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CADTH Reference List

Directly Observed Therapy for Controlled Substances

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Summary of Abstracts

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Key Messages

- We found 2 systematic reviews about the clinical effectiveness of directly observed therapy versus self-administered therapy for people receiving pharmaceutical treatment with controlled substances.
- We did not find any studies about the clinical effectiveness of directly observed therapy versus alternative methods for monitoring or limiting access to doses for people receiving pharmaceutical treatment with controlled substances.
- We found 5 evidence-based guidelines regarding the use of directly observed therapy for people receiving pharmaceutical treatment with controlled substances.

Research Questions

1. What is the clinical effectiveness of directly observed therapy versus self-administered therapy for people receiving pharmaceutical treatment with controlled substances?
2. What is the clinical effectiveness of directly observed therapy versus alternative methods for monitoring or limiting access to doses for people receiving pharmaceutical treatment with controlled substances?
3. What are the evidence-based guidelines regarding the use of directly observed therapy for people receiving pharmaceutical treatment with controlled substances?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were directly observed therapy and controlled substances, including opioids, barbiturates, benzodiazepines, amphetamines, anabolic steroids, and others. An additional search was conducted using a focused set of terms for directly observed therapy to capture additional articles that did not specify the indication. Retrieval was limited to the human population. The search was completed on March 8, 2023, and limited to English-language documents published since January 1, 2013. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings was based on information

available in the abstracts of selected publications. Open access full-text versions of evidence-based guidelines were reviewed when available, and relevant recommendations were summarized.

Table 1: Selection Criteria

Criteria	Description
Population	People receiving pharmaceutical treatment with controlled substances (e.g., opioid agonist therapies, narcotics, stimulants, benzodiazepines)
Intervention	Directly observed therapy (i.e., patient is observed while taking a dose of pharmaceutical treatment to ensure treatment adherence)
Comparator	Q1: Self-administered therapy (i.e., patients are not observed while taking a dose of pharmaceutical treatment) Q2: Alternative methods for monitoring or limiting access to doses (e.g., video directly observed therapy, supervision by non-health care professionals, controlled substance dispenser, lock box systems) Q3: Not applicable
Outcomes	Q1 and Q2: Clinical benefits and harms (e.g., mortality, quality of life, functional status, severity of symptoms, patient participation, risk for diversion, adverse events) Q3: Recommendations regarding best practices (e.g., appropriate patient populations and clinical settings, observation protocols, advice on the individualization of observation methods based on patient needs, strategies to mitigate harms, adverse events, and misuse)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Two systematic reviews were identified regarding the clinical effectiveness of directly observed therapy versus self-administered therapy for people receiving pharmaceutical treatment with controlled substances.[1,2] No relevant literature was identified about the clinical effectiveness of directly observed therapy versus alternative methods for monitoring or limiting access to doses for people receiving pharmaceutical treatment with controlled substances. Five evidence-based guidelines regarding the use of directly observed therapy for people receiving pharmaceutical treatment with controlled substances were identified.[3-7] No relevant health technology assessments, randomized controlled trials, or non-randomized studies were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

Two systematic reviews[1,2] were identified regarding the clinical effectiveness of directly observed therapy versus self-administered therapy for people receiving opioid agonist therapies. Both systematic reviews reported uncertainty about the effects of observed treatment compared to unobserved treatment due to the low quality of evidence.[1,2] One systematic review[1] found no difference in retention, abstinence at the end of treatment, diversion of medication, and the incidence of adverse effects between people who received supervised and unsupervised treatments. The systematic review also found insufficient evidence to suggest that regular supervision of treatment was protective of death.[1] The systematic review by Hov and colleagues[2] found uncertain effects of observed versus unobserved treatment in patients receiving opioid maintenance treatment on retention, use of illicit opioids, patients' satisfaction, and the incidence of adverse events.

