Complex Diagnostic and Treatment Issues in Psychotic Symptoms Associated with Narcolepsy

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ABSTRACT

Narcolepsy is an uncommon chronic, neurological disorder characterized by abnormal manifestations of rapid eye movement sleep and perturbations in the sleep-wake cycle. Accurate diagnosis of psychotic symptoms in a person with narcolepsy could be difficult due to side effects of stimulant treatment (e.g., hallucinations) as well as primary symptoms of narcolepsy (e.g., sleep paralysis and hypnagogic and/or hypnapompic hallucinations). Pertinent articles from peer-reviewed journals were identified to help understand the complex phenomenology of psychotic symptoms in patients with narcolepsy. In this ensuing review and discussion, we present an overview of narcolepsy and outline diagnostic and management approaches for psychotic symptoms in patients with narcolepsy.

OVERVIEW OF NARCOLEPSY

Individual who experience rapid eye movement (REM) phenomena, such as hallucinations, associated with narcolepsy may be misdiagnosed as having schizophrenia,[1] and such misdiagnosis tends to occur even in childhood.[2] Treatment of narcoleptic symptoms, such as excessive daytime sleepiness (EDS), with stimulant medications (e.g., amphetamine and methylphenidate) may result in new-onset psychotic symptoms related to

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initiation (or dose escalation) of such medications.

In children, emotional reactions to frightening hallucinatory phenomena (and to sleep paralysis) can be misconstrued as sleep terrors, nightmares, or panic attacks.[3] Children may resist going to bed or falling asleep due to prior frightening hallucinatory experiences (negative associations), and parents could perceive this as oppositional behavior. Children and adolescents with narcolepsy report embarrassment, academic decline, loss of self worth, and avoidance of social situations that might precipitate cataplexy or draw attention to the patient's somnolence.[3]

Narcolepsy may be misdiagnosed as epilepsy due to the presence of sleep attacks and/or unresponsiveness during periods of hypersomnolence or cataplexy.[4] In adults, diagnostic confusion may exist between attention deficit hyperactivity disorder (ADHD) and hypersomnias of central origin (idiopathic hypersomnia and narcolepsy), especially when the conditions co-occur and self-report questionnaires are used.[5]

When underlying narcolepsy remains undiagnosed and the patient presents with vivid hallucinations, the patient may experience legal consequences (e.g., false accusations, work-place conflicts) due to impaired reality testing.[6] Family and friends may misconstrue patients with narcolepsy as being emotionally unstable, lazy, and irresponsible,[7] often leading to feelings of guilt and anger in the patient as well as poor self esteem.

Clinicians should be aware that perceptual disturbances like hypnic hallucinations restricted to awakening and falling asleep are not sufficient to diagnose the patient with a psychotic disorder. A detailed sleep history with focus on timing and relationship of such hallucinations to sleep can provide a clue to the true nature of these symptoms. Furthermore, a primary psychotic disorder, such as schizophrenia, can occur comorbidly with narcolepsy, leading to a diagnostic and therapeutic challenge for clinicians.

NARCOLEPSY AND PSYCHOSIS

Narcolepsy is an uncommon chronic, neurological disorder characterized by chronic sleepiness, markedly disorganized sleep-wake behaviors, and abnormal manifestations of REM sleep.[8] Incidence of narcolepsy usually peaks in adolescence or early adulthood, and prevalence in the general population appears to vary with ethnicity and familial risk. The estimated prevalence is as low as 0.002 percent in the Israeli population, as high as 0.02 percent in the Japanese population, and up to five percent in families with significant genetic predisposition.[9] The age of onset varies from early childhood to the 50s, with two peaks: a larger peak that occurs at around 15 years of age and a smaller peak at approximately 36 years of age.[10]

The pathophysiology of narcolepsy appears to be related to deficiency of hypocretin neurons in the hypothalamus secondary to a degenerative process like gliosis.[11] According to the *International Classification of Sleep Disorders* (*ICSD*) criteria,[12] narcolepsy is usually diagnosed by the following classic tetrad of symptoms: EDS, inability to move after awakening in conscious state (sleep paralysis), sudden loss of muscle tone (cataplexy), and REM phenomena (e.g., hypnagogic and hypnapompic hallucinations).

