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Literature Review

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Pharmacological management of disrupted sleep due to Methamphetamine use: a literature review

Abstract

Objective: To review the literature on pharmacological management of disrupted sleeping patterns due to Methamphetamine use.

Data sources: A PubMed search of human studies published in English through July 2020 was conducted using the broad search terms "Methamphetamine" and "Sleep".

Study selection: 105 articles were identified and reviewed; 2 studies met the inclusion criteria.

Data extraction: Study design, sample size, medications dose and duration, and sleep related outcomes were reviewed.

Data synthesis: This is some evidence for Modafinil and Mirtazapine for disrupted sleep due to Methamphetamine use, however it is limited by small sample size of the studies.

Conclusion: Treatment of disrupted sleep due to Methamphetamine use, remains challenging. Modafinil and mirtazapine appear to show promise, but further research is warranted before making any evidence-based recommendations.

Keywords: methamphetamine, sleep

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Abbreviations: NSDUH, national survey on drug use and health; ACSA, amphetamine cessation symptom assessment; VAS, visual analogue scale

Introduction

Methamphetamine is a synthetic drug, also known as meth, crystal, "ice" or speed, commonly used in the United States. It is a central nervous system stimulant, can be injected, snorted, inserted rectally, or ingested orally, though smoking is the most common way, it is used probably because of rapid onset of action.[1] It has been suggested that effects can be observed within 15 seconds after smoking as compared to 20-30 minutes with swallowing or 3-5 minutes with snorting. According to the 2018 National Survey on Drug Use and Health (NSDUH) for national indicators of substance use and mental health among people aged 12 or older in the civilian, non-institutionalized population of the United States, approximately 1.9 million people aged 12 or older used Methamphetamine in the past year. This number of past year Methamphetamine users corresponds to 0.7 percent of the population.[2]

Because of significant similarity with other stimulants like amphetamines and cocaine etc., it is classified under stimulant use disorders in DSM-V.[3] Clinical manifestations related to Methamphetamine use are mediated through increased release of Dopamine, Norepinephrine and Serotonin and their reuptake blockade. Dopamine being the major target, responsible for drug seeking and impulsive behaviors. Acute effect of Methamphetamine includes feeling of wellbeing rush, increased energy and alertness, reduced fatigue and decreased need for sleep, increased body temperature, heart rate and respiratory rate, increase in sweating, GI symptoms including nausea, vomiting or stomach cramps, decrease in appetite, increased sexual behaviors, psychotic symptoms and cardiovascular effects like myocardial infarction and risk of cardiac arrhythmias etc.[4,5] Long term use of Methamphetamine causes neurotoxicity especially of Dopaminergic and Serotonergic neurons and can result in psychiatric disorders including mood and anxiety issues, worsening of psychosis and cognitive disorders etc.[6]

Sleep disturbance is commonly observed in methamphetamine users and there appears to be a bidirectional relationship between substance use disorders and sleep problems.Sleep disturbance is also considered as a major risk factor for relapse of methamphetamine use.[7] Sleep disruption can be observed during different phases of Methamphetamine use, i.e. duringthe active use of Methamphetamine, during withdrawal orin abstinence state[8] with insomnia more commonly present during the active use with increased sleep onset latency and decreased total sleep time,[9] and on the other end, hypersomnia during the immediate withdrawal period which is also compounded by sleep deprivation or sleep debt accumulated over previous days of usage.Herrmann et.al., measured dose-dependent effects of Methamphetamine on sleep using polysomnography, a more objective tool to monitor sleep indices.Methamphetamine use was associated with increased sleep latency (which is time taken to fall asleep), decreased sleep efficiency (time sleeping divided by total time in bed), decreased time spent in NREM 2 sleep and REM sleep, with decreased number of REM periods.[10] Methamphetamine withdrawal has been associated with REM rebound.

Though, sleep disturbances are common, and medications are commonly used to ameliorate sleep issues but till date there are no FDA approved medications for treatment of sleep problems in Methamphetamine.So, the purpose of this study was to review the available literature regarding the pharmacological management of sleep disturbances in patients with Methamphetamine use disorder.

Methods

A PubMed search of human studies published in English through July 2020 was conducted using the broad terms: "Methamphetamine" and "Sleep" and studies related to pharmacological management of sleep problems in Methamphetamine use disorder were selected.

Inclusion criteria

a. Randomized controlled trials, open labeled trials, and retrospective chart reviews.

b. Age of subjects 18 or older.

c. Sleep as primary outcome measure.

d. Number of subjects greater than 9.

e. Subjects meeting criteria for DSM Methamphetamine dependence and/or Methamphetamine use disorder.

