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What is This?
The Use of Pentobarbital in Cases of Severe Delirium: A Case Series

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Abstract
Delirium is a common syndrome present at the end of life and causes significant distress for patients and families. Sleep disruption is a common precipitating factor for delirium and restoration of sleep may be instrumental in attenuating symptoms. In this cases series, we present three patients who were unresponsive to escalating doses of standard delirium medications, but whose delirium resolved once improved sleep was achieved using Pentobarbital. In a fourth patient, delirium was successfully treated where neuroleptics were contraindicated. Pentobarbital has been shown to reduce the time to sleep onset, decrease the number of body movements during sleep and spontaneous awakenings and increase the total sleep time. Pentobarbital may provide an additional treatment option for patients whose delirium is refractory to standard management approaches.

Keywords
delirium, sleep disruption, pentobarbital, nembutal, sleep quality, palliation

Introduction
Of all the symptoms at the end of life, perhaps none is more distressing for patients and their families than delirium.¹-⁴ Delirium is often challenging to diagnose and treat, a frequent complication of advanced disease and an independent predictor of mortality.⁵-⁷ In addition, delirium is observed in the majority of the patients prior to death.³,⁸

Standard treatment of delirium first involves the identification and correction of reversible causes such as infection, medications, and electrolyte abnormalities. Current evidence supports the use of dose-limited haloperidol or atypical antipsychotics in the management of delirium.⁹,¹⁰ Patients with fulminant delirium refractory to usual doses of antipsychotics or in whom adequate doses of antipsychotics are contraindicated are more challenging. In several such cases, we have successfully utilized the short-acting barbiturate pentobarbital to promote sleep, with resulting improvement in symptoms of delirium. The relationship between sleep and delirium is well established. Links between rapid eye movement (REM) deficiency and delirium in neurodegenerative diseases and intensive care unit (ICU) patients have been proposed.¹¹-¹⁴ In our experience, pentobarbital-treated patients often awake with an intact sensorium, improved cognition, and little drug-induced somnolence, suggesting that the drug’s efficacy in patients with delirium may be due in large part to sleep-modifying effects.

The following cases describe a series of hospice patients who were diagnosed with delirium according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. These patients were assessed for reversible causes of delirium, including laboratory workup and medication review. In all the cases, the presentation of delirium included a sleep–wake cycle disturbance that was refractory to treatment with haloperidol or atypical antipsychotics. Delirium subsequently improved with pentobarbital treatment, often within a short period of time.

Case Series
Case 1: LK
LK was a 91-year-old female with stage IV breast cancer, coronary artery disease, and congestive heart failure admitted to the hospice inpatient unit with a several-week history of increasing confusion, weakness, and falls. Family reported mental slowing, “not making sense,” and increased daytime somnolence. Medications had been unchanged for more than 2 weeks prior to admission.

The patient presented with intermittent agitation, fragmented sleep, and variable levels of alertness. Workup for delirium,
including standard laboratories and urinalysis, was unremarkable. On day 1, she was started on quetiapine 50 mg at bedtime, but required an additional 25 mg along with multiple breakthrough doses of haloperidol for sleeplessness, agitation, and confusion. From days 2 to 6, doses of haloperidol to 8 mg were given at bedtime, with additional haloperidol during the night for continued confusion, fragmented sleep, and altered mental status. On day 7, LK received 100 mg of pentobarbital at bedtime. Staff reported next morning that she was mentally “much better,” having slept without interruption. Pentobarbital was continued as a scheduled medication at bedtime for 2 more nights, resulting in more restful sleep. She became alert, appropriate, and socially engaged, with improvement in appetite and energy as well. Pentobarbital was discontinued after 3 nights and quetiapine was resumed at bedtime, with continued resolution of delirium.

Case 2: JC

JC was a 79-year-old male with Stage IV non-small cell lung cancer, chronic obstructive pulmonary disease, diabetes mellitus, anxiety, and hypertension, who required admission to the hospice inpatient unit following a 2-week history of confusion, anxiety, weakness, and falls. He also had worsening sleep, restlessness, frequent awakenings, and vivid and distressing dreams or perceptions. He had had no medication additions or changes in at least a week prior to admission; earlier records were unavailable.

