This paper was commissioned for the Committee on Study and Recommendations on the HIMS, FADAP, and Other Drug and Alcohol Programs within the USDOT, whose work was supported by the Federal Aviation Administration. Opinions and statements included in the paper are solely those of the individual author, and are not necessarily adopted, endorsed, or verified as accurate by the Committee on the Study and Recommendations on the HIMS, FADAP, and Other Drug and Alcohol Programs within the USDOT or the National Academies of Sciences, Engineering, and Medicine.

Impairment Effects: Pharmacotherapies for Alcohol Use Disorder (AUD) and Opioid Use Disorder (OUD) Treatment

INTRODUCTION

Alcohol is a psychoactive substance with dependence-producing properties that can lead to dependence or alcohol use disorder (AUD). Worldwide, 3 million deaths every year result from AUD. This represents 5.3% of all deaths around the world (World Health Organization (WHO), 2022). In the United States, alcohol causes 10% of deaths among 15 to 49 year olds (National Center for Drug Abuse Statistics (NCDAS), 2023).

Similarly, opioid dependence is a chronic relapsing disorder that is associated with increased risk of repeated abuse and death due to overdose. Worldwide, about 0.5 million deaths are attributable to drug use. More than 70% of these deaths are related to opioids, with more than 30% of those deaths caused by overdose.(World Health Organization, 2023) In 2018, an estimated 2 million people had an opioid use disorder (OUD). In 2010, There were 15.5 million opioid-dependent people globally in 2010. (Degenhardt et al., 2014) In the United States, the number of adolescent and adult individuals with OUD in 2019 was estimated between 6.7–7.6 million. (Keyes et al., 2022)

The impact of AUD/OUD on the transportation industry is substantial. According to the National Survey on Drug Use and Health (NSDUH), the rate of past month heavy alcohol use within the transportation industry is 8.8%, while the rate of past-month illicit drug use is 5.9% (Bush, & Lipari, 2015). According to the National Safety Council (National Safety Council (NSC), 2018) 13.9% of those working in the transportation industry have a substance use disorder.

Pilots are of particular concern within the transportation industry. According to the National Transportation Safety Board (NTSB) Aviation Accident Database from 2013 to 2017 (National Transportation Safety Board (NTSB), 2020), there were a total of 1,042 aviation accidents in the United States in which the flying pilot was fatally injured. Of those, 91% had available toxicology test results. During the 5 years ending in 2017, 266 (28%) fatally injured pilots tested positive for at least one potentially impairing drug, 144 (15%) pilots tested positive for at least one drug indicating a potentially impairing condition, 94 (10%) pilots' test results indicated evidence of use of at least one controlled substance, and 47 (5%) tested positive for an illicit drug. Sedating pain relievers, a category that includes opioids, was the second most common

category of potentially impairing drugs at 5.3%, after sedating antihistamines. Of the 50 pilots who tested positive for sedating pain relievers, 46 were positive for at least one opioid.

Availability of non-punitive programs aimed at return-to-duty for transportation workers is critically important for early recognition and treatment of AUD/OUD. Early diagnosis and treatment generally portend better long-term outcomes. Focusing only on control measures and removal of affected transportation workers likely reduces the acceptance of these individuals to seek support and may increase the risk of continued unsafe operations. An important development in available treatment of AUD/OUD is medication for addiction treatment (alternatively known as medication assisted therapies and medication assisted treatment; MAT).

MAT refers to the use of medications, typically in combination with counseling and behavioral therapies, to provide treatment of AUD and OUD with the goal of full recovery. Several medications have been approved by the Food and Drug Administration (FDA) for use in MAT. MAT is a recognized standard of care in AUD/OUD for relapse prevention in the United States, Europe, and Australia (Haber et al., 2021), and is endorsed by the World Health Organization (World Health Organization (WHO), 2009, 2023), the Agency for Healthcare Research and Quality (AHQR; (Jonas et al., 2014)) and the Substance Abuse and Mental Health Services Administration (SAMHSA)(Substance Abuse and Mental Health Services Administration (SAMHSA), 2015b). For example, buprenorphine and buprenorphine with naloxone are established first-line medications for the treatment of OUD per the American Psychiatric Association (Kleber et al., 2007), the World Federation of Societies of Biological Psychiatry guidelines, (Soyka et al., 2017; Soyka, Kranzler, et al., 2011), the New South Wales clinical guidelines (NSW Government, 2011), the British Association for Psychopharmacology guidelines (Lingford-Hughes et al., 2012), and WHO guidelines (World Health Organization (WHO), 2009). As this report will detail, research shows that a combination of medication and therapy are especially beneficial in the treatment of AUD and OUD. Specifically, MAT can help sustain recovery.

Despite the recognition of MAT as “first line” treatment for AUD/OUD, none of the FDA approved medications are currently allowed for use by pilots who are in recovery. The Federal Aviation Administration (FAA) special issuance program that permits a pilot in recovery to return to the cockpit prohibits the use of any of the FDA approved MAT medications. Furthermore, treatment programs where pilots are seen for inpatient rehabilitation avoid prescription of MATs in the treatment of these individuals. It is conceivable that the resistance to pilots in recovery receiving MAT is due to the perception that they likely have ‘lesser’ or incomplete recovery if they are taking or ‘relying upon’ such medications to maintain abstinence.

This review was unable to identify any FAA documentation (i.e., official guidance or procedures) used by the FAA in determining the suitability of medications for use by pilots. Efforts were made to locate such documentation online and through direct communications with the Office of the Federal Air Surgeon. [Informal conversations with former FAA personnel indicate that disallowance of medications is based upon a review of medications that have been approved by the FDA for a minimum of 1 year. The key criterion for disapproval is determination by FAA’s internal aviation medicine experts that the medications pose a risk to

flight operations.] There is no available documentation showing that the FAA has considered the suitability of MATs for use by pilots. It does not appear that there have been any instances of a pilot receiving a special issuance FAA Airman Medical Certificate who was receiving MAT.

In contrast to the FAA policy, the Flight Attendant Drug and Alcohol Program (FADAP) program manual (Flight Attendant Drug and Alcohol Program (FADAP), 2023) stipulates that, "flight attendants should be evaluated for and have access to medication assisted therapies for alcohol and opiate dependence as one tool of a comprehensive treatment plan" (page 14). It is recommended that MAT be used as part of a "whole-patient approach" and not in isolation. The benefits of MAT are outlined in the manual, and all flight attendants in treatment should be provided with information about benefits/limitation of MAT, side effects, and instructions for use. The FADAP provides AUD/OUD information on their website, and endorses the use of MAT under a physician's care (Flight Attendant Drug and Alcohol Program (FADAP), 2023).

This chapter provides a review of the current status of MAT for AUD and OUD. The review addresses the efficacy and safety of the medications approved by the FDA for relapse prevention and/or maintenance of abstinence for individuals with AUD/OUD. A particular focus of this report is the evidence related to the neurocognitive and neuropsychiatric effects of MAT. A further objective of the review is the identification of gaps in the evidence, and recommendations for future research.

This report is intentionally focused more on the safety implications of MAT than providing a comprehensive review of the evidence demonstrating the efficacy of MAT. For a review of efficacy of MAT for AUD and OUD the reader is referred to the most recent reviews (Chou et al., 2020; Ghanem et al., 2022; Lim et al., 2022; Mason, & Heyser, 2021; Ray et al., 2020). For each of the medications approved by the FDA for AUD/OUD, this report provides; (1) a summary of evidence surrounding the efficacy of the medication, (2) review of common CNS side effects, and (3) review of published studies investigating the neurocognitive and/or performance effects of the medication.

This report will not include a discussion of off-label, non-FDA-approved, medications such as topiramate, ondansetron, gabapentin, mifepristone, baclofen, oxytocin, or varenicline. For these medications there is some empirical evidence to support their use in MAT but their efficacy and safety has not been established by the FDA (Bold et al., 2019; Falk et al., 2019; Fischler et al., 2022; Garbutt, 2018; Garbutt et al., 2021; Johnson et al., 2008; Johnson et al., 2007; Leung et al., 2015; Mason et al., 2012; Mason et al., 2014; Myrick et al., 2008; Pedersen et al., 2013; Vendruscolo et al., 2015). Additionally, this report will not evaluate the cost or other economic issues and will be limited to MATs for AUD and OUD (as there are no FDA approved MATs for other substance use disorders). Furthermore, this report will not evaluate the literature regarding comorbid substance use and other psychiatric disorders (i.e., "dual diagnosis").

MAT FOR AUD: GENERAL COMMENTS

Although the focus here is pharmacotherapy or MAT for the treatment of AUD, MAT typically includes psychosocial interventions and treatment of underlying psychiatric comorbidities. Psychosocial interventions, including brief interventions, motivational enhancement therapy,

cognitive behavioral therapy, other behavioral approaches, family therapies, and 12-step facilitation have all been shown to be effective components of AUD treatment and may reduce alcohol consumption and improve abstinence rates (Kranzler, Ciraulo, & Zindel, 2014). Some patients may respond to psychosocial interventions and others to MAT alone, but most patients benefit from a combination of these approaches (Ray et al., 2020; Substance Abuse and Mental Health Services Administration (SAMHSA), 2015b). The most recent review (van Amsterdam et al., 2022) concluded that MAT is effective to treat AUD with or without psychotherapy and that psychotherapy can best be offered in combination with pharmacotherapy.

FDA APPROVED MAT FOR ALCOHOL USE DISORDER

There are currently three FDA-approved medications for AUD: disulfiram (Antabuse®), naltrexone (oral: Revia® and long-acting injectable: Vivitrol®), and acamprosate (Campral®). According to a study of the National Prescription Audit database (Mark et al., 2009), prescriptions of these medications is increasing over time, with acamprosate as the market leader. Within one large United States health plan (Baser et al., 2011), of 15,502 patients treated with an FDA-approved medication, acamprosate had the most prescribers (n = 8958), followed by disulfiram (n = 3492), oral naltrexone (n = 2391), and extended-release injectable naltrexone (n = 661).

The mechanisms of action differ, such that disulfiram causes negative physical effects after consuming alcohol, while naltrexone tempers the reinforcing or pleasurable effects of alcohol, and acamprosate normalizes dysregulation in neurochemical systems implicated in alcohol dependence.

Disulfiram

Approved by the FDA as an alcohol abuse deterrent in 1949, disulfiram (Antabuse®) disrupts the metabolism of alcohol, resulting in an unpleasant reaction, which can be severe whenever an individual taking disulfiram consumes alcohol. As such, it is an alcohol antagonist drug.