Five evidence-based guidelines regarding the use of directly observed therapy for people receiving pharmaceutical treatment with controlled substances were identified.[3-7] Three guidelines provide recommendations regarding directly observed therapy for people receiving treatment for opioid use disorder.[3,4,7] The guideline developed by the Royal Australian College of General Practitioners[5] provides recommendations about directly observed therapy for opioid use in general practice. The National Institute for Health and Care Excellence guideline[6] recommends using directly observed therapy for people in prisons when administrating Schedule 2 and 3 medicines and any medicine that would not be self administered. A detailed summary of the guideline recommendations can be found in Table 2.

Table 2: Summary of Recommendations in Included Guidelines

Guideline development group (year)	Summary of recommendations
Canadian Coalition of Seniors' Mental Health (2020) [3]	"If renal function is adequate, daily witnessed ingestion of slow-release oral morphine may be considered with caution for those older adults in whom buprenorphine and methadone maintenance have been ineffective or could not be tolerated. Careful supervision of initiation onto short-acting morphine first is recommended, prior to transition to maintenance with the long-acting 24-hour formulation." (p. 125 to 126) Quality of Evidence: Low; Strength of Recommendation: Weak.
British Columbia Centre of Substance Use and B.C. Ministry of Health (2017)[4]	"For patients who have been unsuccessful with first- and second-line treatment options, opioid agonist treatment with slow-release oral morphine (prescribed as once-daily witnessed doses) can be considered. Slow-release oral morphine should only be prescribed by experienced addiction practitioners who hold a Section 56 exemption to prescribe methadone or only after specialist consultation." (p. 13) Quality of Evidence: Moderate; Strength of Recommendation: Strong.
Royal Australian College of General Practitioners (2017)[5]	"If alternatives to opioid treatment fail, have limited benefit or are inappropriate, then supervised opioid treatment may remain an acceptable long-term therapeutic option." (p. 1)
National Institute for Health and Care Excellence (2016)[6]	"Directly observe the administration of all Schedule 2 and 3 medicines [a] and medicines for tuberculosis." (p. 238) "Directly observe the administration of any medicine that is not in possession[b]." (p. 238)

Guideline development group (year)	Summary of recommendations
Government of Australia (2014)[7]	**Recommendations for outpatients with unsanctioned use of opioids (Methadone)** "All doses of methadone should be supervised, where possible, and a clinician (doctor, nurse, pharmacist) should review the patient daily during the first week of treatment, corresponding to the greatest risk period for methadone-related overdose. The review provides an opportunity to assess intoxication (e.g., sedation, constricted pupils) or withdrawal symptoms, side effects, other substance use and the patient's general well-being." (p. 23) "When induction of methadone, take account of pharmacy availability for supervision of dosing and monitoring of response." (p. 23)
	Buprenorphine "It is easier to supervise the dosing of the film preparation, compared to tablets, of buprenorphine-naloxone." (p. 24) **Recommended induction for outpatients using heroin and/or short-acting pharmaceutical opioids (Buprenorphine)** "Initial doses should be supervised, and a clinician (doctor, nurse, pharmacist) should review the patient daily during the first few days of treatment while the dose is stabilised. The review provides an opportunity to assess intoxication (e.g., sedation, constricted pupils) or withdrawal symptoms, side effects, other substance use and the patient's general well-being." (p. 25)

[a]Refer to National Institute for Health and Care Excellence's guideline on controlled drugs (NG46).

[b]In possession medicine refers to self-administered drugs (p. 204).

References

Health Technology Assessments

No literature identified.

Systematic Reviews

1. Saulle R, Vecchi S, Gowing L. Supervised dosing with a long-acting opioid medication in the management of opioid dependence. *Cochrane Database Syst Rev*. 2017 Apr 27;4(4):CD011983. PubMed

2. Hov L, Mosdol A, Ding Y, Stromme H, Vist GE. Unsupervised Intake of Medicines for Individuals in Opioid Maintenance *(NIPH Systematic Reviews: Executive Summaries)*. Oslo (NO): Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2016. PubMed

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

3. Rieb LM, Samaan Z, Furlan AD, et al. Canadian Guidelines on Opioid Use Disorder Among Older Adults. *Can Geriatr J.* 2020 Mar 30;23(1):123-134. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7067148/pdf/cgj-8-123.pdf. Accessed 2023 Mar 14. PubMed
   Refer to Recommendations:19 (pages 126-127)

4. A Guideline for the Clinical Management of Opioid Use Disorder. Vancouver (BC): British Columbia Centre on Substance Use and B.C. Ministry of Health; 2017: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/bc_oud_guidelines.pdf. Accessed 2023 Mar 14.
   Refer to Recommendation 10 (page 13).

