Opioids for Agitation in Advanced Alzheimer’s Disease

Anna Borisovskaya1,2*, Soo Borson1 and Mary K. Foster2

1Department of Psychiatry, University of Washington School of Medicine, USA
2Veterans Affairs Medical Center, USA
3Department of Psychiatry and Behavioral Sciences, University of Washington, USA

INTRODUCTION

Agitation, aggression, and unsafe resistance to care are common in Alzheimer’s disease (AD), especially in the advanced stages of dementia [1]. While nonpharmacological management, such as looking for and modifying environmental triggers, is an essential component of care, many patients will require medications and a substantial fraction will need serial medication trials with no guarantee of success. Psychotropic medications are typically required when manifest suffering cannot be improved by these means and/or when the patient’s behavior poses a threat to the patient’s or caregivers’ safety. The limitations of psychotropic medications in the treatment of agitation in AD have been much publicized, leaving major gaps in therapeutic efficacy for many patients. The following case illustrates the potential benefits of short acting opioid medications for management of intractable agitation in dementia, a little explored strategy that deserves formal study.

CASE PRESENTATION

A 61-year-old man with young-onset AD was admitted to the inpatient psychiatry unit for treatment of severe behavioral disturbance. He presented with guarded affect, disorganized speech and thought, disrupted sleep, and advanced functional decline. He often spoke to the unseen presence in the room. He required assistance with feeding, toileting, and dressing. He was prone to episodes of agitation during which he assumed threatening postures and used foul language. He was extremely resistive to personal care. Collateral sources described the patient as “a debonair gentleman” prior to the onset of AD, a man who loved music, dressed well, and was pleasant in interactions with friends and family. He was unable to provide any meaningful history of his life or illness. Formal cognitive tests couldn’t be performed due to his inability to understand what was asked of him. His Functional Assessment Staging of Alzheimer’s Disease (FAST) stage was 6d (moderately severe dementia with urinary incontinence). There was no indication of any significant medical problems, and routine laboratory workup revealed no abnormalities.

By this time, his intractable agitation had prevented discharge to any long-term care setting for over eight months. His dementia was progressing, as evidenced by the development of fecal incontinence and sparse speech. He spent most of his time sitting...
on the bed, picking at his clothing. He was given plush toys and appeared to enjoy playing with them.

After an episode of agitation during which multiple staff and security had to assist with changing his soiled undergarments, we reassessed his care. An ethics consultant recommended that he not be changed forcefully, despite the risk of skin breakdown from prolonged exposure to excretions.

We discontinued lorazepam and tapered off trazodone, both of which had been overly sedating at doses ineffective for controlling agitation. Though evidence of physical pain was lacking, we elected a trial of short-acting opioid (oxycodone 5 mg three times a day). At the time, we considered that opioids can modulate emotions, anxiety, and stress in addition to addressing pain [3], and we hoped that oxycodone would address his obvious distress, even if this distress was not caused by pain. What we have not considered at the time was that agitation is often the only expression of pain in patients with severe dementia [4], and that while he did not have any obvious sources of pain, he might have been in pain nonetheless. Unfortunately, we did not use potentially useful scales such as the Pain Assessment in Advanced Dementia (PAINAD) [5] to evaluate the patient’s pain level, but in retrospect he would have scored 6 prior to the administration of oxycodone, with 0 for breathing independent of vocalization, 1 for negative vocalization, 2 for facial expression, 1 for body language, and 2 for consolability items.

Upon initiation of oxycodone, we monitored him for side effects such as sedation, fatigue, falls, and constipation. None of them were observed. The staff unanimously reported rapid improvements in agitation and manageability. A brief discontinuation trial to assess the specificity of oxycodone’s effect led to rapid behavioral deterioration, and resumption produced sustained improvement in the patient’s behavioral control, affect, acceptance of personal care, and sleep. The Clinical Global Impression (CGI) scale demonstrated global improvement of 2 (much improved) with no adverse observable effects. In retrospect, he would have scored 0 on the PAINAD scale. He was maintained on the same dose of oxycodone over the next three months, with sufficient improvement to allow successful transfer to a long-stay dementia care unit.

**DISCUSSION**

Severe agitation is a highly distressing complication of advanced dementia that often responds poorly to psychotropic medications and environmental interventions, leading to prolonged hospitalizations and poor outcomes [1]. We discuss a little explored treatment with short-acting opioids, potentially useful for those patients who failed conventional treatments such as antipsychotics and antidepressants.

There are several reasons why oxycodone was effective in ameliorating agitation in this otherwise very difficult to treat patient. He may have in fact been in pain, which we have not recognized while we were treating him. A growing body of literature is supporting the strategy of addressing pain as expressed by agitation in persons with dementia. A large recent study of 352 patients with moderate to severe dementia and significant behavioral disturbances who were treated with variable pain medications demonstrated significant improvements in verbal agitation, restlessness, and pacing [6]. While no robust clinical guidelines for treatment of pain in dementia exist, there is evidence that addressing pain in patients with advanced dementia and agitation may be helpful, and we may have initiated treatment for pain in our patient sooner had we considered this possibility earlier on [7]. Another reason why the patient improved may have been a direct effect of an opioid on his mood. Functional magnetic resonance imaging (fMRI) study of how opioids influence activation in the brain reveal effects in multiple regions including anterior cingulate cortex, medial and inferior frontal gyri, and precuneus, all of which are engaged in processing of emotional stimuli. Activation of insular cortex, also observed in this study, also plays a role in the production of affective states [3].

Further study of treating patients with advanced dementia and behavioral disturbance with opioids would be of interest to all who are involved in the care of these patients. While treatment of pain is increasingly recognized as potentially beneficial to address agitation in advanced dementia, consideration should be given to the hypothesis that even patients with no pain may benefit due to opioids’ effects on emotional and reward circuitry in the brain. Short-acting opioids may also offer a better benefit-to-risk-ratio than antipsychotics [8], whose association with increased morbidity and mortality in dementia is widely acknowledged [9].

**CONCLUSION**

Short-acting opioids present an attractive option for pharmacological treatment of severe agitation in dementia and should be rigorously studied. Though the evidence base for this treatment is sparse, opioids may be considered where conventional psychopharmacological and behavioral strategies have failed and high-risk behavioral dyscontrol endangers safety and quality of life.

**REFERENCES**

8. Brown B. Broadening the search for safe treatments in dementia.