Sangroula et al., Int J Ment Health Psychiatry 2018, 4:1
DOI: 10.4172/2471-4372.1000155

International Journal of Mental Health & Psychiatry

Case Report

A SCITECHNOL JOURNAL

Methylphenidate in the Treatment of Medication-induced Excessive Daytime Sleepiness: A Unique Case Report and Review of Literature

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Abstract

Background: Excessive daytime sleepiness (EDS) is defined as an inability to remain alert and maintain wakefulness for a majority of wakeful periods during the day. It commonly presents as subjective complaints of excessive daytime drowsiness, fatigue, or low energy occurring at inappropriate times, almost every day for at least three months. Medication-induced EDS is one of the very common encounters in psychiatric practice.

Case Presentation: We present a case of a 56-year old male with a long history of bipolar I and anxiety disorders finally stabilized after multiple medications trials with a combination of different psychotropic medications, including mood stabilizers and benzodiazepine. The patient developed severe EDS which significantly interfered his functioning and did not improve with trials of behavioral modifications and adjustment of the medications. Interestingly, the addition of low dose methylphenidate not only resulted in successful resolution of EDS without changing the only effective regimen but also, improved concentration and distractibility.

Conclusion: To the best of our knowledge, this is the first case reported in the literature suggesting possible benefits of the judicious use of methylphenidate in selected patients with medication-induced EDS. However, clinical judgment should be made on a case-by-case basis for clinical utility and larger research studies are recommended for more conclusive results. Nonetheless, behavioral modification, sleep hygiene education, medication switch, and dose/timing adjustment should always be the first line strategies in the management of EDS induced by the medication.

Keywords

Methylphenidate; Excessive daytime sedation; EDS

Introduction

Excessive daytime sleepiness (EDS) is defined as an inability to remain alert and maintain wakefulness for the majority of wakeful periods during the day. It usually presents as subjective complaints of excessive daytime drowsiness, fatigue, or low energy occurring at inappropriate times, almost daily for at least three months, and interferes with functioning [1]. In general population, its prevalence is about 10-25% [2].

A cross-sectional study conducted in Finland among 11,385 subjects evidenced that daytime sleepiness was more common in females than males (11% versus 6.7%). Additionally, 25 % of subjects with EDS were found to have moderate to severe depression, while 11% were hypnotic or tranquilizer users, 9% reported insufficient sleep, and 3% were diagnosed with narcolepsy [3]. EDS is a common complaint among psychiatric patients because sedation is one of the most frequently reported side effects of psychotropic medications. Moderate level of sedation is often a desirable side effect, especially if the patient has poor sleep or insomnia. Nevertheless, when it becomes severe enough to affect daytime functioning despite having a satisfactory level of improvement in the target symptoms, it needs to be addressed appropriately.

Though stimulants have been used to treat EDS secondary to narcolepsy, obstructive sleep apnea, and circadian sleep disorders, it is less frequently used to treat medication-induced sedation, because most of these cases are managed effectively by various other strategies, as mentioned in the discussion below. Moreover, clinicians are reluctant to use stimulants like amphetamines and methylphenidate, especially in bipolar patients because of its risk for abuse liability and of its predisposition for mania. [4,5].

Methylphenidate, first synthesized in 1944, classified as a central nervous system (CNS) stimulant, increases concentrations of norepinephrine and dopamine by facilitating their release and inhibiting reuptake [4,6]. It is believed to act on dorso-lateral prefrontal cortex of the brain to improve attention, concentration, executive function, and wakefulness. Increase in dopamine and norepinephrine concentrations in the medial prefrontal cortex and the hypothalamus, are reported to improve symptoms of depression, fatigue, and sleepiness [4]. After oral administration, methylphenidate is rapidly absorbed by the gastrointestinal tract, reaching peak concentration within 1-2 hours. Roughly, 80% of the drug is excreted as ritilinic acid while less than 1% is excreted unchanged [6]. It has been approved by the Food and Drug Administration (FDA) for treatment of attention deficit hyperactivity disorder and narcolepsy.