Pharmacology

Disulfiram blocks aldehyde dehydrogenase, which causes an accumulation of acetaldehyde when alcohol is ingested. Aldehyde dehydrogenase is a hepatic enzyme of the major oxidative pathway of alcohol metabolism, converting acetaldehyde to acetate. When acetate builds up, physical reactions can include diaphoresis, palpitations, facial flushing, nausea, vertigo, hypotension, and tachycardia. This aggregation of symptoms is known as the disulfiram-alcohol reaction and discourages alcohol intake. The reaction is proportional to both the dose of disulfiram and alcohol. Unlike other medications approved to treat alcohol use disorder, disulfiram does not directly affect opiate, gaba-aminobutyric acid, or glutamate receptors in the brain. Disulfiram blocks dopamine-beta-hydroxylase in the brain, thereby increasing dopamine levels and reducing noradrenaline levels.

Efficacy

There is modest evidence of disulfiram's efficacy. A meta-analysis of 22 randomized clinical trials (RCTs) showed an increase in total abstinence, percentage of abstinent days, mean days without alcohol, time to first drink, and a decreased likelihood of relapse with disulfiram as compared with no-treatment control.(Skinner et al., 2014) Subgroup analyses comparing blinded and non-blinded RCTs indicated that only the open-label trials showed a significant superiority of disulfiram over no-treatment controls (g = .70), whereas the RCTs with blinded designs showed no significant difference from no-treatment controls (g = .01). Double-blind studies with disulfiram are nearly impossible because of the aversive reaction induced by the drug – replicating such a reaction with placebo would require the same mechanism of action as the medication (e.g., the placebo and disulfiram would both have the threat of an aversive reaction).

The target population for disulfiram is patients who desire abstinence and who do not have liver disease, psychotic disorders, or seizure disorder. Motivation for supervised medication administration, either by a caregiver or medical professional, is essential (Allen, & Litten, 1992; Chick et al., 1992; Fuller et al., 1986). Studies show supervised ingestion provides significantly better outcomes than with unsupervised disulfiram use (Skinner et al., 2014). Support might additionally include the use of incentives, contracts, cooperation from family, the use of regular reminders, and behavioral counseling to improve adherence.

Safety

In terms of safety, a meta-analysis (Skinner et al., 2014) concluded that there were no differences between disulfiram and control groups in deaths or serious adverse events requiring hospitalization. There were, however, significantly more adverse events reported for disulfiram than for controls. Drowsiness is the most common side effect but occurs in a small number and is transient. Extreme caution should be exercised in those with a history of cardiovascular disease or psychosis.

Disulfiram is contraindicated in the presence of severe myocardial disease or coronary occlusion, psychoses, and hypersensitivity to disulfiram or to other thiuram derivatives used in pesticides and rubber vulcanization (LIVA Krakow Pharmaceutical Company, 2012). Because of the possibility of an accidental disulfiram-alcohol reaction, disulfiram should be used with extreme caution in patients with any of the following conditions: diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis, hepatic cirrhosis or insufficiency. Hepatic toxicity including hepatic failure resulting in transplantation or death have been reported (LIVA Krakow Pharmaceutical Company, 2012).

Optic neuritis, peripheral neuritis, polyneuritis, and peripheral neuropathy may occur following administration of disulfiram (LIVA Krakow Pharmaceutical Company, 2012). Multiple cases of hepatitis, as well as hepatic failure resulting in transplantation or death, have been reported with administration of disulfiram. In a small number of patients, a transient mild drowsiness, fatigability, impotence, headache, acne form eruptions, allergic dermatitis, or a metallic or garlic-like aftertaste may be experienced during the first two weeks of therapy (LIVA Krakow Pharmaceutical Company, 2012). These complaints usually disappear spontaneously with the continuation of therapy, or with reduced dosage. Psychotic reactions have been noted,

attributable in most cases to high dosage, combined toxicity (with metronidazole or isoniazid), or to the unmasking of underlying psychoses in patients stressed by the withdrawal of alcohol (LIVA Krakow Pharmaceutical Company, 2012).

The suggested duration of treatment with disulfiram is contingent on the patient establishing stable, long-term abstinence from alcohol (Substance Abuse and Mental Health Services Administration (SAMHSA), 2009). Disulfiram therapy may continue for months or years, depending on patient factors. Importantly, prolonged disulfiram use does not produce tolerance. A 3-year study (Bottlender, & Soyka, 2005) followed 103 individuals who had completed treatment for AUD and found that 43% were abstinent and another 12% were deemed improved. Treatment drop-out was a significant predictor of relapse. A 9-year study of 180 patients with chronic alcohol dependence (Krampe et al., 2006) concluded that the beneficial action of long-term (12- to 20-month) supervised disulfiram therapy was psychological, not pharmacological, because placebo worked as well as disulfiram. Nevertheless, the likelihood of remaining continuously abstinent years after termination of MAT was related to duration of supervised MAT with either disulfiram or placebo. It may be advisable to restart treatment in association with any high-risk situations, like holidays, etc. No withdrawal syndrome is associated with discontinuing disulfiram, but disulfiram–alcohol reactions may occur within 2 weeks of discontinuing the medication (Substance Abuse and Mental Health Services Administration (SAMHSA), 2009).

Cognitive studies

Please see Table 1 for a review of studies that relate to performance and subjective changes related to MAT for AUD. Generally, individuals maintained on MAT for AUD or OUD generally perform more poorly on cognitive tasks than normal healthy controls (Darke et al., 2012; Darke et al., 2000; McDonald et al., 2013; Messinis et al., 2009; Prigatano, 1980; Rapeli et al., 2007; Rapeli et al., 2009; Saroj et al., 2020; Soyka et al., 2008), but better than untreated individuals with AUD/OUD (Nikraftar et al., 2021; Saroj et al., 2020).

A review of specific studies (Table 1) suggests that there is limited evidence that disulfiram significantly impacts cognitive performance. Assessment in the chronic phase, after weeks of treatment, whether in healthy controls or individuals with AUD, suggests no effect of disulfiram on cognitive performance, and the suggestion of possible improvement.

Table 1. Cognitive Effects of MAT for AUD

Study First Author	Treated Sample	Comparison	Dose	Duration of Treatment	Time between MAT dose and test	Cognitive Domain or Subjective Rating	Study Findings
Disulfiram							
Peeke (1979)	7 HC	Baseline	0.5 g/day	2 weeks	N/A	ATT(2),MTR(1), PS(1),VP(2), LM(1),O(1), SR(1)	Better on PS
Gilman (1996)	11 AUD	37 AUD	250 mg/day	17-30 days	N/A	EX(1),MTR(1), O(1)	NS
Prigatano (1980)	15 AUD	9 AUD	250 mg/day	2 weeks	N/A	ATT(2), EX(1),LM(2), MTR(2)	NS
Naltrexone							
Swift (1994)	19 HC	12 HC	50 mg	N/A	30-60 mins	ATT(3), LM(1),PS(2), SR(1)	NS
Chaves (1988)	19 HC	18 HC	50 mg	N/A	60 mins	LM(2)	NS
Hatsukami (1986)	13 HC (overweight)	15 HC (overweight)	300 mg/day	4 and 7 weeks	N/A	ATT(1), EX(1), LM(4),PS(2), SR(1)	NS
van Steenbergen (2017)	18 HC	22 HC	50 mg	N/A	76 mins	EX(2)	Better on post-error accuracy, slower post-error
Malcom (1987)	36 HC (overweight)	Placebo	200 mg/day	8 weeks	N/A	SR(1)	NS
Nestor (2019)	21 AUD	35 HC	50 mg	N/A	2 hours	EX(1)	NS

McCaul (2000)	23 AUD	Baseline	0, 50 mg, 100 mg	8 days	N/A	ATT(1),PS(1), SR(1)	Worse SR, PS
Johnson (2003)	23 AUC	Placebo	50 mg, 100 mg	23 days	N/A	LM(1),PS(2), SR(2)	NS
Acamprosate							
Schneider (1999)	12 HC	Placebo	2g/day	7 days	N/A	ATT(1),LM(2),O(1)	Worse on 1 LM
Schneider (1998)	12 HC	Placebo	2g/day	7 days	N/A	ATT(4),SR(1)	NS
Johnson (2003)	23 AUC	Placebo	2 g/day, 3 g/day	23 days	N/A	LM(1),PS(2), SR(2)	Increased fatigue on 3g
Soyka (1998)	5 AUC	Baseline	1998 mg/day	6 months	N/A	ATT(3)	Better on 2 ATT

Note. AUD = alcohol use disorder, HC = healthy control, N/A = not applicable, Unk = unknown, NS = Not significantly different from comparison group/condition, ATT = attention and working memory, EX = executive functioning, LM = learning/memory, MTR = motor skills, PS = processing speed, SR = subjective report, VP = visuoperceptual or visual cognitive, O = other.

Box 1. Domain Tests Listed in Tables

Attention/working memory: ACT, ART, CFF, CPT, CTA, CTT, DAT, DCT, DMTS, DRT, DSpan, DVT, GDSA, IntegNeuro, LNS, Mackworth Clock Test, MAT, Modified CPT, n-Back, PAL, PASAT, PRM, PVT, Ruff 2 & 7 Selective Attention Test, SRT, SSP, SSPT, SWM, TAP, Time Estimation, UFOV, VIGIL, VST

Executive Functioning: AGN, AM, Category Test, CGT, Color Trails, FDT, IGT, IntegNeuro KST, Mazes and Switching of Attention, PES, Similarities, SOC, SSRT, Stroop Test, TAP Go/NoGo, TOL, Trails B, WCST

Language: BNT, COWAT, FAS, IntegNeuro (Word Generation), Multiple Choice Vocabulary Test, NART, NCCEA, RWT, Semantic Fluency, Spot the Real Word, WAIS-R/III (Vocabulary)

Learning/Memory: BSRT, BVMT-R, BVRT, CVLT, Delayed Recall, Free Recall Verbal Memory, HVLT, IntegNeuro (Memory Recall and Recognition), LM, Memory and Location of TPT, Memory for Facts and Dates, MPD, Pattern Learning, Prose Recall, RAVLT, RBANS (Complex Figure Task), Rivermead Behavioral Memory Test, ROCFT, Six Object Memory Test, Verbal Learning Test, VLMT, WIT (recall and recognition), WMP, WMS, WSL

Motor Skills: FTT, IntegNeuro (Motor Tapping), PPT, TPT

Processing Speed/Reaction Time: BACS, Binary Choice Reaction Time, Choice Reaction Time, Color Trails Part 1, Continuous Reaction Time, DSST, IntegNeuro (Choice Reaction Time), MSMRT, OTMT, RVIPT, SRRT, SSRT, SS, Stroop Color and Word Conditions, Trails A, Visual Search

Subjective Report: Beschwerde-Liste, MCQ, Mood Rating Scale, PCAG, POMS, SDQ, VAS

