Current Sleep Medicine Reports (2022) 8:147–159
https://doi.org/10.1007/s40675-022-00227-4

HYPERSOMNIA DISORDERS (DT PLANTE, SECTION EDITOR)

An Update on the Misuse and Abuse Potential of Pharmacological Treatments for Central Disorders of Hypersomnolence

Quang Ngo[1] · David T. Plante[1,2]

Accepted: 22 August 2022 / Published online: 19 September 2022
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract

Purpose of Review All medications currently approved for the treatment of central disorders of hypersomnolence, with the exception of pitolisant, are scheduled substances. There is a perceived and real potential for misuse and abuse of traditional stimulants and sodium oxybate, with generally less concern for modafinil. Pitolisant and solriamfetol are newer approved agents with unique pharmacological profiles. In our paper, we aim to review the misuse and abuse potential of new and existing treatments for narcolepsy and idiopathic hypersomnia.

Recent Findings Available preclinical, clinical, and post-marketing surveillance data on pitolisant, solriamfetol, and modafinil suggest that these agents have a very low potential for misuse and abuse. Agents that have high potential for misuse, specifically stimulants and sodium oxybate, most likely carry lower risks when used to treat narcolepsy or idiopathic hypersomnia compared to risks of misuse in the general population or among other neuropsychiatric conditions.

Summary Approved therapies for central disorders of hypersomnolence carry low yet varying risks for misuse and abuse. Further studies in patients diagnosed with central disorders of hypersomnolence are required to comprehensively assess the misuse and abuse potential of these therapeutic agents.

Keywords Narcolepsy · Idiopathic hypersomnia · Excessive daytime sleepiness · Substance abuse · Abuse liability · Addiction

Introduction

Narcolepsy and idiopathic hypersomnia are central disorders of hypersomnolence marked by excessive daytime sleepiness (EDS) and account for substantial morbidity and impairment in quality of life [1]. Although conventional stimulants (e.g., methylphenidate and amphetamine) have been the cornerstone of treatment for EDS since the 1930s [2], many providers are often hesitant to prescribe these drugs long term due to concerns of misuse and abuse.

These concerns are not entirely unfounded. Methylphenidate and amphetamine have "black box" warnings and are commonly abused in certain populations and diverted for illicit use as a result of their dopaminergic and rewarding properties [3]. These stimulants are classified as schedule II medications by the Drug Enforcement Agency (DEA) and are associated with numerous public health problems and nonmedical use including inhalation and intravenous injection (see Table 1 for a list of schedules and their definitions) [4, 5]. In 2016, the prevalence of prescription stimulant misuse was 2.1% in the USA [6] with over 7500 overdose fatalities involving pharmaceutical stimulants, a 33% increase from the previous year [7]. Though there is a considerable amount of research on the abuse and diversion of prescription stimulants in ADHD patients [8], there are fewer investigations into the risk of individuals diagnosed with a central disorder of hypersomnolence [9].

Similar concerns have been raised about other treatments for narcolepsy and idiopathic hypersomnia. Sodium oxybate

This article has been edited by Dr. Alon Avidan, as Dr. David Plante is Section Editor for the topical collection Hypersomnia Disorders.

This article is part of the Topical Collection on *Hypersomnia Disorders*

✉ David T. Plante
dplante@wisc.edu

1 University of WI School of Medicine and Public Health, Madison, WI, USA

2 Department of Psychiatry, Wisconsin Psychiatric Institute and Clinics, University of WI – Madison, 6001 Research Park Blvd, Madison, WI 53719, USA

Table 1 Definitions for schedule I–V drugs

Schedule	Definition
Schedule I	The drug or other substance has a high potential for abuse. The drug or other substance has no currently accepted medical use in treatment in the USA. There is a lack of accepted safety for use of the drug or other substance under medical supervision
Schedule II	The drug or other substance has a high potential for abuse. The drug or other substance has a currently accepted medical use in treatment in the USA or a currently accepted medical use with severe restrictions. Abuse of the drug or other substances may lead to severe psychological or physical dependence
Schedule III	The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II. The drug or other substance has a currently accepted medical use in treatment in the USA. Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence
Schedule IV	The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III. The drug or other substance has a currently accepted medical use in treatment in the USA. Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III
Schedule V	The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule IV. The drug or other substance has a currently accepted medical use in treatment in the USA. Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV

(SXB) (Xyrem®) is a sodium salt of GHB, an illicit street drug with an extensive history of abuse and criminal misuse [10]. Xyrem®, as well as the recently approved lower-sodium oxybate analog (Xywav®), are schedule III medications that are prescribed through a risk management program in order to minimize abuse [11]. Modafinil, a nonamphetamine stimulant prescribed for narcolepsy, has emerged as a "smart drug" among university students, raising concerns about its misuse and diversion [12].

Advances in the understanding of the mechanisms of narcolepsy and the need for medications with minimal or no abuse potential have led to the development of new pharmacological agents. Pitolisant, a first in class histamine 3 receptor (H3R) antagonist/inverse agonist, was recently approved for the treatment of EDS and cataplexy associated with narcolepsy. Solriamfetol, a dopamine and norepinephrine reuptake inhibitor, was also recently approved for the treatment of EDS associated with narcolepsy or obstructive sleep apnea. Since current evidence-based guidelines for the treatment of central disorders of hypersomnolence have supported the efficacy of these new drugs [13], an updated, comprehensive review of their misuse and abuse potential is warranted.

This review is intended to provide clinicians with heightened confidence in managing central disorders of hypersomnolence by reviewing current knowledge and recent findings on the misuse and abuse potential of existing and recently Food and Drug Administration (FDA)-approved therapies. This review focuses on the misuse and abuse potential of non-stimulants relative to traditional stimulants. An overview of each pharmacological agent's mechanism of action; efficacy and safety profile; preclinical and clinical abuse liability; and if available, post-marketing surveillance data is described to present a comprehensive, updated assessment of each agent's misuse and abuse liability profile.

Defining Misuse and Abuse Liability

Prescription drug misuse is defined as any use of a prescription medication that is outside of the manner and intent for which it was prescribed including overuse, diversion, use to get high, having multiple prescribers or nonprescribed sources, and concurrent use of alcohol, illicit substances, or nonprescribed controlled medications. Misuse is a necessary but not a sufficient criteria for a substance use disorder [14].

Prescription drug abuse/dependence is the misuse of a prescription drug meeting the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria as a substance use disorder, which can be specified as mild, moderate, or severe [15]. Of note, substance use disorder (DSM-5) has formally replaced the terms substance abuse and substance dependence (DSM-IV) though these terms will be used interchangeably in this review.

Methods

A search for evidence-based studies published in peer review journals was conducted using PubMed. A qualitative review was performed because the number of articles pertaining to misuse and abuse liability for each medication was relatively small, and the diversity of misuse and abuse liability studies spanned across pre-clinical models, clinical studies, and post-marketing surveillance, thus precluding a quantitative analysis. We initially considered articles that met the criteria including the following key concepts: "misuse," "abuse," "dependence," "narcolepsy," "hypersomnia," and "excessive daytime sleepiness." The search term also included the therapeutic drug of interest: pitolisant, solriamfetol, sodium oxybate, and modafinil. Primary sources and sources published from 2017 to 2022 were preferred when considering the

misuse and abuse liability of each therapeutic drug, though secondary sources and relevant bibliographies augmented the background information for each drug. See Table 2 for a summary of drugs discussed in this review.

