

CASE IN POINT

Scheduled Acetaminophen to Minimize Neuropsychiatric Symptoms in Wernicke-Korsakoff Syndrome

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To manage the physical, cognitive, and emotional symptoms of a veteran hospitalized for Wernicke-Korsakoff syndrome secondary to chronic alcohol overuse, acetaminophen was administered in place of psychoactive medications.

Alcohol is the most common substance misused by veterans.¹ Veterans may misuse alcohol as a result of mental illness or posttraumatic stress disorder (PTSD), having difficulties adjusting to civilian life, or because of heavy drinking habits acquired before leaving active duty.² One potential long-term effect of chronic alcohol misuse is Wernicke-Korsakoff syndrome (WKS), a neuropsychiatric condition secondary to a deficiency of thiamine.³ The disease is characterized by altered mental status, oculomotor findings, and ataxia.³ Patients with WKS may exhibit challenging behaviors, including aggression, disinhibition, and lack of awareness of their illness.⁴ Due to long-standing cognitive and physical deficits, many patients require lifelong care with a focus on a palliative approach.³

The mainstay of pharmacologic management for the neuropsychiatric symptoms of WKS continues to be psychoactive medications, such as antipsychotics, benzodiazepines, antidepressants, and anticonvulsant medications.^{4,6} Though atypical antipsychotic medications remain the most widely used, they have a high adverse effect (AE) profile.^{5,6} Among the potential AEs are metabolic syndrome, anticholinergic effects, QTc prolongation, orthostatic hypotension, extrapyramidal effects, sedation, and falls. There also is a US Food and Drug Administration boxed warning for increased risk of mortality.⁷ With the goal of improving and maintaining patient safety, pharmacologic

interventions with lower AEs may be beneficial in the management of the neuropsychiatric symptoms of WKS.

This case describes a veteran who was initially hospitalized due to confusion, ataxia, and nystagmus secondary to chronic alcohol overuse. The aim of the case was to consider the use of acetaminophen in place of psychoactive medications as a way to manage neuropsychiatric symptoms of WKS even when pain was not present.

CASE PRESENTATION

A veteran presented to the local US Department of Veterans Affairs (VA) emergency department (ED) due to their spouse's concern of acute onset confusion and ambulatory difficulties. The veteran's medical history included extensive alcohol misuse, mild asthma, and diet-controlled hyperlipidemia. On initial evaluation, the veteran displayed symptoms of ataxia and confusion. When asked why the veteran was at the ED, the response was, "I just came to the hospital to find my sister." Based on their medical history, clinical evaluation, and altered mental status, the veteran was admitted to the acute care medical service with a presumptive diagnosis of WKS.

On admission, the laboratory evaluation revealed normal alanine transaminase (ALT) and aspartate transaminase (AST) levels but markedly elevated γ -glutamyl transferase (GGT) consistent with alcohol toxicity. COVID-19 testing was negative.

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Magnetic resonance imaging (MRI) of the brain revealed evidence of alterations in the mammillary bodies and moderately severe cortical and cerebellar volume loss suggestive of long-standing alcohol use.

The veteran was hospitalized for 12 days and treated with high-dose IV thiamine, which resulted in improvement of their ophthalmic disorder (nystagmus) and ataxia. However, they continued to exhibit poor recall, confusion, and occasional agitation characterized by verbal outbursts and aggression toward the staff.

The veteran's spouse worked full time and did not feel capable of providing the necessary follow-up care at home. The safest discharge plan found was to transfer the veteran to the local VA community living center (CLC) for physical therapy and further support of their marked cognitive decline and agitation.

Following admission to the CLC, the veteran was placed in a secured memory unit with staff trained specifically on management of veterans with cognitive impairment and behavioral concerns. As the veteran did not have decisional capacity on admission, the staff arranged a meeting with the spouse. Based on that conversation, the goals of care were to focus on a palliative approach and the hope that the veteran would one day be able to return home to their spouse.

At the CLC, the veteran was initially treated with thiamine 200 mg orally once daily and albuterol inhaler as needed. A clinical psychologist performed a comprehensive psychological evaluation on admission, which confirmed evidence of WKS with symptoms, including confusion, disorientation, and confabulation. There was no evidence of cultural diversity factors regarding the veteran's delusional beliefs.