Baseline laboratory values were unremarkable. On days 1-2, lorazepam 2 mg and haloperidol 2 mg were added at bedtime to his usual dose of risperidone 0.5 mg. Nighttime agitation persisted, requiring multiple breakthrough medications including haloperidol and lorazepam. On days 3 and 4, risperidone was discontinued and replaced with haloperidol 4 and then 6 mg at bedtime. Additional Haloperidol was given throughout the day, but he still required nighttime breakthrough doses of haloperidol and lorazepam for confusion and agitation, and sleep remained interrupted. Staff described “rough nights,” garbled speech, and difficulty maintaining attention.

On days 4 to 6, JC received pentobarbital 100 mg at bedtime along with lorazepam and haloperidol. He slept well, with rare awakenings, and reported resolution of the vivid dreams or perceptions that had been problematic. Staff described him as “surprisingly awake and alert” in the morning. His mood and appetite improved and mental status returned to baseline. Pentobarbital was discontinued after 3 nights, with continuation of his baseline doses of haloperidol and lorazepam without return of symptoms of delirium.

Case 3: JM

JM was a 65-year-old male with a history of prostate cancer metastatic to bone, mild baseline cognitive impairment, and prior, though not recent, alcohol and illicit drug abuse. He was admitted to the hospice inpatient unit after a several-week history of agitation and increased confusion.

At admission, the patient was nonverbal and uncooperative. He appeared to have hallucinations, evidenced by reaching, picking, and continued attempts to get out of the bed. Laboratory values were unremarkable, except for mild elevation of aspartate aminotransferase, and increased alkaline phosphatase consistent with his known bone metastases. His level of consciousness varied from lethargy to severe psychomotor agitation, with persistently interrupted sleep throughout his first 7 days of inpatient treatment. Bedtime and overnight medications during that time included various combinations of escalating doses of diazepam (15 mg), clonazepam (1 mg), haloperidol (13 mg), and chlorpromazine (250 mg) as well as frequent daytime breakthrough doses of lorazepam, haloperidol, and chlorpromazine without improvement in sleep quality or alertness, decrease in agitation, or a meaningful wake state.

On his eighth night, medications were changed from chlorpromazine 150 mg and diazepam 15 mg at bedtime (despite which he had required 6 breakthrough doses of additional medications for delirium between 10 PM and 5 AM the previous night) to chlorpromazine 150 mg and pentobarbital 100 mg. He slept until 4:30 AM without additional medication, except for a single dose of pain medication. By the next day he was described as “very alert, old self, per family.” He was continued on pentobarbital 100 mg for a total of 7 nights, during which time his mental status returned to baseline, oral intake improved to 100% of meals, and the need for breakthrough doses of medication decreased significantly. After 7 nights he was transitioned to quetiapine with trazodone at bedtime, without return of delirium.

Case 4: PG

PG was a 67-year-old female with primary peritoneal cancer, metastatic to omentum and mediastinum, admitted to the hospice inpatient unit for management of delirium. She reported a 2-week history of poor sleep, vivid dreams, and nightmares, which had progressed to include daytime hallucinations, distressing to both her and her family. She was on multiple QT prolonging medications, including dronedarone, methadone, citalopram, and ondansetron. Haloperidol doses to 4 mg at bedtime had been tried in the home, without improvement in sleep or symptoms of delirium.

Upon admission, the patient was noted to have mental slowing, daytime somnolence, and trouble maintaining focus. Baseline laboratory values were unremarkable. Because of concerns regarding QT prolongation, pentobarbital 100 mg was added to the 4 mg of haloperidol already scheduled at bedtime, rather than increased doses or trials of alternate antipsychotics. She woke on day 2 reporting that she “slept well,” had more energy, and felt mentally clear. Family also noticed a significant improvement in cognitive function. On day 2, haloperidol 4 mg was scheduled at night without pentobarbital. The patient reported she did not sleep well, staff characterized her night as “restless” and an additional breakthrough dose of haloperidol was given during the night, without effect.
During days 3 to 5, the patient received pentobarbital 100 mg alone at bedtime, without haloperidol and slept well, reporting no dreams or hallucinations and rare awakenings not requiring use of breakthrough medications. On day 6, an attempt was made to replace her bedtime pentobarbital with haloperidol and trazodone. Sleep was again poor, and the patient eventually required a breakthrough dose of pentobarbital 100 mg before finally falling asleep for the remainder of the night. On day 7, haloperidol and clonazepam were tried, with poor sleep and increased difficulty thinking clearly the next day. Pentobarbital 100 mg was resumed on day 8, with return of uninterrupted sleep and improvement in energy and cognitive function. No further attempts were made to discontinue the pentobarbital, and the patient continued to sleep well without return of hallucinations, disturbing dreams, or other symptoms of delirium.

