ((cognitive near therap*) or (behavio* near therap*))) or (KW ((cognitive near/2 therap*) or (behavio* near therap*))) | 8 |

| # | Query | Results |
|---|---|---|
| S3 | (DE "Psychotherapy" OR DE "Adlerian Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Affirmative Therapy" OR DE "Analytical Psychotherapy" OR DE "Autogenic Training" OR DE "Brief Psychotherapy" OR DE "Brief Relational Therapy" OR DE "Child Psychotherapy" OR DE "Client Centered Therapy" OR DE "Conversion Therapy" OR DE "Couples Therapy" OR DE "Eclectic Psychotherapy" OR DE "Emotion Focused Therapy" OR DE "Existential Therapy" OR DE "Experiential Psychotherapy" OR DE "Expressive Psychotherapy" OR DE "Eye Movement Desensitization Therapy" OR DE "Feminist Therapy" OR DE "Geriatric Psychotherapy" OR DE "Gestalt Therapy" OR DE "Group Psychotherapy" OR DE "Guided Imagery" OR DE "Humanistic Psychotherapy" OR DE "Hypnotherapy" OR DE "Individual Psychotherapy" OR DE "Insight Therapy" OR DE "Integrative Psychotherapy" OR DE "Interpersonal Psychotherapy" OR DE "Logotherapy" OR DE "Narrative Therapy" OR DE "Network Therapy" OR DE "Persuasion Therapy" OR DE "Primal Therapy" OR DE "Psychoanalysis" OR DE "Psychodrama" OR DE "Psychodynamic Psychotherapy" OR DE "Psychotherapeutic Counseling") OR (DE "Psychotherapeutic Techniques" OR DE "Rational Emotive Behavior Therapy" OR DE "Reality Therapy" OR DE "Relationship Therapy" OR DE "Solution Focused Therapy" OR DE "Strategic Therapy" OR DE "Supportive Psychotherapy" OR DE "Transactional Analysis" or DE "Psychotherapeutic Techniques" OR DE "Active Listening" OR DE "Animal Assisted Therapy" OR DE "Autogenic Training" OR DE "Brief Relational Therapy" OR DE "Centering" OR DE "Cotherapy" OR DE "Dream Analysis" OR DE "Empty Chair Technique" OR DE "Ericksonian Psychotherapy" OR DE "Free Association" OR DE "Guided Imagery" OR DE "Life Review" OR DE "Mirroring" OR DE "Morita Therapy" OR DE "Motivational Interviewing" OR DE "Mutual Storytelling Technique" OR DE "Network Therapy" OR DE "Paradoxical Techniques" OR DE "Psychodrama") or TI (psychotherap* or "psycho-therap*") or (AB (psychotherapy* or "psycho-therap*") or KW (psychotherap* or "psycho-therap*") | 246,441 |
| S2 | MM "Heroin Addiction" | 277 |
| S1 | (DE "Opiates" OR DE "Codeine" OR DE "Heroin" OR DE "Morphine" OR DE "Papaverine") OR (DE "Narcotic Drugs" OR DE "Opioid Analgesics") | 28,385 |

