

# Naltrexone Initiation in the Inpatient Setting for Alcohol Use Disorder: A Systematic Review of Clinical Outcomes

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## Abstract

Alcohol use disorder (AUD) is a highly prevalent health issue in the United States. The number of those receiving medication-assisted treatment (MAT) is limited, despite strong evidence for their effectiveness. The inpatient setting may represent an important opportunity to initiate MAT. The goal of this study was to summarize the data on *naltrexone* initiation in the emergency department or inpatient setting for the management of AUDs. We searched [ClinicalTrials.gov](http://ClinicalTrials.gov), Ovid EBM Reviews, Ovid Embase, Ovid Medline, Ovid PsycINFO, Scopus, and Web of Science from inception through October 31, 2019. Search strategies were created using a combination of keywords ([Supplemental Appendix 1](#), available online at <http://www.mcpiqjournal.org>) and standardized index terms related to naltrexone therapy for medically hospitalized patients with AUD. Two uncontrolled pre-post study designs evaluated naltrexone prescription rates, 30-day readmission rates, and rehospitalization rates. Two authors independently abstracted data on study characteristics, results, and study-level risk of bias. The research team collaborated to assess the strength of evidence across studies. Two studies reported that implementing a protocol for naltrexone initiation increased MAT rates, with one study noting a substantial decrease in 30-day hospital readmissions. Overall, we found that there is a paucity of data on naltrexone initiation in the inpatient setting for AUDs. This likely reflects the nature of current clinical practice and prescriber comfortability. There is a need for further studies evaluating MAT initiation in the inpatient setting. Furthermore, efforts to increase provider knowledge of these therapeutic options are in need of further exploration.

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Alcohol use disorder (AUD) is a highly prevalent and critical health issue in the United States. Alcohol-induced death rates have accelerated overall and particularly in women.<sup>1</sup> In 2018, an estimated 14.8 million persons had AUD, corresponding to 5.4% of the population. Of this group, only 4.6% received treatment in a specialty treatment facility (hospital, rehabilitation center, or mental health facility).<sup>2</sup> It is estimated that 20% of patients who attend the emergency department (ED) suffer from an AUD.<sup>3</sup> Hospitalists frequently encounter alcohol withdrawal admissions and are often tasked with providing short counseling sessions on AUD owing to time constraint. Furthermore, up to

50% of patients admitted for alcohol withdrawal will be readmitted for the same reason within 30 days.<sup>4</sup>

Alcohol use disorder treatment is highly heterogeneous, with a large proportion of patients spontaneously remitting and some needing long-term psychosocial and medication interventions.<sup>3</sup> Compared with other substance use disorders, AUD has several US Food and Drug Administration (FDA)-approved and off-label pharmacological options available to assist patients with sobriety. Currently, there are 3 FDA-approved medication-assisted treatment (MAT) options: naltrexone, acamprosate, and disulfiram. These agents have been studied in renal and hepatic insufficiency, pregnancy

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## ARTICLE HIGHLIGHTS

- Alcohol use disorder and the related comorbidities are commonly encountered in the inpatient setting, with this patient population representing a source of frequent readmissions.
- Therapeutic options to reduce relapse are available but rarely used in the hospital setting.
- Naltrexone and other medication-assisted treatment options are well studied in the outpatient setting; however, there are few studies exploring their initiation in the inpatient medical setting.

and lactation, central nervous system toxicity, and drug abuse and therefore can be tailored to specific patient populations, depending on their comorbidities.<sup>5</sup> For example, acamprosate can be used in liver failure but not in renal insufficiency whereas naltrexone should be avoided in liver failure but is permitted in renal insufficiency. Dosing and routes can also influence which MAT to use. Two additional agents that have been approved by the European Medicines Agency include nalmefene and gamma-hydroxybutyrate. The efficacy of nalmefene has not been found to be any better than placebo in clinical trials in the United States.<sup>6</sup> The abuse potential of gamma-hydroxybutyrate has led to caution with prescribing in Europe, and it is not FDA approved for AUD.<sup>7</sup>