Pitolisant

Research suggests that histamine, a neurotransmitter that promotes wakefulness, may play an important role in narcolepsy [16]. Preclinical studies have demonstrated that histamine may be important for regulating normal sleep–wake behavior and may play a complementary role with hypocretin [16, 17]. Discovered in the 1980s, the histamine-3 receptor (H3R) is a presynaptic auto receptor that inhibits histamine release and regulates the release of other neurotransmitters [18]. H3Rs are concentrated in the basal ganglia, globus pallidus, hippocampus, and cortex and play an important role in cognition compared to H1R and H2R which have mostly peripheral functions [19, 20].

Pitolisant is a first-of-its-class drug that acts on presynaptic H3Rs through antagonist/inverse agonist activity [21]. This competitive action enhances release of histamine and other wake-promoting neurotransmitters such as dopamine, acetylcholine, and norepinephrine [22, 23]. In narcoleptic animal models, it has been shown to promote wakefulness and decrease episodes of REM sleep, thus circumventing orexin deficiency [22]. In contrast to known drugs of abuse (e.g., amphetamine, cocaine) and wake-promoting agents (e.g., modafinil, armodafinil), pitolisant does not work primarily through dopamine and does not cause an increase of dopamine in the nucleus accumbens [24].

Pitolisant is currently the only H3R antagonist/inverse agonist approved for the treatment of EDS in patients with narcolepsy. Results from key clinical trials including Harmony I, Harmony III, and Harmony-CTP led to the approval of pitolisant for the treatment of narcolepsy in 2019 [20]. Pitolisant is available as oral tablets and demonstrates effectiveness after a 2–3-week titration, though clinical response can take up to 8 weeks [20]. A recent systematic review on the efficacy of pitolisant in the treatment of narcolepsy showed that pitolisant is efficacious in reducing EDS and cataplexy compared to placebo and that adverse side effects were less common and shorter in duration compared to modafinil-treated patients [25].

Pitolisant is generally well tolerated. Safety assessed from pooled studies shows that the frequency of side effects is similar to modafinil. The most common adverse side effects include headache, insomnia, nausea, and anxiety [26]. Pitolisant inhibits CYP2D6 and induces CYP3A4, CYP1A2, and CYP2B6 [27]. Pitolisant has been reported to cause QT prolongation, and it is recommended to avoid other concomitant drugs that may prolong the QT interval [28].

Preclinical Abuse Liability Studies

Preclinical research into H3Rs and its role in drug abuse has been controversial [29]. However, studies of animal models administered pitolisant show that it has no reinforcing properties and does not potentiate the behavioral effects of psychostimulants such as cocaine or methamphetamine [30–32]. Unlike amphetamine, modafinil, and solriamfetol, pitolisant has no effect on striatal dopamine, locomotion, behavioral sensitization, or food intake, which are common features in compounds with abuse potential [24, 33].

Clinical Human Abuse Liability Studies

As a new therapeutic agent, information on the human abuse liability of pitolisant is limited. At present, there is only one published study on the human abuse potential of pitolisant. Setnik et al. [34••] investigated the human abuse potential of pitolisant in a randomized, double blind, active and placebo controlled, crossover study of adults who were nondependent, recreational stimulant users ($n = 38$). Therapeutic (35.6 mg) and supratherapeutic (213.6 mg) doses of pitolisant were compared against placebo and phentermine (60 mg), a schedule IV positive control. Mean drug liking ("at this moment") was significantly lower for pitolisant than phentermine at both therapeutic and supratherapeutic doses. Drug liking of pitolisant (at both doses) was similar to placebo. For key secondary measures overall drug liking and willingness to take the drug again, pitolisant had an abuse potential profile similar to that of placebo and significantly lower than that of phentermine. Unlike phentermine, pitolisant did not demonstrate clinically significant increases in blood pressure or heart rate. Pitolisant, even at supratherapeutic levels, was shown to be no different from placebo in terms of abuse potential or safety.

Based on the findings above and from preclinical data, pitolisant is the only treatment for EDS in narcolepsy that has been approved by the FDA without being scheduled as a controlled substance. There are currently no studies that examine the human abuse potential of pitolisant in patients diagnosed specifically with a central disorder of hypersomnolence. There are currently no published post-marketing surveillance studies assessing misuse and abuse of pitolisant.

Solriamfetol

Solriamfetol (formerly known as JZP-110) is a dopamine and norepinephrine reuptake inhibitor that was approved by the FDA in 2019 for EDS associated with treated obstructive sleep apnea (OSA) (37.5–150 mg/day) or narcolepsy [35]. In a phase III study, solriamfetol demonstrated robust wake-promoting effects in a dose-dependent fashion in OSA

Table 2 Summary of medications used to central disorders of hypersomnolence

Drug name and schedule	Mechanism of action	FDA-approved indications	Administration	Adult dosing[a]	Warning and precautions	Side effects	Misuse and abuse potential
Pitolisant *(Not scheduled)*	Selective histamine 3 (H_3) receptor antagonist/inverse agonist	EDS and cataplexy associated with narcolepsy	4.45 mg and 17.8 mg	Initiate with 8.9 mg once daily, titrate to 17.8 mg once daily by week 2; recommended dose range: 17.8–35.6 g	QT interval prolongation	Most common: headache, nausea, anxiety	Abuse potential is similar to that of placebo and lower than that of phentermine [34••]
Solriamfetol *(Schedule IV)*	Dopamine and norepinephrine reuptake inhibitor	Narcolepsy, OSA	75 mg and 150 mg oral tablets	Start at 75 mg once daily; recommended range 75–150 mg; double at intervals of at least 2 days; maximum recommended dose: 150 mg once daily	Blood pressure and heart rate increases; use caution in treating patients with a history of psychosis or bipolar disorder	Most common: headache, nausea, decreased appetite, insomnia, and anxiety	Abuse potential is similar or lower to that of phentermine [44••]
Sodium oxybate and lower-sodium (calcium, magnesium, potassium, sodium) oxybate oral solution *(Schedule III)*	GABA-B receptor agonist	Cataplexy and EDS in patients 7 years of age and older with narcolepsy	Oral solution, 0.5 mg/mL	Start at 4.5 g per night administered orally divided into two doses; 2.25 g at bedtime and 2.25 g 2–4 h later; increase dosage by 1.5 g per night at weekly intervals to the effective dosage range of 6–9 g per night orally; doses higher than 9 g have not been studied	CNS depression; increased depression and suicidality; impaired motor and cognitive function; high sodium content	Most common: nausea, dizziness, vomiting, somnolence, enuresis, and tremors	Abuse potential less than that of pentobarbital but greater than that of triazolam [68]; abuse potential is similar to or greater than ethanol [69]; post-marketing surveillance indicates low risk of misuse and abuse [11, 70••]; evaluation of the Xyrem® REMS program reports success in monitoring and mitigation [71•]