## PsychINFO search update – Date: Sept 13, 2023

EBSCOhost

Print Search History
Wednesday, September 13, 2023 4:32:38 PM

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S77 | S75 NOT S76 | Limiters - Publication Year: 2017-2023; Population Group: Human<br>Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - APA PsycInfo | 848 |
| S76 | S8 AND S61 | Limiters - Publication Year: 2017-2023; Population Group: Human<br>Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - APA PsycInfo | 2,661 |
| S75 | S70 NOT S74 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - APA PsycInfo | 3,911 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S74 | S71 NOT S73 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 683 |
| S73 | S71 AND S72 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 96 |
| S72 | S14 AND S61 | Limiters - Publication Year: 2017-2023; Population Group: Human Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 3,509 |
| S71 | S14 AND S61 | Limiters - Publication Year: 2017-2023; Population Group: Animal Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 779 |
| S70 | S14 AND S61 | Limiters - Publication Year: 2017-2023 Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 4,594 |
| S69 | S8 AND S61 | Limiters - Publication Year: 2017-2023 Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 3,559 |
| S68 | S67 NOT S66 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 3,345 |
| S67 | S61 AND S65 | Limiters - Publication Year: 2017-2023 Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 3,807 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S66 | S61 AND S65 | Limiters - Publication Year: 2017-2023; Population Group: Animal<br>Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 462 |
| S65 | S19 OR S63 OR S64 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 26,707 |
| S64 | S16 AND S62 | Expanders - Apply related words; Apply equivalent subjects<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 7,109 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S63 | TI (((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone))) OR AB ((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone)) OR KW ((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 25,009 |
| S62 | (DE “Addiction” OR DE “Drug Addiction” OR DE “Drug Abuse”) OR (DE “Substance Use Disorder” OR DE “Prescription Drug Misuse”) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 78,280 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S61 | S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 1,580,037 |
| S60 | (DE "Housing" OR DE "Assisted Living" OR DE "Dormitories" OR DE "Group Homes" OR DE "Retirement Communities" OR DE "Shelters") or (DE "Mental Health Services" OR DE "Community Mental Health Services" OR DE "Psychological First Aid" OR DE "School Based Mental Health Services") or (DE "Volunteers") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 80,935 |
| S59 | (DE "Social Support") or (DE "Psychosocial Rehabilitation" OR DE "Psychosocial Readjustment" OR DE "Therapeutic Social Clubs" OR DE "Vocational Rehabilitation") or (DE "Social Programs" OR DE "Needle Exchange Programs" OR DE "Outreach Programs") or (TI "income-assistance" OR AB "income-assistance" OR KW "income-assistance") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 82,908 |
| S58 | TI ((housing or houses or volunteer* or "voluntary worker*" or wraparound or "wrap around" or "occupation* guidance")) OR AB ((housing or houses or volunteer* or "voluntary worker*" or wraparound or "wrap around" or "occupation* guidance") OR KW (housing or houses or volunteer* or "voluntary worker*" or wraparound or "wrap around" or "occupation* guidance")) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 68,532 |
| S57 | (DE "Vocational Education") or (DE "Occupational Guidance") or (TI (vocation* or "individual placement and support" or "supported employment) OR AB (vocation* or "individual placement and support" or "supported employment) OR KW (vocation* or "individual placement and support" or "supported employment)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 32,749 |
| S56 | (TI ("harm reduction" or "reduc* harm") OR AB ("harm reduction" or "reduc* harm") OR KW ("harm reduction" or "reduc* harm")) or (DE "Harm Reduction") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 8,076 |
| S55 | (TI ((education* OR literacy) N2 (lecture* or program* or film* or intervention*)) OR AB ((education* OR literacy) N2 (lecture* or program* or film* or intervention*)) OR KW ((education* OR literacy) N2 (lecture* or program* or film* or intervention*))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 63,629 |
| S54 | (TI (voucher* or reinforcement or "reinforc* schedule*") OR AB (voucher* or reinforcement or "reinforc* schedule*") OR KW (voucher* or reinforcement or "reinforc* schedule*")) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 48,483 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S53 | (TI (biofeedback or "covert sensiti?ation" or "aversi* stimulation") OR AB (biofeedback or "covert sensiti?ation" or "aversi* stimulation") OR KW (biofeedback or "covert sensiti?ation" or "aversi* stimulation")) or (DE "Reinforcement" OR DE "Differential Reinforcement" OR DE "Negative Reinforcement" OR DE "Noncontingent Reinforcement" OR DE "Positive Reinforcement" OR DE "Primary Reinforcement" OR DE "Punishment" OR DE "Reinforcement Amounts" OR DE "Reinforcement Schedules" OR DE "Reward Learning" OR DE "Reward Sensitivity" OR DE "Rewards" OR DE "Secondary Reinforcement" OR DE "Self-Reinforcement" OR DE "Social Reinforcement") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 59,849 |
| S52 | (TI ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* N2 drug)) OR AB ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* N2 drug)) OR KW ("electrostimulation therap*" or "electro-therap*" or electrotherap* or "electric* stimulation" or (stimulat* N2 drug)) or (DE "Electrical Stimulation" OR DE "Electrical Brain Stimulation" OR DE "Electroconvulsive Shock" OR DE "Nerve Stimulation") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 20,599 |
| S51 | (TI ("case care" or "contingency management" or "contingency therapy") OR AB ("case care" or "contingency management" or "contingency therapy") OR KW ("case care" or "contingency management" or "contingency therapy")) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 1,953 |
| S50 | (TI ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery") OR AB ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery") OR KW ("Narcotics Anonymous" or "Methadone Anonymous" or LifeRing or "SMART Recovery")) | Expanders - Apply related words; Apply equivalent subjects Search modes - SmartText Searching | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 10 |
| S49 | (TI (withdraw* or abstinen* or abstain*) OR AB (withdraw* or abstinen* or abstain*) OR KW (withdraw* or abstinen* or abstain*) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 66,388 |
| S48 | (TI ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*") OR AB ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*") OR KW ("prevention program*" or "supervis* consumption" or "formal intervention*" or "motivate* or enhance*")) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 18,725 |
| S47 | (DE "Motivation" OR DE "Achievement Motivation" OR DE "Affiliation Motivation" OR DE "Agency" OR DE "Animal Motivation" OR DE "Aspirations" OR DE "Craving" OR DE "Drug Seeking" OR DE "Educational Incentives" OR DE "Employee Motivation" OR DE "Extrinsic Motivation" OR DE "Fear of Success" OR DE "Goals" OR DE "Hunger" OR DE "Incentives" OR DE "Intrinsic Motivation" OR DE "Monetary Incentives" OR DE "Needs" OR DE "Procrastination" OR DE "Self-Expansion" OR DE "Sex Drive" OR DE "Social Motivation" OR DE "Temptation" OR DE "Thirst" OR DE "Volition") or TI (incentive* or motivation*) or AB (incentive* or motivation*) or KW (incentive* or motivation*)/freq=2 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 252,132 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S46 | TI (peerneedle* or "peer needle*" or "relapse prevention") or AB (peerneedle* or "peer needle*" or "relapse prevention") or KW (peerneedle* or "peer needle*" or "relapse prevention") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 4,862 |
| S45 | TI (((needle* or syringe*) N3 exchang*) or (safe* N1 injection*)) or AB (((needle* or syringe*) N3 exchang*) or (safe* N1 injection*)) or KW (((needle* or syringe*) N3 exchang*) or (safe* N1 injection*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 1,218 |
| S44 | ((MM "Relaxation Therapy") OR (DE "Rehabilitation" OR DE "Cognitive Rehabilitation" OR DE "Criminal Rehabilitation" OR DE "Neuropsychological Rehabilitation" OR DE "Neurorehabilitation" OR DE "Occupational Therapy" OR DE "Physical Therapy" OR DE "Psychosocial Rehabilitation" OR DE "Rehabilitation Centers" OR DE "Telerehabilitation")) OR (MM "Bibliotherapy") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 51,859 |
| S43 | DE "Support Groups" OR DE "Twelve Step Programs" or MM "Faith Healing" or (MM "Prayer") OR (MM "Meditation") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 12,259 |
| S42 | TI ((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social) N2 (treatment or therap* or program* or intervention* or service*)) or AB((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social) N2 (treatment or therap* or program* or intervention* or service*)) or KW ((behavio* or psychosocial or "psycho-social" or psychoeducation* or "psycho-education*" or psychiatric or psychological or social) N2 (treatment or therap* or program* or intervention* or service*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - SmartText Searching | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 18 |
| S41 | TI (psychological* N2 debrief*) or AB (psychological* N2 debrief*) or KW (psychological* N2 debrief*) | Expanders - Apply related words; Apply equivalent subjects Search modes - SmartText Searching | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 72 |
| S40 | TI ("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanalys* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor) or AB ("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanalys* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor) or KW ("problem solving" or operant* or "discussion group*" or "insight oriented" or "client centered" or counsel* or insight* or paradox* or psychoanalys* or psychodynamic* or psychodrama* or "psycho-drama*" or "role play*" or transactional or befriend* or mentor* or sponsor) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 492,058 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S39 | TI (((mutual or peer or recovery) N1 support) or (stress N2 manag*)) or AB (((mutual or peer or recovery) N1 support) or (stress N2 manag*)) or KW (((mutual or peer or recovery) N1 support) or (stress N1 manag*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - SmartText Searching | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 56 |
| S38 | TI ("12 step" or "twelve-step") or AB ("12 step" or "twelve-step") or KW ("12 step" or "twelve-step") or DE "Self-Help Techniques" OR DE "Self-Management" or TI ("self-help" or (support* N2 group*)) or AB ("self-help" or (support* N2 group*)) or KW ("self-help" or (support* N2 group*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 38,033 |
| S37 | TI ("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*") or AB ("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*") or KW ("street nurse*" or "street outreach" or "street clinic*" or "safer inhalation" or "crack kit*") or MM "Outreach Programs" | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 1,245 |
| S36 | TI ("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical") or AB ("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical") or KW ("case management" or outreach or nonpharmacological or "non-pharmacological" or nonpharmaceutical or "non-pharmaceutical") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 20,600 |
| S35 | TI (((art or music or sound or colo?r) N2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap*or "psychedelic therapy")) or AB (((art or music or sound or colo?r) N2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap*or "psychedelic therapy")) or KW (((art or music or sound or colo?r) N2 therap*) or (relig* or prayer* or spiritual* or meditat* or aromatherap* or bibliotherap*or "psychedelic therapy")) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 136,694 |
