# Sleepless and paranoid

Nick Eilbeck, MD, and Marijo Tamburrino, MD

Mr. Q, age 44, presents with disorientation, paranoid delusions, and auditory and visual hallucinations that began after his sleep started to deteriorate 6 months ago. What could be causing his insomnia?

## CASE Worsening insomnia

Mr. Q, age 44, presents for evaluation of altered mental status characterized by disorientation, impaired attention and concentration, paranoid delusions, and prominent auditory and visual hallucinations. His initial Folstein Mini-Mental State Examination (MMSE) score is 7 of 30, indicating severe impairment. He further describes a recent history of nausea, intermittent vomiting, and anorexia. He takes hydrocodone/acetaminophen, 5/500 mg, 4 times daily for lower back and joint pain. Additionally, he has a pacemaker, which was placed when Mr. Q was in his late 30s to treat sinus bradycardia.

Mr. Q's fiancée describes his 6-month history of worsening sleep disturbance, noting insomnia, fractured sleep, dream enactment, and daytime fatigue. During this time, Mr. Q averaged 3 to 4 hours of sleep nightly without daytime naps. Ten days ago, he stopped sleeping completely and his cognitive function decompensated rapidly. He became increasingly paranoid, believing government agents had been dispatched to kill him. Several days before admission, Mr. Q developed auditory and visual hallucinations. He reports that he hears voices warning him of Armageddon and sees reincarnated spirits of deceased relatives. He describes his mood as "fine" and "okay" and lacks insight into his psychiatric symptoms other than his sleeplessness.

Mr. Q's family says he has a history of transient mild depression after his older brother died from an unknown neurologic disease 3 years ago. Mr. Q did not receive pharmacotherapy or psychotherapy but his symptoms resolved. His family says that Mr. Q has been using marijuana daily for several years, but they are unaware of other substance use. They deny a family history of psychiatric illness.

On physical examination, Mr. Q appears thin, agitated, and in mild distress. He has a fever of 99.2°F. His blood pressure drops intermittently from a baseline of 120/70 mm Hg to 100/60 mm Hg, at which point he experiences transient normal sinus tachycardia. Neurologic examination reveals psychomotor agitation and diffuse myoclonic tremor.

**Which is the most likely cause of Mr. Q's insomnia?**

a) psychotic disorder
b) mood disorder with manic features
c) substance intoxication or withdrawal
d) underlying medical condition

## The authors' observations

The differential diagnosis for insomnia is vast and includes circadian rhythm disorders, parasomnias, pain conditions, cardiopulmonary insufficiency, neurologic disease,

Dr. Eilbeck is a Third-Year Resident and Dr. Tamburrino is Professor and Chair, Department of Psychiatry, University of Toledo College of Medicine, Toledo, OH.

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Table 1

**Differential diagnosis of insomnia**

| Type of disorder | Examples |
|---|---|
| Sleep disorders | Narcolepsy, REM sleep disorder, periodic limb movement disorder, restless leg syndrome, parasomniac conditions |
| Psychiatric disorders | Mania or hypomania, psychosis, substance intoxication or withdrawal, dementia, delirium |
| Neurologic disorders | Stroke, malignancy, infection or abscess, metabolic or viral encephalopathy, seizure disorder, prion disease |
| Somatic conditions | Cardiorespiratory disease, central or obstructive sleep apnea, congestive heart failure (Cheyne-Stokes respiration), pain, nocturnal movement disorder, gastroesophageal reflux disease, nocturia |
| Other causes | Jet lag, shift work, environment, lifestyle, medication |

REM: rapid eye movement

**Source:** Reference 1

**Clinical Point**

**Manic episodes may present with sleeplessness and may encompass cognitive and perceptual deficits, including delusions**

and psychiatric illness (***Table 1***).[1] Insomnia could be caused or worsened by a medication (***Table 2***). Pervasive paranoid thinking can contribute to insomnia, although Mr. Q's sleep disturbance preceded his persecutory delusions. Manic episodes also may present with sleeplessness and may encompass cognitive and perceptual deficits, including delusions and hallucinations. Although most patients with bipolar I disorder are diagnosed before age 30,[2] many are not. Mr. Q had no family history of psychiatric illness and lacked other mania symptoms, such as elevated mood, grandiosity, talkativeness, increased goal-directed activity, or pleasure-seeking behavior. Furthermore, Mr. Q's psychomotor agitation was uncharacteristic of mania and he reported fatigue rather than a decreased need for sleep. Opioid withdrawal can precipitate insomnia, psychosis, tremulousness, and autonomic dysfunction. However, Mr. Q gave no history of opioid abuse and took his medication as prescribed. Furthermore, the opioid was continued throughout his hospitalization. Similarly, Mr. Q's pattern of cannabis use had not varied over the past several years. Acute substance intoxication or withdrawal would not explain the chronicity of Mr. Q's insomnia in the months preceding his presentation. Urine toxicology was negative for other illicit substances and his blood alcohol concentration was 0%. The quality and course of Mr. Q's symptoms indicated a delirium from sleep deprivation, which likely was caused by an underlying medical or neurologic condition.