Table 2 (continued)

Drug name and schedule	Mechanism of action	FDA-approved indications	Administration	Adult dosing[a]	Warning and precautions	Side effects	Misuse and abuse potential
Modafinil *(Schedule IV)*	Weak dopamine reuptake inhibitor	EDS associated with narcolepsy	100 mg or 200 mg tablets	200 mg/day, given as a single dose in the morning; doses of 400 mg/day have been well tolerated	Serious rash (including SJS); angioedema and anaphylaxis; multi-organ hypersensitivity reactions; persistent sleepiness; use caution in patients with psychosis, depression, or mania; consider increased monitoring of cardiovascular disease	Most common: headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, and dyspepsia	Clinical studies demonstrate that modafinil is distinctly different from other amphetamine-like agents [98]; abuse potential may be similar to methylphenidate based on DAT occupancy [103]; 10% of patients may display amphetamine-like withdrawals [104]; post-marketing surveillance is not up to date, though historically has not seen any misuse or abuse in the population

[a]Recommended dosing for the treatment of symptoms associated with narcolepsy

patients with EDS [36]. In this same patient population, solriamfetol has also been shown to improve measures of functioning, quality of life, and work productivity [37]. In patients with narcolepsy with EDS, a recent study demonstrated robust effects of solriamfetol for up to 52 weeks of treatment without rebound sleepiness or withdrawal-related adverse effects after abrupt discontinuation [38].

Side effects including headache, nausea, nasopharyngitis, insomnia, dry mouth, and anxiety are common during titration but frequently resolve with maintenance therapy. Approximately 10% of patients discontinue therapy because of adverse events [38]. Increase in blood pressure and heart rate are severe adverse effects that should be monitored during therapy [39]. Coadministration of dopaminergic drugs should be used with caution though possible interactions have not been evaluated [40].

Preclinical Abuse Liability Studies

As a modulator of dopamine (DA) and norepinephrine (NE), it is important to compare solriamfetol to two existing classes of medications with similar mechanisms of action, modafinil and amphetamine. Unlike modafinil, which mainly binds to the dopamine transporter (DAT) and inhibits release of dopamine, solriamfetol inhibits reuptake at both the DAT and norepinephrine transporter (NET) [41, 42]. This dual activity at NET and DAT may help explain differences in the therapeutic effects and abuse potential of solriamfetol versus modafinil/armodafinil [42].

The mechanism by which solriamfetol induces wakefulness is also different from d-amphetamine [43]. In contrast to d-amphetamine, an equipotent wake-promoting dose of solriamfetol is not accompanied by stereotyped behavior or pronounced locomotor activity, nor does it produce rebound hypersomnia [43]. These findings are reinforced by another study that demonstrated solriamfetol is neither a potent nor efficacious monoamine releaser when compared to amphetamine [42]. In rat brain synaptosomes, the highest solriamfetol concentration tested resulted in a submaximal release of DA and serotonin (5-HT) with no effects on NE. The differences in interaction at monoamine transporters between solriamfetol (reuptake inhibitor) versus amphetamine (monoamine releaser) may help explain differences in the therapeutic effects and abuse potential of solriamfetol [42].

Clinical Human Abuse Liability Studies

As a new therapeutic agent, information on the human abuse of solriamfetol is limited. To date, there is only one human abuse potential study of solriamfetol. Carter et al. [44••] recently evaluated solriamfetol in a randomized, double blind, placebo-controlled, crossover study in adults with a history of recreational polydrug use ($n = 43$). Solriamfetol (300, 600, and 1200 mg) was evaluated against placebo and the schedule IV stimulant phentermine (45 and 90 mg) as a positive control. Peak liking at the moment was significant greater for solriamfetol (at all doses) than placebo but was significantly less than phentermine 90 mg. More than half of the participants did not report next day overall drug liking after supratherapeutic doses of solriamfetol (600 and 1200 mg). Participants were significantly less likely to take to take solriamfetol again (at all doses) compared to phentermine (at all doses). Positive drug effects with solriamfetol were consistently lower than phentermine whereas negative effects (disliking, anxiety, agitation) were consistently higher than phentermine. The overall findings of this investigation indicate that the abuse potential of solriamfetol is similar to or lower than phentermine. There were no serious adverse events observed with solriamfetol despite inclusion of supratherapeutic doses of 600 and 1200 mg, the latter being four times the highest planned therapeutic dose.

Solriamfetol is schedule IV as its subjective response and side effect profile is similar to that of phentermine. There are currently no studies examining the human abuse potential of pitolisant in patients diagnosed with a central disorder of hypersomnolence. There are currently no published post-marketing surveillance studies assessing the misuse and abuse prevalence of solriamfetol.

Sodium Oxybate

Sodium oxybate (SXB) (Xyrem®) is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of GABA that acts a rapid central nervous system (CNS) depressant. GHB is found in the brain and throughout peripheral tissues [11]. SXB has therapeutic benefits for both cataplexy and EDS though it is not well understood and believed to be due to GABA-B receptor agonist activity. This differs from ethanol and sedative hypnotics such as benzodiazepines, which act via the GABA-A subtype [45, 46].

SXB was approved in 2002 by the US FDA and considered a first of its kind for treatment of both EDS and cataplexy in patients with narcolepsy, and since then has been considered a first-line therapy for patients with narcolepsy [47, 48]. In other countries such as Australia and Italy, SXB has also been approved for use in alcohol withdrawal syndrome and abstinence maintenance [47]. The efficacy of SXB for cataplexy and EDS in patients with narcolepsy is well established in clinical trials [49–51]. In the USA, SXB is classified as a schedule III substance, with illicit use subject to schedule I penalties [11].

The specific mechanism by which SXB reduces symptoms in narcoleptic patients is not well understood. Improved

sleep may be related to decreased time spent in wake and N1 and increases in stage N2 and N3 resulting in deeper sleep [52]. The therapeutic efficacy of SXB gradually emerges over time and persists after metabolization of the drug. This delay effect suggests that the therapeutic mechanism may be mediated indirectly through possible interactions of GABA-B receptors and disinhibition of dopamine release [53, 54].

SXB is generally well tolerated in patients with narcolepsy with mild to moderate side effects that are dose dependent [55]. Commonly reported side effects include nausea, vomiting, headache, dizziness, and enuresis. Rare side effects include psychosis, anxiety, and suicidal ideation [56]. There is concern about the safety margin of SXB; impaired consciousness and respiratory depression have been reported at doses 2 to 3 times the maximum recommended dose [57]. In addition, abuse or misuse of GHB in combination with other substances may lead to severe side effects such as respiratory depression, seizures, altered mental status, and death [58].

Based on the safety profile and risks associated with its illicit counterpart GHB, SXB is only available through the Xyrem® Risk Evaluation and Mitigation (REMS) program which was designed to mitigate the risk of its misuse and abuse. It is a requirement that prescribers enroll in the program. A central pharmacy dispense the medication to enrolled patients after being fully instructed on the proper use and risks associated with SXB [59]. This same REMS program also oversees the newer lower-sodium oxybate analog (Xywav®), given its similar risks of misuse and abuse.