| S34 | DE "Alternative Medicine" OR DE "Acupuncture" OR DE "Aromatherapy" OR DE "Faith Healing" OR DE "Folk Medicine" OR DE "Shamanism" or TI ((traditional* or Native* or aboriginal* or indigenous or ceremon*) near/2 (heal* or medicine or medical*)) or AB ((traditional* or Native* or aboriginal* or indigenous or ceremon*) near/2 (heal* or medicine or medical*)) or KW ((traditional* or Native* or aboriginal* or indigenous or ceremon*) near/2 (heal* or medicine or medical*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 10,007 |
| S33 | MM "Mind Body Therapy" or TI ("relaxation therap*" or "relaxation technique*" or "talk therapy") or AB ("relaxation therap*" or "relaxation technique*" or "talk therapy") or KW ("relaxation therap*" or "relaxation technique*" or "talk therapy") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 2,606 |
| S32 | TI ("community mental health" or "community care" or "therapeutic communit*" or "confrontational intervention*" or "assertive community treatment" or "clubhouse*" or "early intervention*") or AB ("community mental health" or "community care" or "therapeutic communit*" or "confrontational intervention*" or "assertive community treatment" or "clubhouse*" or "early intervention*") or KW ("community mental health" or "community care" or "therapeutic communit*" or "confrontational intervention*" or "assertive community treatment" or "clubhouse*" or "early intervention*") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 37,384 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S31 | TI (commun* N3 (service* OR center* OR centre* OR network* OR psychiatr* OR psychology OR reinforc*)) or AB (commun* N3 (service* OR center* OR centre* OR network* OR psychiatr* OR psychology OR reinforc*)) or KW (commun* N3 (service* OR center* OR centre* OR network* OR psychiatr* OR psychology OR reinforc*)) | Expanders - Apply related words; Apply equivalent subjects Search modes - SmartText Searching | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 1 |
| S30 | MM "Couples Therapy" or (DE "Family Therapy" OR DE "Conjoint Therapy" OR DE "Strategic Family Therapy" OR DE "Structural Family Therapy") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 30,222 |
| S29 | TI ((marital or marriage or family or families or support* or group or couple* or interpersonal) near/2 therap*) or AB ((marital or marriage or family or families or support* or group or couple* or interpersonal) near/2 therap*) or KW ((marital or marriage or family or families or support* or group or couple* or interpersonal) near/2 therap*) | Expanders - Apply related words; Apply equivalent subjects Search modes - SmartText Searching | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 274,749 |
| S28 | TI (cope or (coping near/2 skill*) or "self-control training" or "structured counsel*") or AB (cope or (coping near/2 skill*) or "self-control training" or "structured counsel*") or KW (cope or (coping near/2 skill*) or "self-control training" or "structured counsel*") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 33,465 |
| S27 | (MM "Cognitive Therapy" OR DE "Coping Behavior" OR DE "Coping Style") or (DE "Counseling" OR DE "Community Counseling" OR DE "Cross Cultural Counseling" OR DE "Educational Counseling" OR DE "Genetic Counseling" OR DE "Gerontological Counseling" OR DE "Grief Counseling" OR DE "Group Counseling" OR DE "Marriage Counseling" OR DE "Microcounseling" OR DE "Multicultural Counseling" OR DE "Occupational Guidance" OR DE "Pastoral Counseling" OR DE "Peer Counseling" OR DE "Premarital Counseling" OR DE "Psychotherapeutic Counseling" OR DE "Rehabilitation Counseling" OR DE "School Counseling") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 134,810 |
| S26 | MM "Cognitive Therapy" or TI (social near/2 skil*) or AB (social near/2 skil*) or KW (social near/2 skil*) | Expanders - Apply related words; Apply equivalent subjects Search modes - SmartText Searching | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 4 |
| S25 | TI (sociali?ation or (social near/2 adjust*) or (social near/2 support*)) or AB (sociali?ation or (social near/2 adjust*) or (social near/2 support*)) or KW (sociali?ation or (social near/2 adjust*) or (social near/2 support*)) or (DE "Socialization" OR DE "Political Socialization" OR DE "Professional Socialization" OR DE "Reintegration") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 33,704 |
| S24 | (TI (cognitive N2 therap*) OR (behavio* N2 therap*))) OR (AB ((cognitive N1 therap*) or (behavio* N1 therap*))) OR (KW ((cognitive N2 therap*) or (behavio* N1 therap*))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 103,499 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S23 | (DE "Psychotherapy" OR DE "Adlerian Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Affirmative Therapy" OR DE "Analytical Psychotherapy" OR DE "Autogenic Training" OR DE "Brief Psychotherapy" OR DE "Brief Relational Therapy" OR DE "Child Psychotherapy" OR DE "Client Centered Therapy" OR DE "Conversion Therapy" OR DE "Couples Therapy" OR DE "Eclectic Psychotherapy" OR DE "Emotion Focused Therapy" OR DE "Existential Therapy" OR DE "Experiential Psychotherapy" OR DE "Expressive Psychotherapy" OR DE "Eye Movement Desensitization Therapy" OR DE "Feminist Therapy" OR DE "Geriatric Psychotherapy" OR DE "Gestalt Therapy" OR DE "Group Psychotherapy" OR DE "Guided Imagery" OR DE "Humanistic Psychotherapy" OR DE "Hypnotherapy" OR DE "Individual Psychotherapy" OR DE "Insight Therapy" OR DE "Integrative Psychotherapy" OR DE "Interpersonal Psychotherapy" OR DE "Logotherapy" OR DE "Narrative Therapy" OR DE "Network Therapy" OR DE "Persuasion Therapy" OR DE "Primal Therapy" OR DE "Psychoanalysis" OR DE "Psychodrama" OR DE "Psychodynamic Psychotherapy" OR DE "Psychotherapeutic Counseling") OR (DE "Psychotherapeutic Techniques" OR DE "Rational Emotive Behavior Therapy" OR DE "Reality Therapy" OR DE "Relationship Therapy" OR DE "Solution Focused Therapy" OR DE "Strategic Therapy" OR DE "Supportive Psychotherapy" OR DE "Transactional Analysis" or DE "Psychotherapeutic Techniques" OR DE "Active Listening" OR DE "Animal Assisted Therapy" OR DE "Autogenic Training" OR DE "Brief Relational Therapy" OR DE "Centering" OR DE "Cotherapy" OR DE "Dream Analysis" OR DE "Empty Chair Technique" OR DE "Ericksonian Psychotherapy" OR DE "Free Association" OR DE "Guided Imagery" OR DE "Life Review" OR DE "Mirroring" OR DE "Morita Therapy" OR DE "Motivational Interviewing" OR DE "Mutual Storytelling Technique" OR DE "Network Therapy" OR DE "Paradoxical Techniques" OR DE "Psychodrama") or TI (psychotherap* or "psycho-therap*") or (AB (psychotherapy* or "psycho-therap*") or KW (psychotherap* or "psycho-therap*") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 250,976 |
| S22 | S19 or S20 or S21 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 415,177 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S21 | TI (((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone))) OR AB ((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone)) OR KW ((“use” or using or disorder* or abuse* or dependen* or addict* or abusing) N3 (“multiple drug*” or polydrug* or “street drug*” or “designer drug*” or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or “Co-Gesic” or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or “MS Contin” or Nalbuphine or narcotic* or Norco or Nubain or “Nucynta ER” or “Opana ER” or opiate* or opioid* or opium or Onsolis or Oramorph or “Ora-Morph” or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or “Oxymorphone hydrochloride” or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or “Targiniq ER” or Tramadol or TussiCaps or Tussionex or “Tuzistra XR” or Vicodin or Vicoprofen or Vituz or “Xartemis XR” or Xodol or “Xtampza ER” or “Zohydro ER” or Zolvit or Zutripro or Zydone))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 25,009 |
| S20 | TI (abuse* or dependen* or addict* or abusing) or AB (abuse* or dependen* or addict* or abusing) or KW (abuse* or dependen* or addict* or abusing) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 407,547 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S19 | MM "Heroin Addiction" | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 7,326 |
| S18 | S16 or S17 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 55,056 |
| S17 | TI (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co-Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) or AB (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co-Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) or KW (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co-Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 50,907 |
| S16 | (DE "Opiates" OR DE "Codeine" OR DE "Heroin" OR DE "Morphine" OR DE "Papaverine") OR (DE "Narcotic Drugs" OR DE "Opioid Analgesics") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 29,046 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S15 | S14 NOT S8 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 8,256 |
| S14 | S3 OR S4 OR S13 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 34,421 |
| S13 | S11 AND S12 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 32,111 |
| S12 | S1 OR S9 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 55,908 |
| S11 | S2 OR S5 OR S10 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 434,339 |
| S10 | (DE “Addiction” OR DE “Drug Addiction” OR DE “Drug Abuse”) OR (DE “Substance Use Disorder” OR DE “Prescription Drug Misuse”) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 78,280 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S9 | TI (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co-Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) or AB (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co-Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) or KW (Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or "Co-Gesic" or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or "Targiniq ER" or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 50,907 |
| S8 | S3 OR S4 OR S7 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 26,165 |
| S7 | S1 AND S6 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 17,004 |
| S6 | S2 OR S5 | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 419,010 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S5 | TI (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) OR AB (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) OR KW (PWUD or PWID or "people who use drugs" or (("use" or using or users) N3 (illicit* or illegal* or inject*))) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 17,273 |
| S4 | DE "Opioid Use Disorder" OR DE "Heroin Use Disorder" OR DE "Morphine Dependence" | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 6,335 |
| S3 | TI ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) OR AB ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) OR KW ((addict* or dependen* or abuse* or abusing or disorder*) N3 ("multiple drug*" or polydrug* or "street drug*" or "designer drug*" or Abstral or Actiq or Alfentanil or Anexsia or Astramorph or Avinza or Butrans or carfentan* or Codeine or Co-Gesic or Demerol or Diamorphine or Dilaudid or Dolophine or Duragesic or Embeda or Endocet or Exalgo or Fentanyl or Fentora or heroin or Hycet or Hycodan or Hydrocodone or Hydromet or hydromorphone or Hysingla or Ibudone or Kadian or Liquicet or Lorcet or Lortab or Maxidone or meperidine or Morphabond or "MS Contin" or Nalbuphine or narcotic* or Norco or Nubain or "Nucynta ER" or "Opana ER" or opiate* or opioid* or opium or Onsolis or Oramorph or "Ora-Morph" or Oxaydo or Oxecta or Oxycet or oxycodone or OxyContin or "Oxymorphone hydrochloride" or Palladone or Pentazocine or Percocet or Percodan or Pethidine or Reprexain or Rezira or Roxanol* or Roxicet or Roxicodone or Roxycodone or Sublimaze or Sufentanil or Tapentadol or Targiniq ER or Tramadol or TussiCaps or Tussionex or "Tuzistra XR" or Vicodin or Vicoprofen or Vituz or "Xartemis XR" or Xodol or "Xtampza ER" or "Zohydro ER" or Zolvit or Zutripro or Zydone)) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 17,630 |