Hypnagogic hallucinations occur during the "falling asleep" phase (more common) and hypnapompic hallucinations occur during the "awakening from sleep" phase (less common). Diagnosis of narcolepsy without cataplexy can be made in the presence of EDS if one of the associated symptoms (hypnagogic hallucinations, automatic behaviors, sleep paralysis, and/or disrupted sleep) is present together with the following polysomnographic abnormalities: average sleep latency less than eight minutes or presence of two sleep-onset REM periods (SOREMPs) during the multiple sleep latency test (MSLT).

The regular MSLT consists of five naps at two-hour intervals, usually scheduled after six hours of sleep the night prior to MSLT. SOREMPs are associated with onset of REM sleep within 15 minutes after sleep onset. Human leukocyte antigen (HLA) typing showing the association with HLA DQB1*0602 is supportive of the diagnosis, but the specificity of DQB1*0602 positivity is low for narcolepsy. Low CSF hypocretin levels (110pg/mL; one-third of mean control value) can often aid in diagnosis, especially if cataplexy is present.[13] Most low levels of CSF hypocretin tend to correlate with narcolepsy associated with cataplexy and HLA DQB1*0602 positivity.[14]

Multiple case reports describe the difficulties of diagnosing psychotic symptoms in presence of narcolepsy.[15–17] Psychotic symptoms in patients with narcolepsy have the following three possible explanations: co-occurring primary psychotic illness (e.g., schizophrenia),[15,20] an iatrogenic occurrence due to treatment with stimulants,[16] or a narcoleptic psychosis viewed as delusional elaboration of hypnic hallucinations.[1,17] Patients with narcolepsy who experience prominent REM phenomena, such as hypnic hallucinations, may attach significance to a particular vivid hallucination, often followed by attempts to explain the hallucination. This could lead to delusional explanations of such hallucinatory experiences. Such patients may exhibit bizarre and disorganized behaviors suggestive of a primary psychotic illness. Patients with episodes of sleep paralysis in narcolepsy have described such episodes as "electricity shooting through the body" and described vivid visual hallucinations (e.g., "aliens standing next to my bed"). These episodes were associated with ensuing patient narratives, such as being "abducted by aliens." It appears that these narratives have significant cultural influences.[21] A specific example of this is in patients who experience breathing difficulties and sleep paralysis. These events have

been described by patients as a person sitting on their chests (vivid hallucination). The specific description of who is "sitting" on the patient's chest within the narrative may vary from culture to culture (e.g., an old hag or witch may be described by a patient in Newfoundland or the US while "kanashibari," a term related to supernatural powers, may be described by a patient in Japan).[22]

It has been suggested that about seven percent of patients with a diagnosis of schizophrenia actually have a psychotic variant of narcolepsy;[1] however, larger studies to confirm these findings are lacking. Although an earlier study showed that patients with schizophrenia were four times as likely to have narcolepsy-associated antigens, such as HLA DR15 and DQ6, compared to normal controls,[23] there appears to be insufficient evidence at this time to suggest any shared pathology between narcolepsy and psychotic illnesses. In this regard, studies into rare genetic syndromes, such as succinic semialdehyde dehydrogenase deficiency (g-hydroxybutyric aciduria), which present with neurological deficits (e.g., hypotonia, seizures, impaired language development, psychotic symptoms in adolescence and late-adulthood, and sleep difficulties consistent with narcolepsy) may help provide further insights into possible neurobiological interactions between psychosis and narcolepsy.[24] However, Walterfang et al[25] argue against a specific narcoleptic form of psychosis in an extensive review. They point out that the following pathological mechanisms are largely absent in primary psychotic disorders compared to narcolepsy: significant REM sleep phenomena, associations with HLA antigens like HLA DR15, DQ6 and DQB1*0602 (an allele of DQ1), TNF-alpha gene polymorphisms, and evidence of hypocretin neuron disruption.[25]

Thus, the key diagnostic challenges in co-occurring narcolepsy and psychosis would be the following: A) to distinguish the psychosis-like symptoms of narcolepsy (REM sleep-related hallucinations) from positive symptoms of schizophrenia, and/or B) to establish a temporal relationship between initiation of stimulant medications and onset and continuation of psychotic symptoms or, conversely, reduction in psychotic symptoms upon cessation of stimulants.