Visuoperceptual, Visuospatial, Visual Cognitive: BD, Categorization Reaction Time, Hidden Figures Test, Koh's BD, ROCFT, SPM, Thurstone Concealed Figures

Other: HRII, MWIT, Reading Comprehension, Vocabulary and Picture Completion premorbid estimate from WAIS-R, WAIS FSIQ

Notes. ACT = Attentional Capture Test, AGN = Affective Go/NoGo (CANTAB), AM = Austin Maze, ART = Act & React Test System ART-90, BACS = Brief Assessment of Cognition Symbol Coding Test, BD = Block Design (WAIS), BVMT-R = Brief Visuospatial Memory Test – Revised, BVRT = Benton Visual Retention Test, BNT = Boston Naming Test, BSRT = Buschke Selective Reminding Test, CANTAB = Cambridge Neuropsychological Test Automated Battery, CFF = critical flicker fusion threshold-test, CGT = Cambridge Gambling Task (CANTAB), COWAT = Controlled Oral Word Association Test, CPT = Continuous Performance Test, CTA = Computerized Test of Attention, CTT = Critical Tracking Task or

Compensatory Tracking Task, CVLT = California Verbal Learning Test, DAT = Divided Attention Task, DCT = Digit Cancellation Test, DMTS = Delayed Match to Sample (CANTAB), DRT = Digit Recall Task, DSpan = Digit Span (WAIS-R/III), DSST = Digit Symbol Substitution Test, DTS1 = Vienna Test System Determination Test, DVT = Digit Vigilance Test, FAS = Phonemic Fluency Test, FDT = Five Digit Test, FTT = Finger Tapping Test, GDSA = Goal-Directed Serial Alternation, HRII = Halstead-Reitan Impairment Index, HVLT = Hopkins Verbal Learning Test, IGT = Iowa Gambling Test, KST = Key Search Test, LNS = Letter Number Sequencing Test (WAIS/WSM-III), LM = Logical Memory, MAT = Mental Arithmetic Test, MCQ = Memory Complaint Questionnaire, MPD = Memory for Persons Data, MSMRT = Multiple-Discrimination-Multiple-Response Reaction Time, MWIT = Mehrfachwahl-Wortschatz Intelligence Test, NART = National Adult Reading Test, NCCEA = Neurosensory Center Comprehensive Examination for Aphasia, PASAT = Paced Auditory Serial Addition Test, PAL = Paired Associate Learning (CANTAB), PCAG = Pentobarbital Chlorpromazine Alcohol Group, OTMT = Oral Trailmaking Test, PES = Post-Error Slowing, POMS = Profile of Mood States, PPT = Purdue Pegboard Test, PRM = Pattern Recognition Memory (CANTAB), PVT = Psychomotor Vigilance Task, RAVLT = Rey Auditory Verbal Learning Test, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, ROCFT = Rey Osterrieth Complex Figure Test, RVIPT = Rapid Visual Information Processing Task, RWT = Regensburger Word Fluency Test, SDQ = Single Dose Questionnaire, SOC = Stockings of Cambridge (CANTAB), SPM = Standard Progressive Matrices, SRT = Seashore Rhythm Test, SRTT = Simple Reaction Time Test, SS = Symbol Search (WAIS-III), SSP = Spatial Span Task (CANTAB, WMS-III), SSPT = Speech Sounds Perception Test, SSRT = Stop Signal Reaction Time, SWM = Spatial Working Memory (CANTAB), TAP = Test of Attentional Performance, TOL = Tower of London, TPT = Tactual Performance Test, TPT = Tactual Performance Test, Trails A = Trailmaking Test Part A, Trails B = Trailmaking Test Part B, UFOV = Useful Field of View Test, VAS = Visual Analog Scale, VLMT = Verbal Learning and Memory Test, VIGIL = VIGIL Computerized Vigilance Test, VST = Visual Search Task, WAIS = Wechsler Adult Intelligence Scale, WAIS-R = Wechsler Adult Intelligence Scale – Revised, WCST = Wisconsin Card Sorting Test, WIT = Wilde Intelligence Test, WMP = Word Memory Paradigm, WMS = Wechsler Memory Scale, WSL = Word Sequence Learning Test

Driving studies

In terms of driving, according to the FDA approved package insert, caution should be exercised when beginning treatment with disulfiram. In a small number of patients, a transient mild drowsiness and/or fatigue may be experienced during the first two weeks of therapy. These complaints usually disappear spontaneously with the continuation of therapy, or with reduced dosage (Duramed Pharmaceuticals Inc, 2010). There are no empirical studies specifically addressing the impact of disulfiram on driving performance.

Naltrexone

Naltrexone (Revia®) was first approved by the FDA for AUD in 1994 (with later approval in 2006 as an extended-release intramuscular injectable; Vivitrol®) for alcohol dependence and has been shown to decrease relapse to heavy drinking and total alcohol consumption (Anton et al., 2006).

Pharmacology

Naltrexone blocks the mu-opioid receptor (and it is also a weaker antagonist of the kappa and delta-opioid receptors). Naltrexone reduces the urge to consume alcohol through two mechanisms - suppression of alcohol-mediated beta-endorphin stimulation of dopamine neurons in the nucleus accumbens and reduction of beta-endorphin disinhibition of the tonic inhibition of dopamine cells by gamma-aminobutyric acid neurons in the ventral tegmental area. With extended-release injectable naltrexone, peak blood levels occur approximately 2 hours after injection and a second peak occurs approximately 2 days later. About 14 days after injection, blood levels slowly begin to decline.

In terms of the duration of treatment, the FDA label states that naltrexone should be taken for up to 3 months to treat AUD. In a study with Veterans who had completed induction on naltrexone (Greenstein et al., 1983), at least 30 days of naltrexone therapy was necessary for significant improvement at 1-month follow-up. Longer periods of treatment were not necessarily associated with greater gains. Two controlled studies (Hernandez-Avila et al., 2006; Kranzler et al., 2003) support the use of periodic or targeted dosing (i.e. targeted to situations identified by the patients as being high risk for heavy drinking). As such, following abstinence, it may be beneficial to take naltrexone at times when there is high risk of relapse, such holidays or during a personal tragedy. Discontinuation of oral naltrexone is not associated with a withdrawal syndrome, and it is not necessary to taper the dose.

Research has not yet clearly defined the optimal duration of treatment with injectable naltrexone. Some recommend that healthcare providers consider discontinuing injectable naltrexone once a patient has achieved stable abstinence from alcohol and has established a sound plan and support for ongoing recovery. Like oral naltrexone, injectable naltrexone may be useful for short periods when a patient in stable recovery is at particular risk for relapse to problem alcohol use. When discontinuing treatment, patient education is paramount, including possible enhanced sensitivity to opioids after discontinuing treatment and the importance of not taking any opioid medications for at least 30 days from the date of last injection (Substance Abuse and Mental Health Services Administration (SAMHSA), 2009).

Efficacy

Early systematic reviews concluded that naltrexone is effective for lowering overall drinking, heavy alcohol consumption, and improving controlled consumption (Bouza et al., 2004; O'Malley, 1996) In a review of 11 double-blind, placebo-controlled trials, oral naltrexone, combined with psychosocial interventions, reduced relapse rates at 3 months (Bouza et al., 2004). Of note, most studies were done with individuals who entered the study abstinent. Short-term outcomes included lower relapse rates (38% with naltrexone versus 60% with placebo), lower rate of return to drinking (61% versus 69%), reduced craving for alcohol, and fewer total drinking days. Naltrexone was reported to be especially useful in patients who have a history of relapses. (O'Malley, 1996). Extended-release injectable naltrexone is approved for use only in patients who can refrain from drinking for several days before treatment begins. In a 6-month RCT, those taking extended-release injectable naltrexone had a 25% reduction in heavy drinking

days compared to placebo. (Garbutt et al., 2005). [A heavy drinking day is defined as a day on which alcohol consumption is equal to or greater than 5 drinks in men and 4 drinks in women.]

Meta-analytic studies have convincingly demonstrated the efficacy of naltrexone in decreasing total alcohol consumption and relapse to heavy drinking (Jonas et al., 2014; Rosner et al., 2010). Rosner et al. (Rosner et al., 2010) found, based on a total of 50 RCTs with 7793 patients, that naltrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group and decreased drinking days by about 4%. Significant effects were also demonstrated for reducing the number of heavy drinking days and amount of alcohol consumed, while effects on return to any drinking was not significantly different between groups.

There is evidence that male gender and requiring abstinence for a period before beginning treatment improves outcome for those taking naltrexone (Garbutt et al., 2014; Maisel et al., 2013; O'Malley et al., 2007). It has also been reported that family history of AUD and the presence of the OPRM1 Asn40Asp polymorphism may moderate outcome for users of naltrexone (Garbutt et al., 2014). There is limited evidence for other moderators impacting treatment benefit for naltrexone, including: a sweet-liking phenotype, and high craving for alcohol, both of which are associated with a positive response to naltrexone, particularly in combination (Garbutt et al., 2016; Jonas et al., 2014), as well as the presence of baseline depression (Kiefer et al., 2005) and smoking status (Schacht et al., 2017).

Safety

Reported side effects of naltrexone are mainly gastrointestinal problems and sedative effects (Rosner et al., 2010). Side effects reportedly can be mitigated by taking naltrexone with food and building up the dose. Naltrexone has been administered to AUD patients for 6 months to 1 year with no additional safety concerns (Balldin et al., 2003; O'Malley et al., 2003).

According to the package insert (Alkermes Inc, 2010), in controlled clinical trials of naltrexone administered to adults with AUD, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more frequent in patients treated with naltrexone than in patients treated with placebo (1% vs. 0). Depression-related events associated with premature discontinuation of study drug were also more common in patients treated with naltrexone (~1%) compared to placebo-treated patients (0). In a 24-week, placebo-controlled pivotal trial in 624 AUD patients, depressed mood was reported by 10% of patients treated with naltrexone 380 mg, as compared to 5% of patients treated with placebo injections (Alkermes Inc, 2010).

Relevant adverse events seen most frequently in association with naltrexone therapy for AUD (i.e., those occurring in ≥5% and at least twice as frequently with VIVITROL than placebo) include dizziness or syncope and somnolence or sedation (Alkermes Inc, 2010).

When considering all treatment-emergent clinical adverse reactions, regardless of causality, occurring in ≥5% of patients with AUD, for which the incidence was greater in the naltrexone group than in the placebo group, 21% of naltrexone-treatment patients complained of headache

versus 18% in the placebo group, 13% complained of dizziness versus 4% of the placebo group, and 5% complained of somnolence versus 1% of the placebo group (Alkermes Inc, 2010).

