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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

# Naltrexone for Alcohol Addiction: Clinical Effectiveness, Cost Effectiveness, and Guidelines


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## Research Questions

1. What is the clinical effectiveness of injectable extended-release naltrexone for the treatment of alcohol dependency disorder?
2. What is the cost effectiveness of injectable extended-release naltrexone for the treatment of alcohol dependency disorder?
3. What are the evidence-based guidelines regarding the use of injectable extended-release naltrexone for the treatment of alcohol dependency disorder?

## Key Findings

One systematic review with a meta-analysis, four randomized controlled trials, two non-randomized studies, and one evidence-based guideline were identified regarding the clinical effectiveness of naltrexone for alcohol addiction. No relevant economic evaluations were identified.

## Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were injectable extended-release naltrexone and alcohol dependency. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and May 23, 2019. Internet links were provided, where available.

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

### Table 1: Selection Criteria

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| **Population** | Patients with alcohol dependency disorder or addiction |
| **Intervention** | Injectable extended-release naltrexone (Vivitrol) |
| **Comparators** | Q1-2: Placebo;<br>Other forms of naltrexone (e.g., oral naltrexone);<br>Acamprosate;<br>Naltrexone in combination with acamprosate<br>Q3: No comparator |
| **Outcomes** | Q1: Clinical effectiveness (e.g., emergency department visits, reduction in symptoms, safety, Prevention of relapse, adverse events, reduced drinking)<br>Q2: Cost effectiveness outcomes<br>Q3: Guidelines |
| **Study Designs** | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines |

## Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

One systematic review with meta-analysis, four randomized controlled trials, and two non-randomized studies were identified regarding the clinical effectiveness of naltrexone for alcohol addiction. In addition one evidence-based guideline was identified regarding the clinical effectiveness of naltrexone for alcohol addiction. No relevant health technology assessments or economic evaluations were identified.

Additional references of potential interest are provided in the appendix.

## Overall Summary of Findings

One systematic review with meta-analysis,[1] four randomized controlled trials,[2-5] and two non-randomized studies[6-7] were identified regarding the clinical effectiveness of injectable extended-release naltrexone (XR-NTX) for alcohol addiction.

The authors of the systematic review with meta-analyses did not find any significant benefits of XR-NTX to prevent relapse to heavy drinking but did find a reduction in heavy drinking days.[1] Alternatively, they did find that oral naltrexone and acamprosate had the best evidence for improving alcohol consumption outcomes for patients.[1]

The authors of one randomized trial compared XR-NTX to oral naltrexone for alcohol use disorders in veterans and found no significant difference in therapeutic effect or adherence.[2] The authors of a second randomized controlled trial aimed to assess the feasibility and safety of XR-NTX for alcohol use disorder in HIV clinics in comparison to standard treatment.[3] They found that XR-NTX was a safe treatment and had a better retention rate than standard care.[3] The authors of two other randomized controlled trials[4.5] aimed to assess if XR-NTX reduced alcohol consumption and while one found that XR-NTX decreased alcohol consumption among HIV prison inmates transitioning to the community[4] the other found no significant difference in alcohol use or cocaine use among patients with these disorders.[5]

The authors of one non-randomized study found that XR-NTX reduced alcohol consumption among patients with alcohol use-disorders.[6] The authors of a second non-randomized study,[7] aimed to compare long-acting injectable naltrexone with oral naltrexone within a population of veterans with alcohol use disorders and found that the oral naltrexone was associated with lower 30-day alcohol-related hospital admission than long-acting injectable naltrexone.[7]

One guideline by the Washington Department of Veteran Affairs and Department of Defense recommends the use of oral or extended-release naltrexone for patients with moderate to severe alcohol use disorders.[8]

## References Summarized

### Health Technology Assessments

No literature identified.

## Systematic Reviews and Meta-analyses

1. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol-use disorders in outpatient settings. Comparative Effectiveness Review No. 134. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2012-00008-I.) AHRQ Publication No. 14-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2014 May: https://effectivehealthcare.ahrq.gov/topics/alcohol-misuse-drug-therapy/research. Accessed 2019 Jun 7.

## Randomized Controlled Trials

2. Busch AC, Denduluri M, Glass J, et al. Predischarge injectable versus oral naltrexone to improve postdischarge treatment engagement among hospitalized veterans with alcohol use disorder: a randomized pilot proof-of-concept study. *Alcohol Clin Exp Res.* 2017 Jul;41(7):1352-1360.
PubMed: PM28605827

3. Korthuis PT, Lum PJ, Vergara-Rodriguez P, et al. Feasibility and safety of extended-release Naltrexone treatment of opioid and alcohol use disorder in HIV clinics: a pilot/feasibility randomized trial. *Addiction*. 2017 Jun;112(6):1036-1044.
PubMed: PM28061017

