Toward Rational Use of Benzodiazepines in Posttraumatic Stress Disorder

To the Editor: A recent study in the *Journal* by Lund et al[1] has provided important data: benzodiazepines are still prescribed to 30.6% of an American veteran posttraumatic stress disorder (PTSD) population, although from 1999 to 2009 there was a 17% decline. In a comment,[2] Capehart encourages this trend, assuming that this decline may reflect greater use of evidence-based therapies. Indeed, expert consensus guidelines[3,4] recommend against the use of benzodiazepines in PTSD, even though there is only 1 randomized controlled trial (RCT) that did not find a significant advantage of benzodiazepines over placebo.[5] Furthermore, PTSD is highly comorbid with substance disorders and therefore prone to detrimental addiction effects,[6–8] and benzodiazepine-induced anterograde amnesia has been proposed to interfere negatively with exposure-based psychotherapies.[9] Substantial ambivalence exists regarding the proper use of benzodiazepines in PTSD, as illustrated by a prescription frequency variation of 14.7%–56.8% among 137 facilities in the United States.[10] Moreover, the preponderance of clinical research on selective serotonin reuptake inhibitors (SSRIs) in PTSD has made some wonder why benzodiazepines are prescribed at all.[2]

Still, preclinical evidence has offered promising potential. In particular, data from studies on the *reconsolidation phase* of memory, which is activated by reexposure to conditioned stimuli, show that specific traumatic memory is fragile and prone to disruption,[11] as demonstrated with propranolol in humans.[12,13] The animal research finding that midazolam is capable of obliterating long-term fear is promising for the use of benzodiazepines in PTSD.[14] Rodent studies have repeatedly shown that the immediately reduced contextual fear responding produced by systemic midazolam does not recover over time following reexposure.[14–17] This effect seems to depend on the age of the memory; a longer interval between the initial acquisition of fear memories and their reactivation may require longer reactivation periods and higher doses to weaken them.[17] The effects of benzodiazepines on blockade of traumatic memory reconsolidation therefore deserve further attention.

In fact, new pharmacologic strategies are requisite as current PTSD therapies remain unsatisfactory. One needs to bear in mind that the magnitude of the effects of SSRIs is limited and remission is rarely achieved.[4,18] Furthermore, the latest *Cochrane Review*[19] concludes that there is no clear evidence to show that any particular class of medication is more effective in PTSD or better tolerated than any other. The bulk of trials showing efficacy to date have been with SSRIs, but there is a paucity of literature on benzodiazepines. The 1990 RCT by Braun et al[5] is extensively cited in psychiatric literature to demonstrate the notion that benzodiazepines are ineffective in PTSD, but has very low power (N = 10), confounding withdrawal effects, and it included only treatment-refractory, chronic PTSD patients who were unresponsive to several antidepressants. To date, there is no evidence on the effects of benzodiazepines on reconsolidation of traumatic memory in PTSD.

Lund and colleagues[1] accurately mention that simply advocating against current benzodiazepine use in PTSD, without providing alternative strategies, is not an option. Future research is warranted; finding the optimal memory reactivation length may become a great clinical challenge of trial-and-error, as benzodiazepine administration may time-dependently both inhibit and promote forgetting in PTSD.

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