| # | Query | Limiters/Expanders | Last Run Via | Results |
|---|---|---|---|---|
| S2 | TI (abuse* or dependen* or addict* or abusing) or AB (abuse* or dependen* or addict* or abusing) or KW (abuse* or dependen* or addict* or abusing) | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 407,547 |
| S1 | (DE "Opiates" OR DE "Codeine" OR DE "Endogenous Opiates" OR DE "Heroin" OR DE "Morphine" OR DE "Papaverine") OR (DE "Opiates" OR DE "Narcotic Drugs" OR DE "Narcotic Agonists" OR DE "Narcotic Antagonists" OR DE "Opiates" OR DE "Opioid Analgesics") | Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo | 32,299 |

## Embase (via Elsevier) – Date: Feb 14, 2023

1946 – 2023-02-14

| # | Query | Results |
|---|---|---|
| 110 | #109 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) | 2,345 |
| 109 | #107 NOT #108 | 14,146 |
| 108 | #107 AND [conference abstract]/lim | 3,998 |
| 107 | #103 NOT #106 | 18,144 |
| 106 | #104 NOT (#104 AND #105) | 3,218 |
| 105 | 'human'/mj | 689,373 |
| 104 | 'animal'/mj | 3,251 |
| 103 | #63 AND #102 | 40,864 |
| 102 | #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 | 3,920,399 |
| 101 | 'animal assisted therapy'/exp/mj | 903 |
| 100 | 'housing'/exp/mj OR 'community care'/exp/mj OR 'volunteer'/exp/mj | 79,188 |
| 99 | 'social care'/exp/mj OR 'income assistance':ti,ab,kw | |
| 98 | housing:ti,ab,kw OR houses:ti,ab,kw OR volunteer*:ti,ab,kw OR 'voluntary worker*':ti,ab,kw OR wraparound:ti,ab,kw OR 'wrap around':ti,ab,kw OR ((occupation* NEAR/1 guidance):ti,ab,kw) | 350,213 |
| 97 | 'vocational education'/exp/mj OR 'vocational rehabilitation'/exp/mj OR 'vocational guidance'/exp/mj OR (((vocation* OR 'individual placement') NEAR/2 support*):ti,ab,kw) OR 'supported employment':ti,ab,kw | 13,836 |
| 96 | 'harm reduction':ti,ab,kw OR ((reduc* NEAR/2 harm):ti,ab,kw) OR 'harm reduction'/exp/mj | 12,043 |
| 95 | ((education* OR literacy) NEAR/2 (lecture* OR program* OR film* OR intervention*)):ti,ab,kw | 98,016 |
| 94 | voucher*:ti,ab,kw OR reinforcement:ti,ab,kw OR ((reinforc* NEAR/2 schedule*):ti,ab,kw) | 52,759 |
| 93 | biofeedback:ti,ab,kw OR 'covert sensiti?ation':ti,ab,kw OR ((aversi* NEAR/1 stimulation):ti,ab,kw) OR 'reinforcement (psychology)'/exp/mj | 44,083 |
| 92 | 'electrostimulation therap*':ti,ab,kw OR 'electrotherap*':ti,ab,kw OR electrotherap*:ti,ab,kw OR ((electric* NEAR/2 stimulation):ti,ab,kw) OR ((stimulat* NEAR/2 drug):ti,ab,kw) OR 'electrotherapy'/exp/mj | 208,148 |
| 91 | 'case care':ti,ab,kw OR 'contingency management':ti,ab,kw OR 'contingency therapy':ti,ab,kw | 1,725 |
| 90 | 'narcotics anonymous':ti,ab,kw OR 'methadone anonymous':ti,ab,kw OR lifering:ti,ab,kw OR 'smart recovery':ti,ab,kw | 221 |

| # | Query | Results |
|---|---|---|
| 89 | ((withdraw* OR abstain* OR abstinance) NEAR/2 (program* OR intervention OR 'use' OR 'using' OR therap* OR support*)):ti,ab,kw | 7,411 |
| 88 | ('prevention program*':ti,ab,kw OR supervis*:ti,ab,kw) AND consumption:ti,ab,kw OR 'formal intervention*':ti,ab,kw | 3,274 |
| 87 | 'motivation'/exp/mj OR incentiv*:ti,ab,kw OR motivation*:ti,ab,kw | 204,578 |
| 86 | 'preventive health service'/exp/mj | 13,174 |
| 85 | peerneedle*:ti,ab,kw OR 'peer needle*':ti,ab,kw OR 'relapse prevention':ti,ab,kw | 5,420 |
| 84 | (((needle* OR syringe*) NEAR/3 exchang*):ti,ab,kw) OR ((safe* NEAR/1 injection*):ti,ab,kw) | 3,299 |
| 83 | ((behavio* OR psychosocial OR 'psycho social' OR psychoeducation* OR 'psycho education*' OR psychiatric OR psychological OR social) NEAR/2 (treatment OR therap* OR program* OR intervention* OR service*)):ti,ab,kw | 175,808 |
| 82 | (psychological* NEAR/2 debrief*):ti,ab,kw | 231 |
| 81 | 'problem solving':ti,ab,kw OR operant*:ti,ab,kw OR 'discussion group*':ti,ab,kw OR 'insight oriented':ti,ab,kw OR 'client centered':ti,ab,kw OR counsel*:ti,ab,kw OR insight*:ti,ab,kw OR paradox*:ti,ab,kw OR psychoanalys*:ti,ab,kw OR psychodrama*:ti,ab,kw OR psychodynamic*:ti,ab,kw OR 'psycho drama*':ti,ab,kw OR 'role play*':ti,ab,kw OR transactional:ti,ab,kw OR befriend*:ti,ab,kw OR mentor*:ti,ab,kw OR sponsor:ti,ab,kw | 1,050,145 |
| 80 | (((mutual OR peer OR recovery) NEAR/1 support):ti,ab,kw) OR ((stress NEAR/2 manag*):ti,ab,kw) OR 'stress management'/exp/mj | 23,263 |
| 79 | '12 step':ti,ab,kw OR 'twelve step':ti,ab,kw OR ((support* NEAR/2 group*):ti,ab,kw) OR 'self help'/exp/mj OR 'self help':ti,ab,kw | 38,085 |
| 78 | 'street nurse*':ti,ab,kw OR 'street outreach':ti,ab,kw OR 'street clinic*':ti,ab,kw OR 'safer inhalation':ti,ab,kw OR 'crack kit*':ti,ab,kw OR 'naloxone kit':ti,ab,kw | 458 |
| 77 | 'case management':ti,ab,kw OR outreach:ti,ab,kw OR nonpharmacological:ti,ab,kw OR 'non pharmacological':ti,ab,kw OR nonpharmaceutical:ti,ab,kw OR 'non pharmaceutical':ti,ab,kw | 65,658 |
| 76 | (((art OR music OR sound OR colo?r) NEAR/2 therap*):ti,ab,kw) OR relig*:ti,ab,kw OR prayer*:ti,ab,kw OR spiritual*:ti,ab,kw OR meditat*:ti,ab,kw OR aromatherap*:ti,ab,kw OR bibliotherap*:ti,ab,kw OR 'psychedelic therapy':ti,ab,kw | 120,893 |
| 75 | (((traditional* OR native* OR aboriginal* OR indigenous OR ceremon*) NEAR/2 (heal* OR medicine OR medical*)):ti,ab,kw) OR 'medicine, traditional'/exp/mj | 132,075 |
| 74 | ((traditional OR complementary OR holistic OR natur* OR alternative OR native) NEAR/2 (medicine* OR therap* OR mental*)):ti,ab,kw | 146,470 |
| 73 | 'alternative medicine'/exp/mj OR 'relaxation therap*':ti,ab,kw OR 'relaxation technique*':ti,ab,kw OR 'talk therapy':ti,ab,kw | 43,696 |
| 71 | (commun* NEAR/3 (service* OR center* OR centre* OR network* OR psychiatr* OR psychology OR reinforc*)):ti,ab,kw | 70,242 |
| 70 | ((marital OR marriage OR family OR families OR support* OR group OR couple* OR interpersonal) NEAR/2 therap*):ti,ab,kw | 70,111 |
| 69 | cope:ti,ab,kw OR ((coping NEAR/2 (skill* OR behavio*)):ti,ab,kw) OR (('self control' NEAR/1 training):ti,ab,kw) OR 'structured counsel*':ti,ab,kw | 65,581 |
| 68 | 'coping behavior'/exp/mj OR 'counseling'/exp/mj OR 'social adaptation'/exp/mj | 119,453 |
| 67 | 'cognitive therapy'/exp/mj OR 'behavior therapy'/exp/mj OR ((social NEAR/2 skill*):ti,ab,kw) | 53,109 |
| 66 | sociali?ation:ti,ab,kw OR ((social NEAR/2 adjust*):ti,ab,kw) OR ((social NEAR/2 support*):ti,ab,kw) OR 'socialization'/exp/mj | 86,895 |
| 65 | ((cognitive NEAR/2 therap*):ti,ab,kw) OR ((behavio* NEAR/2 therap*):ti,ab,kw) | 51,996 |
| 64 | 'psychotherapy'/exp/mj OR 'psychiatric treatment'/exp/mj OR psychotherap*:ti,ab,kw OR 'psycho therap*':ti,ab,kw | 239,973 |
| 63 | #57 AND #61 OR #60 OR #62 | 101,324 |

| # | Query | Results |
|---|---|---|
| 62 | (('use' OR using OR disorder* OR abuse OR dependen* OR addict*) NEAR/3 ('multiple drug*' OR 'polydrug*' OR 'street drug*' OR 'designer drug*' OR abstral OR actiq OR alfentanil OR anexsia OR astramorph OR avinza OR butrans OR carfentan* OR codeine OR 'co gesic' OR demerol OR diamorphine OR dilaudid OR dolophine OR duragesic OR embeda OR endocet OR exalgo OR fentanyl OR fentora OR heroin OR hycet OR hycodan OR hydrocodone OR hydromet OR hydromorphone OR hysingla OR ibudone OR kadian OR liquicet OR lorcet OR lortab OR maxidone OR meperidine OR morphabond OR 'ms contin' OR nalbuphine OR narcotic* OR norco OR nubain OR 'nucynta er' OR 'opana er' OR opiate* OR opioid* OR opium OR onsolis OR oramorph OR 'ora morph' OR oxaydo OR oxecta OR oxycet OR oxycodone OR oxycontin OR 'oxymorphone hydrochloride' OR palladone OR pentazocine OR percocet OR percodan OR pethidine OR reprexain OR rezira OR roxanol* OR roxicet OR roxicodone OR roxycodone OR sublimaze OR sufentanil OR tapentadol OR 'targiniq er' OR tramadol OR tussicaps OR tussionex OR 'tuzistra xr' OR vicodin OR vicoprofen OR vituz OR 'xartemis xr' OR xodol OR 'xtampza er' OR 'zohydro er' OR zolvit OR zutripro OR zydone')):ti,ab,kw | 75,252 |
| 61 | abuse*:ti,ab,kw OR dependen*:ti,ab,kw OR addict*:ti,ab,kw OR abusing:ti,ab,kw | 2,426,657 |
| 60 | 'opiate addiction'/exp/mj OR 'heroin dependence'/exp/mj OR 'morphine addiction'/exp/mj | 21,555 |
| 57 | 'morphine derivative'/exp/mj OR 'fentanyl'/exp/mj OR 'narcotic agent'/exp/mj OR 'opiate'/exp/mj | 179,351 |