In an open-label study of 570 alcoholics seeking treatment, the most commonly reported new-onset events were nausea (naltrexone group, 9.8%; reference group, 0.0%) and headache (naltrexone group, 6.6%; reference group, 1.7%) (Croop, Faulkner, & Labriola, 1997). Other symptoms included: dizziness (4.4% versus 0.4%), fatigue 3.6% versus 0.4%, nervousness 3.8% versus 0%, insomnia 3% versus 0%, anxiety 2% versus 0.8%, somnolence 2% versus 0.4%, and depression 1.4% versus 1.7% (Croop, Faulkner, & Labriola, 1997).

Cognitive studies

A review of studies investigating neurocognitive effects (Table 1) shows no neurocognitive effects associated with acute dosing of naltrexone in healthy controls. However, there do appear to be some subjective CNS-related changes, such as fatigue and sleepiness occurring at 2 to 8 hours after treatment and persisting for 2 to 3 hours. There is no evidence of neurocognitive compromise with chronic treatment, nor are there subjective difficulties in the chronic phase at typical doses.

Driving studies

Both the oral and long-acting injectable forms of naltrexone carry package insert warnings against driving or operating heavy machinery due to possible dizziness until it is determined how the drug affects each individual (Alkermes Inc, 2010; Duramed Pharmaceuticals Inc, 2013).

A study of 10 individuals with AUD receiving treatment of 3 monthly injections of extended-release naltrexone (Lapham, & McMillan, 2011) found that the percentage of vehicular failures-to-start due to elevated breath alcohol (i.e., unable to drive due to alcohol level with an alcohol ignition interlock device) decreased while on treatment from 3.1% to 1.29%.

Acamprosate

Acamprosate (Campral®) was approved by the FDA in 2004 with demonstrated primary effectiveness for maintaining abstinence from alcohol. The target population for acamprosate includes patients who desire continued sobriety after a period of abstinence.

Pharmacology

The mechanism of action for acamprosate is unknown. It appears to involve modulation of the glutamatergic neurotransmitter system to counteract the imbalance between the glutamatergic and GABAergic systems associated with chronic alcohol exposure and alcohol withdrawal. Unlike disulfiram and naltrexone, acamprosate is not affected by liver function and is therefore safe for use in those individuals with liver disease. Acamprosate is contraindicated in patients with severe renal impairment (Forest Pharmaceuticals Inc, 2005). The suggested duration of treatment with acamprosate is at the discretion of the medical provider. A study (O'Malley et al., 1996) of 80 individuals with AUD who had discontinued 12 weeks of treatment with naltrexone found that the effect of naltrexone therapy on abstinence rates persisted only through the first

month of follow-up, suggesting that more than 12 weeks of treatment may be needed to maintain gains. The effectiveness and safety of acamprosate have been evaluated for up to 1 year (Substance Abuse and Mental Health Services Administration (SAMHSA), 2009). It is recommended that discontinuation of acamprosate may be considered once stable abstinence has been achieved, along with diminished craving, and a plan for ongoing recovery. Acamprosate therapy also may be discontinued if a patient is not adhering to the medication regimen. Acamprosate should not be discontinued just because a patient returns to alcohol use (Substance Abuse and Mental Health Services Administration (SAMHSA), 2009).

Efficacy

A systematic review (Bouza et al., 2004) of 33 studies found that acamprosate was associated with significantly improved abstinence rates and cumulative days of abstinence. The medication was also associated with significantly improved treatment compliance. Meta-analytic reviews have demonstrated the efficacy of acamprosate (Jonas et al., 2014; Maisel et al., 2013; Rosner et al., 2008) in terms of reduction in return to drinking (Jonas et al., 2014) and improving abstinence (Maisel et al., 2013; Rosner et al., 2008).

Better outcomes have been demonstrated in those with greater length of sobriety before treatment initiation (Karpyak et al., 2014; Soyka, & Muller, 2017). Acamprosate has been shown to be especially effective in those with negative emotional state-based craving (relief drinkers) and has also been shown to reverse alcohol-related changes in sleep architecture and help with sleep deprivation-induced cravings (Karpyak et al., 2014; Soyka, & Muller, 2017). Other moderators of outcome include having a stated goal of abstinence (Berger et al., 2013), baseline craving intensity (Ho et al., 2022), baseline serum glutamate levels (Nam et al., 2015), baseline somatic stress (Kiefer et al., 2005), and various genetic polymorphisms and metabolomic profiles (Ho et al., 2022; Karpyak et al., 2014).

Safety

In controlled clinical trials, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but occurred more frequently in treated patients than in patients treated with placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in year-long studies) (Forest Pharmaceuticals Inc, 2005). Completed suicides occurred in 3 of 2272 (0.13%) patients in the pooled acamprosate group from all controlled studies and in 2 of 1962 patients (0.10%) in the placebo group.

Adverse events coded as "depression" were reported at similar rates in acamprosate-treated and placebo-treated patients in early trials. Adverse symptoms, including nausea, depression, and anxiety, while accounting for discontinuation in less than 1% of patients, were nevertheless more commonly cited in association with discontinuation in acamprosate-treated patients than in placebo-treated patients (Forest Pharmaceuticals Inc, 2005).

In spontaneously reported adverse events, dizziness was reported at a rate greater than the placebo group in controlled clinical trials; 4% for those on a dose of 1332 mg/day, 3% for those on a dose of 1998 mg/day, and 3% for the placebo groups (Forest Pharmaceuticals Inc, 2005).

Cognitive studies

It has been theorized that acamprosate may have neuroprotective effects (De Witte et al., 2005; Koob et al., 2002). However, as reviewed in Table 1, there is no evidence to support this theory. In healthy individuals no differences were found between those administered acamprosate over 7 days and those receiving placebo on a cognitive test battery (with the exception of an isolated finding of reduced recall on a memory task). Similarly, no differences were found on self-report measures of cognitive functioning. There was one study which reported increased subjective fatigue after 23 days of treatment but no cognitive or other subjective complaints (Johnson, 2003).

Driving studies

Per the FDA approved package insert, patients are advised against driving or operating heavy machinery until they are reasonably certain that acamprosate does not affect their ability to engage in such activities (Forest Pharmaceuticals Inc, 2005). There are no empirical studies specifically addressing the impact of acamprosate on driving performance.

Summary of FDA-Approved MAT for AUD

MAT for AUD appears to be relatively effective and safe. The drug labels for all three of the FDA approved medications carry a warning indicating that caution should be exercised when driving or operating machinery until the individual taking the medication has enough time and experience on the medication to understand its potential effects. Driving performance after taking these medications has not been studied using a dedicated driving study. Available evidence suggests that subjective changes such as increased somnolence, dizziness and fatigue occur in a small percentage of individuals taking the medication but are likely transitory. There is no evidence that these medications have significant neurocognitive effects.

MAT FOR OUD: GENERAL COMMENTS

Currently there are three medications approved by the U.S. Food and Drug Administration (FDA) for treatment of OUD. These include the full opioid agonist methadone (Dolophine® or generic or oral concentrate, Methadose® or generic), the partial opioid agonist buprenorphine, and the long-acting injectable opioid antagonist naltrexone (Vivitrol®). The following buprenorphine products are FDA approved for the treatment of OUD: generic buprenorphine/naloxone sublingual tablets, buprenorphine sublingual tablets (Subutex®), buprenorphine/naloxone sublingual films or buccal or tablet (Suboxone®), buprenorphine/naloxone sublingual film (Cassipa®), buprenorphine/naloxone sublingual tablets (Zubsolv®), buprenorphine/naloxone buccal film (Bunavail®), buprenorphine implants (Probuphine®), and buprenorphine extended-release injection (Sublocade®).

The most widely used MATs for OUD are methadone and buprenorphine. These are also the most well-studied (Sugarman et al., 2022). Another approach is complete detoxification and induction to the antagonist medication, naltrexone. In a national study of 70,538 Medicare beneficiaries with OUD during the pandemic from September 2019 to February 2021, the most

frequent MAT prescribed was methadone (2.84% of the sample), followed by buprenorphine (0.12%); there were no naltrexone prescriptions.

Some patients may respond to psychosocial interventions and others to MAT alone, but most patients benefit from a combination of these approaches (Amato et al., 2011; Ray et al., 2020).

Methadone

Approved by the Food and Drug Administration (FDA) in 1947 for analgesic and antitussive uses, methadone (Methadose®, Dolophine®) was shown to be effective in treating opiate addiction in the mid-1960s and was approved by FDA for this use in late 1972. It now has indications for detoxification treatment of opioid addiction, maintenance treatment of opioid addiction, and management of pain severe enough to require daily, around-the-clock, long-term term opioid treatment and for which alternative treatment options are inadequate (Roxane Laboratories Inc, 2014). Detoxification is defined as using methadone "as a substitute narcotic drug in decreasing doses to reach a drug free state in a period not to exceed 21 days" in order to "withdraw an individual who is dependent on heroin or other morphine-like drugs from the use of these drugs." Maintenance, the provision of which is restricted to methadone treatment programs, involves using methadone "at relatively stable doses" for more than 21 days along with the appropriate social and medical services. Methadone, a pharmaceutical opioid, is currently marketed as oral concentrate (10 mg/ml), oral solution (5 and 10 mg/5ml), tablet (5, 10, and 40 mg), injection (10mg/ml) and powder (50, 100, and 500 mg/bottle for prescription compounding).

Pharmacology

Methadone hydrochloride is a mu-agonist, synthetic opioid analgesic with multiple actions qualitatively like those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. It acts to modulate various neurochemical activities involved in analgesia, euphoria, and sedation. Methadone is also a non-competitive antagonist to the *N*-methyl-d-aspartate (NMDA) receptor, possibly further adding to its benefits for neuropathic pain.

Methadone maintenance treatment has the longest successful track record in patients addicted to opioids for more than a year and has been shown to control withdrawal symptoms and improve functionality (Substance Abuse and Mental Health Services Administration (SAMHSA), 2012). Methadone maintenance is considered a long-term treatment for OUD even though it has been used on a short-term basis to detoxify patients from opioids (Douaihy, Kelly, & Sullivan, 2013). It has potential for abuse, and there are no protective factors for overdosing. Benefits include the reduction or elimination of opiate withdrawal symptoms and drug-seeking behavior, no euphoric, tranquilizing, or analgesic effects, no change in tolerance levels over time, and minimal side effects. Methadone is slow acting, usually lasting between 24-36 hours. Federal regulations require that methadone initially be given daily under observation for either 6 or 7 days per week (Substance Abuse and Mental Health Services Administration (SAMHSA), 2015a). In closely monitored settings such as inpatient programs, multiple split doses can be administered per day based on patients' symptoms at peak blood levels. Outpatient programs are limited in this approach because patients can be monitored only when they are at the site.