Preclinical and Clinical Abuse Liability Studies

Extensive literature exists on the dependence and abuse potential of GHB which shares very similar pharmacology to SXB, and thus studies can be extrapolated to its pharmaceutical counterpart. GHB produces dose-related increases in dissociate-like effects, sedative-like effects, and drug liking in humans without a history of sedative abuse [60]. Prolonged GHB administration also leads to the development of physical dependence as demonstrated in both animal models (e.g., [61, 62]) and humans [63]. Preclinical studies have shown that GHB is self-administered in mice [64], induces conditioned place preference in rats [65], and has shown greater preference and intake in genetically bred ethanol-preferring rats [66]. Furthermore, the neurobiological pathways of GHB dependence and withdrawal are complex and cannot be related to a single mechanism, creating complications in withdrawal management such that no single drug class (e.g., benzodiazepine) is sufficient to prevent life-threatening complications [67].

In a randomized, double-blinded placebo-controlled, comparative abuse study in adults with a history of substance use, GHB significantly increased same-day measures of positive drug effects (liking and good effects) relative to placebo; overall, the abuse potential of GHB was found to be less than that of pentobarbital but greater than that of triazolam [68]. In another comparative abuse study of recreational nonmedical users of ethanol and sedative-hypnotics, drug liking was significantly greater for GHB compared to placebo; same day liking and good effects were similar to that of ethanol, whereas next day measures of abuse potential (including liking, good effects, and take again) were significantly greater for GHB [69].

Post-marketing Surveillance Studies

The prevalence of SXB misuse and abuse is well documented through post-surveillance studies and data monitoring. The incidence of SXB abuse was evaluated by Mayer et al. in 2018 [70••] in the largest post-authorization, non-interventional surveillance study to date (narcolepsy type 1 $n = 670$, other indications $n = 60$). The study, conducted between May 2006 and September 2016, enrolled any patient, irrespective of diagnosis, who had been prescribed SXB by a sleep specialist. Incidence of higher-than-recommended doses (< 4%) and misuse was low (e.g., early refill requests, inappropriate dose adjustment requests, use by other household members, continued use after drug termination). 35.5% of patients reported consumption of alcohol though few reported drinking daily (23, 3.4%). Three cases of adverse events were concluded to be associated with misuse or abuse. Prior to this study, the most recent post-marketing data available for SXB covered the period between market introduction in 2002 to 2008, during which approximately 26,000 patients worldwide received SXB [11]. During this period, there were 4 cases (0.039%) that satisfied DSM-IV criteria for substance dependence, 10 cases (0.039%) that satisfied DSM-IV criteria for substance abuse, two confirmed cases (0.008%) of sexual assault involving SXB, 8 cases (0.031%) of overdose with suicidal intent, and five incidents of diversion. Although post-marketing data may be subject to underreporting, both surveillance studies to date indicate a low risk of abuse and misuse of SXB.

There have been several recent evaluations on the effectiveness of the Xyrem® REMS program. Data monitoring [71•] from enrolled prescribers ($n = 4524$) showed that: no patients were shipped SXB under one or more than one name or after being disenrolled; no individual patient had overlapping active prescriptions; and all notifications regarding potential abuse ($n = 31$), misuse ($n = 343$), or diversion ($n = 22$) were discussed with prescribers. Overall, the results show that the REMS program is successfully identifying and documenting suspected incidents of abuse, misuse, early refill requests, and diversion, with information conveyed to prescribers in real time. As education is a foundational pillar

of the REMS program, the data also revealed knowledge gaps in patients and prescribers when it comes to safety risks (e.g., all prescribers knew that CNS depression was a risk of SXB in combination with alcohol but not all prescribers knew it was a risk from SXB alone). This is contrasted with findings from a cross sectional-survey [72] distributed to healthcare professionals in 2020 which concluded that prescribers had excellent knowledge of SXB with respect to minimizing risks, including CNS depression and potential for abuse and misuse, though the low sample size ($n = 31$) limits generalization. Furthermore, this study reported a limited understanding of how to best improve prescriber educational interventions, though suggests that face to face education may be more effective than written guidance.

Modafinil

Modafinil is a wake-promoting agent with a pharmacological profile that is unlike that of traditional stimulants. Modafinil is a racemic mixture of two active isomers, whereas armodafinil is the R isomer only, leading to differences in pharmacokinetics and a longer half-life [73]. The precise mechanism of action of this class of drug is unclear though studies have demonstrated that it directly prevents dopamine reuptake and indirectly activates the release of orexin and histamine [74]. It has been investigated in a large number of patients with narcolepsy in rigorous, double blind, placebo controlled studies [75, 76]. Modafinil has been approved by the FDA to treat EDS in narcolepsy, obstructive sleep apnea, and shift work sleep disorder and is also often prescribed off-label for other indications [77]. It is classified as a schedule IV medication as overdose may cause seizures or cardiac arrhythmias, a danger shared by classic stimulants which are schedule II [78].

Studies show that modafinil is an exceptionally weak but very selective, dopamine transporter inhibitor. Modafinil binds to and disrupts cell-membrane dopamine transporter (DAT) leading to direct prevention of dopamine reuptake, elevated extracellular dopamine concentrations, increased stimulation of dopaminergic and adrenergic receptors, and wakefulness [41]. It has also been postulated to increase signaling in orexin and histamine pathways [79], with animal studies also suggesting a glutamatergic effect [80]. Relative to classic stimulants which also act through catecholaminergic mechanisms, modafinil has a lower propensity for causing euphoric effects [81]. These differences may be due to differences in DAT selectivity and interaction, pharmacokinetics, or the nature of each compound's interaction with DAT [82].

Much of the research on modafinil has shown that it is well tolerated [83, 84]. Long-term studies have shown no evidence of tolerance [84], though rare cases of tolerance have been reported [85]. Other studies have demonstrated that modafinil causes symptoms of withdrawal and return of sleepiness in patients with narcolepsy after 9 weeks of use [86]. Compared to classic stimulants, modafinil has a lower incidence of anxiety, hypertension, jitteriness, and severe tachycardia [78]. The most common side effect is headache (11%) and rare allergic reactions including Stevens-Johnson syndrome have also been reported [78]. Risk of overdose is low; a retrospective review of 87 cases of supratherapeutic doses of modafinil showed no serious or death-related overdose effects [87].

Preclinical Abuse Liability Studies

Modafinil has been shown to share discriminative stimulus properties with cocaine. This has been documented in rodents [88, 89] and rhesus monkeys [90, 91]. Similar results have been reported in rats exposed to d-amphetamine [92]. Modafinil at higher doses reinstates cocaine-induced conditioned place preference following extinction in rats suggesting that modafinil may induce relapse in humans [93]. Modafinil alone may have rewarding properties as it has been shown to induce behavioral sensitization and establish conditioned place after single and repeated injections in mice [89, 94, 95]. More recent studies suggest that modafinil induces rapid-onset behavioral sensitization that is mediated by D1 and D2 receptors located in the ventral tegmental area and nucleus accumbens, a brain region associated with rewarding effects and abuse [96, 97].