5. The Royal Australian College of General Practitioners (RACGP). Prescribing drugs of dependence in general practice, Part C1: Opioids. East Melbourne (AU): RACGP; 2017: https://www.racgp.org.au/getattachment/f0eb9c77-58fc-4e7f-bec6-5b570bc68534/Part-C1.aspx. Accessed 2023 Mar 14.
   Refer to: Key Principles for Appropriate Opioid Prescribing in General Practice (page 1).

6. National Institute for Health and Care Excellence. Physical health of people in prison *(NICE guideline NG57)* 2016; https://www.nice.org.uk/guidance/ng57/evidence/full-guideline-pdf-2672652637. Accessed 2023 Mar 14.
   Refer to Recommendations 47 and 48 (page 238).

7. Gowing L, Ali R, Dunlop A, Farrell M, Lintzeris N. National guidelines for medication-assisted treatment of opioid dependence. Canberra (AU): Australian Government, Department of Health and Aged Care; 2014: https://www.health.gov.au/resources/publications/national-guidelines-for-medication-assisted-treatment-of-opioid-dependence. Accessed 2023 Mar 14.
   Refer to Sections A4.2.1 (a)- Recommended Regimen for Outpatients with Unsanctioned Use of Opioids (page 23); A4.2.2 Buprenorphine-Key Principles (page 24); A.4.2.2(a)- Recommended Induction Regimen for Outpatients Using Heroin and/or Short-Acting Pharmaceutical Opioids (page 25).

Appendix 1: References of Potential Interest

Systematic Reviews

Controlled Substances Not Specified

Ryan R, Santesso N, Lowe D, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. *Cochrane Database Syst Rev.* 2014 Apr 29;2014(4):CD007768. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007768.pub3/full. Accessed 2023 Mar 14.PubMed

Non-Randomized Studies

Alternative Outcomes- Treatment Initiation

Abrahamsson T, Widinghoff C, Lilliebladh A, Gedeon C, Nilvall K, Hakansson A. Interim buprenorphine treatment in opiate dependence: A pilot effectiveness study. *Subst Abus.* 2016;37(1):104-9. PubMed

Multiple Interventions- Directly Observed Therapy with Psychosocial Intervention

Dhawan A, Chopra A. Does buprenorphine maintenance improve the quality of life of opioid users? *Indian J Med Res*. Jan 2013;137(1):130-5. PubMed

Guidelines and Recommendations

Alternative Methodology

Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder. Toronto (ON): Centre for Addiction and Mental Health; 2021: https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf. Accessed 2023 Mar 14.
Refer to Sections: B2: Prescribing Buprenorphine/Naloxone (page 23) and B5- Prescribing Injectable Opioid Agonist Therapy (page 31).

Guidance for Injectable Opioid Agonist Treatment for Opioid Use Disorder. Vancouver (BC): British Columbia Centre on Substance Use; 2021: https://www.bccsu.ca/wp-content/uploads/2021/07/BC_iOAT_Guideline.pdf. Accessed 2023 Mar 14.
Refer to Models of Care in BC (page 23); Table 2- Summary of Clinical Recommendations (page 28); Prescribing Injectable Hydromorphone (pages 32-33).

The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update. Rockville (MD): American Society of Addiction Medecine; 2020: https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline. Accessed 2023 March 21.
Note: OTP refers to Opioid Treatment Programs may include medically supervised opioid withdrawal and maintenance treatment (page 6).
Refer to Sections: Part 2 Treatment Options, recommendations 4 and 7 (page 11); Part 4 Methadone, recommendation 4 (page 12).