Longer duration of treatment is generally predictive of better outcome. In one study conducted in New York City, it was found that patients who stayed in treatment a year or more abused substances less than those who left treatment earlier (Hartel, & Schoenbaum, 1998). Decisions concerning treatment duration ideally are made jointly between the patient and the treatment team (Substance Abuse and Mental Health Services Administration (SAMHSA), 2012). A review of the literature surrounding post-discharge outcomes (Magura, & Rosenblum, 2001) found universally high rates of relapse after methadone treatment is discontinued.

A phased approach to treatment with methadone is recommended (Substance Abuse and Mental Health Services Administration (SAMHSA), 2012), including the (1) acute, (2) rehabilitative, (3) supportive-care, (4) medical maintenance, (5) tapering (optional), and (6) continuing-care phases. The duration of the entire treatment program is quite variable and depends on patient and other factors. At least 2 years of continuous treatment is recommended, in addition to continued abstinence, before a patient would enter the medical maintenance phase. In addition, random drug testing and callbacks of medication are recommended during the medical maintenance phase to ensure that patients are compliant (Substance Abuse and Mental Health Services Administration (SAMHSA), 2012). Appointments with the treatment facility are recommended every 1 to 3 months during the continuing care phase. The duration of this and other phases are variable. Patients can be maintained long-term on methadone with physicians in the community.

Efficacy

The benefits of methadone maintenance treatment for OUD are well documented, including a significant reduction in the use of opiates, relative to placebo. A recent meta-analysis (Lim et al., 2022) found that patients treated with methadone, have higher retention rates in treatment than non-pharmacotherapeutic control groups. Earlier meta-analyses likewise have found superior retention in treatment and superior outcomes in terms of opioid abuse with methadone compared to placebo (Connock et al., 2007; Farre et al., 2002; Ferri, Davoli, & Perucci, 2011; Johansson, Berglund, & Lindgren, 2007); they have also found that high doses of methadone were more effective than low doses in the reduction of illicit opioid use (Castells et al., 2009; Connock et al., 2007; Farre et al., 2002) with a proposal of doses starting at 50 mg/day or higher (Farre et al., 2002). Amato and colleagues (Amato et al., 2013) conducted a review of the literature and found that relative to placebo, methadone decreased severe withdrawal and reduced dropouts. Cochrane reviews (Mattick et al., 2002, 2003, 2009) have likewise concluded that methadone is an effective MAT for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilize opioid replacement therapy. In the context of correctional facilities, treatment with methadone has been found to significantly increase community treatment engagement, reduce illicit opioid use and reduce injection drug use (Ferri, Davoli, & Perucci, 2011; Johansson, Berglund, & Lindgren, 2007; Moore et al., 2019; Sharma et al., 2016).

One notable moderator of outcome includes concomitant psychosocial treatment (Liu, & Li, 2023). Another moderator is dose level. High doses tend to be more efficacious than lower ones in the achievement of sustained heroin abstinence (Castells et al., 2009).

Safety

Because OUD is associated with a high risk of premature death, many studies have examined this issue. A systematic review of the topic concluded that methadone maintenance therapy reduces mortality, as well as HIV risk (Connock et al., 2007). Various meta-analyses (Ma et al., 2019; Santo et al., 2021; Sordo et al., 2017) have found that retention in methadone treatment is associated with substantial reductions in the risk for all-cause and overdose mortality.

Few adverse events are reported in methadone trials (Mattick et al., 2014). The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating (Roxane Laboratories Inc, 2014). These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable. (Roxane Laboratories Inc, 2014). According to the package insert, methadone can cause respiratory depression, arrhythmia, and interactions with antidepressants (Roxane Laboratories Inc, 2014). The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred. Methadone can be fatal in overdose and can increase risk of severe liver disease with the concomitant use of other substances such as alcohol or sedative-hypnotics such as benzodiazepines and barbiturates (Douaihy, Kelly, & Sullivan, 2013).

According to the FDA approved package insert, methadone may impair the mental or physical abilities needed to drive a car or operate machinery (Roxane Laboratories Inc, 2014). The basis for this warning is not reported.

Cognitive studies

A list of studies investigating the performance and subjective effects of MAT for OUD is presented in Table 2.

Adverse acute effects of methadone are apparent on measures of attention/working memory, executive functioning, language, learning/memory, and subjective measures (of sedation and cognitive functioning). There is some suggestion that larger doses may exacerbate these effects, relative to smaller doses (Strand, Ramaekers, et al., 2019).

Mindt and colleagues (Mindt et al., 2022), in their recent review of the literature on methadone and buprenorphine, concluded that, relative to healthy controls, those treated with methadone generally perform significantly worse on measures of attention, working memory, executive functioning, learning and memory, processing speed, visual cognitive abilities, and language, with small to large effect sizes. Comparisons between those treated with methadone and those currently using opioids (or those who have OUD but are abstinent) were inconclusive, but most studies show better performance with methadone treatment, or no difference. Longitudinal studies report either improvement over time in various cognitive domains, or no significant change (Mindt et al., 2022).

Table 2. Cognitive Effects of Naltrexone for OUD

Study First Author	Treated Sample	Comparison	Dose or Average Dose	Duration of Treatment	Time between MAT dose and test	Cognitive Domain or Subjective Rating (# tests)	Study Findings of MAT
Naltrexone							
Swift (1994)	7 HC	Baseline	0.5 g/day	2 weeks	N/A	ATT (3), LM(1), PS(1)	Improvement on PS
Hatsukami (1986)	13 HC (overweight)	15 HC (overweight)	300 mg/day	4 and 7 weeks	N/A	ATT(1), LM(2), PS(1), SR(1)	NS
van Steenbergen (2017)	18 HC	22 HC	50 mg	N/A	76 mins	EX(1)	NS
Malcom (1987)	36 HC (overweight)	Placebo	200 mg/day	8 weeks	N/A	SR(1)	NS
Chaves (1988)	19 HC	18 HC	50 mg	N/A	60 mins	LM(2)	NS
van Steenbergen (2017)	18 HC	22 HC	50 mg	N/A	76 mins	EX(1)	Improvement on post-error accuracy, slower post-error
Rawson (2001)	62 OUD	Baseline	50 mg	6 months	N/A	SR(1)	Improvement on fatigue, vigor, confusion
Kosten (2020)	67 OUD seeking buprenorphine discontinuation	Baseline	XR-NTX	22 days 36 days	N/A	ATT(3), LG(1), PS(1)	Improvement in 3 ATT, 1 PS
Saroj (2020)	20 OUD	30 HC	Unk	6 months	N/A	ATT, EX(2), LG(1) PS(1), LM(1)	NS except more errors on

							recognition test
Messinis (2009)	32 OUD	34 HC	50 mg	At least 3 months	NA	ATT(1), EX(1), LG(3), LM(2), PS(2)	NS
Methadone							
Aniskin (2011)	23 OUD abstinent	24 HC	Unk	At least 1 year	N/A	EX(1), PS(2)	Worse
Appel (1976)	24 OUD	24 HC 24 OUD abstinent	Unk	At least 11 months	N/A	PS(1)	NS
Appel (1982)	24 OUD	24 HC 24 OUD abstinent	100 mg	28.5-32.2 months	N/A	ATT(1)	NS
Baldacchino (2015)	29 OUD	28 HC	Unk	1.3 years	4–6 hours	EX(3)	Worse on 2 EX
Balcacchino (2019)	29 OUD	28 HC	Unk	1.3 years	4-6 hours	ATT(5), LG(1)	Worse on LG and 2 ATT
Battistella (2012)	16 OUD	16 HC 16 OUD abstinent	Unk	Unk	N/A	LM(2)	NS
Bracken (2012)	22 OUD	14 HC	9 @ <80mg 13 @ >80mg	16.1 months	N/A	ATT(1), PS(1), SR(2)	Worse on ATT, PS
Chang (2015)	42 OUD	37 HC	35.37 mg	Unk	N/A	ATT(1), EX(1)	Worse
Chesher (1989)	26 OUD	19 HC 19 OUD abstinent	85 mg	>6 months	1 hour	ATT(1)	NS
Constantinou (2010)	16 OUD 16 OUD abstinent	16 HC	Unk	Unk	N/A	ATT(1), EX(1)	NS

Curran (1999)	18 OUD	Placebo	43.5 mg	At least 6 months	40-80 mins	ATT(1), LM(2), MTR(1) PS(2),SR(1)	NS, Worse SR
Darke (2000)	30 OUD	30 HC	78.6 mg	60 months	N/A	ATT(1), EX(1), LG(2), LM(3), PS(2), VP(1)	Worse on all except 1 LG
Fadardi (2010)	53 OUD	71 HC	Unk	48 months	N/A	EX(1)	Worse
Gordon (1970)	18 OUD	20 HC	100 mg/day	At least 1 year	N/A	PS(2)	Better
Grevert (1977)	30 OUD	26 HC	52 mg/day	1 month 3 months	After dose	ATT(2), LM(1), SR(1)	NS
Gruber (2006)	17 OUD	Baseline, 2 months	68 mg/kg	16 days	N/A	EX(2), LG(2), LM(3), PS(3), VP(1)	Improvement over time in 2 LM, 1 PS
Liao (2014)	65 OUD	64 HC 264 OUD abstinent	30-60 mg	6 months	N/A	EX(1), PS(1)	NS, Better than OUD abstinent on EX
Lin (2012)	27 OUD	23 HC	Unk	At least 6 months	N/A	ATT(2), EX(2), LG(3), LM(3), PS(1), VP(3)	Worse on 1 EX, 2 VP
Lintzeris (2006)	8 OUD	Baseline	10 mg	3.8 years	0,1,3,5 hours	LM(1)	Worse
McKegney (1990)	45 OUD	Baseline, 2 months	Unk	Unk	N/A	ATT(2), EX(2), LM(1), PS(1), MTR(2)	Improvement in 1 EX over time
Mintzer (2002)	18 OUD	21 HC	Unk	45.4 months	N/A	ATT(1), EX(2), LM(1), PS(2)	Worse on all except LM
Moskowitz (1985) as cited in Lenne (2000)	15 OUD	16 OUD abstinent	60-100 mg	6 months	Before and after dose	ATT(4), PS(1)	Worse on PS
Piratsu (2006)	30 OUD	21 HC	Unk	12 months	N/A	EF(3),LM(1),O(1)	Worse
Prosser (2009)	10 OUD	14 HC 13 OUD abstinent		At least 6 months	N/A	ATT(1),LG1)	Worse on ATT than HC and OUD abstinent