## Embase search update – Date: Aug 17, 2023

| # | Query | Results |
|---|---|---|
| 114 | #112 NOT #106 AND [2017-2023]/py | 184 |
| 113 | #112 NOT #106 | 520 |
| 112 | #111 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) | 2,597 |
| 111 | #109 NOT #110 | 14,680 |
| 110 | #109 AND [conference abstract]/lim | 3,925 |
| 109 | #108 NOT #102 | 18,605 |
| 108 | #7 AND #98 | 18,605 |
| 107 | #105 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [01-01-2023]/sd NOT [18-08-2023]/sd | 213 |
| 106 | #105 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) | 2,502 |
| 105 | #103 NOT #104 | 14,722 |
| 104 | #103 AND [conference abstract]/lim | 4,198 |
| 103 | #99 NOT #102 | 18,920 |
| 102 | #100 NOT (#100 AND #101) | 3,320 |
| 101 | 'human'/mj | 689,379 |
| 100 | 'animal'/mj | 3,353 |
| 99 | #59 AND #98 | 18,920 |
| 98 | #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 | 3,920,399 |
| 97 | 'animal assisted therapy'/exp/mj | 903 |
| 96 | 'housing'/exp/mj OR 'community care'/exp/mj OR 'volunteer'/exp/mj | 79,188 |
| 95 | 'social care'/exp/mj OR 'income assistance':ti,ab,kw | 63,120 |
| 94 | housing:ti,ab,kw OR houses:ti,ab,kw OR volunteer*:ti,ab,kw OR 'voluntaryworker*':ti,ab,kw OR wraparound:ti,ab,kw OR 'wrap around':ti,ab,kw OR ((occupation* NEAR/1 guidance):ti,ab,kw) | 350,213 |
| 93 | 'vocational education'/exp/mj OR 'vocational rehabilitation'/exp/mj OR 'vocational guidance'/exp/mj OR (((vocation* OR 'individual placement') NEAR/2 support*):ti,ab,kw) OR 'supported employment':ti,ab,kw | 13,836 |

| # | Query | Results |
|---|---|---|
| 92 | 'harm reduction':ti,ab,kw OR ((reduc* NEAR/2 harm):ti,ab,kw) OR 'harm reduction'/exp/mj | 12,043 |
| 91 | ((education* OR literacy) NEAR/2 (lecture* OR program* OR film* OR intervention*)):ti,ab,kw | 98,016 |
| 90 | voucher*:ti,ab,kw OR reinforcement:ti,ab,kw OR ((reinforc* NEAR/2 schedule*):ti,ab,kw) | 52,759 |
| 89 | biofeedback:ti,ab,kw OR 'covert sensiti?ation':ti,ab,kw OR ((aversi* NEAR/1stimulation):ti,ab,kw) OR 'reinforcement (psychology)'/exp/mj | 44,083 |
| 88 | 'electrostimulation therap*':ti,ab,kw OR 'electrotherap*':ti,ab,kw OR electrotherap*:ti,ab,kw OR ((electric* NEAR/2 stimulation):ti,ab,kw) OR ((stimulat* NEAR/2 drug):ti,ab,kw) OR 'electrotherapy'/exp/mj | 208,148 |
| 87 | 'case care':ti,ab,kw OR 'contingency management':ti,ab,kw OR 'contingency therapy':ti,ab,kw | 1,725 |
| 86 | 'narcotics anonymous':ti,ab,kw OR 'methadone anonymous':ti,ab,kw OR lifering:ti,ab,kw OR 'smart recovery':ti,ab,kw | 221 |
| 85 | ((withdraw* OR abstain* OR abstinance) NEAR/2 (program* OR intervention OR 'use' OR 'using' OR therap* OR support*)):ti,ab,kw | 7,411 |
| 84 | ('prevention program*':ti,ab,kw OR supervis*:ti,ab,kw) AND consumption:ti,ab,kw OR 'formal intervention*':ti,ab,kw | 3,274 |
| 83 | 'motivation'/exp/mj OR incentiv*:ti,ab,kw OR motivation*:ti,ab,kw | 204,578 |
| 82 | 'preventive health service'/exp/mj | 13,174 |
| 81 | peerneedle*:ti,ab,kw OR 'peer needle*':ti,ab,kwOR 'relapse prevention':ti,ab,kw | 5,420 |
| 80 | (((needle* OR syringe*) NEAR/3 exchang*):ti,ab,kw) OR ((safe* NEAR/1injection*):ti,ab,kw) | 3,299 |
| 79 | ((behavio* OR psychosocial OR 'psycho social' OR psychoeducation* OR 'psycho education*' OR psychiatric OR psychological OR social) NEAR/2 (treatment OR therap* OR program* OR intervention* OR service*)):ti,ab,kw | 175,808 |
| 78 | (psychological* NEAR/2 debrief*):ti,ab,kw | 231 |
| 77 | 'problem solving':ti,ab,kw OR operant*:ti,ab,kw OR 'discussion group*':ti,ab,kw OR 'insight oriented':ti,ab,kw OR 'client centered':ti,ab,kw OR counsel*:ti,ab,kw OR insight*:ti,ab,kw OR paradox*:ti,ab,kw OR psychoanalys*:ti,ab,kw OR sychodrama*:ti,ab,kw OR psychodynamic*:ti,ab,kw OR 'psycho drama*':ti,ab,kw OR 'role play*':ti,ab,kw OR transactional:ti,ab,kw OR befriend*:ti,ab,kw OR mentor*:ti,ab,kw OR sponsor:ti,ab,kw | 1,050,145 |
| 76 | (((mutual OR peer OR recovery) NEAR/1 support):ti,ab,kw) OR ((stress NEAR/2 manag*):ti,ab,kw) OR 'stress management'/exp/mj | 23,263 |
| 75 | '12 step':ti,ab,kw OR 'twelve step':ti,ab,kw OR ((support* NEAR/2 group*):ti,ab,kw) OR 'self help'/exp/mj OR 'self help':ti,ab,kw | 38,085 |
| 74 | 'street nurse*':ti,ab,kw OR 'street outreach':ti,ab,kw OR 'street clinic*':ti,ab,kw OR 'safer inhalation':ti,ab,kw OR 'crack kit*':ti,ab,kw OR 'naloxone kit':ti,ab,kw | 458 |
| 73 | 'case management':ti,ab,kw OR outreach:ti,ab,kw OR nonpharmacological:ti,ab,kw OR 'non pharmacological':ti,ab,kw OR nonpharmaceutical:ti,ab,kw OR 'non pharmaceutical':ti,ab,kw | 65,658 |
| 72 | (((art OR music OR sound OR colo?r) NEAR/2 therap*):ti,ab,kw) OR relig*:ti,ab,kw OR prayer*:ti,ab,kw OR spiritual*:ti,ab,kw OR meditat*:ti,ab,kw OR aromatherap*:ti,ab,kw OR bibliotherap*:ti,ab,kw OR 'psychedelic therapy':ti,ab,kw | 120,893 |
| 71 | (((traditional* OR native* OR aboriginal* OR indigenous OR ceremon*) NEAR/2 (heal* OR medicine OR medical*)):ti,ab,kw) OR 'medicine, traditional'/exp/mj | 132,075 |
| 70 | ((traditional OR complementary OR holistic OR natur* OR alternative OR native) NEAR/2 (medicine* OR therap* OR mental*)):ti,ab,kw | 146,470 |
| 69 | 'alternative medicine'/exp/mj OR 'relaxation therap*':ti,ab,kw OR 'relaxation technique*':ti,ab,kw OR 'talk therapy':ti,ab,kw | 43,696 |
| 68 | 'community mental health':ti,ab,kw OR 'community care':ti,ab,kw OR 'assertive community treatment':ti,ab,kw OR clubhouse*:ti,ab,kw OR 'therapeutic communit*':ti,ab,kw OR 'confrontational intervention*':ti,ab,kw OR 'early intervention*':ti,ab,kw | 56,187 |
| 67 | (commun* NEAR/3 (service* OR center* OR centre* OR network* OR psychiatr* OR psychology OR reinforc*)):ti,ab,kw | 70,242 |
| 66 | ((marital OR marriage OR family OR families OR support* OR group OR couple* OR interpersonal) NEAR/2 therap*):ti,ab,kw | 70,111 |