Naltrexone, a long-acting opioid antagonist, is one of the most extensively studied medications to treat any substance use disorder, with several decades of research supporting its use<sup>5,8,9</sup> and an FDA approval dating back to 1994.<sup>10</sup> Naltrexone is unique in that it is available in both oral and long-acting injectable forms. In addition to evidence suggesting effectiveness in reduction of heavy drinking, this medication has a relatively benign adverse effect profile, and remains a first-line pharmacological treatment choice for AUDs. The mechanism proposed is a reduction of dopamine release from the nucleus accumbens in the setting of opioid receptor occupancy.<sup>11,12</sup> An important caveat is that attention must be paid to the patient's medication and substance use history to ensure there is no co-occurring use of opioids, prescribed

or illicit, as naltrexone can precipitate opioid withdrawal in those who are actively using, and should be avoided in such patients. However, naltrexone is also approved for opioid abstinence, making it a dual purpose medication in patients with both alcohol and opioid use disorders.

A 2005 Cochrane review of 50 randomized controlled trials (RCTs), including 7793 patients, found that naltrexone reduced the risk of heavy drinking to 83% of that in the placebo group<sup>13</sup> and was associated with an overall decrease in drinking days. Although its effectiveness has been adjudged as equivalent to that of acamprosate,<sup>8</sup> naltrexone is given as a once daily dose vs thrice daily, making it more convenient for daily use. These features combined with its favorable safety profile have led to naltrexone's role as a first-line agent for MAT of AUDs, prompting investigation into its potential value as a pre-discharge intervention for patients who are admitted for alcohol withdrawal.

Despite these favorable findings, there appears to be limited use of naltrexone in the acute setting when a patient is evaluated in the ED or admitted to the hospital.

The inpatient setting offers an opportunity to initiate treatment and possibly prevent substance use disorder progression, which may otherwise go untreated if left unaddressed. Furthermore, deferring treatment with naltrexone or other MAT to the outpatient setting may lead to patients being lost to follow-up and a missed opportunity to initiate a potentially beneficial medication. There is a lack of data on the implications of inpatient vs outpatient initiation of MAT. In our review, we focus on studies investigating the initiation of naltrexone in the inpatient setting.

The objective of this study was to systematically review the published literature on naltrexone (oral or injectable) initiated in the acute setting for the management of AUDs.

## METHODS

## Data Sources

We searched [ClinicalTrials.gov](https://www.clinicaltrials.gov), Ovid EBM Reviews, Ovid Embase (1974+), Ovid Medline (1946+, including epub ahead of print, in-process, and other nonindexed citations),

Ovid PsycINFO (1806+), Scopus (1970+), and Web of Science (1975+) from initiation to October 31, 2019. We also sought additional studies by reviewing the reference lists of the included articles. Search strategies were created using a combination of keywords (Supplemental Appendix 1, available online at <http://www.mcpiqjournal.org>) and standardized index terms related to naltrexone therapy for medically hospitalized patients with AUD.

### Data Selection

We included both RCTs and non-RCTs in which naltrexone was initiated during hospital course or upon discharge and was compared with a placebo as well as studies in which readmissions were identified. Studies without measurable outcomes, studies performed in outpatient, residential, or partial outpatient programs, studies in which psychiatric comorbidity was the primary focus, and those that examined use of naltrexone for anything other than AUD were excluded.

### Data Extraction, Quality, and Applicability Assessment

Two authors (N.M.M., J.M.) independently abstracted data on study design; setting; population characteristics (sex, age, race/ethnicity, comorbid conditions, and coronary anatomy); eligibility and exclusion criteria; numbers of patients screened, eligible, enrolled, and lost to follow-up; method of outcome assessment; and results for each outcome. Each study was assessed for bias independently, and consensus was reached by discussion. Disagreements in study selection and issues related to data extraction were resolved by discussion with a senior coauthor (R.W.K.).