Prosser (2006)	29 OUD	29 HC 27 OUD abstinent	Unk	6.44 years	N/A	EX(1),LG(2), LM(1)	Worse than on 1 LG, LM, Better than abstinent on LM
Qiu (2011)	31 OUD	24 HC	Unk	Unk	N/A	EX(1)	Worse
Rapeli (2007)	16 OUD	17 HC	53.4 mg	14.3 days	3-6 hours	ATT(3),EX(1), LM(2)	Worse on 2 ATT, EX, 2 LM
Rapeli (2009)	13 OUD	15 HC	72.9 mg, 125.7	21-213 days	3-6 hours	ATT(2),LG(1), LM(2),SR(1)	Worse on 1 ATT, SR
Rapeli (2011)	12 OUD	14 HC	71 mg, 127 mg, 135 mg	20-405 days	3-6 hours	ATT(3),EX(1), LM(1)	Worse
Rothenberg (1977)	12 OUD	12 HC	20-70mg 0 mg 5 mg 10 mg	At least 1 month	2.25 hours	ATT (1), 1 PS	Better on PS, HC slower as dose increases
Silberstein (1993)	81 OUD	Baseline	Unk	At least 47 months	N/A	ATT(1),EX(2),LM(1), MTR(2) PS(1)	Better on 1 EX over time
Soyka (2010)	77 OUD	35 Short-term MMT vs 42 Long-term MMT		>30 days or >6 months	N/A	ATT(2), EX(3)LG(3), LM(2), PS(1), VP(2)	Long-term MMT better on 2 LG and 1VP
Soyka (2011)	24 OUD	25 HC	Unk	8-10 weeks	N/A	ATT(5)	Worse on 4 ATT
Specka (2000)	54 OUD	54 HC	93 mg	18 months	N/A	ATT(6)	Worse on 3 ATT
Strand (2019)	22 HC	Placebo	5 mg 10 mg	Unk	2 hours	ATT(4), PS(2), SR(2)	Worse on 3 ATT, 1 PS on high dose, Worse 2 SR

Verdejo (2005)	18 OUD	23 OUD abstinent	83.82 mg	38.66 months	N/A	ATT(1), EX(4), LG(3),PS(1)	Worse
Wang (2014)	32 OUD	25 HC, 17 OUD	70.86 mg	7.61 years	5.17 hours	ATT(5),EX(2),LG(2),LM(2) MTR(1), PS(1)	Worse than HC on 1 EX, Better than OUD abstinent on ATT,EX,MTR
Wang (2018)	47 OUD	Baseline	42.91 mg	Unk	12 weeks	ATT(1), LM(3)	Better on 3 LM
Buprenorphine							
Ghosh (2022)	24 OUD 17 OUD	20 HC	5.3 mg 5.6 mg	3 months 6 months	N/A	ATT(2), EX(3), PS(1), VP(1)	Worse on 2 ATT
Jensen (2008)	20 HC	Baseline	0.6 mg IV		Before infusion and 20, 60, 105, 150, 210 and 480 min after	EX(1), MTR(1) PS(1)	Worse
Lintzeris (2006)	8 OUD	Baseline	2 or 8 mg (sublingual)	1.5 years	3 hours	LM(1)	Better
MacDonald (1989)	12 HC	Placebo, Baseline	0.3 mg	Unk	Pre-dose, 1.5 hours,4 hours 8 hours	ATT(2), PS(2), SR(1)	Worse on 1 ATT, 2 PS, SR through 8 hours
Manner (1987)	7 HC	Baseline	7.5 ug-kg	N/A	0, 5, 10, 20, 30, 45, 60, 90, 120, and 180	ATT(1), SR(1)	Worse

					mins after dose		
Messinis (2009)	18 OUD	34 HC 32 OUD abstinent	6.78 mg	18-28 weeks	N/A	ATT(1), EX(1),LG(2), LM(2)PS(2)	Worse than HC on 1 EX, 2 LM, NS with OUD abstinent
Mintzer (2004)	8 OUD	8 mg vs 32 mg	8/2, 16/4, and 32/8 mg	7-10 days	12 hours before dose, 1 hour after dose, 6 hours after dose	ATT(3),EX(1), LM(1),PS(2)	Higher dose worse on LM
Piratsu (2006)	18 OUD	21 HC	Unk	12 months	N/A	EF(3),LM(1),O(1)	Worse on LM
Rapeli (2007)	17 OUD	17 HC	15.8 mg 3.9 mg of naloxone	11 days	3-6 hours	ATT(3),EX(1), LM(2)	Worse on 2ATT, 2LM
Rapeli (2009)	15 OUD	15 HC	17.3 mg, 22.7 mg (80% got naloxone)	19-224 days	3-6 hours	ATT(2),LG(1), LM(2),SR(1)	Worse on 2 ATT, SR
Rapeli (2011)	14 OUD	14 HC	16 mg, 20 mg 21 mg (79% got naloxone)	21-414 days	3-6 hours	ATT(3),EX(1), LM(1)	Worse on 2 ATT, LM, Better improvement over time on 1 ATT
Saarialho-Kere (1987)	12 HC	Baseline	0.4 mg (sublingual)	8 days	Before dose, 2	PS(1), SR(1)	Worse

					and 4 hours after		
Saroj (2020)	20 OUD	30 HC	Unk	At least 6 months	N/A	ATT(3), EX(2). LG(1), LM(1), PS(1)	Worse on 2 ATT, 2 EX
Scott (2017)	20 OUD	Baseline	4-16 mg (with naloxone)	6 months	N/A	ATT(2),EX(2),LG(2), LM(2), MTR(1), PS(3)	NS
Shmygalev (2011)	30 OUD	90 HC	7.7 mg	26 months	6 hours	ATT(1)	NS
Singhal (2008)	19 OUD	Baseline	4 mg (sublingual) + 2 additional 2 mg	At least 1 month	2 hours and next day	ATT(1), EX(1), LM(1), PS(2)	Better on 2 PS, 1 EX
Singhal (2007)	19 OUD	Baseline	4 mg/day + 3 additional 2 mg	At least 1 month	2 hours and next day	SR(1)	NS
Soyka (2011)	22 OUD	25 HC	Unk	8-10 weeks	N/A	ATT(5)	Worse on 3 ATT
Strand (2019)	22 HC	Placebo	0.2 mg 0.4 mg (sublingual)	N/A	2 hours	ATT(4), PS(2), SR(2)	Worse on 4 ATT, 1 PS, 2 SR
Zacny (1997)	16 HC	Placebo	0, 0.075, 0.15 or 0.3 mg/70 kg	N/A	before injection, and 15, 60, 120, 180, 240 and 300 min after injection	SR(3), LM(1), PS(2)	Worse on 2 SR, 2 PS

Note. OUD = opioid use disorder, HC = healthy control, XR-NX = extended-release injectable naltrexone, MMT = methadone maintenance therapy, Unk = Unknown, N/A = Not Applicable, NS = Not significantly different from comparison group/condition, ATT = attention, vigilance, working memory, EX = executive functioning, LG = language, LM = learning/memory, MTR = motor, PS = processing speed, SR = subjective report, VP = visuoperceptual or visual cognitive.

Driving studies

The methadone FDA approved package insert carries a warning against driving or operating heavy machinery until or if one is tolerant to any potential mental or physical effects (Roxane Laboratories Inc, 2014).

During an over-the-road driving test conducted 4 hours after methadone (5 mg or 10 mg) administration in 22 healthy volunteers, there were no acute effects on measures of lane position control (i.e., standard deviation of lateral position and mean lateral position) or on measures of speed control (i.e., standard deviation of speed) (Strand, Vindenes, et al., 2019). The investigators noted that driving tests were stopped twice during methadone 10 mg and once during placebo due to subjective sleepiness.

In OUD patients maintained on methadone for 3 months (Lenne et al., 2003), there were no differences between methadone and control participants in a driving simulator on measures of standard deviations of lateral position, speed, steering wheel angle, or reaction time.

Thirty OUD patients maintained 18.6 months on methadone, matched to a group of controls on age, sex and intelligence, were examined with the ART 2020 battery, a computer based cognitive test battery which includes several driving related tasks (Schindler et al., 2004). Testing was conducted 22 hours post-dosing Compared to controls, methadone-maintained patients had significantly slower decision and reaction times on a task (DR2) involving presentation of a city drive video sequence during which subjects press a right-side pedal to "drive" and react to stimuli by pressing on a left-side brake pedal. There were no differences from controls on a task where subjects are briefly shown images of traffic situations and then asked questions on relevant details.

Another study conducted with the ART 2020 test reported on the performance of 40 patients with an approximately 70-month history of OUD, maintained on either methadone (52.7 mg) or buprenorphine (mean: 13.4 mg) for about 20 months compared to age, sex, and intelligence matched non-OUD controls (Baewert et al., 2007). On the DR2 task described above patients reportedly performed worse than controls. Investigators reported that the buprenorphine group generally performed slightly better than the methadone group on the ART 2020 tests.

Buprenorphine

Buprenorphine and buprenorphine with naloxone were approved in 2002 by the FDA with two buprenorphine products (Suboxone® and Subutex®) for the treatment of narcotic addiction. Both products are administered as sublingual tablets. Suboxone® is a combination product with buprenorphine and naloxone in a 4:1 ratio. Between 2010 and 2017, FDA approved additional buprenorphine formulations: Butrans® (extende- release transdermal film containing buprenorphine), Zubsolv® (buprenorphine/naloxone sublingual tablets), and Sublocade® (buprenorphine extended-release injection).

For OUD, buprenorphine is typically started at least 12 to 24 hours after abstaining from opiate use when withdrawal symptoms have begun and for the first two days of treatment under direct observation of a health-care provider. In the United States, the combination formulation of buprenorphine/naloxone is usually prescribed to discourage potential misuse by injection.

The target population for buprenorphine includes patients for whom treatment in a methadone clinic is not appropriate or is less convenient. This is because buprenorphine is not required to be dispensed through opioid treatment programs and can be prescribed in any clinical setting by prescribers with Drug Enforcement Agency certification. An advantage of buprenorphine is that it can be combined with the antagonist naloxone to deter misuse of the medication. Also, as a partial opioid agonist, it has a better safety profile than methadone (Fairley et al., 2021; Thomas et al., 2014) and therefore may be a preferable MAT for OUD in those with various health comorbidities.

Pharmacology

Buprenorphine affects different types of opioid receptors in different ways. Depending on the receptor, it acts as an agonist, partial agonist, or antagonist. In the treatment of OUD, buprenorphine is an agonist/antagonist such that it relieves withdrawal symptoms from other opioids and induces some euphoria, but also blocks the ability for many other opioids, including heroin, to cause an effect. Unlike full agonists like heroin or methadone, buprenorphine has a ceiling effect, such that taking more medicine will not increase the effects.

Before starting buprenorphine, individuals are generally advised to wait long enough after their last dose of opioid until they have some withdrawal symptoms to allow for the medication to bind the receptors. If taken too soon, buprenorphine can displace other opioids bound to the receptors and precipitate an acute withdrawal episode. The dose of buprenorphine is then adjusted until symptoms improve.