| # | Query | Results |
|---|---|---|
| 65 | cope:ti,ab,kw OR ((coping NEAR/2 (skill* OR behavio*)):ti,ab,kw) OR (('self control' NEAR/1 training):ti,ab,kw) OR 'structured counsel*':ti,ab,kw | 65,581 |
| 64 | 'coping behavior'/exp/mj OR 'counseling'/exp/mj OR 'social adaptation'/exp/mj | 119,453 |
| 63 | 'cognitive therapy'/exp/mj OR 'behavior therapy'/exp/mj OR ((social NEAR/2 skill*):ti,ab,kw) | 53,109 |
| 62 | sociali?ation:ti,ab,kw OR ((social NEAR/2 adjust*):ti,ab,kw) OR ((social NEAR/2 support*):ti,ab,kw) OR 'socialization'/exp/mj | 86,895 |
| 61 | ((cognitive NEAR/2 therap*):ti,ab,kw) OR ((behavio* NEAR/2 therap*):ti,ab,kw) | 51,996 |
| 60 | 'psychotherapy'/exp/mj OR 'psychiatric treatment'/exp/mj OR psychotherap*:ti,ab,kw OR 'psycho therap*':ti,ab,kw | 239,973 |
| 59 | #55 AND #57 OR #56 OR #58 | 101,324 |
| 58 | (('use' OR using OR disorder* OR abuse OR dependen* OR addict*) NEAR/3 ('multiple drug*' OR 'polydrug*' OR 'street drug*' OR 'designer drug*' OR abstral OR actiq OR alfentanil OR anexsia OR astramorph OR avinza OR butrans OR carfentan* OR codeine OR 'co gesic' OR demerol OR diamorphine OR dilaudid OR dolophine OR duragesic OR embeda OR endocet OR exalgo OR fentanyl OR fentora OR heroin OR hycet OR hycodan OR hydrocodone OR hydromet OR hydromorphone OR hysingla OR ibudone OR kadian OR liquicet OR lorcet OR lortab OR maxidone OR meperidine OR morphabond OR 'ms contin' OR nalbuphine OR narcotic* OR norco OR nubain OR 'nucynta er' OR 'opana er' OR opiate* OR opioid* OR opium OR onsolis OR oramorph OR 'ora morph' OR oxaydo OR oxecta OR oxycet OR oxycodone OR oxycontin OR 'oxymorphone hydrochloride' OR palladone OR pentazocine OR percocet OR percodan OR pethidine OR reprexain OR rezira OR roxanol* OR roxicet OR roxicodone OR roxycodone OR sublimaze OR sufentanil OR tapentadol OR 'targiniq er' OR tramadol OR tussicaps OR tussionex OR 'tuzistra xr' OR vicodin OR vicoprofen OR vituz OR 'xartemis xr' OR xodol OR 'xtampza er' OR 'zohydro er' OR zolvit OR zutripro OR zydone)):ti,ab,kw | 75,252 |
| 57 | abuse*:ti,ab,kw OR dependen*:ti,ab,kw OR addict*:ti,ab,kw OR abusing:ti,ab,kw | 2,426,657 |
| 56 | 'opiate addiction'/exp/mj OR 'heroin dependence'/exp/mj OR 'morphine addiction'/exp/mj | 21,555 |
| 55 | 'morphine derivative'/exp/mj OR 'fentanyl'/exp/mj OR 'narcotic agent'/exp/mj OR 'opiate'/exp/mj | 179,351 |
| 54 | #53 AND [english]/lim | 31,165 |
| 53 | #51 NOT #52 | 33,641 |
| 52 | #51 AND [conference abstract]/lim | 7,448 |
| 51 | #47 NOT #50 | 41,089 |
| 50 | #48 NOT (#48 AND #49) | 3,218 |
| 49 | 'human'/mj | 689,373 |
| 48 | 'animal'/mj | 3,251 |
| 47 | #7 AND #46 | 40,864 |
| 46 | #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 | 3,920,399 |
| 45 | 'animal assisted therapy'/exp/mj | 903 |
| 44 | 'housing'/exp/mj OR 'community care'/exp/mj OR 'volunteer'/exp/mj | 79,188 |
| 43 | 'social care'/exp/mj OR 'income assistance':ti,ab,kw | 63,120 |
| 42 | housing:ti,ab,kw OR houses:ti,ab,kw OR volunteer*:ti,ab,kw OR 'voluntary worker*':ti,ab,kw OR wraparound:ti,ab,kw OR 'wrap around':ti,ab,kw OR ((occupation* NEAR/1 guidance):ti,ab,kw) | 350,213 |
| 41 | 'vocational education'/exp/mj OR 'vocational rehabilitation'/exp/mj OR 'vocational guidance'/exp/mj OR (((vocation* OR 'individual placement') NEAR/2 support*):ti,ab,kw) OR 'supported employment':ti,ab,kw | 13,836 |
| 40 | 'harm reduction':ti,ab,kw OR ((reduc* NEAR/2 harm):ti,ab,kw) OR 'harm reduction'/exp/mj | 12,043 |
| 39 | ((education* OR literacy) NEAR/2 (lecture* OR program* OR film* OR intervention*)):ti,ab,kw | 98,016 |
| 38 | voucher*:ti,ab,kw OR reinforcement:ti,ab,kw OR ((reinforc* NEAR/2 schedule*):ti,ab,kw) | 52,759 |