### Data Synthesis and Analyses

Owing to small sample size and heterogeneity of the included studies, we performed a qualitative narrative synthesis of results. Risk of bias in all included studies was assessed using the Cochrane-validated ROBINS-I assessment tool,<sup>14</sup> which is specifically designed for assessing the risk of bias in nonrandomized trials (Supplemental Appendix 2, available online at <http://www.mcpiqjournal.org>).

## RESULTS

A total of 2102 records were identified. All results were exported to a citation manager, in which 984 obvious duplicates were removed, leaving 1118 unique citations. Forty full-text articles were assessed for eligibility (Figure). A total of 2 trials met the inclusion criteria. Both trials were uncontrolled pre- and postintervention studies in which providers were educated about naltrexone prescribing. Both trials were adjudged to have a serious risk of bias (Table). Naltrexone prescription rates in addition to 30-day hospital readmissions and 30-day ED revisits were the common outcomes.

### Naltrexone Prescription Rates

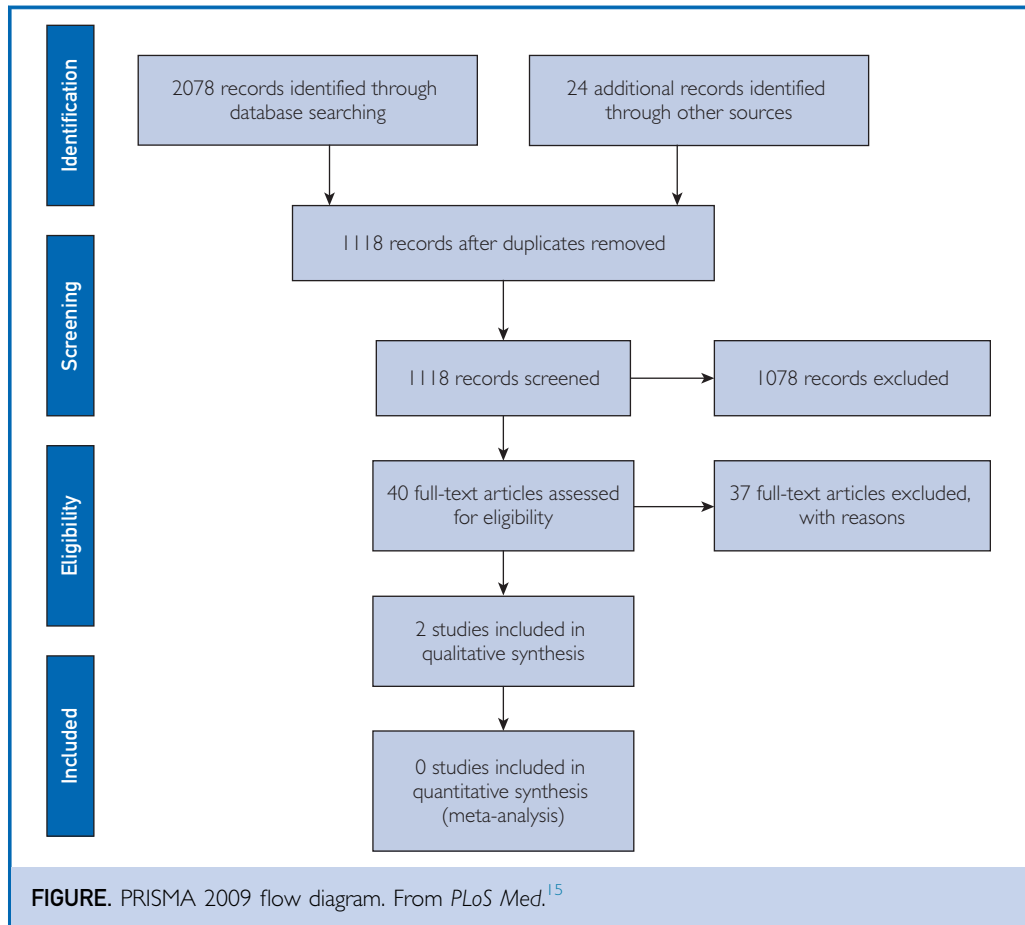
Two studies examined prescription rates of naltrexone pre- and post-educational intervention. Wei et al<sup>16</sup> implemented a discharge planning tool for all patients admitted with an alcohol-related diagnosis. This intervention led to an increase in oral naltrexone-prescribing rates from 0% to 64% ( $P < .001$ ). Likewise, Stephens et al<sup>17</sup> developed an algorithm for assessing eligibility for oral naltrexone, which included the addition of related smart phrases to the electronic medical record. An increase in naltrexone-prescribing rates from 1.6% to 28.1% was noted after these interventions.

