# Letters to the Editor

## Thyroid Augmentation of Mirtazapine: A Case Report

**Sir:** Depression is a common but debilitating illness in the United States with a prevalence rate ranging from 4.8% to 9.2% in primary care practice.[1] Fortunately, there are many antidepressant medications to treat patients with depression. However, up to 46% of patients treated with antidepressants do not adequately respond to treatment.[2] A smaller number—5% to 10%—will continue to experience depression despite numerous therapeutic interventions.[3] Clinicians are then left to treat these patients who do not experience a full response using a number of treatment options.

We describe the case of a patient diagnosed with depression who, having not previously responded to 2 classes of antidepressants, partially responded to a third class and achieved remission with thyroid hormone augmentation. To our knowledge, augmentation of mirtazapine with thyroid hormone has not previously been reported.

***Case report.*** Ms. A, a 33-year-old woman, was diagnosed with a major depressive episode, severe without psychotic features (DSM-IV criteria). Her symptoms included a loss of energy, decreased concentration, insomnia, anxiety, guilt, and a feeling of hopelessness. She was experiencing an inability to take care of her family, had quit her job as an aerobics instructor, and had stopped her college studies. She had no previous psychiatric history and enjoyed good physical health. Ms. A denied the use of alcohol, tobacco, or illicit substances. She was taking hydrochlorothiazide, 25 mg/day, for essential hypertension and denied the concurrent use of over-the-counter medications. Her family physician had prescribed her nortriptyline, 100 mg/day, which she took for 6 weeks prior to stopping it due to bothersome side effects and not feeling better. Her physician then started her on fluoxetine, 20 mg/day, shortly after stopping nortriptyline treatment. Early on, she felt that the fluoxetine made her anxiety worse; fluoxetine caused her headaches, nausea, loose stools, and an overall feeling of restlessness. This trial was cut short after a week. Ms. A then was referred to the psychiatry service, but in the lapse overdosed with a combination of trazodone given to her for insomnia and the remaining supply of fluoxetine. She was initially admitted to the medical intensive care unit, where her condition was stabilized prior to her transfer to the psychiatry service.

Once Ms. A was at the psychiatry ward, it was decided after initial workup to initiate a trial of mirtazapine, 15 mg, to target her constellation of depressive and anxious symptoms. Because mirtazapine potentially induces orthostatic hypotension, the medication was given at bedtime to diminish the possibility that such an effect would be problematic. The treatment team also felt that mirtazapine would be a good choice given Ms. A's previous problems with continued loose stools following treatment with fluoxetine. Buspirone, 5 mg t.i.d., was also started to help treat her anxiety. Over the next 10 days, mirtazapine was titrated up to 30 mg/day, and her mood improved slightly. Ms. A's suicidal ideation had dissipated, and she readily contracted for safety and was discharged home.

At the first outpatient follow-up appointment, Ms. A voiced wanting to discontinue buspirone, which she did not feel was helping her. She also was impatient with regard to not feeling better despite reassurance about the time necessary for antidepressants to begin to work. She did not feel she could wait a full 8 weeks for a fair therapeutic trial. A decision was made to augment her mirtazapine with levothyroxine ($T_4$) at 50 µg/day titrated up to 200 µg/day over the following 2 weeks. Prior to initiation of treatment with $T_4$, her thyroid-stimulating hormone level was checked and found to be within normal limits (0.71 µIU/mL). Over the next 2 to 3 weeks, Ms. A noted a significant improvement. She started back to school, began to exercise again, and took the reins in the daily running of the household. Her mirtazapine dosage was increased to 45 mg/day, and the daily $T_4$ dosage was tapered by 25 µg/week. Ms. A continues to participate in bimonthly supportive therapy and is maintained on mirtazapine, 45 mg daily, with no noted adverse side effects.

A number of options exist for clinicians to treat patients who do not adequately respond to antidepressants. Those options include switching to a different class of antidepressant, augmenting with lithium or thyroid hormone, combining classes of antidepressants, electroconvulsive therapy, steroid suppression therapy, and/or augmenting with atypical antipsychotics.[4] Other options include addition of psychostimulants, buspirone, pindolol, yohimbine, and tryptophan.[5] Transcranial magnetic stimulation is a recent arrival to the list of treatment options.[3] Joffe[2] points out that substitution or switching classes is the most widely used treatment for patients who fail to respond to an antidepressant and the most widely used by both psychiatrists and family physicians. He states that there is no evidence in the literature suggesting that substitution is more efficacious than augmentation or combination strategies.[2]