## EVALUATION Inconclusive results

Routine laboratory studies reveal mild normocytic anemia and mild hypokalemia. Liver panel, renal function, cardiac profile, brain natriuretic peptide level, folate and vitamin B12 levels, thyroid studies, and human immunodeficiency virus serology are negative or within normal limits. Urinalysis reveals the presence of ketones, indicative of Mr. Q's recent anorexia. Chest radiography and CT imaging of the head, abdomen, and pelvis also are unremarkable. MRI is contraindicated because of Mr. Q's implanted pacemaker. Pulse oximetry does not suggest apneic events. Mr. Q and his family refuse a lumbar puncture, which precludes cerebrospinal fluid (CSF) analysis. Electroencephalography (EEG) records normal patterns of wakefulness oscillating with transient periods of stage 1 sleep. A detailed family interview reveals that Mr. Q's older brother had a history of epilepsy and died at age 49 following a prolonged hospitalization for recurrent seizures and similar insomnia symptoms. History from the patient's paternal lineage is not available.

Table 2

**Medications that can cause or exacerbate insomnia**

| Class/category | Medication(s) |
|---|---|
| Stimulants | Bupropion, dextroamphetamine, methylphenidate |
| Decongestants | Pseudoephedrine, phenylephrine |
| Antihypertensives or antiarrythmics | α- and β-antagonists |
| Respiratory medications | Albuterol, theophylline |
| Hormones | Corticosteroids, thyroid medications |
| Anticonvulsants | Lamotrigine |
| Medications that induce rebound insomnia | Benzodiazepines, sedative-hypnotics, opioids |
| Nonprescription medications | Caffeine, alcohol, nicotine, illicit psychostimulants |

**How would you initially manage Mr. Q's psychiatric symptoms?**

a) administer a benzodiazepine
b) begin an antipsychotic
c) administer a sedative-hypnotic agent
d) start a melatonin receptor agonist or melatonin supplementation

## The authors' observations

American Psychiatric Association practice guidelines[3] do not support first-line use of benzodiazepines for non-alcohol withdrawal-related delirium. Benzodiazepines are ineffective for treating delirium and may exacerbate symptoms.[4] Laboratory evidence confirmed Mr. Q has no history of alcohol or benzodiazepine use. Although treating the underlying cause of delirium is essential, prescribing a sedative-hypnotic medication such as zolpidem for Mr. Q's insomnia may worsen his condition. These agents are known to impair cognition and may induce or intensify psychosis.[5] Melatonin and melatonin receptor agonists, such as ramelteon, promote sleep by regulating the sleep-wake rhythm through their action on melatonin receptors in the hypothalamus.[6] Recently, a randomized control trial (RCT)[7] found melatonin protected against delirium in hospitalized patients age ≥65. However, no RCT has examined use of exogenous melatonin or melatonin receptor agonists to treat delirium. In Mr. Q's case, we chose to administer haloperidol. First- and second-generation antipsychotics have shown efficacy in treating acute delirium. Although more clinical experience has accumulated using first-generation agents such as haloperidol, a 2007 Cochrane meta-analysis[8] demonstrated equal benefit with second-generation antipsychotics, while noting a decreased incidence of adverse effects.

## TREATMENT Adverse effects

Mr. Q receives an IM injection of haloperidol, 5 mg, for severe agitation, followed 15 hours later by IM aripiprazole, 9.75 mg. Within hours of receiving aripiprazole, Mr. Q develops hyperkinetic perioral and tongue movements. He initially is diagnosed with acute reactionary dystonia, although closer examination reveals myoclonus consistent with his overall presentation. Additionally, his QTc interval increases by 120 ms. Subsequently, all antipsychotics are stopped. We prescribe lorazepam, 1 mg IM every 4 hours as needed, for agitation. Mr. Q receives 2 consecutive doses of lorazepam, although neither effectively reduces his agitation or promotes sleep. Mr. Q is not assessed with positron-emission tomography (PET) or polysomnography.

continued

## Clinical Point

**A sedative-hypnotic may worsen Mr. Q's condition because these agents may impair cognition or induce or intensify psychosis**