### Thirty-Day Hospital Readmissions

Both studies examined all-cause inpatient readmissions at 30 days. Wei et al<sup>16</sup> found that rates of readmission decreased from 23.4% (15 of 64) to 8.2% (4 of 49) ( $P = .042$ ) after the implementation of the naltrexone-prescribing program. Stephens et al<sup>17</sup> found rehospitalization rates of 10.2% (13 of 128) preintervention and 11.4% (13 of 114) postintervention ( $P = .75$ ). In a subgroup analysis of those counseled about naltrexone use in the postintervention group, rehospitalization rates decreased from 26.2% (11 of 42) to 2.8% (2 of 72) ( $P < .001$ ).

### Thirty-Day All-Cause ED Visits

Thirty-day ED revisits were examined in 2 studies. Wei et al<sup>16</sup> found that 18.8% of patients (12 of 39) eligible for naltrexone before intervention had an ED revisit within 30 days.



This figure decreased to 6.1% (3 of 16) post-intervention ( $P = .056$ ). Stephens et al<sup>17</sup> found 25.8% (33 of 128) vs 19.3% (22 of 114) of patients ( $P = .23$ ) after intervention had an ED revisit. In a subgroup analysis, patients who received counseling about naltrexone before discharge were noted to have a lower odds ratio of ED revisit (odds ratio, 0.21; 95% CI, 0.07 to 0.60).

## DISCUSSION

### Summary of Evidence

The objective of this study was to review the published literature on naltrexone initiated in the inpatient setting for the management of AUDs. Two small pre-post intervention trials showed some promise with regard to increasing naltrexone prescription rates with appropriate provider education and a trend toward lower 30-day readmission rates and

rehospitalization rates in those prescribed naltrexone. Both studies used oral naltrexone, and results may not be applicable to the use of the long-acting intramuscular formulation. Barriers to initiation identified in the studies included general relative contraindications or contraindications such as current opioid use, opioid use disorder, or severe liver dysfunction. However, a lack of knowledge among prescribers needs to be addressed, and simple interventions were found to increase prescribing rates in these 2 studies. This lack of knowledge could be as simple as providers having a poor understanding of drug mechanism, indications, or side effects due to a lack of familiarity with the drug.

Ultimately, this systematic review reveals a paucity of evidence regarding naltrexone initiation in the inpatient medical setting. Given the dearth of information published on the topic, it begs the question as to whether there

TABLE. Assessed Risk of Bias in Evaluated Studies

Bias	Stephens et al <sup>17</sup>	Wei et al <sup>16</sup>
Bias due to confounding	Serious	Serious
Bias in selection	Serious	Serious
Bias in the classification of interventions	Moderate	Moderate
Bias due to deviations from intended interventions	Low	Low
Bias due to missing data	Serious	Serious
Bias in the measurement of outcomes	Serious	Serious
Bias in the selection of the overall result	Serious	Serious
Overall bias	Serious	Serious

are shortcomings in the standards of care for patients with AUD. Although it has been previously described that MAT of AUD is underprescribed,<sup>18</sup> the reasons for this are likely multifaceted. Patients suffering from substance use disorder represent a clinically challenging population, whose care is complicated by ambivalence to engage in treatment as well as low adherence, loss to follow-up, and low levels of insurance. This cohort also frequently experiences multiple comorbidities, especially psychiatric illnesses, and management of AUDs can fall to the wayside as acute crises take priority in the inpatient setting.<sup>19,20</sup> Unfortunately, it is also likely that the social stigma associated with AUD, a lack of understanding of AUD as a treatable condition, and a lack of clinician familiarity with pharmacotherapy for AUD are contributing factors in the low treatment rates observed.