Clinical Human Abuse Liability Studies

In a human abuse potential study of adults with a history of polysubstance abuse, drug liking of modafinil was significantly greater than placebo. Compared to methylphenidate, study findings (including the lack of a response on the Amphetamine Scale of the Addiction Research Center Inventory) were consistent with preclinical data suggesting that modafinil is not an amphetamine-like agent [98]. Wisor et al. [41] postulated that modafinil's lack of sustaining abstinence in cocaine [99, 100] and methamphetamine-dependent users [101, 102] makes it a poor pharmacological mimetic and substitute, and thus distinct in its abuse and addiction potential relative to cocaine and methamphetamine. A DAT occupancy study using positron emission topography (PET) imaging in humans show that modafinil is close to methylphenidate in terms of dopaminergic transmission, suggesting that the abuse potential of modafinil may be near the same level as methylphenidate [103]. In a clinical trial comparing modafinil to pitolisant, 10% of patients displayed amphetamine-like withdrawal symptoms [104]. No clinical studies have been conducted assessing modafinil's abuse liability in patients with a central disorder of hypersomnolence.

Post-marketing Surveillance

Post-marketing surveillance of modafinil is limited. A historical surveillance from 1999 to 2003 did not detect any generalized or persistent misuse or abuse of modafinil [105]. Case reports of modafinil misuse and abuse are rare. Subjects had a history of alcohol dependence [106], benzodiazepine dependence [107], schizoaffective disorder [85, 107], and ADHD [108]. To our knowledge, there are no reported cases of abuse or misuse in patients prescribed modafinil for a central disorder of hypersomnolence.

Conclusion

With the exception of pitolisant, all medications currently approved by the FDA for the treatment of central disorders of hypersomnolence are controlled substances; hence, there has been a need to treat symptoms of excessive daytime sleepiness and/or cataplexy using novel pharmacological agents with a lower potential for abuse. There is wide variability in the literature on the general misuse and abuse of the therapeutic agents discussed above with even less studies specifically evaluating the liability in patients with narcolepsy or idiopathic hypersomnia.

While data is limited, agents that have high potential for misuse in the general population or in other conditions such as ADHD may have lower risk among patients treated for a central disorder of hypersomnolence, particularly when safeguards are in place. A study evaluating patients prescribed methylphenidate or amphetamine for narcolepsy or idiopathic hypersomnia reported no patients misusing their stimulant medication [9] though a related study reported an increase in alcohol or polysubstance misuse in the high-dose group [109]. Sodium oxybate, a schedule III substance, demonstrates high liability in preclinical and clinical models, though the low prevalence of misuse and abuse in post-marketing surveillance studies demonstrate that there are effective risk mitigation systems in place. Preclinical and clinical studies on modafinil, a schedule IV substance, report mixed results on abuse potential, though post-marketing surveillance has not detected generalized or persistent misuse or abuse of this agent [105]. Initial research into solriamfetol, a schedule IV substance, and pitolisant, a nonscheduled substance, show promise as the human abuse liability studies thus far have demonstrated a benign subjective response and side effect profile. These novel compounds will continue to benefit from additional clinical liability studies and post-marketing surveillance to assess long-term risks and benefits.

In considering a therapeutic option for the treatment of a central disorder of hypersomnolence, misuse and abuse potential is one of many considerations in selecting the most appropriate therapeutic agent. Other important considerations include the patient's age, allergies, prior adverse effects, comorbidities, convenience of administration, and goals of care. Though not discussed in this review, special consideration should be taken for pregnant and pediatric populations. The choice of treatment also depends on the specific disorder and the symptoms that are being targeted. Careful consideration into the misuse and abuse potential of a therapeutic agent in conjunction with the latest evidence-based guidelines [13] provides heightened confidence in prescribing currently available, FDA-approved treatments.

Declarations

Conflict of Interest Dr. Plante has served as a consultant for Teva Pharmaceuticals Australia, a consultant for Harmony Biosciences, and consultant/medical advisory board member for Jazz Pharmaceuticals. Dr. Plante has also received research support from the AASM Foundation, NIA, NINR, the Great Lakes Center for Occupational Health and Safety, and the Madison Educational Partnership. Dr. Plante also has a patent application pending not related to this work. Mr. Ngo has no conflicts of interest to declare.

Human and Animal Rights and Informed Consent This review did not directly involve human participants or animals and is thus exempt from Institutional Review Board or Institutional Animal Care and Use Committee oversight.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Jennum P, Ibsen R, Knudsen S, Kjellberg J. Comorbidity and mortality of narcolepsy: a controlled retro- and prospective national study. Sleep. 2013;36:835–40.
2. Rasmussen N. America's first amphetamine epidemic 1929–1971. Am J Public Health. 2008;98:974–85.
3. Rabiner DL, Anastopoulos AD, Costello EJ, Hoyle RH, Esteban McCabe S, Swartzwelder HS. The misuse and diversion of prescribed ADHD medications by college students. J Atten Disord. 2009;13:144–53.
4. Jaffe SL. Intranasal abuse of prescribed methylphenidate by an alcohol and drug abusing adolescent with ADHD. J Am Acad Child Adolesc Psychiatry. 1991;30:773–5.
5. Parran TV Jr, Jasinski DR. Intravenous methylphenidate abuse: prototype for prescription drug abuse. Arch Intern Med. 1991;151:781–3.
6. Kaye S, Darke S. The diversion and misuse of pharmaceutical stimulants: what do we know and why should we care? Addiction. 2012;107:467–77.
7. Seth P, Scholl L, Rudd RA, Bacon S. Overdose deaths involving opioids, cocaine, and psychostimulants - United States, 2015–2016. MMWR Morb Mortal Wkly Rep. 2018;67:349–58.

8. Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, Utzinger L, Fusillo S. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. J Am Acad Child Adolesc Psychiatry. 2008;47:21–31.
9. Mantyh WG, Auger RR, Morgenthaler TI, Silber MH, Moore WR. Examining the frequency of stimulant misuse among patients with primary disorders of hypersomnolence: a retrospective cohort study. J Clin Sleep Med. 2016;12:659–62.
10. Dijkstra BAG, Beurmanjer H, Goudriaan AE, Schellekens AFA, Joosten EAG. Unity in diversity: a systematic review on the GHB using population. Int J Drug Policy. 2021;94:103230.
11. Wang YG, Swick TJ, Carter LP, Thorpy MJ, Benowitz NL. Safety overview of postmarketing and clinical experience of sodium oxybate (Xyrem): abuse, misuse, dependence, and diversion. J Clin Sleep Med. 2009;5:365–71.
12. Sharif S, Guirguis A, Fergus S, Schifano F. The use and impact of cognitive enhancers among university students: a systematic review. Brain Sci. 2021;11:355.
13. Maski K, Trotti LM, Kotagal S, Robert AR, Rowley JA, Hashmi SD, Watson NF. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17:1881–93.
14. Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain. 2013;154:2287–96.
15. Hasin DS, O'Brein CP, Auriacombe M, Borges G, Bucholz K, Budney A, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry. 2013;170(8):834–51. https://doi.org/10.1176/appi.ajp.2013.12060782.
16. Scammell TE, Jackson AC, Franks NP, Wisden W, Dauvilliers Y. Histamine: neural circuits and new medications. Sleep. 2019;42:zsy183.
17. Anaclet C, Parmentier R, Ouk K, et al. Orexin/hypocretin and histamine: distinct roles in the control of wakefulness demonstrated using knock-out mouse models. J Neurosci. 2009;29:14423–38.
18. Parsons ME, Ganellin CR. Histamine and its receptors. Br J Pharmacol. 2006;147:S127–35.
19. Martinez-Mir MI, Pollard H, Moreau J, Arrang JM, Ruat M, Traiffort E, Schwartz JC, Palacios JM. Three histamine receptors (H1, H2 and H3) visualized in the brain of human and non-human primates. Brain Res. 1990;526:322–7.
20. Harwell V, Fasinu PS. Pitolisant and other histamine-3 receptor antagonists-an update on therapeutic potentials and clinical prospects. Medicines (Basel). 2020;7:E55.
21. Schwartz J-C. The histamine H3 receptor: from discovery to clinical trials with pitolisant. Br J Pharmacol. 2011;163:713–21.
22. Lin J-S, Dauvilliers Y, Arnulf I, et al. An inverse agonist of the histamine H(3) receptor improves wakefulness in narcolepsy: studies in orexin-/- mice and patients. Neurobiol Dis. 2008;30:74–83.
23. Ligneau X, Perrin D, Landais L, et al. BF2.649 [1-{3-[3-(4-Chlorophenyl)propoxy]propyl}piperidine, hydrochloride], a nonimidazole inverse agonist/antagonist at the human histamine H3 receptor: preclinical pharmacology. J Pharmacol Exp Ther. 2007;320:365–75.
24. Uguen M, Perrin D, Belliard S, Ligneau X, Beardsley PM, Lecomte JM, Schwartz JC. Preclinical evaluation of the abuse potential of pitolisant, a histamine H_3 receptor inverse agonist/antagonist compared with modafinil. Br J Pharmacol. 2013;169:632–44.
25. Fabara SP, Ortiz JF, Anas Sohail A, Hidalgo J, Altamimi A, Tama B, Patel UK. Efficacy of pitolisant on the treatment of narcolepsy: a systematic review. Cureus. 2021;13:e16095.
26. Romigi A, Vitrani G, Lo Giudice T, Centonze D, Franco V. Profile of pitolisant in the management of narcolepsy: design, development, and place in therapy. Drug Des Devel Ther. 2018;12:2665–75.
27. Syed YY. Pitolisant: first global approval. Drugs. 2016;76:1313–8.
28. Winter W, Wanaski SP, Patroneva A, Dayno JM. 0744 cardiac safety profile of pitolisant in patients with narcolepsy. Sleep. 2020;43:A283.
29. Pallardo-Fernández I, Muñoz-Rodríguez JR, González-Martín C, Alguacil LF. Histamine H3 receptor gene variants associated with drug abuse in patients with cocaine use disorder. J Psychopharmacol. 2020;34:1326–30.
30. Brabant C, Charlier Y, Navacerrada MES, Alleva L, Tirelli E. Action of pitolisant on the stimulant and rewarding effects of cocaine in mice. Eur J Pharmacol. 2016;791:552–9.
31. Huyts B, Brabant C, Tirelli E. Pitolisant and intravenous cocaine self-administration in mice. Eur J Pharmacol. 2019;851:63–8.
32. Kitanaka J, Kitanaka N, Hall FS, et al. In vivo evaluation of effects of histamine H3 receptor antagonists on methamphetamine-induced hyperlocomotion in mice. Brain Res. 2020;1740:146873.
33. Krief S, Berrebi-Bertrand I, Nagmar I, et al. Pitolisant, a wake-promoting agent devoid of psychostimulant properties: preclinical comparison with amphetamine, modafinil, and solriamfetol. Pharmacol Res Perspect. 2021;9:e00855.
34.•• Setnik B, McDonnell M, Mills C, Scart-Grès C, Robert P, Dayno JM, Schwartz J-C. Evaluation of the abuse potential of pitolisant, a selective H3-receptor antagonist/inverse agonist, for the treatment of adult patients with narcolepsy with or without cataplexy. Sleep. 2020;43:zsz252. **This study evaluates the human abuse potential of pitolisant through a randomized, double blind, placebo-controlled, crossover design study of 38 nondependent stimulant users. This article is highly of interest as it is currently the only published study on the human abuse potential of pitolisant. The study design is consistent with FDA guidance for abuse potential assessment.**
35. Jazz Pharmaceuticals (2019) sunosi.ca.PM-en.pdf. In: Jazz Pharmaceuticals . Jazz Pharmaceuticals, Inc.; Palo Alto, CA: 2019. Inc. Sunosi™ (solriamfetol) tablets prescribing information. https://pp.jazzpharma.com/pi/sunosi.ca.PM-en.pdf. Accessed 10 May 2022.
36. Schweitzer PK, Mayer G, Rosenberg R, Malhotra A, Zammit GK, Gotfried M, Chandler P, Baladi M, Strohl KP. Randomized controlled trial of solriamfetol for excessive daytime sleepiness in OSA. Chest. 2021;160:307–18.
37. Weaver TE, Drake CL, Benes H, et al. Effects of solriamfetol on quality-of-life measures from a 12-week phase 3 randomized controlled trial. Ann Am Thorac Soc. 2020;17:998–1007.
38. Malhotra A, Shapiro C, Pepin J-L, et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. Sleep. 2019;43:zsz220.
39. Videnovic A, Amara AW, Comella C, et al. Solriamfetol for excessive daytime sleepiness in Parkinson's disease: phase 2 proof-of-concept trial. Mov Disord. 2021;36:2408–12.
40. Kaufman MB. Pharmaceutical approval update. P T. 2019;44:337–9.
41. Wisor J. Modafinil as a catecholaminergic agent: empirical evidence and unanswered questions. Front Neurol. 2013;4:139.
42. Baladi MG, Forster MJ, Gatch MB, Mailman RB, Hyman DL, Carter LP, Janowsky A. Characterization of the neurochemical and behavioral effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. J Pharmacol Exp Ther. 2018;366:367–76.