Table 3

**DSM-IV-TR diagnostic criteria for opioid withdrawal**

| |
|---|
| A. Either of the following:<br>1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer)<br>2. Administration of an opioid antagonist after a period of opioid use |
| B. ≥3 of the following, developing within minutes to several days after criterion A:<br>1. dysphoric mood<br>2. nausea or vomiting<br>3. muscle aches<br>4. lacrimation or rhinorrhea<br>5. pupillary dilation, piloerection, or sweating<br>6. diarrhea<br>7. yawning<br>8. fever<br>9. insomnia |
| C. The symptoms of criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning |
| D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder |

**Source:** Reference 11

## Clinical Point

**Familial fatal insomnia is an autosomal dominant disease caused by a point mutation in the prion protein gene**

**What is the likely cause of Mr. Q's persistent insomnia?**

a) cardiovascular disease
b) encephalitis
c) a neurodegenerative process
d) infection
e) malignancy

### The authors' observations

There was no evidence of neurologic disease on Mr. Q's CT scan and EEG was within normal limits. Other imaging and laboratory studies did not reveal possible infection, malignancy, or cardiovascular disease. Despite its rarity, we considered the possibility of a prion disease, given Mr. Q's unique presentation and family history. Familial fatal insomnia (FFI) is an autosomal dominant disease caused by a point mutation in the prion protein gene. Prion proteins are theorized to play a role in myelin stability. The aberrant isoform produced in FFI is structurally misfolded so that it resists degradation by proteolytic enzymes. The accumulation of irregular prion proteins in the medial thalamic nucleus results in progressive neurodegeneration. Patients with FFI present with increasingly severe insomnia, mild fever, dysautonomia, spontaneous myoclonus, cognitive dysfunction, and hallucinations.[9] Generally, patients die from sudden cardiorespiratory failure or ensuing infections 9 to 24 months after symptom onset. In vivo, FFI diagnosis is suggested by a loss of sleep spindles on polysomnogram and by decreased thalamic metabolism on PET scan. Other imaging modalities and testing, including EEG and CSF analysis, lack sensitivity and/or specificity.[10]

### OUTCOME Improvement, discharge

On his fourth hospital day, Mr. Q's symptoms begin to remit spontaneously. His gastrointestinal (GI) upset improves and the following night he sleeps for approximately 4 hours. As his sleep improves, his delusional thinking and hallucinations resolve. Orientation, memory, and concentration gradually improve. Before discharge, his MMSE score is 24 out of 30, indicating improved cognition. His heart rate, blood pressure, and body temperature normalize and his myoclonus improves. Mr. Q is discharged after 6 days in the

hospital and returns home. He follows up with his primary care physician, denies any recurrence of sleep disturbance, and reports that his cognition and perception have returned to his baseline.

## The authors' observations

Spontaneous resolution of Mr. Q's symptoms excludes an FFI diagnosis. We reconsidered the possibility of substance-induced insomnia. Most compelling was how quickly Mr. Q's insomnia abated after hospitalization, even though he received no specific treatment. His protracted nausea and vomiting resolved just before his overall condition improved. We hypothesized that Mr. Q's GI upset may have impaired absorption of his prescribed opioid, leading to acute withdrawal symptoms (***Table 3***).[11] Symptoms of severe opioid withdrawal include psychosis, autonomic instability, and myoclonus.[12] Another possibility is that opioid withdrawal may have caused Mr. Q's GI upset, in which case we would search for a cause of decreased intestinal absorption or suspect a history of opioid abuse. Mr. Q's daily marijuana use raises the risk of comorbid substance abuse or dependence. Chronic pain and long-term opioid use can result in chronic insomnia, which may account for Mr. Q's sleep disturbance in the months before his presentation.[12]


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## Related Resources

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### Drug Brand Names

Albuterol • Proventil, Ventolin
Aripiprazole • Abilify
Bupropion • Wellbutrin, Zyban
Dextroamphetamine • Dexadrine
Haloperidol • Haldol
Hydrocodone/Acetaminophen • Vicodin
Lamotrigine • Lamictal
Lorazepam • Ativan
Methylphenidate • Methylin, Ritalin
Phenylephrine • Neo-Synephrine
Pseudoephedrine • Sudafed
Ramelteon • Rozerem
Theophylline • Elixophyllin, Slo-Phyllin
Zolpidem • Ambien

### Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

## Clinical Point

**Mr. Q's GI upset may have impaired absorption of his prescribed opioid, leading to acute withdrawal symptoms**

# Bottom Line

Insomnia can be a feature of many psychiatric conditions or may precipitate psychiatric presentations. Chronic insomnia can lead to decreased concentration, fatigue, delirium, and psychotic symptoms such as hallucinations. Attention to phenomenology, course, and treatment response can narrow the differential diagnosis.