In the clinical setting, referrals for addiction medicine or chemical dependency treatment are often provided, yet patients are often lost to follow-up and may begin drinking shortly after discharge, only to be readmitted with a similar clinical picture. Given the opportunity to make substantial interventions in the hospital setting, more research is needed to determine whether the initiation of MAT before discharge is of benefit. Indeed, there are ample data to suggest that hospitalized patients are more motivated to change their behavior, creating an opportunity for a “teachable moment,”<sup>7,21</sup> yet this will require both

time and resources as well as a multidisciplinary approach.<sup>16</sup>

Although there are factors to predict readmission,<sup>4</sup> clinical management received by most patients largely remains the same regardless of risk stratification. The use of a multidisciplinary approach may allow for the creation of protocols that can direct care toward the most vulnerable patients. One such protocol is the initiation of naltrexone or other MAT at discharge. However, as evident by our systematic review, there remains a lack of evidence to equip hospitalists with the confidence to do so. Nonetheless, this remains an important research topic given the safety and efficacy of MAT.<sup>22,23</sup>

Medical teams frequently interact with patients diagnosed with AUD and therefore play an important role in establishing initial steps to treatment, which may promote abstinence from drinking and subsequent reductions in hospitalizations. Prescribing MAT along with referral to substance abuse counselors, psychiatrists, and chemical dependency treatment centers may be effectively integrated into patient care when approached in a standardized manner. Limited evidence supports protocolization or enhancements through the electronic medical record to increase prescribing and to reduce 30-day rehospitalization rates.<sup>24</sup> Naltrexone may be a promising way to help break the readmission cycle in patients with AUD who are interested in taking medication. Additionally, it is important to consider the patient’s comorbidities and goals of care when discussing initiation of naltrexone, as it has shown the most benefit in reducing heavy drinking days as opposed to abstinence and may not be the best MAT choice for all patients. More research is needed to further investigate the utility of prescribing naltrexone upon discharge and its effect on outcomes such as readmission rate, relapse rate, and successful follow-up for chemical dependency treatment.

### Limitations

Given the paucity of literature on this topic, combined with the high degree of heterogeneity between the studies chosen, we are unable to draw meaningful conclusions about the efficacy of inpatient naltrexone initiation. Our findings highlight a need for further

investigation into this topic, ideally in the form of an RCT assessing outcomes related to readmission rates, relapse rates, and rates of successful referral for chemical dependency treatment. Furthermore, our decision to focus only on studies involving inpatient medical admissions does create a notable limitation of available studies for review. We acknowledge the high prevalence of psychiatric comorbidities in patients suffering from AUD and recognize that future studies could benefit from including cohorts of patients admitted for medical as well as psychiatric primary diagnoses.

## CONCLUSION

Naltrexone initiation at the time of medical hospitalization may be a promising way to help improve outcomes related to AUD and to break the readmission cycle in patients with AUD who are interested in taking medication with the goal of reducing heavy drinking. More research is needed to confirm the utility of prescribing naltrexone upon discharge and its effect on outcomes. No studies have looked at the inpatient application of long-acting naltrexone to date.

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## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: <http://www.mcpiqjournal.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** AUD = alcohol use disorder; FDA = US Food and Drug Administration; MAT = medication-assisted treatment; RCT = randomized controlled trial

**Potential Competing Interests:** The authors report no competing interests.

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