4. Springer SA, Di Paola A, Azar MM, Barbour R, Krishnan A, Altice FL. Extended-release Naltrexone reduces alcohol consumption among released prisoners with HIV disease as they transition to the community. *Drug Alcohol Depend*. 2017 05 01;174:158-170.
PubMed: PM28334661

5. Pettinati HM, Kampman KM, Lynch KG, et al. A pilot trial of injectable, extended-release Naltrexone for the treatment of co-occurring cocaine and alcohol dependence. *Am J Addict*. 2014 Nov-Dec;23(6):591-597.
PubMed: PM25251201

## Non-Randomized Studies

6. Crevecoeur-MacPhail D, Cousins SJ, Denering L, Kim T, Rawson RA. Effectiveness of extended release Naltrexone to reduce alcohol cravings and use behaviors during treatment and at follow-up. *J Subst Abuse Treat*. 2018 Feb;85:105-108.
PubMed: PM29174308

7. Beatty A, Stock C. Efficacy of long-acting, injectable versus oral naltrexone for preventing admissions for alcohol use disorder. *Ment Health Clin*. 2017 May;7(3):106-110.
PubMed: PM29955507

## Economic Evaluations

No literature identified.

## Guidelines and Recommendations

8. Management of Substance Use Disorders Work Group. VA/DoD clinical practice guideline for the management of substance use disorders. Version 3.0. Washington (DC): Department of Veterans Affairs, Department of Defense; 2015 Dec: https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf Accessed 2019 Jun 7.
*See: VI Recommendations. D. Treatment, pages 25 & 33*

# Appendix — Further Information

## Previous CADTH Reports


9. Naltrexone for alcohol dependence: clinical effectiveness. (*CADTH rapid response: reference list*). Ottawa (ON): CADTH; 2017 Jan: https://www.cadth.ca/naltrexone-alcohol-dependence-clinical-effectiveness. Accessed 2019 Jun 7.

10. Injectable extended-release naltrexone to treat opioid use disorder. (*CADTH issues in emerging health technologies; issue 163*). Ottawa (ON): CADTH; 2017 Aug: https://www.cadth.ca/dv/ieht/injectable-extended-release-naltrexone-treat-opioid-use-disorder. Accessed 2019 Jun 7.


## Systematic Reviews and Meta-Analyses

*Route of Administration Unspecified*


11. Canidate SS, Carnaby GD, Cook CL, Cook RL. A systematic review of naltrexone for attenuating alcohol consumption in women with alcohol use disorders. *Alcohol Clin Exp Res*. 2017 03;41(3):466-472.
PubMed: PM28247556


*Alternative Outcome – Health Care Utilization*


12. Hartung DM, McCarty D, Fu R, Wiest K, Chalk M, Gastfriend DR. Extended-release Naltrexone for alcohol and opioid dependence: a meta-analysis of healthcare utilization studies. *J Subst Abuse Treat*. 2014 Aug;47(2):113-121.
PubMed: PM24854219


## Randomized Controlled Trials – Protocol Paper


13. Malone M, McDonald R, Vittitow A, et al. Extended-release vs. oral naltrexone for alcohol dependence treatment in primary care (XON). *Contemp Clin Trials*. 2019 Jun;81:102-109.
PubMed: PM30986535

14. Collins SE, Saxon AJ, Duncan MH, et al. Harm reduction with pharmacotherapy for homeless people with alcohol dependence: protocol for a randomized controlled trial. *Contemp Clin Trials*. 2014 Jul;38(2):221-234.
PubMed: PM24846619


## Non-Randomized Studies

*Alternative Population*


15. Notzon DP, Kelly MA, Choi CJ, et al. Open-label pilot study of injectable naltrexone for cannabis dependence. *Am J Drug Alcohol Abuse*. 2018 02 Nov;44(6):619-627.
PubMed: PM29420073

*No Comparator*

16. Collins SE, Duncan MH, Smart BF, et al. Extended-release naltrexone and harm reduction counseling for chronically homeless people with alcohol dependence. *Subst Abus*. 2015;36(1):21-33.
PubMed: PM24779575

*Alternative Outcome*

17. Chang G, Crawford M, Pitts M, Schein AZ, Goodwin K, Enggasser JL. Adherence to extended release naltrexone: Patient and treatment characteristics. *Am J Addict*. 2018 09;27(6):524-530.
PubMed: PM30106489

## Qualitative Studies

18. Aletraris L, Bond Edmond M, Roman PM. Adoption of injectable naltrexone in U.S. substance use disorder treatment programs. *J Stud Alcohol Drugs.* 2015 Jan;76(1):143-151.
PubMed: PM25486403

## Review Articles

19. Blum K, Modestino EJ, Badgaiyan RD, et al. Analysis of evidence for the combination of pro-dopamine regulator (KB220PAM) and naltrexone to prevent opioid use disorder relapse. *EC Psychol Psychiatr*. 2018 Aug;7(8):564-579.
PubMed: PM30417173

20. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. *JAMA*. 2018 08 28;320(8):815-824.
PubMed: PM30167705