National Injectable Opioid Agonist Treatment for Opioid Use Disorder Clinical Guideline. [Vancouver (BC)]: Canadian Research Initiative in Substance Misuse (CRISM); 2019: https://crism.ca/projects/ioat-guideline/. Accessed 2023 Mar 14.
Refer to: Summary of Clinical Practice Guideline (page 20); Section 3.3.iii Medication Provision (pages 31-32).

The Royal Australian College of General Practitioners (RACGP). Prescribing drugs of dependence in general practice, Part B – Benzodiazepines. East Melbourne (AU): RACGP; 2015: https://www.racgp.org.au/getattachment/1beeb924-cf7b-4de4-911e-f7dda3e3f6e9/Part-B.aspx. Accessed 2023 Mar 14.
Refer to Section 1.6.3- Accountable Prescribing of Benzodiazepines (page 17).

Unclear Methodology

Lintzeris N, Hayes V, Arunogiri S. Interim guidance for the delivery of medication assisted treatment of opioid dependence in response to COVID-19: a national response. Sydney (AU): Royal Australasian College of Physicians; 2020: https://www.racp.edu.au/docs/default-source/news-and-events/covid-19/interim-guidance-delivery-of-medication-assisted-treatment-of-opiod-dependence-covid-19.pdf. Accessed 2023 Mar 14.
Refer to: Table 1 Guide to Supervised and Unsupervised Dosing Conditions for OAT During COVID-19 Pandemic (pages 7-8).

Guidelines for South Australian Pharmacists Dispensing Medication Assisted Treatment for Opioid Dependence (MATOD). Adelaide (AU): Government of South Australia, SA Health; 2016: https://www.sahealth.sa.gov.au/wps/wcm/connect/8875c9804008e393b7ffbf4826472d56/Pharmacist+Guidelines+for+SA+Pharmacists+Dispensing+MATOD+FINAL+Jan+2016.pdf. Accessed 2023 Mar 14.
Refer to Sections: 2.6.9 Diversion (page 25); 2.6.10- Supervised Dosing Procedure for Buprenorphine/Naloxone Film (page 25); 3.1.1-Supervised Dosing (pages 37-38).

Cunningham C, Fishman M. The ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Rockville (MD): American Society of Addiction Medicine; 2015: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-pocketguide.pdf. Accessed 2023 Mar 14.
Refer to Sections: Treatment Settings (page 4); Methadone (page 6); Buprenorphine (page 7)

Not Specific to Directly Observed Therapy

National Institute for Health and Care Excellence. Controlled drugs: safe use and management *(NICE guideline NG46)* 2016; https://www.nice.org.uk/guidance/ng46. Accessed 2023 Mar 14.
Refer to Sections: 7.6-Recommendations (page 82).

Supervised dosing with a long acting opioid medication for the management of prescription opioid dependence. [Geneva (CH)]: World Health Organization, Mental Health Gap Action Programme (mhGAP); 2015: https://cdn.who.int/media/docs/default-source/mental-health/mhgap/substance-use-disorders/supervised-dosing-with-a-long-acting-opioid-medication-to-reduce-opioid-use-and-related-harm-in-the-management-of-prescription-opioid-dependence.pdf. Accessed 2023 March 14.
Refer to Recommendations (page 26).

Review Articles

Chou R, Korthuis PT, Weimer M, et al. Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings *(Technical Brief No. 28).* Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2016: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/opioid-use-disorder_technical-brief.pdf. Accessed 2023 Mar 14.
Note: This is a technical brief.
Refer to: Appendix F- Details of Trials for Guiding Question 3 (pages F-1 to F-18).

Pietras S, Azur M, Brown J. Review of medication-assisted treatment guidelines and measures for opioid and alcohol use. Washington (DC): U.S. Department of Health and Human Services, Assistant Secretary for Planning and Evaluation, Office of Disability, Aging and Long-Term Care Policy; 2015: https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//146866/MATguidelines.pdf. Accessed 2023 Mar 14.
Refer to: Table A4- Diversion Control (page A-13).