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Fluoxetine and Trazodone Combination Pharmacotherapy Resulting in Severe Irritability, Anger, Anxiety, and Anorexia: Probable Adverse Drug Interaction

To the Editor: Trazodone is commonly used as an off-label hypnotic.[1] Although its efficacy data as a hypnotic are mixed, trazodone is second only to nonbenzodiazepine drugs and is used by up to 1% of Americans each month.[2,3] The popularity of trazodone as a hypnotic is most likely due to lack of known abuse potential unlike the majority of other hypnotics.[3] Some data, however, suggest worse outcomes when trazodone is combined with strong cytochrome P450 (CYP) 2D6 inhibitors such as fluoxetine.[4] The following case report describes a probable drug-drug interaction between trazodone and fluoxetine resulting in exacerbation of symptoms, which rapidly resolved after discontinuation of trazodone.

Case report. Mr A is a 24-year-old male military service member in deployed settings who presented to a military deployed field behavioral health outpatient clinic in September 2015 with symptoms of insomnia, mood swings, anxiety, and irritability for 2 months. Symptoms had recently worsened in the context of increased work demands. Mr A was started on fluoxetine 10 mg for unspecified depressive disorder (*DSM-5* criteria) and increased to 20 mg after a week. He was also provided behavioral strategies to improve his initiation and maintenance insomnia. At a 2-week follow-up appointment, he had 50% subjective improvement in his mood swings and irritability but still had insomnia despite implementing behavioral techniques. He also complained of no reduction in anxiety. He was started on trazodone 50 mg, and at 1-week follow-up, he was sleeping for 8 hours per night. At that time, his irritability had resolved, and he reported euthymia. However, his anxiety symptoms remained, leading to an increase in the fluoxetine dose to 40 mg. Mr A returned 2 weeks later and reported no improvement in anxiety symptoms and a recurrence of his irritability, but he continued to sleep well. The fluoxetine was increased to 60 mg to help address the recurrence of irritability and his ongoing anxiety symptoms. He was maintained on trazodone 50 mg nightly.

Mr A presented to the clinic after 5 days on the fluoxetine 60-mg dose. He reported severe irritability, anger, worsened anxiety, and complete loss of appetite that began 1 day after the increase in the fluoxetine dose. Mr A had skipped all 3 meals during 1 of the days and had since been forcing himself to eat. Given the timing and patterns of these symptoms, an adverse drug-drug reaction was suspected between trazodone and fluoxetine. Trazodone was stopped due to its much shorter half-life in comparison to fluoxetine with the hope of a more rapid resolution. At a 1-week follow-up appointment, Mr A reported that he had complete resolution of his irritability, anger, anxiety, and anorexia symptoms on the second day after discontinuing trazodone. He was maintained on fluoxetine 60 mg and transitioned to hydroxyzine 100 mg for insomnia. Immediately after these changes, he was transferred to another military camp and was lost to follow-up.

This case describes a dose-related type of adverse drug reaction.[5] The temporal and dose-dependent relationship of symptoms and subsequent resolution by discontinuation of trazodone places it in the probable category.[5,6] One study[4] showed that adolescent psychiatric patients taking combination trazodone with strong CYP 2D6 inhibitors including fluoxetine and paroxetine were 6 times less likely to respond to treatment and 3 times more likely to experience self-harm. The authors[4] speculate that the response was the result of increased accumulation of meto-chlorophenylpiperazine (mCPP), the active trazodone metabolite. Excess levels of mCPP have been shown to increase dysphoria, anxiety, and agitation.[7] The present case illustrates the need for high clinical suspicion, as these drug-drug reaction symptoms can mimic index psychiatric symptoms. Similar adverse events may serve as an important clinical signal for what could be an easily missed adverse drug reaction. Clinicians may consider alternative combinations of medications given the results from prior studies[4] and this report.

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