STIMULANT-INDUCED PSYCHOSIS

A recent review by the US Food and Drug Administration (FDA) of all pharmaceutical company-sponsored trials reveals that "transient psychotic states" (hallucinosis) occur in 0.25 percent of children on stimulants (1 in 400). These hallucinations tend to wane 3 to 7 days after discontinuation of the stimulant.[26]

A more recent review of manufacturers' data by the FDA in children at risk of psychosis and/or mania with stimulants showed an average rate of adverse events, such as psychosis and mania, at 1.48 per 100 persons in a year. A total of 865 case reports of psychosis, mania, or similar events were identified in post-marketing surveillance with the most common symptoms of hallucinations related to stimulants being "visual and/or tactile" hallucinations.[27]

Another review found the presence of psychotic symptoms in chronic amphetamine-dependent patients to be as high as 40 percent, mostly at higher doses. One to 15 percent of these patients experienced continued psychotic symptoms even after several days of abstinence.[28]

Psychosis during treatment of narcolepsy with stimulants is dose dependent (i.e., it is less likely at low doses and more likely at high doses and with chronic treatment).[28] However, most patients with narcolepsy treated with high-dose methylphenidate for an extended period of time do not develop psychosis.[29,30]

Chronic use of stimulants results in reduction in dopamine transporter density[31,32] and possibly a persistent hyperdopaminergic state. Although it can be argued that this persistent hyperdopaminergic state could be responsible for evolving psychotic symptoms in patients with narcolepsy and chronic stimulant therapy, vulnerability studies have not established duration criteria that define such a relationship.

Whether emergence of psychosis in patients treated for narcolepsy with licit doses of stimulants might indicate an underlying biological vulnerability to psychosis is largely unknown. A common neurobiological pathway for such a model is unclear, although it is possibly mediated via the dopaminergic system,[33,34] and genetic factors also appear to have a mediating role in emergence of psychotic symptoms during treatment with stimulants.[35]

A systematic review of stimulant psychosis showed that 50 to 70 percent of patients with schizophrenia or history of acute psychosis with stimulants show a worsening in response to a single dose of stimulant, even when such patients have been adherent with an antipsychotic medication. The authors point out that although the long-term effect of stimulants on sensitization is unknown, continued antipsychotic treatment at low doses may prevent the development of chronic, persistent psychosis.[36] This conclusion may thus have therapeutic implications for patients with comorbid narcolepsy and psychotic disorder.

DIFFERENTIATING CORE SYMPTOMS OF PSYCHOSIS FROM SYMPTOMS OF NARCOLEPSY

Criteria for distinguishing whether psychotic symptoms represent hypnic experiences of narcolepsy or a primary psychotic disorder have been elaborated in a study comparing 148 narcoleptic patients to 21 patients with acute schizophrenia and 128 healthy controls.[37] In this study, hallucinations in narcolepsy (compared to hallucinations in schizophrenia) were sleep-related (up to 80% of the experiences) and were associated with other symptoms of narcolepsy; they were posture-dependent (increased in supine position), unlike in schizophrenia

wherein hallucinations are not posture-dependent; and the content of hallucinations in narcolepsy was of "visual-kinetic" quality (e.g., "I felt like I was flying or falling," or "I felt like someone was in the room with me"), whereas in schizophrenia, hallucinations are mostly auditory.

A recent study utilizing schedules for clinical assessment in neuropsychiatry (SCAN 2.1) to compare psychotic symptoms between 60 patients with narcolepsy, 102 patients with schizophrenia, and 120 matched population controls concluded that hallucinations in patients with narcolepsy, compared to patients with schizophrenia, tend to be sleep-related, multimodal or holistic in nature (i.e., combination of visual, auditory, tactile), and were associated with reduced frequency of concurrent delusions.[38] Compared to population controls, patients with narcolepsy were not shown to have increased prevalence of formal psychotic disorders in this study.

Early reports of dream-like or hallucinatory experiences in narcolepsy noted the preponderance of the following descriptions: flying, falling, and skimming or sliding during cataplexy episodes.[39,40] Such visual-kinetic experiences could represent REM sleep intrusion into wakefulness, often accompanied by nonvolitional REM leading to sensations of flying. Such vivid visual-kinetic experiences are rare in patients with schizophrenia.

DIAGNOSTIC AND TREATMENT COMPLEXITIES

According to the American Academy of Sleep Medicine (AASM), practice parameters for treatment of narcolepsy,[41] modafinil, sodium oxybate, amphetamine, methamphetamine, dextroamphetamine, methylphenidate, and selegiline are effective treatments for excessive sleepiness. The AASM practice parameters recommend tricyclic antidepressants and fluoxetine for cataplexy, sleep paralysis, and hypnagogic hallucinations associated with narcolepsy. Levels of recommendations, however, within these parameters are varied for each of these medications due to differences in published clinical evidence supporting their uses.