Exclusion criteria

a. Axis I psychiatric diagnoses, dependence on other substances except for nicotine, currently on methadone or buprenorphine, history of epilepsy.

Results

Literature search: Search yielded 105 articles, titles and abstracts were reviewed but only 2 met the inclusion criteria.

In a study by C. McGregor et al., authors evaluated the effectiveness of Modafinil and Mirtazapine in treating sleep disturbances in subjects going through the Methamphetamine withdrawal. Mirtazapine was chosen because of its antidepressant and antianxiety effects, which are commonly encountered problems in Methamphetamine withdrawal along with improving sleep disturbances. Modafinil was chosen on the other end, because of its wake promoting characteristics as hypersomnolence is a commonly observed symptom in acute Methamphetamine withdrawal state. There is also some data available for effectiveness of Modafinil in cocaine dependence, so authors wanted to evaluate its effectiveness in Methamphetamine withdrawal. 13 subjects were enrolled into the Mirtazapine group (60mg) and 14 subjects were enrolled into Modafinil group (400mg), and data was compared with TAU (Treatment as usual) group which had 22 subjects. TAU group subjects received Pericyazine (2.5-5mg) which is an older sedating phenothiazine antipsychotic. Subjects completed Amphetamine Cessation Symptom Assessment (ACSA), Beck Depression Inventory II (BDI II), Visual Analogue Scale (VAS) for general wellbeing, and St. Mary's Hospital Sleep Questionnaire to assess sleep patterns. The Mirtazapine group was found to have increased total hours of sleep, increased nighttime sleep but also increased daytime sleep, along with increased nocturnal awakenings as compared to the Modafinil group. There were no differences in terms of sleep quality between the groups. Sleep patterns were compared between Modafinil and Mirtazapine groups only. Overall, both Mirtazapine and Modafinil groups were also found to have less severe withdrawal symptoms as compared to TAU groups. Both were found to be well tolerated, and overall Modafinil appeared to be clinically more effective as subjects were less fatigued and had great depth of sleep with lesser awakening as compared to Mirtazapine. Modafinil group was also found to have less craving as compared to Mirtazapine or TAU group.[11]

In another randomized controlled trial by Mahoney et al, 18 subjects with DSM-IV diagnosis of Methamphetamine dependence were enrolled in 7 days inpatient study. On day 1, they were randomized to receive one dose of Modafinil 200 mg on day 6 or 7th of study with counter condition of placebo on day before or after. Day 1-4 were utilized for subjects to be familiar with the testing environment. Several self-reported forms like Epworth Sleepiness Scale (ESS), Pittsburg Sleep Quality Index (PSQI), Beck Depression Inventory II (BDI-II), Sleep quality and craving visual analogue scale (VAS) were used throughout these 7 days. MSLT – Mean sleep latency test, an objective measure of tendency to fall asleep during the day was conducted between days 5 and 7, with 5th day assessment as baseline, 6^{th,} or 7th day assessment after Modafinil or Placebo. Modafinil helped improve the sleep latency, baseline mean sleep latency was 12.1±3.5 minutes, as compared to 16.0±4.6 following Modafinil administration, results achieved statistical significance with p value <0.001.No difference noted between placebo and baseline. There was another interesting finding in the study, positive correlation was found between likelihood of taking a nap and desire or craving for Methamphetamine, meaning subjects who were less sleepy, didn't desire or crave for Methamphetamine.[12]

Discussion

Mirtazapine increased total hours of sleep, increased nighttime sleep but also increased daytime sleep, along with increased nocturnal awakenings as compared to the Modafinil in treating sleep disturbances during Methampehtamine withdrawal. There were no differences in terms of sleep quality between Mirtazapine and Modafinil group. Modafinil group subjects were less fatigued, had great depth of sleep with lesser awakening and less cravings. There is positive correlation between likelihood of taking a nap and desire or craving for Methamphetamine. Modafinil improved sleep latency.