We report an interesting case of bipolar I disorder with coexisting anxiety disorder stabilized on a combination of psychotropic medications which caused excessive sedation affecting functioning. Attempts to improve sleep hygiene, dose modification and changing medication schedules were ineffective and the patient continued to be drowsy during the day. Finally, EDS was treated successfully with low dose methylphenidate under mood stabilizer coverage without changing the patients preexisting medications. To the best of our knowledge, this is the first case in the literature reporting the possible effectiveness of low dose methylphenidate in the treatment of medication-induced EDS.

Method

The medical record of the case was thoroughly reviewed. The case was discussed among the authors and thorough review of the related literature was done in “PUBMED” and “up-to-date” to formulate the discussion.

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Received: November 25, 2017 **Accepted:** January 12, 2018 **Published:** January 19, 2018

Case presentation

The patient is a 56-year old single, unemployed, Caucasian, male with a long- standing bipolar 1 disorder for more than 30 years and generalized anxiety disorder for 7 years. The patient was struggling with multiple relapses of his manic and depressive symptoms since 1980's with several hospitalizations and two suicidal attempts, and was treated with multiple psychotropic medications, including trials of all mood stabilizers and atypical antipsychotics, without satisfactory results. Patient was assessed in outpatient clinic in April 2012 when he presented with irritability, distractibility, grandiosity, over-talkativeness, mood swings, and high energy level. He denied any depressive or psychotic symptoms, and denied suicidal or homicidal ideation, intent, or plan during that visit. No any significant medical conditions including thyroid, CNS, hepatic, renal, cardiac or respiratory diseases were reported and patient denied a history of allergy to medications. Family history was negative for any medical, psychiatric and neurodegenerative conditions. The mental status exam was found to be significant for irritable mood being argumentative with staff, loud and hyper-verbal, poor insight and poor judgment. His medications were adjusted as risperidone 1 mg/day orally (PO) at bedtime (HS), valproic acid 500 mg/day extended-release PO in the morning (AM), clonazepam 0.5 mg PO twice daily (BID) as needed (PRN), and benztropine 0.5 mg/day PO HS. Since then, patient's symptoms had been relatively stable without the need for inpatient psychiatric hospitalization. However, his compliance had been poor with frequent refusal to the recommended treatment which he attributed to the side effects of the medications, mainly excessive daytime sedation. Despite this he reported that he was sleeping adequately at night (an average of 7-8 hours at night). The patient reported ongoing stressors including but not limited to unemployment, financial crises, relationship issues, and his mental health problems. He also denied any illicit substance use history including alcohol and tobacco, and his repeated urine toxicology was negative. The patient appeared to have dysphonic speech, and was suspected to be tardive dysphonia. Risperidone was decreased to 0.5 mg HS to reduced sedation, while benztropine and clonazepam PRN were continued, and valproic acid was adjusted to 250 mg AM and 500 mg HS.

The patient continued to complain EDS on subsequent visits. He was offered referral to neurologist and evaluation of his sleep including polysomnography to rule out other causes of EDS. However, he declined referral, instead visited different doctors for his speech difficulty where he was then diagnosed with tardive dysphonia. On the subsequent office visits, he continued to endorse progressive problems with excessive daytime drowsiness, despite getting normal sleep at night. Several attempts were made to adjust the medication dosages and schedules without success.

On one of the visits (March, 2014), risperidone was stopped, and the patient was started on lurasidone 20 mg/day with bupropion sustained released 100 mg/day which resulted in the relapse of his bipolar symptoms while he continued to complain of daytime sedation. Lurasidone was then stopped, and he was started on quetiapine 12.5 mg/day PO HS, which was increased to 25 mg/day PO HS. With the above changes, patient's psychiatric symptoms became fairly stable and dysphonia improved which was evidenced by his improved speech. Hence, the patient chose to continue combination of quetiapine and valproic acid though it increased sedation significantly. The dose of quetiapine was reduced to minimum effective (25 mg one third to one half tablet BID every 2-3 days), while valproic acid was continued at 250 mg AM and 500 mg HS, along with benztropine and clonazepam PRN at their previous dosages and schedules.

After starting quetiapine, sedation became more problematic. The patient reported excessive day time drowsiness and somnolence interfering with his functioning. For instances, he reported several fall episodes, being very sleepy during the day, burned his hands, and almost set his kitchen on fire due to daytime sedation. He tried drinking coffee to keep himself alert during the day without success. Attributing these incidents to the sedative effects of his medications, the patient tried self- adjusting the medicines by decreasing to minimally effective dose and by limiting the number of medications taken at one time. Despite all these measures, he was unable to function during the daytime due to excessive sedation.