43. Hasan S, Pradervand S, Ahnaou A, Drinkenburg W, Tafti M, Franken P. How to keep the brain awake? The complex molecular pharmacogenetics of wake promotion. Neuropsychopharmacol. 2009;34:1625–40.
44.•• Carter LP, Henningfield JE, Wang YG, Lu Y, Kelsh D, Vince B, Sellers E. A randomized, double-blind, placebo-controlled, crossover study to evaluate the human abuse liability of solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor. J Psychopharmacol. 2018;32:1351–61. **This study evaluates the human abuse potential of solriamfetol in a randomized, double blind, placebo-controlled, crossover design study of 43 adults with a recent history of recreational polydrug use. This article is highly of interest as it currently the only published study on the human abuse potential of solriamfetol. The study design is consistent with FDA guidance for abuse potential assessment.**
45. Whiting PJ. GABA-A receptor subtypes in the brain: a paradigm for CNS drug discovery? Drug Discov Today. 2003;8:445–50.
46. Trudell JR, Messing RO, Mayfield J, Harris RA. Alcohol dependence: molecular and behavioral evidence. Trends Pharmacol Sci. 2014;35:317–23.
47. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin an American Academy of Sleep Medicine report. Sleep. 2007;30:1705–11.
48. Roth T, Dauvilliers Y, Guinta D, Alvarez-Horine S, Dynin E, Black J. Effect of sodium oxybate on disrupted nighttime sleep in patients with narcolepsy. J Sleep Res. 2017;26:407–14.
49. Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev. 2012;16:431–43.
50. Xu X-M, Wei Y-D, Liu Y, Li Z-X. Gamma-hydroxybutyrate (GHB) for narcolepsy in adults: an updated systematic review and meta-analysis. Sleep Med. 2019;64:62–70.
51. Maski K, Trotti LM, Kotagal S, Robert AR, Swick TJ, Rowley JA, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2021;17(9):1895–945. https://doi.org/10.5664/jcsm.9326.
52. Black SW, Yamanaka A, Kilduff TS. Challenges in the development of therapeutics for narcolepsy. Prog Neurobiol. 2017;152:89–113.
53. Huang Y-S, Guilleminault C. Narcolepsy: action of two γ-aminobutyric acid type B agonists, baclofen and sodium oxybate. Pediatr Neurol. 2009;41:9–16.
54. Cruz HG, Ivanova T, Lunn M-L, Stoffel M, Slesinger PA, Lüscher C. Bi-directional effects of GABA(B) receptor agonists on the mesolimbic dopamine system. Nat Neurosci. 2004;7:153–9.
55. US Xyrem® Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep. 2002;25:42–9.
56. Plazzi G, Ruoff C, Lecendreux M, Dauvilliers Y, Rosen CL, Black J, Parvataneni R, Guinta D, Wang YG, Mignot E. Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-withdrawal multicentre study and open-label investigation. Lancet Child Adolesc Health. 2018;2:483–94.
57. Robinson DM, Keating GM. Sodium oxybate: a review of its use in the management of narcolepsy. CNS Drugs. 2007;21:337–54.
58. Carter LP, Pardi D, Gorsline J, Griffiths RR. Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem): differences in characteristics and misuse. Drug Alcohol Depend. 2009;104:1–10.
59. Wu J, Juhaeri J. The US Food and Drug Administration's Risk Evaluation and Mitigation Strategy (REMS) program - current status and future direction. Clin Ther. 2016;38:2526–32.
60. Oliveto A, Gentry WB, Pruzinsky R, Gonsai K, Kosten TR, Martell B, Poling J. Behavioral effects of gamma-hydroxybutyrate (GHB) in humans. Behav Pharmacol. 2010;21:332–42.
61. Weerts EM, Goodwin AK, Griffiths RR, Brown PR, Froestl W, Jakobs C, Gibson KM. Spontaneous and precipitated withdrawal after chronic intragastric administration of gamma-hydroxybutyrate (GHB) in baboons. Psychopharmacology. 2005;179:678–87.
62. Goodwin AK, Griffiths RR, Brown PR, Froestl W, Jakobs C, Gibson KM, Weerts EM. Chronic intragastric administration of gamma-butyrolactone produces physical dependence in baboons. Psychopharmacology. 2006;189:71–82.
63. Brunt TM, Koeter MW, Hertoghs N, van Noorden MS, van den Brink W. Sociodemographic and substance use characteristics of gamma hydroxybutyrate (GHB) dependent inpatients and associations with dependence severity. Drug Alcohol Depend. 2013;131:316–9.
64. Martellotta MC, Cossu G, Fattore L, Gessa GL, Fratta W. Intravenous self-administration of gamma-hydroxybutyric acid in drug-naive mice. Eur Neuropsychopharmacol. 1998;8:293–6.
65. Martellotta MC, Fattore L, Cossu G, Fratta W. Rewarding properties of gamma-hydroxybutyric acid: an evaluation through place preference paradigm. Psychopharmacology. 1997;132:1–5.
66. Colombo G, Agabio R, Diaz G, Fà M, Lobina C, Reali R, Gessa GL. γ-Hydroxybutyric acid intake in ethanol-preferring sP and -nonpreferring sNP rats. Physiol Behav. 1998;64:197–202.
67. Kamal RM, van Noorden MS, Franzek E, Dijkstra BAG, Loonen AJM, De Jong CAJ. The neurobiological mechanisms of gamma-hydroxybutyrate dependence and withdrawal and their clinical relevance: a review. Neuropsychobiology. 2016;73:65–80.
68. Carter LP, Richards BD, Mintzer MZ, Griffiths RR. Relative abuse liability of GHB in humans: a comparison of psychomotor, subjective, and cognitive effects of supratherapeutic doses of triazolam, pentobarbital, and GHB. Neuropsychopharmacol. 2006;31:2537–51.
69. Johnson MW, Griffiths RR. Comparative abuse liability of GHB and ethanol in humans. Exp Clin Psychopharmacol. 2013;21(2):112–23. https://doi.org/10.1037/a0031692.
70.•• Mayer G, Plazzi G, Iranzo Á, Ortega-Albás J, Quinnell T, Pesch H, Serralheiro P, Schlit A-F, Wuiame D, Bentz JWG. Long-term compliance, safety, and tolerability of sodium oxybate treatment in patients with narcolepsy type 1: a postauthorization, non-interventional surveillance study. Sleep. 2018;41:zsy128. **This study evaluates the safety and abuse potential of SXB in sleep disordered patients through the largest post authorization, surveillance study to date. This investigation provides long-term, real-world data on the use of SXB in clinical practice and helps inform the overall safety and abuse potential of SXB alongside clinical trial data. This study is limited by its observational nature and cannot be directly compared to clinical trial data, though the safety profile of SXB observed in this study is similar to previous reports.**
71.• Strunc MJ, Black J, Lillaney P, Profant J, Mills S, Bujanover S, Thorpy MJ. The Xyrem® (sodium oxybate) Risk Evaluation and Mitigation Strategy (REMS) program in the USA: results from 2016 to 2017. Drugs - Real World Outcomes. 2021;8:15–28. **This study evaluates the REMS Program and its efficacy in providing SXB to patients with medical needs in a controlled manner. This study highlights the real-world systems in place that can effectively minimize the safety risks associated with**

SXB and helps inform the overall safety and abuse potential of SXB when it is properly prescribed.