Sleep is result of interplay between multiple brain regions, regulated by multiple neurochemicals. Serotonin, norepinephrine, histamine, orexin, acetylcholine, and dopamine are considered primarily wake promoting neurochemicals in contrast to adenosine, GABA which are considered sleep promoting agents. Serotonin neurons project from the dorsal raphe nucleus to cortex and promotes wakefulness. Their activity is highest during wakefulness, decreases during non-REM sleep and pretty much absent during REM.Norepinephrine containing neurons are primarily located in locus coeruleus and project widely throughout brain, highly activated during wakefulness, decreased discharge during non-REM and close to absent activity in REM sleep. Histamine neurons follows the same trend as of serotonin and norepinephrine neurons, active during wakefulness, decreased activity doing non-REM sleep and absent during REM sleep. Histamine containing neurons are primarily concentrated in tuberomammillary nucleus. Orexin containing neurons project widely from hypothalamus to several different brain regions including serotonin/histamine and norepinephrine neurons, widely active during wakefulness and absent activity during non-REM sleep and REM sleep.Acetylcholine neurons are found in 2 major brain areas, basal forebrain and pedunculopontine tegmental/laterodorsal will tegmental nuclei in brainstem. These neurons are highly active during wakefulness and REM sleep, activity diminishes during non-REM sleep. The precise mechanism of action of dopaminergic neurons is not very clear, as they are very active during wakefulness and REM sleep but not during non-REM sleep. Dopaminergic neurons are highly concentrated in substantia nigra and ventral tegmental area and in hypothalamus. Both

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adenosine and GABA are inhibitory neurochemicals. GABA neurons have widespread projections in brain, helps turning off the wake on neurons and promote sleep.[13]

So, any disorder/medication or illicit drugs, which affect these neurochemicals, can affect sleep in any possible way. Amphetamines are like drugs, promotes wakefulness because they primarily interact with dopaminergic and norepinephrinergic neurons, increases the release of these chemicals in brain and produce hyperarousal states. This has also been a hypothesis for sleep problems observed in Methamphetamine users. Chronic use of Methamphetamine and acute intoxication both induce wakefulness and cause insomnia, but reverse is observed in acute Methamphetamine withdrawal, where hypersomnia is commonly observed. Acute withdrawal generally lasts for 7 days or so, but chronic use leads to neurotoxicity and symptoms associated with that can persist for months. Hypersomnia as a part of withdrawal can resolve in few days but followed thereafter by Insomnia which can become chronic in nature.

As it has been suggested before that sleep issues are important risk factor for relapse, especially the REM sleep rebound, studied more in alcohol relapse but could be a factor in other drug use disorders as most of the illicit drugs of abuse including Methamphetamine cause REM suppression during active use.[10] So, improving sleep in drug use disorders can have significant impact in promoting and maintaining abstinence from illicit drugs including Methamphetamine.

Based on small evidence as mentioned above, Modafinil has shown some evidence to improve daytime sleepiness in abstinent Methamphetamine dependent subjects and also shown to reduce the craving and desire for Methamphetamine, as well as the likelihood of using meth or whether meth would make the participant feel better. There was a study though, which failed to find any significant difference between Modafinil and placebo in terms of treatment retention, withdrawal severity or sleep outcome but it was not adequately powered, sample was too small to detect any difference.[14]

Mirtazapine was not found to be much effective in improving sleep quality as compared to placebo. It's efficacy against Methamphetamine withdrawal symptoms also appears to be questionable. In a small RCT, Mirtazapine was titrated to 30 mg and compared with placebo in treating Methamphetamine withdrawal symptoms, no significant differences in treatment retention, sleep or withdrawal symptoms were found.[15]

Most of the RCTs had considerable limitations such as low number of patients included, short follow- ups, insufficient or missing data on patient characteristics or tolerability so further larger trials are needed.

Use of benzodiazepines or benzodiazepine receptors agonists is generally avoided in this patient population because of risk of abuse, and other drugs like Trazodone, Doxepin, Ramelteon, Gabapentin and newer drugs like Suvorexant/Lemboraxant may be better suitable options but more research is needed.

Conclusion

Methamphetamine use is associated with disrupted sleep patterns i.e., poor sleep quality, lack of sleep, and significant daytime sleepiness.There is positive correlation between likelihood of taking a nap and desire or craving for Methamphetamine as sleep deficiencies can precipitateMethamphetamine use. Addressing disrupted sleep due Methamphetamine use is critical to improve treatment outcomes and retention. Modafinil improved sleep latency and fatigue. Mirtazapine has shown evidence for increased total hours of sleep, increased nighttime sleep and daytime sleep, along with increased nocturnal awakenings as compared to the Modafinil in treating sleep disturbances during Methamphetamine withdrawal. Current literature on pharmacological management of disrupted sleep patterns due to Methamphetamine use is limited due to less numbers of studies and small sample size of studies. Further research is warranted demanding randomized, placebo-controlled double-blind studies for pharmacological management of disrupted sleep associated with Methamphetamine use.

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Conflicts of interest

The authors declare that there is no conflict of interest to declare.

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