It is recommended that patients receive buprenorphine as long as it provides benefit (Martin et al., 2018). As with other treatments, longer duration of treatment with buprenorphine is associated with better outcomes. In a retrospective longitudinal cohort study (Williams et al., 2020), it was found that risk of overdose and other adverse outcomes were highest following buprenorphine discontinuation irrespective of treatment duration. Superior outcomes were evident with treatment duration greater than 15 months.

Maintenance treatment with buprenorphine for opioid addiction consists of three phases: (1) induction, (2) stabilization, and (3) maintenance. No stated requirement exists for observed dosing with buprenorphine, although guidelines strongly recommend dosage monitoring early in treatment (Substance Abuse and Mental Health Services Administration (SAMHSA), 2004, 2015a). During induction and early stabilization daily dosing is recommended (Substance Abuse and Mental Health Services Administration (SAMHSA), 2004). The stabilization phase typically lasts 1 to 2 months. The maintenance phase begins when the patient is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings. The longest period that a patient is on buprenorphine is the maintenance

phase. This period may be indefinite (Substance Abuse and Mental Health Services Administration (SAMHSA), 2004).

Efficacy

Buprenorphine maintenance treatment has been evaluated in randomized clinical trials against placebo, and separately as an alternative to methadone for management of OUD. A Cochrane review (Mattick et al., 2014) which included 31 trials found high quality evidence that buprenorphine was superior to placebo in retention of patients in treatment at all doses. Other systematic reviews and network meta-analysis similarly report higher retention of patients in treatment with buprenorphine than placebo (Lim et al., 2022; Thomas et al., 2014). Based on placebo controlled trials buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) (Mattick et al., 2014).

In a recent trial (Ling et al., 2020), the RECOVER (Remission from Chronic Opioid Use: Studying Environmental and SocioEconomic Factors on Recovery; NCT03604861) investigators enrolled 425 participants from 35 sites. Results showed that those receiving 12-month versus ≤ 2 months buprenorphine extended-release OUD treatment had significantly higher likelihood of sustained abstinence and fewer withdrawal symptoms, lower pain, more positive health-related quality of life, and higher employment versus pre-trial.

The combination of buprenorphine to naloxone in a 4:1 ratio decreases the potential of either being used for opioid abuse or injection use (Indivior Inc, 2021). In a review of the literature on buprenorphine-naloxone in a 4:1 ratio (Mammen, & Bell, 2009), it was concluded that the addition of naloxone does not appear to affect the efficacy of buprenorphine as a maintenance drug. A recent review of 10 studies (Baxley et al., 2023) concluded that craving is reduced over time with buprenorphine and buprenorphine/naloxone.

Fudala and colleagues (Fudala et al., 2003) conducted a double-blind trial which found greater efficacy of buprenorphine/naloxone in combination and buprenorphine alone than placebo (Fudala et al., 2003). Importantly, the rate of adverse events was not significantly different in either treatment group compared with the placebo. The combination of buprenorphine/naloxone in combination and buprenorphine alone reduces the use of opiates as well as the cravings for addicted persons in clinic-based settings (Fudala et al., 2003).

Lintzeris and colleagues compared the buprenorphine-naloxone sublingual film to the tablet formulation via an outpatient double-blind RCT and found outcomes were not significantly different (Lintzeris et al., 2013). There were comparable outcomes and dose equivalence between these two different formulations, but more patients were satisfied with the film formulation (Lintzeris et al., 2013).

Outcomes tend to be improved when delivered in concert with psychosocial and contingency interventions (like financial incentives for opiate-free urine samples) (Connock et al., 2007; Poliwoda et al., 2022). Treatment is effective whether delivered in a primary care or outpatient clinic setting (Connock et al., 2007). One meta-analysis (West, O'Neal, & Graham, 2000) found

that patients receiving buprenorphine were more likely to stay drug-free in studies that included patients with prior methadone experience.

Safety

In a systematic review and meta-analysis evaluating 15 randomized control trials and 35 cohort studies (Santo et al., 2021), the rate of all-cause mortality during treatment with buprenorphine or methadone was more than half of the rate seen during time out of treatment. This association held regardless of patient sex, age, geographic location, HIV status, hepatitis C virus status, or whether drugs were taken through injection (Santo et al., 2021).

According to the package insert, there are no relevant adverse events beyond headache which occurred in 36.4% of those taking sublingual tablets versus 22.4% of the placebo group (Indivior Inc, 2021). The most common adverse event (> 1%) associated with the sublingual administration was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision. The most common adverse events associated with the buccal administration were similar to those observed with sublingual administration of the film (Indivior Inc, 2021).

Many, but not all, post-marketing reports regarding coma and death involved misuse by self-injection or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia.

Buprenorphine has been reported to have the potential of causing a serotonin syndrome if used concomitantly with other serotonergic drugs (Indivior Inc, 2021). Higher doses or most commonly in combination with serotonergic medications can increase this risk. Prescribers are cautioned when adding buprenorphine to antidepressants of the SSRI, SNRI, or TCA class. It is also recommended that tramadol, dextromethorphan, linezolid, cyclobenzaprine and many other medications should also be used cautiously (if at all) in buprenorphine dependent persons (Indivior Inc, 2021; Poliwoda et al., 2022). Concomitant use of buprenorphine and benzodiazepines or other central nervous system depressants increases the risk of adverse reactions including overdose and death (Indivior Inc, 2021). Administration with other CNS depressants raises the risk of severe respiratory depression, muscle cramps, insomnia, and irritability (Indivior Inc, 2021; Poliwoda et al., 2022). Other side effects may include: sleepiness, adrenal insufficiency, QT prolongation, low blood pressure, allergic reactions, constipation, headache, and opioid addiction (Indivior Inc, 2021; Ling et al., 1998). For patients with a history of seizures there is increased seizure risk. A double-blind randomized control trial (Ling et al., 1998) found that adverse events were not dose-related.

Cognitive studies

Refer to Table 2 for a review of studies that relate to performance and subjective changes related to MAT for OUD.

Adverse acute effects of buprenorphine are apparent on measures of attention/working memory, executive functioning, processing speed, and subjective measures (of sedation and cognitive difficulties). Those studies finding improvement acutely are likely due to practice effects.

Mindt and colleagues (Mindt et al., 2022) in a recent review, concluded that, relative to healthy controls, in both cross-sectional and longitudinal studies significantly worse performance was observed on measures of attention, working memory, executive functioning, visual cognitive abilities, learning and memory, and language following treatment with buprenorphine. Effect sizes ranged from small to large. Patients with OUD who were taking buprenorphine and remaining abstinent were found to perform significantly better than those who continued to use opioids.

Driving studies

In a randomized double-blind and crossover study of 12 young adults receiving sublingual buprenorphine 0.4 mg or matched placebo (Saarialho-Kere et al., 1987), no acute effects of buprenorphine were found on a driving simulator consisting of a color television where a winding road was presented on the screen while the subject tried to keep the simulated car on the road using a steering wheel. During the latter half of the task, 60 visual or/and sound stimuli were presented in random order, and the driver had to respond or not respond to them by pressing a button or by pushing a foot pedal. The number of reaction errors and the cumulative reaction time were recorded. Tests were conducted at baseline and repeated at 2 and 4 hours post-dose. Investigators reported no effect of buprenorphine at 2 or 4 hours post-dose on the driving test measures of tracking errors (deviations from the road), nor on tracking percentage (relative length of the track driven off the road).

An on-road driving test study was conducted 4 hours after either 0.2 or 0.4 sublingual buprenorphine in 22 healthy volunteers (Strand, Vindenes, et al., 2019). Investigators reported that at the higher dose of buprenorphine there was a significantly increase in the standard deviation of lateral position relative to placebo. However, the increase in SDLP did not exceed the 95% confidence interval for the change in SDLP associated with a 0.05% BAC, suggesting that the magnitude of increase in weaving did not reach the impairment threshold. Driving tests were stopped once following buprenorphine (0.2 mg) once following placebo due to subjective sleepiness.

In OUD patients maintained on buprenorphine for 3 months (Lenne et al., 2003), there were no differences between patients and control participants on driving simulator measures of standard deviations of lateral position (SDLP), speed and steering wheel angle, or on a secondary reaction time task.

Using the ART 2020 test described above, Schindler and colleagues (Schindler et al., 2004), examined 30 OUD patients, 15 maintained on buprenorphine, and 15 maintained on methadone for between 11 and 18 months, 22 hours following administration of medication. Performance on the ART 2020 test battery was compared to age, sex and intelligence-matched controls. On the driving-related tasks the buprenorphine group did not differ from the controls.

Another study employing the ART 2020 test enrolled 40 patients with an approximately 70-month history of OUD, maintained on either methadone (52.7 mg) or buprenorphine (mean: 13.4 mg) for about 20 months. Patients were compared to controls matched on age, sex and intelligence. Performance was reportedly poorer for patients compared to controls on the DR2 test, but results were not shown separately for methadone and buprenorphine. It was reported that the buprenorphine group had performed significantly better than the methadone group on the DR2 subtest. The authors concluded that the buprenorphine group generally performed slightly better than the methadone group on all tests.

Naltrexone

In 1984 the FDA approved naltrexone for treating heroin addiction (Revia®). An extended-release form, administered in monthly injections was approved in 2010 for OUD (Vivitrol®). An even longer-acting implantable form of naltrexone was developed and approved but was withdrawn from the market because it wasn't commercially viable. As discussed above, regarding its use for AUD, naltrexone is a competitive opioid antagonist, with a high binding affinity for μ-opioid receptors. Because it is an opioid blocker, naltrexone prevents prescription or illicit opioid agents from binding to the μ receptor and leading to euphoria. Thus, it does not alleviate opioid cravings like methadone and buprenorphine but, rather, blocks the euphoric effects of opioids.

Pharmacology

Naltrexone is a pure opiate receptor antagonist and works by primarily binding at the *mu* opioid receptors. By binding to these receptors, it blocks the euphoric (pleasurable or "high") effects linked with opioids. Naltrexone itself has little or no effect in the absence of alcohol or opiates. It is not addictive and does not cause withdrawal symptoms when used in people not physically dependent on opioids or alcohol.

Naltrexone is the least studied MAT for OUD (Sugarman et al., 2022). Oral naltrexone has been evaluated for the treatment of OUD but should not be prescribed, as there is not sufficient evidence to recommend its routine use given very low adherence rates (Minozzi et al., 2011). These concerns were largely eliminated with the long-acting injectable form of naltrexone.

After injection with the extended-release naltrexone depot injection (Vivitrol), initial peak concentrations are reached within 2 hours and reach another peak 2–3 days later. Around day 14 after administration, the concentration starts to slowly decline, with measurable levels still detectable after 1 month (Dunbar et al., 2006).