72. Iranzo A, Serralheiro P, Schuller J-C, Schlit A-F, Bentz JWG. Evaluation of the effectiveness of the risk minimization measures of sodium oxybate in the European Union. Drugs - Real World Outcomes. 2020;7:307–15.
73. Modafinil. LiverTox: clinical and research information on drug-induced liver injury [Internet]. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Modafinil. [Updated 2021 Aug 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548274/.
74. Hashemian SM, Farhadi T. A review on modafinil: the characteristics, function, and use in critical care. J Drug Assess. 2020;9(1):82–6. https://doi.org/10.1080/21556660.2020.1745209.
75. Broughton RJ, Fleming JA, George CF, Hill JD, Kryger MH, Moldofsky H, Montplaisir JY, Morehouse RL, Moscovitch A, Murphy WF. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997;49:444–51.
76. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. Neurology. 2000;54:1166–75.
77. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. Drugs. 2008;68:1803–39.
78. Borghol A, Aucoin M, Onor I, Jamero D, Hawawini F. Modafinil for the improvement of patient outcomes following traumatic brain injury. Innov Clin Neurosci. 2018;15:17–23.
79. Ishizuka T, Murotani T, Yamatodani A. Action of modafinil through histaminergic and orexinergic neurons. Vitam Horm. 2012;89:259–78.
80. Mahler SV, Hensley-Simon M, Tahsili-Fahadan P, LaLumiere RT, Thomas C, Fallon RV, Kalivas PW, Aston-Jones G. Modafinil attenuates reinstatement of cocaine seeking: role for cystine-glutamate exchange and metabotropic glutamate receptors. Addict Biol. 2014;19:49–60.
81. O'brien CP, Dackis CA, Kampman K. Does modafinil produce euphoria? AJP. 2006;163:1109–1109.
82. Schmitt KC, Reith MEA. The atypical stimulant and nootropic modafinil interacts with the dopamine transporter in a different manner than classical cocaine-like inhibitors. PLoS One. 2011;6:e25790.
83. Suhayl N, Burdette W, Kathryn S. Absence of mood switch with and tolerance to modafinil: a replication study from a large private practice. J Affect Disord. 2006. https://doi.org/10.1016/j.jad.2006.01.010.
84. Mitler M, Harsh J, Hirshkowitz M, Guilleminault C. Long-term efficacy and safety of modafinil (PROVIGIL(R)) for the treatment of excessive daytime sleepiness associated with narcolepsy. Sleep Med. 2000;1:231–43.
85. Krishnan R, Chary KV. A rare case modafinil dependence. J Pharmacol Pharmacother. 2015;6:49–50.
86. Greenblatt K, Adams N. Modafinil. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022. [Updated 2022 Feb 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531476/.
87. Carstairs SD, Urquhart A, Hoffman J, Clark RF, Cantrell FL. A retrospective review of supratherapeutic modafinil exposures. J Med Toxicol. 2010;6:307–10.
88. Loland CJ, Mereu M, Okunola OM, et al. R-modafinil (armodafinil): a unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. Biol Psychiatry. 2012;72:405–13.
89. Paterson NE, Fedolak A, Olivier B, Hanania T, Ghavami A, Caldarone B. Psychostimulant-like discriminative stimulus and locomotor sensitization properties of the wake-promoting agent modafinil in rodents. Pharmacol Biochem Behav. 2010;95:449–56.
90. Gold LH, Balster RL. Evaluation of the cocaine-like discriminative stimulus effects and reinforcing effects of modafinil. Psychopharmacology. 1996;126:286–92.
91. Newman JL, Negus SS, Lozama A, Prisinzano TE, Mello NK. Behavioral evaluation of modafinil and the abuse-related effects of cocaine in rhesus monkeys. Exp Clin Psychopharmacol. 2010;18:395–408.
92. Heal DJ, Buckley NW, Gosden J, Slater N, France CP, Hackett D. A preclinical evaluation of the discriminative and reinforcing properties of lisdexamfetamine in comparison to D-amfetamine, methylphenidate and modafinil. Neuropharmacology. 2013;73:348–58.
93. Bernardi RE, Lewis JR, Lattal KM, Berger SP. Modafinil reinstates a cocaine conditioned place preference following extinction in rats. Behav Brain Res. 2009;204:250–3.
94. Wuo-Silva R, Fukushiro DF, Borçoi AR, et al. Addictive potential of modafinil and cross-sensitization with cocaine: a preclinical study. Addict Biol. 2011;16:565–79.
95. Shuman T, Cai DJ, Sage JR, Anagnostaras SG. Interactions between modafinil and cocaine during the induction of conditioned place preference and locomotor sensitization in mice: implications for addiction. Behav Brain Res. 2012;235:105–12.
96. Wuo-Silva R, Fukushiro DF, Hollais AW, et al. Modafinil induces rapid-onset behavioral sensitization and cross-sensitization with cocaine in mice: implications for the addictive potential of modafinil. Front Pharmacol. 2016;7:420. https://doi.org/10.3389/fphar.2016.00420.
97. Wuo-Silva R, Fukushiro-Lopes DF, Fialho BP, et al. Participation of dopamine D1 and D2 receptors in the rapid-onset behavioral sensitization to modafinil. Front Pharmacol. 2019;10:211. https://doi.org/10.3389/fphar.2019.00211.
98. Jasinski DR, Kovacević-Ristanović R. Evaluation of the abuse liability of modafinil and other drugs for excessive daytime sleepiness associated with narcolepsy. Clin Neuropharmacol. 2000;23:149–56.
99. Malcolm R, Swayngim K, Donovan JL, et al. Modafinil and cocaine interactions. Am J Drug Alcohol Abuse. 2006;32:577–87.
100. Dackis CA, Lynch KG, Yu E, Samaha FF, Kampman KM, Cornish JW, Rowan A, Poole S, White L, O'Brien CP. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. Drug Alcohol Depend. 2003;70:29–37.
101. Anderson AL, Li S-H, Biswas K, et al. Modafinil for the treatment of methamphetamine dependence. Drug Alcohol Depend. 2012;120:135–41.
102. Shearer J, Darke S, Rodgers C, Slade T, van Beek I, Lewis J, Brady D, McKetin R, Mattick RP, Wodak A. A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. Addiction. 2009;104:224–33.
103. Kim W, Tateno A, Arakawa R, Sakayori T, Ikeda Y, Suzuki H, Okubo Y. In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [18F] FE-PE2I. Int J Neuropsychopharmacol. 2014;17:697–703.
104. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, Lehert P, Ding C-L, Lecomte J-M, Schwartz J-C. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol. 2013;12:1068–75.

105. Myrick H, Malcolm R, Taylor B, LaRowe S. Modafinil: preclinical, clinical, and post-marketing surveillance—a review of abuse liability issues. Ann Clin Psychiatry. 2004;16:101–9.
106. Cengiz Mete M, Şenormancı Ö, Saraçlı Ö, Atasoy N, Atik L. Compulsive modafinil use in a patient with a history of alcohol use disorder. Gen Hosp Psychiatry. 2015;37:e7-8.
107. Kate N, Grover S, Ghormode D. Dependence on supratherapeutic doses of modafinil: a case report. Prim Care Companion CNS Disord. 2012;14:PCC.11l01333.
108. Alacam H, Basay O, Tumkaya S, Mart M, Kar G. Modafinil dependence: a case with attention-deficit/hyperactivity disorder. Psychiatry Investig. 2018;15:424–7.
109. Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case-control study. Sleep. 2005;28:667–72.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.