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Memantine for Posttraumatic Stress Disorder in an Older Veteran

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To the Editors:

Posttraumatic stress disorder (PTSD) is often along-term, disabling condition, especially in combat veterans who have been exposed to severe, recurrent trauma. Randomized control trial data show the α_1 -adrenergic antagonist, prazosin, to be effective for PTSD-related nightmares and sleep disturbances.¹ Prazosin has also been shown to effectively treat behavioral problems associated with dementia in older adults.² However, medication options might be limited when an older adult with PTSD or dementia, or both, is unable to tolerate prazosin. In this case example, we describe an elderly veteran with severe PTSD symptoms and dementia who was unable to tolerate prazosin but who derived benefit for both his problems by the addition of the uncompetitive *N*-methyl-D-aspartate antagonist, memantine.

Because assessment of PTSD symptoms in persons with cognitive impairment can be a challenge, a Posttraumatic Stress Screen for the Cognitively Impaired (PTSS-CI) has been described for use in long-term care settings.³ It assesses the severity of 8 symptoms of PTSD during the previous week on a 4-point (from 0 to 3) ordinal scale, with higher scores indicating greater severity of symptoms. The PTSS-CI consists of 2 versions, which are administered to the patient and to a knowledgeable informant concurrently. Notably, patient and staff reports of PTSD symptoms have not been found to be influenced by the level of cognitive impairment on the PTSS-CI, and the instrument has been shown to have reliable psychometric properties, as described in the original publication.³

We administered the 2 versions of the PTSS-CI to the veteran and the primary nurse taking care of him, respectively, at 3 different time points. These were before the initiation of memantine therapy in November 2009, at 12 weeks after initiating treatment with memantine in February 2010 (which included a 4-week dose-titration protocol and 8 weeks at the optimal dose recommended), and finally after an additional 6 months of memantine

treatment in early September 2010. At each time point, the PTSS-CI was administered for 2 consecutive weeks, every Friday around 1 P.M., to maintain consistency between assessments.

CASE REPORT

The subject is an 85-year-old white male veteran admitted for rehabilitation after a fractured hip after falling out of bed during a nightmare related to traumatic experiences during World War II. He had been attempting to jump out his "foxhole" when he fell out of bed and described his reexperiencing symptoms as a "nonstop movie playing in my (his) head." His condition had been diagnosed as PTSD, and he was in mental health treatment of PTSD and recurrent major depressive disorder for many decades and had received lifetime compensation and care from the Department of Veterans Affairs for his PTSD-related disability.

In addition to PTSD and depression, the veteran was diagnosed with mild-to-moderate dementia during an evaluation by a multidisciplinary team at the time of admission in June 2009, with Folstein Mini Mental State (MMSE) score of 18 of 30 in June 2009 and a score of 17 of 30 later in August 2009. He had been on a maintenance dose of citalopram 40 mg/d for more than 2 years, and no changes to the specific serotonin reuptake inhibitor (SSRI) were made during the period of treatment described in the next paragraphs. The veteran also received consistent psychotherapeutic support for his mental health problems for the duration of his stay at the skilled nursing facility.

Because the sleep disturbance was most notable at the time of admission, a trial of prazosin 1 mg at bedtime was initiated. However, the veteran was unable to tolerate an upward titration of prazosin beyond a dose of 3 mg because of postural hypotension and repeated falls. The total duration of the prazosin trial had been 5 weeks, of which 3 weeks were at 3 mg/d, without any noticeable improvement in his nightmares. Given his limited ability to tolerate medication adverse effects in general and some evidence of potential benefit from memantine for both cognitive impairment and symptoms of PTSD (details in the next paragraphs), a trial of memantine, instead of a cholinesterase inhibitor, was considered. His self-rated PTSS-CI scores were 20 and 18, and his PTSS-CI scores per informant report were 10 and 15 (range, 0–24) for the 2 consecutive weeks immediately before initiating treatment with memantine. He tolerated the memantine titration protocol well, and the recommended dose of 10 mg twice a day was reached during 4 weeks.

