Influence of chronic barbiturate administration on sleep apnea after hypersomnia presentation: case study

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Introduction
The prevalence of sleep apnea in the western world is approximately 2% in middle-aged women and 3% in middle-aged men, and that of excessive daytime sleeplessness in the general population is between 2% and 10%. In clinical practice, it is often a challenge to differentiate between cases of primary hypersomnia (e.g., narcolepsy, idiopathic hypersomnia, periodic hypersomnias) and cases of secondary hypersomnia (e.g., associated with trauma; neurologic, psychiatric or medical disorders; sleep apnea; and the use or abuse of...
pharmacological agents). Cases with mixed causation, in particular, can present with special difficulties. When numerous factors, such as comorbid disorders, multiple drug therapies, obesity, or the use of respiratory and central nervous system suppressant drugs, may be involved, distinguishing between central, obstructive and mixed sleep apnea becomes diagnostically complex. Moreover, pharmacological agents that depress cerebral function, such as barbiturates, also depress bulbar and carotid body centres and can exacerbate sleep apnea. These factors and drug treatments may obscure and delay the diagnosis of sleep apnea.

We report a complex case of a woman with bipolar spectrum disorder, taking a combination of anticonvulsants, antipsychotics and barbiturates, who presented with hypersomnia. To our knowledge, no other such case has been reported. A MEDLINE search identified 1 case of flurazepam-induced sleep apnea syndrome,3 a complex case of a patient with comorbid conditions who was taking hypnotic agents (i.e., flunitrazepam and triazolam)4 4 cases of obstructive sleep apnea associated with treatment-resistant mania,5 and a case of obstructive sleep apnea following rapid weight gain secondarily to treatment with vigabatrin.6

Case report

A 44-year-old woman with a long history of bipolar spectrum disorder (DSM-IV category: bipolar mood disorder, not otherwise specified) presented with hypersomnia. She had a history of generalized seizures (tonic–clonic) and traits consistent with histrionic and dependent personality disorders. She was successfully treated for many years with the anticonvulsants phenytoin and phenobarbital at therapeutic blood levels; the dosages had not changed for several years. Her psychiatric illness was treated with depot flupenthixol (40 mg every 2 weeks), olanzapine (5 mg at bedtime), and valproic acid (250 mg 3 times a day) for a year without major side effects. An adequate clinical response was achieved in the previous year with subtherapeutic levels of valproic acid. During that year, the patient remained free of psychotic symptoms, and her seizures were under control. She did not exhibit any recurrent affective episodes or anxiety symptoms.

The patient’s body mass index was 35. She had a history of hypertension, but it was under good control with a diuretic. She had developed tubular interstitial nephritis while she was taking lithium, and this necessitated a switch to valproic acid 2 years before the onset of hypersomnia. Kidney function returned to normal within a year of this switch. There was no recent history of viral infections.

The woman’s hypersomnia developed over a 2-week period. Initially, she slept during sessions with her doctor. These episodes increased in intensity and frequency, until they presented as a sustained drowsiness lasting a few hours at a time. Accompanying features included snoring and a generalized hypotonia, without complete alertness between periods of sleep. The patient was arousable by painful stimuli and did not feel refreshed from sleep. The periods of drowsiness were unpredictable and were not accompanied by changes in affect, mood or cognition. An absence of anxiety was noted, and there was no evidence of recent head injury or major life stressors.

By the second week, the disorder was interfering with the patient’s daily activities. Her general physical examination, complete blood count and differential count, urinanalysis, liver profile, and levels of creatinine, thyroid stimulating hormone, urea and electrolytes, random glucose, and various drugs revealed no clinically significant results except for benign elevations of liver enzyme levels; however, they had been high since 1986 and were drug related. Her blood pressure was 130/80 mm Hg, and no cardiac decompensation was noted. A neurological examination revealed sustained drowsiness with diminished reflexes and reduced generalized muscle tone without ataxia. The possibility of repeated attempts at suicide by drug overdose was ruled out with the toxicological examination results. The patient’s history was negative for any substance or alcohol abuse.

By the third week, neurological and sleep disorder consults were obtained. Simultaneously, the dosage of olanzapine was reduced to 2.5 mg at bedtime, depot flupenthixol to 30 mg every 2 weeks and valproic acid to 250 mg twice a day (with no change in the dosages of phenobarbital and phenytoin). A minor improvement in the patient’s hypersomnia was noted with the change in medication. Drug levels of phenytoin, valproic acid and phenobarbital were within a therapeutic range at this time. In collaboration with her neurologist and her family physician, a decision was made to taper the phenobarbital and to discontinue it by week 6. Between week 3 and week 6, the patient was maintained on depot flupenthixol (30 mg every 2 weeks) and the same dosage of phenytoin. An attempt to reintroduce olanzapine and valproic acid made the hypersomnia worse and was abandoned.
By week 7, the patient’s daytime hypersomnia resolved, and she was maintained on depot flupenthixol at a reduced dosage (30 mg every 2 weeks). At week 8, valproic acid (750 mg at bedtime) was reintroduced. At week 12, the patient was finally diagnosed with sleep apnea (obstructive type) using polysomnography. Study results showed a severe apnea index of 95 events per hour; oxygen saturation was compromised for the entire period of the study, and 196 arousal episodes were recorded throughout the night. REM stages were 17%. The sleep apnea was successfully treated with continuous positive airway pressure. The patient had no further periods of daytime hypersomnia in the year after treatment was initiated. Serum levels of valproic acid and phenytoin remained unchanged pre- and post-treatment. 