The optimal length of treatment with oral naltrexone is not known. In general, the longer patients take an effective medication, the better their outcomes (Substance Abuse and Mental Health Services Administration (SAMHSA), 2021). Similarly, the extended-release injectable form, which can be prescribed by any healthcare provider licensed to prescribe medications, should be taken as long beneficial. While there is no physical dependence with naltrexone, evidence shows that many people may require ongoing treatment.

Efficacy

The target population for naltrexone are those who have not used opioids for at least 7 days (or 10 to 14 days for long-acting opioids). In contrast with methadone (due to interactions with the liver), naltrexone is a better option for patients on multiple medications (Koehl, Zimmerman, & Bridgeman, 2019).

Injectable naltrexone is particularly beneficial for patients for whom daily adherence may be a concern and for patients desiring not to receive an opioid agonist (Koehl, Zimmerman, & Bridgeman, 2019). The results of a randomized controlled trial showed that long-acting injectable naltrexone was associated with higher retention to treatment than oral treatment (Sullivan et al., 2019).

Extended-release naltrexone has historically been more successful for those recently leaving longer-term detoxification programs, those involved in structured research studies, and individuals not on parole or probation (Jarvis, Holtyn, Berry, et al., 2018; Jarvis, Holtyn, Subramaniam, et al., 2018).

A systematic review of 14 studies (Kirchmayer et al., 2002) revealed non-statistically significant results for successful completion of treatment, and for use of opioids under treatment, relative to controls. However, use of naltrexone in addition to behavioral treatment significantly decreased the probability of (re-)incarceration.

One systematic review (Jarvis, Holtyn, Subramaniam, et al., 2018) of 34 studies studying extended-release naltrexone concluded that it decreases opioid use. A follow-up systematic review and meta-analysis (Zangiabadian et al., 2022) of 18 studies ranging from 21 to 24 months of treatment with naltrexone found greater retention (63% higher) and greater odds of being opioid-free relative to controls, though results did not reach statistical significance.

A meta-analysis (Bahji, Carlone, & Altomare, 2020) of 11 studies conducted among criminal justice-involved individuals found that naltrexone improved retention in treatment, reduced rates of re-incarceration, reduced opioid relapse, and improved opioid abstinence.

Finally, a network meta-analysis (Lim et al., 2022) found that the likelihood of treatment retention was significantly higher for naltrexone than for controls and showed an average treatment retention of 41% for naltrexone among all included studies. It was the fourth most effective medication for OUD in terms of treatment retention after methadone, slow-release oral morphine, and buprenorphine.

Safety

The adverse events seen most frequently in association with naltrexone therapy in OUD patients (i.e., those occurring in ≥2% and at least twice as frequently with naltrexone than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache (Alkermes Inc, 2010). Relative to 2% of placebo participants, 3% of naltrexone-treated patients complained of headache, and relative to 1% of those taking placebo, 6% of naltrexone-treated patients complained of insomnia (Alkermes Inc, 2010).

Although naltrexone does not reduce respiratory drive, relapse with high-dose opioids may result in accidental overdose death due to diminished opioid tolerance.

Cognitive studies

Please see Table 2 for a review of studies that relate to performance and subjective changes related to naltrexone for OUD. As is apparent from reviewing Table 2, there are generally no significant differences between healthy controls taking naltrexone for 2 to 7 weeks and placebo, either in terms of cognitive performance or subjective experience. Improvements noted in some within-subject designs are likely due to practice effects.

In studies conducted with individuals with OUD, naltrexone treatment tends to result in either improved cognitive performance or no differences from placebo or baseline or healthy controls. Some studies found improvement. Taken together, available evidence suggests that naltrexone does not cause any adverse cognitive sequalae.

Driving studies

There were no driving studies with chronic naltrexone-treated individuals.

Summary of FDA-Approved MAT for OUD

MAT for OUD is relatively effective and has become a standard of care.

A recent review of neurocognitive findings (Mindt et al., 2022) concluded that buprenorphine produces impairment on measures of executive functioning, learning/memory, visual cognitive abilities, attention/working memory, and language, with small to large effect sizes, including studies investigating chronic effects. Similarly, methadone produces impairments on measures of processing speed, executive functioning, learning/memory, visual cognitive abilities, attention/working memory, and language, with small to large effect sizes, including studies investigating chronic effects (Mindt et al., 2022). Findings generally indicate less impairment of cognitive functioning following dosing with buprenorphine compared to methadone. By contrast, naltrexone does not appear to cause adverse effects on cognitive functioning.

In terms of driving performance, all of these drugs carry warnings about driving or operating dangerous machinery. There is evidence demonstrating an acute, adverse effects of buprenorphine on driving. However, these effects of buprenorphine appear to dissipate after about 8 hours. In contrast, for methadone there is evidence for acute and chronic impairment of performance on driving simulation tasks. Comparison studies show less impairment of driving related abilities following buprenorphine compared to methadone. However, there are findings suggesting that the cognitive/driving performance differences between OUD patients and controls (especially healthy controls), may be better explained by sociodemographic variables than the effects of MATs (Strand et al., 2013).

FAA POSITION/POLICY ON MEDICATIONS AND MAT

In the Federal Aviation Administration's "Guide for Aviation Medical Examiners" (accessed at: https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/), several

medications are listed on its “Do Not Issue - Do Not Fly” list to alert examiners of disallowed medications for pilots. This list includes controlled substances (e.g., methadone, buprenorphine) and psychiatric/psychotropic medications (disulfiram, naltrexone, acamprosate). None of the current FDA-approved MATs are available for pilot use.

This policy stands in contrast to expert opinion and current standard of care in treatment of AUD/OUD, espoused by varying organizations including the World Health Organization (World Health Organization (WHO), 2009, 2023), the Agency for Healthcare Research and Quality (AHQR; (Jonas et al., 2014)) and the Substance Abuse and Mental Health Services Administration (SAMHSA)(Substance Abuse and Mental Health Services Administration (SAMHSA), 2015b).

The FAA policy on MAT also appears inconsistent with the objectives of the special issuance program developed to allow pilots in recovery from alcohol dependence/alcohol abuse and other substance dependence/substance abuse to return to the cockpit.

In contrast to the policy on MAT, the FAA has made a determination that four antidepressant medications (fluoxetine, sertraline, citalopram, and escitalopram) could be allowed for use by pilots seeking special issuance certification under their SSRI Special Issuance protocol. This policy allows vetted pilots on a stable dose of one of these four medications to return to the cockpit with additional monitoring of their mental health. The antidepressant medications were determined by the FAA to not have aeromedically significant neurocognitive effects or other risk factors for aviation safety.

To date, no pilot seeking a special issuance for alcohol dependence or other substance dependence has received a special issuance while taking any of the FDA-approved drugs for AUD or OUD. Furthermore, there is no evidence that the FAA has considered permitting a pilot under their current special issuance program to take any of these medications.

SUMMARY AND RECOMMENDATIONS

MAT is universally recognized as generally safe and effective in support of relapse prevention and abstinence among those with AUD/OUD.

Available evidence suggests that these medications have adverse, acute subjective effects that are transitory. There is no evidence that the three drugs approved for AUD (i.e., disulfiram, naltrexone, acamprosate) have any significant adverse neurocognitive effects, though studies are limited. In contrast, there is clear evidence that two of the approved medications for OUD (both methadone and buprenorphine) have lasting adverse cognitive effects. However, evidence also suggests that treated individuals tend to improve over time with treatment. The third FDA-approved medication for OUD, naltrexone, is not associated with adverse cognitive sequalae.

The FDA-approved medications for AUD/OUD carry label warnings that caution should be exercised when driving or operating machinery until the individual taking the medication has enough time and experience on the medication to understand its potential effects. Driving is not well studied among those being treated for AUD. For OUD, there is evidence demonstrating chronic impairments on driving simulation tasks associated with methadone. In contrast, there is

no consistent evidence for impairment on driving simulation tasks with chronic use of buprenorphine, and no evidence of acute or chronic effects for naltrexone.

Collectively, given all of the available evidence, MAT for AUD with FDA-approved medications can be considered safe in terms of both cognitive and driving performance. Compliance and adherence remain major limitations for disulfiram and acamprosate. Injectable naltrexone is an efficacious treatment for AUD that appears to have resolved the issues with compliance and adherence.

Treatment of OUD with MAT is considerably more complicated. For both methadone and buprenorphine chronic effects have been seen on measures of cognitive performance. For methadone there are also chronic effects seen on driving simulators and tests of driving-related abilities. Conservatively, it might be concluded that naltrexone may be the safest alternative for relapse prevention among those with OUD, although more research is needed.

Currently, none of the FDA-approved medications for AUD or OUD are allowed for use by pilots. This stands in contrast to clinical practice recommendations of various national and international medical groups and stands in contrast to the Flight Attendant Drug and Alcohol Program (FADAP), which encourages the use of MAT.

Gaps and Research Needed

Several gaps in the current knowledge base are evident. First, and most relevant to the transportation industry, more research is needed on context-relevant safety. Driving simulation has become acceptable to the Food and Drug Administration in the evaluation of drug impaired driving. Additional studies, with FDA approved MATs for AUD and OUD could lead to more precise labeling with respect to when and if it's safe to operate a motor vehicle after taking these medications. With respect to aviation safety, the effect of these drugs could be further assessed with measures validated as predictors of flight performance, as there are no widely accepted flight simulation scenarios validated for evaluation of drug impairment. In addition, there is increasing use of "real world" digital and electronic assessment tools.

Furthermore, it appears that additional research is needed on the relative effectiveness of different rates of tapering MAT doses (e.g., buprenorphine). The use of buprenorphine to support transition to naltrexone treatment is one aspect worthy of further research (Gowing et al., 2017).

It is also recognized that the research review has been conducted with non-pilots with and without AUD and OUD. One can question the extent to which such data applies to pilots. Pilots, for example, are a group that tend to have higher levels of intelligence and differ from the general population on other attributes (Carretta et al., 2016; Wakcher, Cross, & Blackman, 2003). It is also noteworthy that MAT research to date largely underrepresents females and minorities as well.

There is a dearth of research on how MAT may or may not interact with other medications. For example, in a review of the treatment of co-occurring anxiety disorders and substance use disorders, McHugh (2015) calls for more research on the efficacy and safety of medications used

in those with co-occurring disorders. Questions about potentially altered medication metabolism on dual diagnosis treatment, and cross-tolerance and interactions are concerns.

Finally, while there is some literature, as reviewed herein, that pertains to the necessary duration of treatment with MAT, it is sparse. Optimal duration of treatment is largely unknown because most trials run only long enough to establish initial efficacy. Longer trials are needed comparing different durations of treatment.

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