After the first full day in the CLC, the nursing staff observed anger and agitation that seemed to start midafternoon and continued until around dinnertime. The veteran displayed verbal outbursts, refusal to cooperate with the staff, and multiple attempts to leave the CLC. With the guidance of a geriatric psychiatrist, risperidone 1 mg once daily as needed was initiated, and staff continued with verbal redirec-

tion, both with limited efficacy. After 3 days, due to safety concerns for the veteran, other CLC patients, and CLC staff, risperidone dosing was increased to 1 mg twice daily, which had limited efficacy. Lorazepam 1 mg once daily also was added. A careful medication review was performed to minimize any potential AEs or interactions that might have contributed to the veteran's behavior, but no pharmacologic interventions were found to fully abate their behavioral issues.

After 5 weeks of ongoing intermittent behavioral issues, the medical team again met to discuss new treatment options. A case reported by Husebo and colleagues used scheduled acetaminophen to help relieve neuropsychiatric symptoms of dementia in a patient who exhibited similar behavioral issues and did not respond well to antipsychotics or benzodiazepines.⁸ Although our veteran did not express or exhibit obvious pain, the medical team chose to trial this intervention, and the veteran was started on acetaminophen 650 mg orally 3 times daily. A comprehensive metabolic panel, including GGT and thyroid-stimulating hormone, was performed before starting acetaminophen; no abnormalities were noted. The clinical examination did not reveal physical abnormalities other than ataxia.

After 5 days of therapy with the scheduled acetaminophen, the veteran's clinical behavior dramatically improved. The veteran exhibited infrequent agitated behavior and became cooperative with staff. Three days later, the scheduled lorazepam was discontinued, and eventually they were tapered off risperidone. One month after starting scheduled acetaminophen, the veteran had improved to a point where the staff determined a safe discharge plan could be initiated. The veteran's nystagmus resolved and behavioral issues improved, although cognitive impairment persisted.

Due to COVID-19, a teleconference was scheduled with the veteran's spouse to discuss a discharge plan. The spouse was pleased that the veteran had progressed adequately both functionally and behaviorally to make a safe discharge home possible. The spouse arranged to take family

leave from their job to help support the veteran after discharge. The veteran was able to return home with a safe discharge plan 1 week later. The acetaminophen was continued with twice-daily dosing and was continued because there were no new behavioral issues. This was done to enhance postfacility adherence and minimize the risk of drug-drug interactions. Attempts to follow up with the veteran postdischarge were unfortunately unsuccessful as the family lived out of the local area.

DISCUSSION

Alcohol misuse is a common finding in many US veterans, as well as in the general population.^{1,3} As a result, it is not uncommon to see patients with physical and psychological symptoms related to this abuse. Many of these patients will become verbally and physically abusive, thus having appropriate pharmacologic and nonpharmacologic interventions is important.

In this case study, the veteran was diagnosed with WKS and exhibited physical, cognitive, and emotional symptoms consistent with this disease. Although the physical symptoms improved with thiamine and abstinence from alcohol, their cognitive impairment, verbal outbursts, and aggressive demeanor persisted.

After using antipsychotic and anxiolytic medications with minimal clinical improvement, a trial of acetaminophen 650 mg 3 times daily was instituted. The patient's behavior improved; demeanor became calmer, and they were easily redirected by the nursing staff. Psychological support was again employed, which enhanced and supported the veteran's calmer demeanor. Although there is limited medical literature on the use of acetaminophen in clinical situations not related to pain, there has been research documenting its effect on social interaction.^{9,10}

Acetaminophen is an analgesic medication that acts through central neural mechanisms. It has been hypothesized that social and physical pain rely on shared neurochemical underpinnings, and some of the regions of the brain involved in affective experience of physical pain also have been found to be involved in the experience of social pain.¹¹ Acetaminophen

may impact an individual's social well-being as social pain processes.¹¹ It has been shown to blunt reactivity to both physical pain as well as negative stimuli.¹¹

CONCLUSIONS

A 2019 survey on alcohol and drug use found 5.6% of adults aged ≥ 18 have an alcohol use disorder.¹² In severe cases, this can result in WKS. Although replacement of thiamine is critical for physical improvement, psychological deficits may persist. Small studies have advanced the concept of using scheduled acetaminophen even when the patient is not verbalizing or displaying pain.¹³ Although more research needs to be done on this topic, this palliative approach may be worth considering, especially if the risks of antipsychotics and anxiolytics outweigh the benefits.

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Ethics and consent

The authors report that the patient did not provide informed consent. Details about the patient and case have been changed to avoid identification.

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