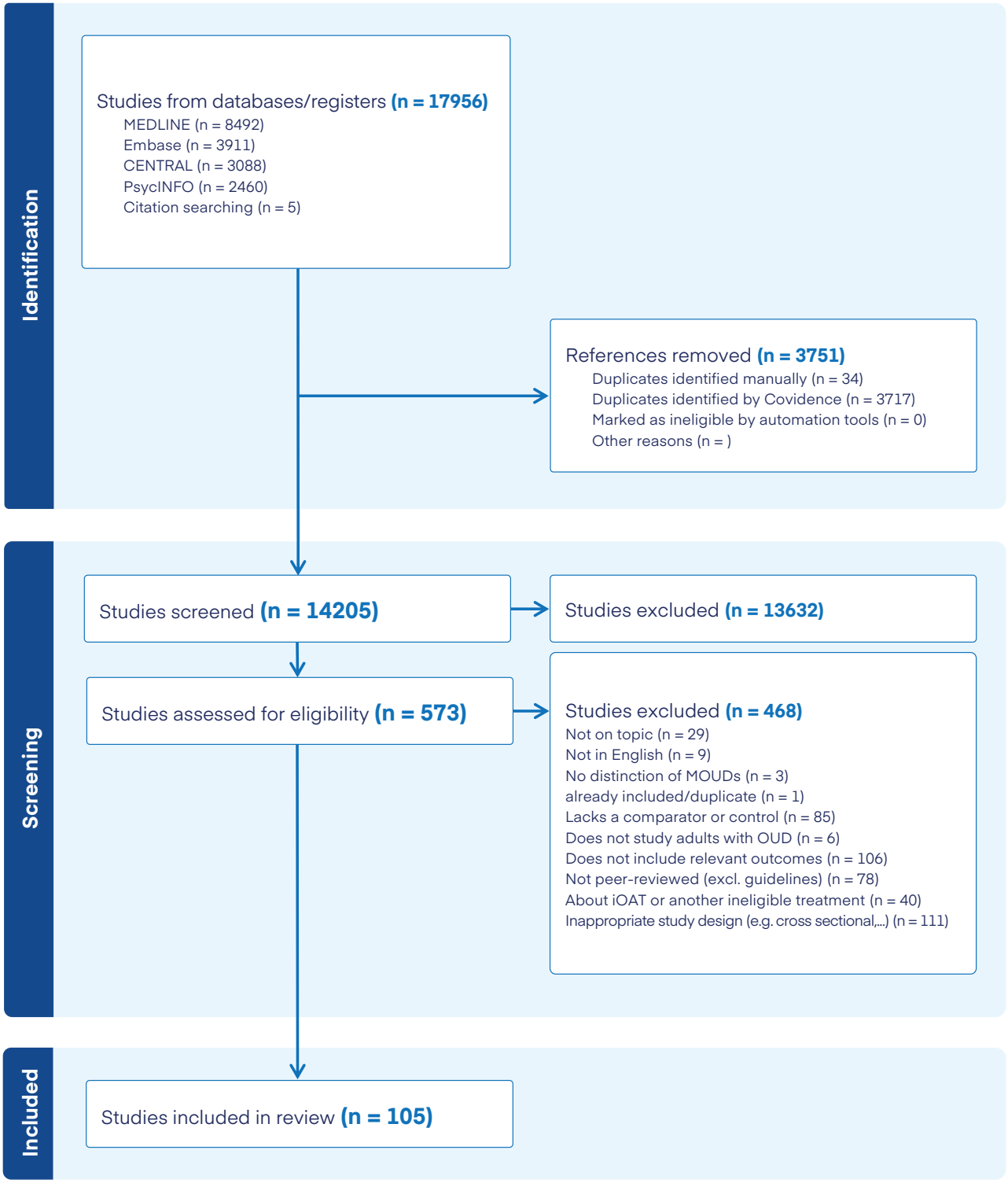
| # | Query | Results |
|---|---|---|
| 37 | biofeedback:ti,ab,kw OR 'covert sensiti?ation':ti,ab,kw OR ((aversi* NEAR/1 stimulation):ti,ab,kw) OR 'reinforcement (psychology)'/exp/mj | 44,083 |
| 36 | 'electrostimulation therap*':ti,ab,kw OR 'electro therap*':ti,ab,kw OR electrotherap*:ti,ab,kw OR ((electric* NEAR/2 stimulation):ti,ab,kw) OR ((stimulat* NEAR/2 drug):ti,ab,kw) OR 'electrotherapy'/exp/mj | 208,148 |
| 35 | 'case care':ti,ab,kw OR 'contingency management':ti,ab,kw OR 'contingency therapy':ti,ab,kw | 1,725 |
| 34 | 'narcotics anonymous':ti,ab,kw OR 'methadone anonymous':ti,ab,kw OR lifering:ti,ab,kw OR 'smart recovery':ti,ab,kw | 221 |
| 33 | ((withdraw* OR abstain* OR abstinance) NEAR/2 (program* OR intervention OR 'use' OR 'using' OR therap* OR support*)):ti,ab,kw | 7,411 |
| 32 | ('prevention program*':ti,ab,kw OR supervis*:ti,ab,kw) AND consumption:ti,ab,kw OR 'formal intervention*':ti,ab,kw | 3,274 |
| 31 | 'motivation'/exp/mj OR incentiv*:ti,ab,kw OR motivation*:ti,ab,kw | 204,578 |
| 30 | 'preventive health service'/exp/mj | 13,174 |
| 29 | peerneedle*:ti,ab,kw OR 'peer needle*':ti,ab,kw OR 'relapse prevention':ti,ab,kw | 5,420 |
| 28 | (((needle* OR syringe*) NEAR/3 exchang*):ti,ab,kw) OR ((safe* NEAR/1 injection*):ti,ab,kw) | 3,299 |
| 27 | ((behavio* OR psychosocial OR 'psycho social' OR psychoeducation* OR 'psycho education*' OR psychiatric OR psychological OR social) NEAR/2 (treatment OR therap* OR program* OR intervention* OR service*)):ti,ab,kw | 175,808 |
| 26 | (psychological* NEAR/2 debrief*):ti,ab,kw | 231 |
| 25 | 'problem solving':ti,ab,kw OR operant*:ti,ab,kw OR 'discussion group*':ti,ab,kw OR 'insight oriented':ti,ab,kw OR 'client centered':ti,ab,kw OR counsel*:ti,ab,kw OR insight*:ti,ab,kw OR paradox*:ti,ab,kw OR psychoanalys*:ti,ab,kw OR psychodrama*:ti,ab,kw OR psychodynamic*:ti,ab,kw OR 'psycho drama*':ti,ab,kw OR 'role play*':ti,ab,kw OR transactional:ti,ab,kw OR befriend*:ti,ab,kw OR mentor*:ti,ab,kw OR sponsor:ti,ab,kw | 1,050,145 |
| 24 | (((mutual OR peer OR recovery) NEAR/1 support):ti,ab,kw) OR ((stress NEAR/2 manag*):ti,ab,kw) OR 'stress management'/exp/mj | 23,263 |
| 23 | '12 step':ti,ab,kw OR 'twelve step':ti,ab,kw OR ((support* NEAR/2 group*):ti,ab,kw) OR 'self help'/exp/mj OR 'self help':ti,ab,kw | 38,085 |
| 22 | 'street nurse*':ti,ab,kw OR 'street outreach':ti,ab,kw OR 'street clinic*':ti,ab,kw OR 'safer inhalation':ti,ab,kw OR 'crack kit*':ti,ab,kw OR 'naloxone kit':ti,ab,kw | 458 |
| 21 | 'case management':ti,ab,kw OR outreach:ti,ab,kw OR nonpharmacological:ti,ab,kw OR 'non pharmacological':ti,ab,kw OR nonpharmaceutical:ti,ab,kw OR 'non pharmaceutical':ti,ab,kw | 65,658 |
| 20 | (((art OR music OR sound OR colo?r) NEAR/2 therap*):ti,ab,kw) OR relig*:ti,ab,kw OR prayer*:ti,ab,kw OR spiritual*:ti,ab,kw OR meditat*:ti,ab,kw OR aromatherap*:ti,ab,kw OR bibliotherap*:ti,ab,kw OR 'psychedelic therapy':ti,ab,kw | 120,893 |
| 19 | (((traditional* OR native* OR aboriginal* OR indigenous OR ceremon*) NEAR/2 (heal* OR medicine OR medical*)):ti,ab,kw) OR 'medicine, traditional'/exp/mj | 132,075 |
| 18 | ((traditional OR complementary OR holistic OR natur* OR alternative OR native) NEAR/2 (medicine* OR therap* OR mental*)):ti,ab,kw | 146,470 |
| 17 | 'alternative medicine'/exp/mj OR 'relaxation therap*':ti,ab,kw OR 'relaxation technique*':ti,ab,kw OR 'talk therapy':ti,ab,kw | 43,696 |
| 16 | 'community mental health':ti,ab,kw OR 'community care':ti,ab,kw OR 'assertive community treatment':ti,ab,kw OR clubhouse*:ti,ab,kw OR 'therapeutic communit*':ti,ab,kw OR 'confrontational intervention*':ti,ab,kw OR 'early intervention*':ti,ab,kw | 56,187 |
| 15 | (commun* NEAR/3 (service* OR center* OR centre* OR network* OR psychiatr* OR psychology OR reinforc*)):ti,ab,kw | 70,242 |
| 14 | ((marital OR marriage OR family OR families OR support* OR group OR couple* OR interpersonal) NEAR/2 therap*):ti,ab,kw | 70,111 |
| 13 | cope:ti,ab,kw OR ((coping NEAR/2 (skill* OR behavio*)):ti,ab,kw) OR (('self control' NEAR/1 training):ti,ab,kw) OR 'structured counsel*':ti,ab,kw | 65,581 |
| 12 | 'coping behavior'/exp/mj OR 'counseling'/exp/mj OR 'social adaptation'/exp/mj | 119,453 |
| 11 | 'cognitive therapy'/exp/mj OR 'behavior therapy'/exp/mj OR ((social NEAR/2 skill*):ti,ab,kw) | 53,109 |