**Discussion**

The above case series describes patients whose sleep disruption and delirium significantly improved with the use of pentobarbital, often within a few days of use. The efficacy of pentobarbital treatment appeared to correlate with the drug’s ability to induce sleep and reduce nocturnal wakening. The drug also caused minimal somnolence upon wakening, likely helpful in reestablishing cognitive clarity. Pentobarbital, a short-acting barbiturate, has been shown to reduce the time to sleep onset, decrease the number of body movements in sleep, reduce the number of spontaneous awakenings, and increase total sleep time.15,16 Although pentobarbital modestly suppresses REM sleep, sleep cycles are preserved, with an increase in the “depth” and “soundness” of sleep. Furthermore, pentobarbital lacks the anticholinergic effects of some neuroleptics that may exacerbate the confusion and cognitive impairment of delirium.17 Typical sleep-inducing doses range from 100 to 200 mg in adults.18

There are multiple risk factors for delirium, although many patients with delirium have no clear toxic or metabolic abnormalities.19 The current approach to delirium emphasizes identification of medical factors rather than less commonly definable factors such as sleep.20,21 The inversion of the sleep–wake cycle in patients with delirium has long been recognized. The interrelationship between sleep and delirium is confounded as there is considerable overlap between the symptoms caused by sleep loss and those associated with delirium.22,23 It is also well established that sleep–wake disturbances are common in patients with serious illness and delirium is a near inevitable consequence of the dying process.8,24-26 Evidence suggests that irreversible delirium is associated with higher rates of sleep disruption.27 A recent prospective study of 105 hospice patients found that poor sleep quality precedes delirium suggesting causality.28 In patients with neurodegenerative disease, delirious behavior has been correlated with disturbances in sleep–wake cycles and REM sleep behavior disorder.11,12,14,29

Whether sleep disturbance is a cause or a consequence of delirium, restoration of sleep–wake cycle may be instrumental in attenuating the symptoms of delirium. Some authors have suggested that the clinical benefit of narcoleptics in the management of delirium may be attributable to their sleep-promoting effects.30 Sleep induction has also been shown to attenuate the symptoms of mania and possibly psychosis.17,30 There is also growing interest in medications such as the sedative dexmedetomidine that decrease the post-intubation and ICU incidence of delirium possibly by promoting a more physiologic sleep–wake cycle in ICU patients.31-33 Dexmedetomidine appears to better preserve quality and quantity of sleep when compared to other agents. Melatonin also may have a role in treating or preventing delirium, possibly related to its role in regulating sleep–wake cycles.34,35

The management of delirium is a challenging issue for clinicians caring for patients near the end of life. In patients with delirium with a history of severe sleep loss, management directed at securing restorative sleep shows promise as a means of achieving symptomatic relief and cognitive improvement. Clearly, there are subsets of patients with delirium whose suffering is refractory to standard management approaches, and other options, such as pentobarbital, may need to be considered. It is possible that the efficacy of such pharmacologic agents to treat delirium may depend on the drug’s ability to restore sleep–wake cycles.

The cases as reported have several limitations. Patient histories were incomplete, specifically with respect to changes in medications in the period preceding the onset of delirium. Delirium management was confounded by the use of medications, such as benzodiazepines and opioids, which may have potentiated delirium. Conversely, other interventions, such as pain control and use of oxygen, may have contributed to the observed clinical improvement in cognition. Although the cases discussed here support a role for pentobarbital in the treatment of refractory delirium, further study is needed to fully characterize the use of this medication and its efficacy.

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