During the consecutive assessments using the PTSS-CI, there were clinically significant decreases in his self-reported PTSS-CI scores as follows: mean (SD) scores of 19.0 (1.4) before memantine therapy, 8.5 (2.5) 12 weeks after initiation of memantine, and 8.0 (1.4) after an additional 6 months (total around 9 months) of treatment ($F_{2,5} = 14.03$, $P = 0.03$). Post hoc tests revealed a significant difference between the mean scores before initiating memantine and after 9 months of therapy (meandifference, 11.0; 95% confidence interval, 4.92–17.09; $t_2 = 7.78$, $P = 0.02$), whereas the difference between the initial and the week 12 assessments bordered on statistical significance ($t_2 = 3.90$, $P = 0.06$). Mean (SD) observer-rated PTSS-CI scores at the 3 time points were 12.5 (3.5) before initiation, 7.5 (0.7) after

12 weeks, and 9.5 (0.7) at 9 months ($F_{2,5} = 2.82$, $P = 0.21$), with no significant post hoc comparisons.

The greatest improvements on the PTSS-CI were seen for the symptoms of hyperarousal (startled easily, feeling as if in danger), and the pattern of improvement was similar on both versions of the scale. Although the patient continued to reexperience symptoms and nightmares, no additional instances of violent behavior associated with nightmares were observed during the course of treatment with memantine. There was also a clinically noticeable improvement in the veteran's cognitive functioning, and his MMSE scores had increased to 22 and 19 of 30 at the time of the first and second post-memantine assessments, respectively.

DISCUSSION

The improvement in PTSD symptoms from the addition of memantine to ongoing SSRI treatment observed for this older veteran is similar to the benefits from memantine described in a case series of Vietnam-era veterans with similar problems.⁴ This younger cohort of veterans, between the ages of 54 and 59, had similar sleep difficulties and nightmares and had persistent symptoms despite pharmacotherapy with different SSRIs. The decision to initiate a trial of memantine in our veteran was facilitated by the presence of a greater degree of cognitive impairment and a greater risk of intolerance to the unpleasant adverse effects of medications than the younger veterans in the previously mentioned case series might have experienced.

The beneficial effect of memantine is believed to be from its actions on the glutamatergic system. A similar explanation has been offered for the improvement in PTSD symptoms observed from the addition of the antiepileptic drug, lamotrigine, to an SSRI.⁵ At this time, it is also unclear whether the added improvement from memantine is from its independent influence on PTSD symptoms or is some form of augmentation of the ongoing SSRI treatment. Memantine augmentation of SSRI therapy has been reported for obsessive-compulsive disorder, another anxiety disorder characterized by recurrent, intrusive, distressing symptoms.⁶

Current reasoning suggests that the therapeutic response for PTSD symptoms from an SSRI (like citalopram), or a medication like memantine, might be associated with its effects on the hypothalamic-pituitary-adrenal axis.⁷ A dysregulation in the hypothalamic-pituitary adrenal axis in response to stress has been most extensively studied in those with PTSD, and correction of an existing imbalance has been observed with treatments that have demonstrated efficacy, including psychotherapy.⁸ Along similar lines, older adults treated with an SSRI for generalized anxiety disorder demonstrated a substantially greater reduction in salivary cortisol levels compared with placebo-treated adults.⁹ Whether a different adrenergic agent instead of prazosin, like the β -blocker propranolol, might have any added benefits in this case remains to be investigated. Administration of propranolol has been shown to significantly reduce physiologic responses during script-driven traumatic imagery in those with PTSD.¹⁰

Our observations should be interpreted in light of the inherent limitations, mostly notable being that these observations were from a single case. Next, the memantine trial was open label, and there was no comparison to a period of treatment with a placebo. Further, statistically significant differences were observed on self-report but not according to the observer ratings and were significant between the first and third assessments only. Finally, although we attempted to be as consistent as possible in obtaining collateral assessments, different nursing staff provided the observer assessments at different time points.

Nonetheless, these observations raise interesting possibilities, especially for older patients with PTSD who might have coexisting cognitive impairment or are unable to tolerate unpleasant adverse effects of certain medications. A lifetime diagnosis of PTSD has been associated with a doubling of the risk of developing dementia later in life, and available data suggest that memantine is a safe and well-tolerated medication, especially by those with dementia.^{11,12} Randomized control trials using validated measures of PTSD and involving well-defined outcomes are needed to comprehensively evaluate whether memantine holds any promise in these clinical situations. Pending the results of such an investigation, this case underscores the possibility of an alternate therapeutic option that might benefit especially older adults with persistent symptoms of PTSD.

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AUTHOR DISCLOSURE INFORMATION

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