| # | Query | Results |
|---|---|---|
| 10 | sociali?ation:ti,ab,kw OR ((social NEAR/2 adjust*):ti,ab,kw) OR ((social NEAR/2 support*):ti,ab,kw) OR 'socialization'/exp/mj | 86,895 |
| 9 | ((cognitive NEAR/2 therap*):ti,ab,kw) OR ((behavio* NEAR/2 therap*):ti,ab,kw) | 51,996 |
| 8 | 'psychotherapy'/exp/mj OR 'psychiatric treatment'/exp/mj OR psychotherap*:ti,ab,kw OR 'psycho therap*':ti,ab,kw | 239,973 |
| 7 | #3 AND #5 OR #4 OR #6 | 92,348 |
| 6 | ((disorder* OR addict* OR dependen* OR abuse* OR abusing) NEAR/3 ('multiple drug*' OR 'polydrug*' OR 'street drug*' OR 'designer drug*' OR abstral OR actiq OR alfentanil OR anexsia OR astramorph OR avinza OR butrans OR carfentan* OR codeine OR 'co gesic' OR demerol OR diamorphine OR dilaudid OR dolophine OR duragesic OR embeda OR endocet OR exalgo OR fentanyl OR fentora OR heroin OR hycet OR hycodan OR hydrocodone OR hydromet OR hydromorphone OR hysingla OR ibudone OR kadian OR liquicet OR lorcet OR lortab OR maxidone OR meperidine OR morphabond OR 'ms contin' OR nalbuphine OR narcotic* OR norco OR nubain OR 'nucynta er' OR 'opana er' OR opiate* OR opioid* OR opium OR onsolis OR oramorph OR 'ora morph' OR oxaydo OR oxecta OR oxycet OR oxycodone OR oxycontin OR 'oxymorphone hydrochloride' OR palladone OR pentazocine OR percocet OR percodan OR pethidine OR reprexain OR rezira OR roxanol* OR roxicet OR roxicodone OR roxycodone OR sublimaze OR sufentanil OR tapentadol OR 'targiniq er' OR tramadol OR tussicaps OR tussionex OR 'tuzistra xr' OR vicodin OR vicoprofen OR vituz OR 'xartemis xr' OR xodol OR 'xtampza er' OR 'zohydro er' OR zolvit OR zutripro OR zydone)):ti,ab,kw | 41,411 |
| 5 | abuse*:ti,ab,kw OR dependen*:ti,ab,kw OR addict*:ti,ab,kw OR abusing:ti,ab,kw | 2,426,657 |
| 4 | 'opiate addiction'/exp/mj OR 'heroin dependence'/exp/mj OR 'morphine addiction'/exp/mj | 22,286 |
| 3 | #1 OR #2 | 464,038 |
| 2 | abstral:ti,ab,kw OR actiq:ti,ab,kw OR alfentanil:ti,ab,kw OR anexsia:ti,ab,kw OR astramorph:ti,ab,kw OR avinza:ti,ab,kw OR butrans:ti,ab,kw OR carfentan*:ti,ab,kw OR codeine:ti,ab,kw OR 'co gesic':ti,ab,kw OR demerol:ti,ab,kw OR diamorphine:ti,ab,kw OR dilaudid:ti,ab,kw OR dolophine:ti,ab,kw OR duragesic:ti,ab,kw OR embeda:ti,ab,kw OR endocet:ti,ab,kw OR exalgo:ti,ab,kw OR fentanyl:ti,ab,kw OR fentora:ti,ab,kw OR heroin:ti,ab,kw OR hycet:ti,ab,kw OR hycodan:ti,ab,kw OR hydrocodone:ti,ab,kw OR hydromet:ti,ab,kw OR hydromorphone:ti,ab,kw OR hysingla:ti,ab,kw OR ibudone:ti,ab,kw OR kadian:ti,ab,kw OR liquicet:ti,ab,kw OR lorcet:ti,ab,kw OR lortab:ti,ab,kw OR maxidone:ti,ab,kw OR meperidine:ti,ab,kw OR morphabond:ti,ab,kw OR 'ms contin':ti,ab,kw OR nalbuphine:ti,ab,kw OR narcotic*:ti,ab,kw OR norco:ti,ab,kw OR nubain:ti,ab,kw OR 'nucynta er':ti,ab,kw OR 'opana er':ti,ab,kw OR opiate*:ti,ab,kw OR opioid*:ti,ab,kw OR opium:ti,ab,kw OR onsolis:ti,ab,kw OR oramorph:ti,ab,kw OR 'ora morph':ti,ab,kw OR oxaydo:ti,ab,kw OR oxecta:ti,ab,kw OR oxycet:ti,ab,kw OR oxycodone:ti,ab,kw OR oxycontin:ti,ab,kw OR 'oxymorphone hydrochloride':ti,ab,kw OR palladone:ti,ab,kw OR pentazocine:ti,ab,kw OR percocet:ti,ab,kw OR percodan:ti,ab,kw OR pethidine:ti,ab,kw OR reprexain:ti,ab,kw OR rezira:ti,ab,kw OR roxanol*:ti,ab,kw OR roxicet:ti,ab,kw OR roxicodone:ti,ab,kw OR roxycodone:ti,ab,kw OR sublimaze:ti,ab,kw OR sufentanil:ti,ab,kw OR tapentadol:ti,ab,kw OR 'targiniq er':ti,ab,kw OR tramadol:ti,ab,kw OR tussicaps:ti,ab,kw OR tussionex:ti,ab,kw OR 'tuzistra xr':ti,ab,kw OR vicodin:ti,ab,kw OR vicoprofen:ti,ab,kw OR vituz:ti,ab,kw OR 'xartemis xr':ti,ab,kw OR xodol:ti,ab,kw OR 'xtampza er':ti,ab,kw OR 'zohydro er':ti,ab,kw OR zolvit:ti,ab,kw OR zutripro:ti,ab,kw OR zydone:ti,ab,kw | 254,927 |
| 1 | 'morphine derivative'/exp/mj OR 'fentanyl'/exp/mj OR 'narcotic agent'/exp/mj OR 'opiate'/exp/mj | 179,351 |

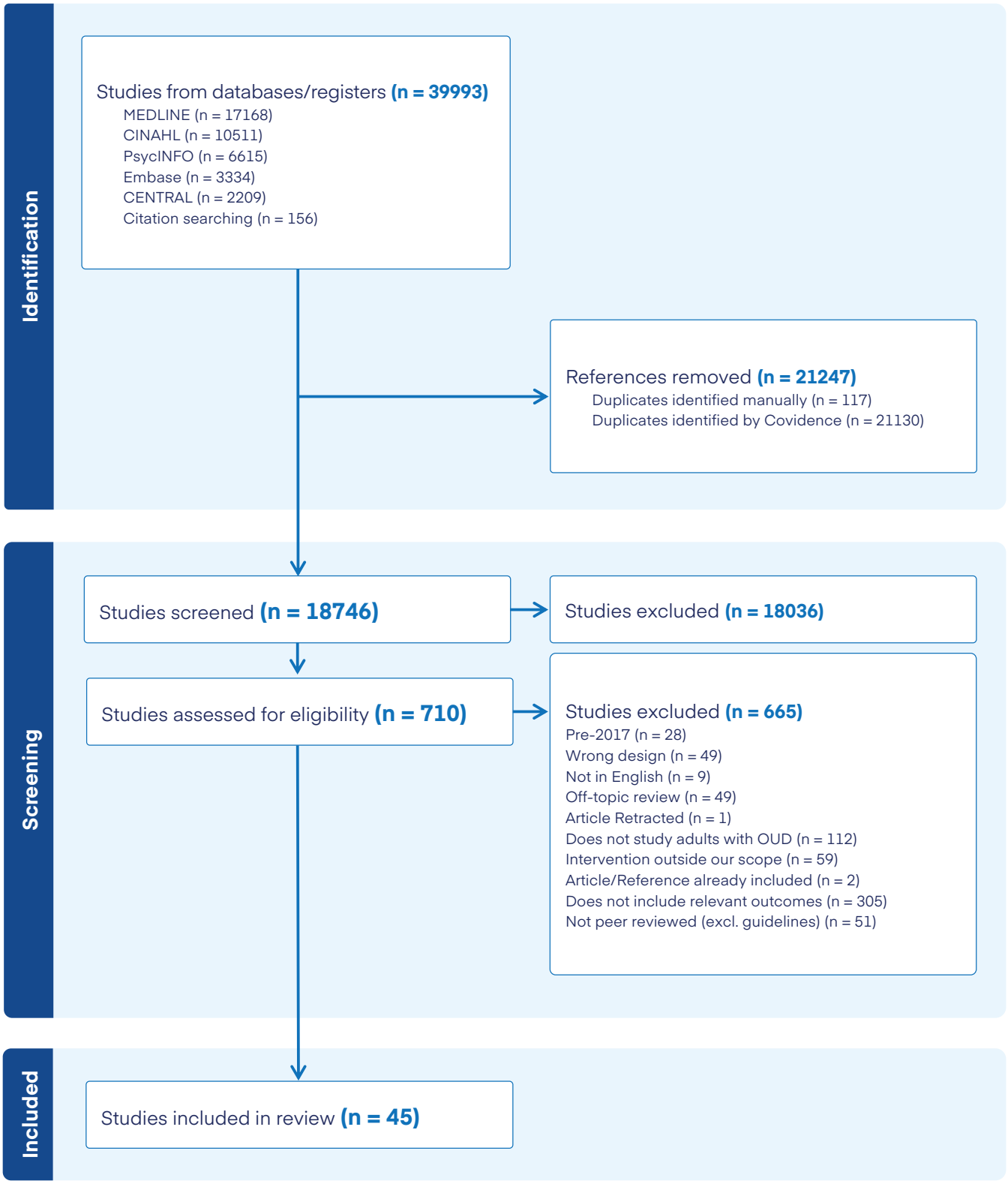
# APPENDIX 5

# Prisma Tables

## A5.1. Pharmacotherapies



## A5.2. Psychosocial and Harm Reduction interventions



# APPENDIX 6

# Data Summary

The full data summary is available at the following link:

2024 Update to CRISM National OUD Guideline - Data summary

# APPENDIX 7

# Grade Tables

The GRADE tables are available at the following link:

2024 Update to CRISM National OUD Guideline – GRADE tables

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