After discussing options for medications, risks, benefits, and side effects, including but not limited to mania or psychosis, he agreed to try methylphenidate instead of recommended neurological work-up. Methylphenidate was started at a low dose (5 mg PO daily for one week), which was then increased to 5 mg PO BID. After 2 weeks, he called the office to thank and report that his day time sleepiness improved tremendously and he was more attentive, energetic, and he was able to focus in his work. On the following visit, he was noted to be slightly agitated and activated but denied manic symptoms; hence the dose of methylphenidate was reduced to 2.5 mg BID or 5 mg daily. He continued to report satisfaction with increase in concentration and decreased daytime sedation, but could only tolerate quetiapine doses less than 25 mg, as he preferred 1/2 tablet PO daily or an alternate day dosing schedule. He showed remarkable improvement in his functioning and his dysphonia improved to the significant extent with the lowest possible dose of quetiapine. He was referred to speech therapy and otolaryngologist, who recommended a trial of serial botulinum injections, but the patient refused. Since December 2016, he has been treated with quetiapine 25 mg HS 1/3 to 1/2 tablet every 2-3 days, valproic acid 250 mg AM and 500 mg HS for bipolar disorder, clonazepam 0.5 mg twice daily PRN for anxiety, benztropine 0.5 mg orally twice daily for prevention of extrapyramidal symptoms, and methylphenidate 5 mg daily or 2.5 mg twice daily for EDS likely secondary to medications. The patient's psychiatric symptom was adequately controlled after adding methylphenidate, enabling him to maintain wakefulness, with the added benefit of increased focus and concentration.

Discussion

Patients often used different terms interchangeably to describe EDS such as sleepiness, tiredness, lack of energy, hypersomnia, and fatigue. In clinical practice, the distinction between terminologies can lead to different diagnostic approaches. For instance, fatigue is defined as a lack of mental or physical energy. This encompasses three parts which present in varying degrees amongst individuals: the lack of capability to initiate activity, the inability to maintain activity, and difficulties with emotional balance, memory, and concentration [7], which is associated with many chronic medical diseases and psychiatric disorders [8]. The use of clinical judgment is critical to distinguish between the two complaints.

While making a diagnosis of EDS and identifying its underlying etiology, it is clinically prudent to rule-out all other causes that may present as daytime sedation, These include: i) obstructive sleep apnea (OSA) and obesity, ii) psychiatric conditions, iii) medications, iv) circadian rhythm and insufficient sleep disorders, v) primary

insomnia, vi) hypersomnia of central origin such as narcolepsy and Kleine-Levin Syndrome, vii) substance use disorders, and viii) other co-morbid medical and neurological conditions [7]. It is important that we address the causes of EDS, as untreated or inappropriately treated EDS can increase the risk of morbidity and mortality, and can affect key areas of functioning at home, work, and school [9].

The management of EDS, irrespective of cause, is best achieved by the systematic approach. The first step in the management is the patient education and behavioral modifications such as keeping a sleep diary, maintaining a good sleep hygiene, sticking to regular sleep schedules, avoiding caffeine or heavy meals in the evening, sleeping in a cool and comfortable room, reducing sources of light and sound, avoiding excessive stimuli prior to bedtime, and regular exercise. Ideally, subjective complaints of daytime sleepiness and measure of sleep architecture should have been evaluated with the use of Epworth Sleepiness Scale (ESS) and Polysomnography (PSG) respectively, in addition to a through laboratory and imaging work-up commonly used to rule out organic causes of EDS. Appropriate diagnostic work-up and ensuring behavioral modification was difficult in our case because of the patient's ambivalence towards diagnostic procedures and treatment recommendations, partial compliance to treatment recommendation, self-management of medications, the hostile and argumentative behavior (on several office visits), which made treatment more challenging. Despite this, the patient's target symptoms were well managed with an effective combination of medications, but left the patient unable to function due to EDS. Hence, clinical prudence was used during the assessment to arrive the diagnosis of medication induced EDS, and was effectively treated with stimulant after extensive modification of the patient's preexisting medications. A trial of methylphenidate proved useful in maintaining alertness and wakefulness, with increased focus and attention, and overall functioning during the daytime.