In the above case, I describe a patient who had partially responded to mirtazapine, had not tolerated buspirone, and was impatient to wait for completion of a full therapeutic trial. Reportedly, 80% of psychiatrists would also not wait a full 8 weeks in making a therapeutic change in a patient not responding.[6] Nelson[5] also points out that augmentation may be a more attractive strategy in severely depressed patients, since it avoids the time lost in tapering one agent while adding a second and can be helpful in an impatient patient. I decided to augment with $T_4$, although triiodothyronine ($T_3$) is more widely used and studied.[2] Joffe is reluctant to interpret the findings over the last 25 to 30 years as indicating that $T_3$ is more effective than $T_4$.[2] I also felt that I was at a point in treatment where an augmenting agent would possibly show efficacy; Nelson[5] writes that agents are rarely added after an extended period (> 1 month). To my pleasure, Ms. A had a favorable response after adding $T_4$, and I continued $T_4$ treatment for another 3 weeks prior to tapering it.

To my knowledge, this is the first reported case of successful augmentation of mirtazapine with thyroid hormone. Single case

reports should be interpreted with caution, but this finding suggests that further studies are needed looking at the benefits of augmentation strategies in combination with mirtazapine. As the number of Americans diagnosed with depression increases, the number of patients prescribed antidepressants will increase as well. In 1998, approximately $5.52 billion were spent on antidepressants.[7] Family physicians will no doubt see the majority of those patients and will be faced with treatment dilemmas in the partial, slow, or nonresponders. These very patients may well benefit from augmentation strategies like the one described here.

Conclusions and opinions expressed are those of the authors and do not necessarily reflect the opinion or policy of the U.S. Government, Department of Defense, Department of the Army, or the U.S. Army Medical Command.



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## Effect of Citalopram on Blood Desipramine Levels

**Sir:** We report a case of treatment-resistant major depression and panic disorder with agoraphobia treated with desipramine and augmented with citalopram without altered blood levels of desipramine.

***Case report:*** Ms. A is a 54-year-old married white woman with DSM-IV major depression and panic disorder with agoraphobia. She has a history of panic attacks since age 20 and had presented 1 year earlier for psychiatric consultation owing to increasing symptoms of depression, which included low mood, poor concentration, suicidal thoughts, and despair. She had difficulty going to large shops and gatherings and also had difficulty leaving home. There was no significant past psychiatric history of hospitalization or suicide attempts. She had been unresponsive to a combination of fluoxetine, 60 mg daily, buspirone, 15 mg t.i.d., and trazodone, 150 mg at bedtime, prescribed by her family physician. Her medical history was significant for hypertension and knee problems. She had been in individual psychotherapy for 2 years. The family history was significant for the mother who had anxiety attacks that had never been treated. There was no past history of drug or alcohol abuse. Results of her laboratory tests had been unremarkable.

The patient was gradually tapered off fluoxetine and started on desipramine treatment, which was titrated over the course of 3 months to a dosage of 300 mg daily in divided doses (serum level = 234 ng/mL). Clonazepam, 1 mg t.i.d., was added to control anticipatory anxiety. With desipramine, the patient's sleep improved and the crying spells were reduced in frequency and intensity. Suicidal thoughts were still present, but decreased in intensity. Regarding symptoms of panic, she indicated, "I still have my moments." Although she wanted to, she was still unable to return to work. Owing to persistence of depressive and panic symptoms, desipramine was augmented with citalopram, 10 mg daily, which was titrated after 1 week to 20 mg daily without side effects. At this time, the clonazepam dosage was decreased to 1 mg b.i.d. The desipramine dosage was maintained at 300 mg daily in divided dosage. The serum desipramine level was 267 ng/mL 1 month after the augmentation. There were no adverse reactions and no marked elevation of the blood level of desipramine with the addition of citalopram.

Different combinations of selective serotonin reuptake inhibitors (SSRIs) and tricyclic amines (TCAs) for treatment-resistant depression vary in efficacy and safety. During coadministration of SSRIs and TCAs, blood levels must be carefully monitored due to elevation of TCA levels.[1] Citalopram has demonstrated superiority to placebo in major depression[2] and in panic disorder.[3] There have been no reports of clinical adverse reactions when citalopram is coadministered with a TCA.[4] In addition, citalopram has demonstrated safety when coadministered with digoxin[5] and warfarin.[6] Further studies are warranted to determine the potential for adverse effects of citalopram in combination with TCAs and other SSRIs.

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