In patients presenting with comorbid narcolepsy and psychotic symptoms, diagnosis of narcolepsy should be confirmed using criteria set forth by AASM in the ICSD-2.[12] Once diagnosis of narcolepsy is confirmed, the question remains as to whether the psychotic symptoms are hypnic hallucinations of narcolepsy, stimulant-induced, or 'chance' comorbidity of a primary psychotic disorder. A clear temporal relationship between initiation or dose increase of a stimulant and a paranoid hallucinatory state is usually present in stimulant-induced psychosis. Therefore, an initial step to establish a temporal relationship between the onset of psychotic symptoms and dose initiation/escalation of stimulants should be undertaken. If such a relationship is unable to be established after a thorough history, patients should be weaned off of stimulants gradually rather than be stopped abruptly to prevent stimulant rebound. This is particularly relevant in patients with narcolepsy who have an underlying mood disorder, such as bipolar disorder, as stimulants can precipitate/mimic affective disequilibrium,[42] although perhaps to a lesser degree than antidepressants. A careful history should, therefore, be obtained for ascertaining the presence of mood-disordered symptoms, including family history of mood disorder.

After stimulants are gradually discontinued, modafinil can be initiated and titrated to 400mg/day to target symptoms of narcolepsy. The mechanism of action of modafinil is yet to be elucidated although it was proposed that GABA, glutamate, histamine, and hypocretin systems are involved.[43] Recently, modafinil has been shown to occupy catecholamine and dopamine transporters in brain.[44] At least four double-blind, randomized trials of modafinil in narcolepsy have shown improvements in sleepiness symptoms, with continuation of improvement seen in a few open-label extension studies.[43] Caution should be exercised as modafinil was shown to be associated with mania[45,46] and psychosis[47] in case reports. Regular monitoring of symptoms of EDS using Epworth Sleepiness Scale (ESS) as well as clinical monitoring for worsening psychosis and/or affective symptoms can be useful.

Armodafinil is an R-enantiomer of modafinil with a longer half-life and was recently approved by the FDA for improving wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS), narcolepsy, and shift work sleep disorder. Armodafinil appears to be well tolerated and efficacious in patients with narcolepsy at 150mg and 250mg doses;[48] however, it will not be commercially available until 2010 pending further clinical data.

If psychotic symptoms persist at least 7 to 10 days after cessation of stimulants, initiation of an antipsychotic medication should be considered. Although any antipsychotic medication can be helpful in targeting psychotic symptoms in such a complex clinical situation, aripiprazole might be potentially useful given its unique mechanism of action as a dopamine (D2) partial agonist, serotonin (5-HT1A) partial agonist, and serotonin (5-HT2A) antagonist. Recent evidence suggests that activation of postsynaptic dopamine (D1 or D2) receptors increases wakefulness, and selective stimulation of dopamine D2 autoreceptors or blockade of dopamine D1 or D2 receptors produces sedation. Activation of serotonergic 5-HT1A receptors leads to increased dopamine release in ventral tegmental area (VTA), which in turn may lead to wakefulness; however, effects of serotonergic 5-HT2A receptor activation are still unclear.[49]

In adult studies, the antipsychotics olanzapine and risperidone were shown to increase Stage 2 sleep and Delta sleep and suppress REM sleep; whereas, quetiapine appears to have

lesser REM suppressant effects.[50,51] Therefore, abrupt discontinuation of these medications can result in REM rebound and REM-related hallucinations. Effects of aripiprazole on REM sleep architecture are unknown.

Possible utility of aripiprazole in comorbid psychosis and narcolepsy was hypothesized in some reviews,[15,16] but there are no published case reports of aripiprazole's effectiveness in this clinical scenario. While aripiprazole is considered to be one of the least sedating atypical antipsychotics, caution should be exercised as it may cause sedation and worsen symptoms of narcolepsy. Case reports exist about worsening psychotic symptoms on aripiprazole.[52,53] Although antiadrenergic effects of aripiprazole appear to be low compared to clozapine, there is a published report on clozapine-induced cataplexy;[54] therefore, it is reasonable to monitor for worsening narcolepsy symptoms (e.g., cataplexy) in patients on aripiprazole. There are no known drug-drug interactions between modafinil and aripiprazole.