Common medications that cause sedation and daytime somnolence are benzodiazepines and non-benzodiazepine sedatives, antipsychotics, antidepressants, antihistamines, anticonvulsants, opioid analgesics, beta-blockers, and barbiturates. Strategies commonly used to decrease medication-induced EDS are: i) modifying medication schedules to multiple dosing or nighttime dosing, ii) reducing to the minimum effective dosage, iii) considering an alternative non-sedating medication, or iv) stopping the medication. Benzodiazepines and non-benzodiazepines induce sedation by increasing gamma-aminobutyric acid (GABA) signaling while mood stabilizing drugs with antiepileptic activity have sedating properties. A serum drug level, when applicable, should be regularly monitored to rule out increased medication concentrations. For instance, patients on valproate need to be monitored for serum ammonia level and liver function test (LFT) to rule out encephalopathy. Antidepressants have both activating and sedating properties, and patients with complaints of EDS may be switched to a morning dosing schedule of an activating antidepressant. Finally, medications prescribed for pain syndromes and tricyclic antidepressants should be used with caution in patients with EDS as they have anticholinergic properties which can induce somnolence [10]. Liver and renal function test should be monitored because reduced metabolism or elimination in the setting of hepatic or renal dysfunction can lead to bioaccumulation of the medication to excessive sedation. In the above case, serum ammonia/valproic acid level, and hepatic/renal function tests were monitored at frequent intervals which were within normal limits. It should also be noted that the concomitant administration of quetiapine and clonazepam, which are eliminated through the CYP3A4 enzyme, may increase the levels of these medications leading to daytime sleepiness [4]. All above- described treatment strategies were applied without success and finally, the addition of a stimulant to decrease day time sedation was considered after discussing the risk and benefits with the patient.

Numerous neurologic and medical disorders often present with EDS. Strokes, tumors, traumatic brain injury, periodic limb movement, multiple sclerosis, and neurosarcoidosis often present with complaints of daytime sedation [10-12]. Many cardiovascular, hematologic, respiratory, and metabolic disorders also present subjective complaints of EDS [10]. After ruling out clinical/subclinical hypothyroidism, and diabetes mellitus through laboratory tests as important causal factors [13,14], Obstructive Sleep Apnea (OSA) was the most likely remaining differential diagnosis in our case. Though ESS was unable to be performed, the likely hood of OSA was considered "Low" based on "STOP-Bang questionnaire" which is an eight-item survey on snoring, tiredness, observed apneas, blood pressure, BMI, age, neck circumference, and gender. It measures the presence of OSA with a good degree of sensitivity [15].

Comorbid depression, anxiety, and substance abuse can present with excessive nighttime sleep, daytime sleepiness, and excessive napping. Patients presenting with depression and anxiety often complain of trouble initiating sleep (early insomnia) or maintaining sleep (middle insomnia) or early morning awakening (late insomnia). This is primarily due to the biologic/vegetative symptoms of a neurochemical imbalance along with behavioral adaptations In contrast, patients with medication-induced sedation often fall asleep on time and can maintain sleep, but complain excessive daytime drowsiness or sleepiness despite adequate sleep during the night. Nonetheless, intoxication or withdrawal from substance of abuse can also mimic daytime sleepiness. A through history, physical examination, and laboratory evaluation including blood alcohol level and urine toxicology will aid better clinical judgment and diagnosis. In our case, clinical studies did not reveal any substance use by history or lab abnormalities indicating EDS related to the substance use disorder.

To the best of our knowledge, no case reports have been reported, thus far, which suggested the effective use of methylphenidate in the treatment of EDS induced by medication; especially when the patient has been hardly stable with existing medications and changes to treatment are not desirable. However, there is extensive literature that supports the use of modafinil to treat excessive daytime sleepiness as it is thought to increase dopamine transmission in wake- promoting areas [17,18]. Rabinstein and colleagues described a case of levodopa-responsive Parkinson's disease who developed EDS that improved with treatment of 400 mg PO daily of modafinil. Several studies have been completed demonstrating the efficacy of modafinil in narcolepsy [19-21]. Another study reported the efficacy of modafinil as an adjuvant in treating depressed patients with symptoms of daytime fatigue and sleepiness [22]. To date, no cases reports exist that describe the use of amphetamines in EDS. In our case, methylphenidate was selected because the patient also reported poor concentration and an inability to focus, in addition to EDS.