The hypersomnia may have been paradoxical, resulting from elevated plasma phenobarbital due to the inhibited metabolism of phenobarbital. An interaction between valproic acid and phenobarbital which would have resulted in elevated levels of plasma phenobarbital is possible, but was not supported by the study results. The therapeutic index of barbiturates is narrow, and may well be altered by advancing age and the concomitant use of other central nervous system depressants. Weight gain, excessive snoring, structural compromise of airways and pre-existing hypertension likely contributed to the development of sleep apnea, which initially presented as hypersomnia.

The most likely explanation was an increased response to phenobarbital, without any appreciable change in serum levels. The therapeutic index of barbiturates is narrow, and may well be altered by advancing age and the concomitant use of other central nervous system depressants. Weight gain, excessive snoring, structural compromise of airways and pre-existing hypertension likely contributed to the development of sleep apnea, which initially presented as hypersomnia.

This case illustrates a very common disorder that can be easily overlooked if not carefully sought. If undiagnosed, sleep apnea may be associated with significant morbidity and even mortality. Initially, the patient in this case appeared to have a common drug interaction between valproic acid and phenobarbital which would have resulted in elevated levels of plasma phenobarbital due to the inhibited metabolism of phenobarbital. However, levels of phenobarbital and valproic acid in this case were similar before and after the patient presented with hypersomnia, and this was puzzling.

A diagnosis of neuroleptic malignant syndrome was ruled out by negative findings of rigidity and hyperthermia, and by normal vital signs. Repeated medical and neurological assessments and a normal electroencephalogram ruled out any seizures or other metabolic or cerebral dysfunction. Her baseline liver enzymes were high, but these had not changed appreciably since 1986. Hypersomnia related to another mental disorder was excluded on the basis of a comprehensive history, investigations and observation over time. She did not meet the criteria for major depression.

A number of possibilities were considered in this case. The hypersomnia may have been paradoxical, with redistribution of the free drug (i.e., phenobarbital); brain levels may have risen, while total plasma levels remained unchanged. However, this is unlikely because the protein-binding capacity of phenobarbital is only 20%–60%. An interaction between valproic acid and phenytoin was suspected, but was also unlikely because there was no overt neurotoxicity and therapeutic drug levels were maintained. As well, the patient had been treated with this combination for a year before she presented with hypersomnia.

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The masked sleep apnea was further exacerbated by the impairment of respiratory muscle function secondary to chronic barbiturate treatment. In addition, the sedative-hypnotic action of barbiturates may inhibit conduction in the reticular formation and reduce the impulses reaching the cerebral cortex. This system is central to the sleep–wake cycle and is intimately linked with respiration. The slow tapering of the barbiturates likely reduced the inhibition at these core anatomical centres, and thus reduced the hypersomnia. The barbiturate must have also caused some instability in the respiratory drive, and this respiratory-suppressant effect was diminished with the barbiturate tapering.

It would appear that this patient initially presented with central sleep apnea, influenced by chronic barbiturate treatment, which was then followed by the unmasking of an underlying obstructive component. The tapering of the other sedating drugs likely improved the hypersomnia somewhat by reducing the central nervous system depressant effects. Given that the reciprocal influence between epilepsy and sleep apnea syndrome may aggravate the prognosis of both processes, the patient’s anticonvulsant medication may have further aggravated pre-existing or latent sleep apnea syndrome. Age may also have increased the severity of the apnea. The role of genetics and sex remains unclear.

This case illustrates the complexity involved in the coadministration of numerous central nervous system depressant drugs and the masked presentation of comorbid disorders such as sleep apnea which can escape early detection. It emphasizes the importance of searching for common, treatable, comorbid disorders in stable outpatients who have predisposing conditions. It also highlights the importance of seeking early consultation for common, treatable, comorbid disorders in stable outpatients who have predisposing conditions.
for complex cases and maintaining a high index of suspicion when patients present with unexplained hypersomnia.

References


6. Lambert MV, Bird JM. Obstructive sleep apnea following rapid weight gain secondary to treatment with vigabatrin (Sabril).


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Dr. Steiner is currently a Professor in Psychiatry and Behavioural Neurosciences at McMaster University and Director of Research in the Department of Psychiatry at St. Joseph’s Hospital in Hamilton. This award is designed to recognize outstanding research achievements by Canadian scientists in the field of neuropsychopharmacology. The award, donated by Hoffmann-La Roche Limited, consists of $5000 and an engraved plaque.

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