If psychotic symptoms improve but narcoleptic symptoms persist on modafinil therapy, a reasonable choice would be to rechallenge the patient with stimulants after explaining the risks and benefits of such medication. In such cases, monitoring for re-emergence of psychotic symptoms is essential. In one study, psychotic symptoms improved upon initiation of stimulants in some patients with narcolepsy, especially when these patients had worsening of symptoms on antipsychotics. These patients were misdiagnosed as having treatment resistant-schizophrenia when actually they had treatable variants of narcolepsy.[1]

Another choice to consider for narcoleptic symptoms is sodium oxybate, either as monotherapy or in addition to modafinil. Sodium oxybate is a sodium salt of the central nervous system (CNS) depressant gamma-hydroxy butyrate (GHB), and it appears to activate excitatory GHB receptors at low doses, stimulate inhibitory gamma-amino butyric acid (GABA) receptors at higher doses, and possibly cause both dopamine and serotonin release. The recommended starting dose is 4.5g a night divided into two equal doses of 2.25g, which may be adjusted up to a maximum of 9g per night in increments of 1.5g per night at 1- to 2-week intervals.[55]

In cases of narcolepsy where cataplexy presents as the major debilitating symptom in addition to EDS, sodium oxybate has demonstrated statistically significant improvements in both symptoms, either as monotherapy or in combination with modafinil, in clinical trials.[56] Clinicians should, however, note that symptoms of psychosis-like paranoia and hallucinations can be potential and infrequent side effects of sodium oxybate. Therefore, use of sodium oxybate in comorbid narcolepsy and psychosis should be avoided as much as possible. If initiated, monitoring for emergence or worsening of psychotic symptoms during the initiation and dose escalation phases should be undertaken.

GHB has high abuse potential, with notoriety for use in "date rape" and "rave parties" by adolescents and young adults. The FDA has, therefore, currently classified sodium oxybate as a schedule I substance.[57] A history of illicit substance dependence in adolescents or adults with narcolepsy can be a deterrent for initiation of sodium oxybate. However, it has been suggested in animal studies,[58] that patients with narcolepsy, in general, have a lower chance of addiction due to a deficiency in hypocretin (orexin), a hypothalamic neuropeptide that regulates sleep-wake cycle, feeding behaviors, and energy homeostasis, and was recently implicated in reward systems.[59,60] Nevertheless, given the concerns over possible diversion and abuse of sodium oxybate, a restricted drug distribution system called Xyrem Success Program was created. This system incorporates a post-marketing surveillance program that includes centralized distribution and dispensing, maintaining a registry of physicians and patients, provision of educational materials for patients and physicians, involvement of trained staff in pharmacies, and a method to track prescription shipments.[61]

Another concern with use of sodium oxybate appears to be its relatively narrow therapeutic index and risk associated with overdose. A recent review indicated that GHB withdrawal syndrome is associated with emergent delirium and psychotic symptoms that are often persistent.[62] Whether patients previously on stimulants who have experienced psychosis are more prone to delirium with sodium oxybate or GHB still remains unclear.

CONCLUSIONS

As a symptom of many psychiatric disorders across the age spectrum, sleep disturbances often complicate the course and treatment of the underlying psychiatric symptoms. Identification of symptoms of narcolepsy assumes importance due to significant implications for diagnosis, treatment, and outcomes. Bizarre descriptions of hypnic hallucinations and sleep paralysis symptoms may lead to diagnostic misinterpretations of patients as psychotic, anxious, and/or depressed. Patients may experience extensive life-threatening medical consequences if REM hallucinations lead to delusional elaboration. When primary psychotic disorders, such as schizophrenia, co-occur with narcolepsy, it can lead to significant diagnostic/therapeutic challenges, as well as worsening in psychosocial impairments (e.g., lack of self care, social withdrawal, and depressed mood). Given such the psychosocial consequences associated with co-occurring narcolepsy and psychosis, clinicians should be mindful of comorbid sleep disorders in psychiatric illnesses and the need for careful attention to routine history taking to prevent misdiagnosis and treatment approaches that may worsen either condition. This discussion regarding diagnosis and treatment of narcolepsy can be useful to monitor both primary psychotic

symptoms and psychotic phenomena associated with narcolepsy, when they co-occur.

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