The use of stimulants in bipolar patients has been controversial. Recently, there is a growing interest in the "vigilance regulation model of mania", which may result in a possible mechanism to manage mania. According to this model, mania or psychomotor excitation may be associated with auto-regulatory control of brain arousal. This

theory arose from the hypothetical relationship between behavior and vigilance: as behavior influences vigilance and vice versa. In other words, stimulating behaviors in excited individuals may be attempted to stabilize a hyper arousal state by increasing external stimulations, where hyper arousal is defined as vigilance [23,24]. It is possible that adding a stimulant medication, although counterintuitive, may be useful in controlling manic episodes. It may be a possible explanation for the continued stability in our patient, without any breakthrough mania, even after the addition of methylphenidate. Similar evidence is reported in a literature review of stimulant use in bipolar patients, who were administered methylphenidate and showed rapid improvement during manic episodes [24]. In a separate open-label trial, the use adjunctive methylphenidate in 14 moderately depressed bipolar I and II patients who were non-responders to antipsychotic and mood stabilizers, reported a reduction in depression and overall symptom severity. In this trial, no manic/hypomanic switches or other psychiatric side effects were reported [25]. The important ongoing study, "Methylphenidate in Mania Project" (MEMAP) will hopefully provide us an in-depth understanding into the utility of stimulants in treating episodes of mania [23].

Methylphenidate has a significant potential for abuse, having a similar pharmacokinetic profile as cocaine. Prevention of abuse liability must be a shared responsibility between the patient, his/her primary social support, and prescriber through education; of the consequences of abuse and addiction, the legal ramifications, and the risk for psychiatric symptoms, and death. Additionally, practitioners and their patients must be aware of the patterns of methylphenidate abuse and its clinical presentations of toxicity. Methylphenidate abuse and toxicity present similar to other CNS stimulants like cocaine and amphetamine. Methylphenidate intoxication produces a clinical picture with a variety of presentations including manic like states, psychosis, depressions, and anxiety. Early signs of abuse may be seen as new onset of euphoria, paranoia, hallucinations, and delusions. Toxicity is both dose and interval dependent. Acute toxicity, at high doses, presents with psychiatric symptoms of extreme anger, threats of aggressive behavior, delirium, hallucinations, and panic states which are transient in course. Neurological symptoms of overdose may present with motor and behavioral changes such as stereotypic movements, teeth grinding, repetitive and disorganized behaviors, and aggressiveness. Psychotic symptoms may often appear with chronic abuse, and can also be present in acute setting [6].

The major limitation of our case was that patient refused to undergo sleep study, and other diagnostic work up suggested. Hence, evaluation of the case and the most likely diagnosis is based on the clinical observation on several visits and the patient's reported history. In addition, scales/questionnaires could not be used for the diagnosis and monitoring of the severity of the problems as patient refused to participate.

Conclusion

We presented an interesting case of bipolar I disorder with coexisting anxiety disorder stabilized on a combination of medications that effectively treated the patient's target symptoms. The patient developed EDS which was the major barrier in the treatment. Notably, it was successfully treated with low dose methylphenidate without changing the patients preexisting medications, as they proved to be the best effective treatment strategy after numerous medication trials to target the symptoms. However, more case reports/case series reports, and clinical studies are needed to explore in depth about the effectiveness of methylphenidate in the treatment of medication-induced EDS. Nonetheless, it is emphasized that behavioral modification, maintaining good sleep hygiene, and educating the patient are the most critical steps to be considered for the systematic management of EDS. A thorough clinical, laboratory, and diagnostic work-up must be completed to rule out other causes of EDS. For the effective management of medication-induced EDS, medication dose and timing adjustment, and switching or stopping the offending medication should be considered before adding stimulants like methylphenidate. The severity of EDS, extent of impairment of functioning, and propensity of abuse liability are important factors to be considered before starting on stimulants. To conclude, careful and judicious decision should be made on case-by-case basis after discussing the risks, benefits, and consequences with the patient.

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