Letters to the Editor

Lack of Sertraline Efficacy Probably Due to an Interaction With Carbamazepine

Sir: We report 2 cases in which concomitant use of a selective serotonin reuptake inhibitor (SSRI), sertraline, and an antiseizure/mood-stabilizing drug, carbamazepine, resulted in a lack of sertraline efficacy at doses 2 to 4 times higher than the minimum effective dose of sertraline, 50 mg/day, under steady-state dosing conditions. This is the first published report of such a reduction.

Case 1. Ms. A, a 33-year-old, physically active white woman with a diagnosis of schizoaffective disorder (bipolar type), had been successfully treated by a combination of haloperidol, 4–6 mg/day, and carbamazepine, 1000 mg/day, for 3 years. When she then developed a depressive episode, sertraline at a dose of 50 mg/day was added to the regimen. However, after a period of 4 weeks, Ms. A did not respond and had to be admitted to the hospital for suicidal thoughts. After a minimum trial of 2 weeks at each dose, the sertraline dose was increased to 100 mg/day, 200 mg/day, and then to 300 mg/day. Within 2 weeks of taking 300 mg/day, Ms. A showed a significant improvement in her sleep, appetite, energy, and concentration. After the start of sertraline treatment, 1 plasma level for carbamazepine (1000 mg/day) and 2 levels for sertraline (one at 200 mg/day and the other at 300 mg/day) were obtained. All plasma levels were obtained under our standard protocol for therapeutic drug monitoring (i.e., a stable dose maintained for at least 5 times the usual half-life of the drug and the sample obtained 10–12 hours after the last dose). Automated gas chromatographic-electron-capture assay[1] performed by the same laboratory was used for both plasma levels of sertraline, with levels below 10 ng/mL not detectable. Ms. A was using no drugs except those mentioned in the case history. Routine laboratory test results were within normal limits.

Case 2. Mr. B, a 25-year-old, physically healthy white man with a long-standing diagnosis of a posttraumatic stress disorder, had been successfully treated with carbamazepine, 400 mg/day, for 13 years. When he then developed major depressive disorder, he was started on sertraline, 50 mg/day. However, Mr. B failed to respond, and, after a minimum trial of 3 weeks at each dose, sertraline was increased to 100 mg/day, 200 mg/day, and finally to 300 mg/day, which resulted in a remarkable improvement in his mood, sleep, energy, and interests. After the start of sertraline treatment, 1 plasma level each was drawn for carbamazepine (400 mg/day) and sertraline (100 mg/day). All plasma levels were obtained under our standard protocol for therapeutic drug monitoring (described above). Sertraline level was measured using automated gas chromatographic-electron-capture assay[1] using the same laboratory as in case 1, with levels below 10 ng/mL not detectable. Ms. B was using no other drugs besides those mentioned in the case history. Routine laboratory test results were within normal limits.

Although blood was drawn 10 to 12 hours after the last dose in the 2 patients, sertraline levels were still significantly lower than the levels observed after 24 hours of the last dose (i.e., trough levels) of sertraline at similar dosages (Table 1). For example, at a dose of 200 mg/day, the first patient had a level of 19 ng/mL, whereas in a young healthy female, average trough levels of sertraline at this dose would be 107 ng/mL.[2] Similarly, the second patient had a level of < 10 ng/mL (nondetectable) at a dose of 100 mg/day of sertraline, whereas in a young healthy male, average trough level of sertraline at this dose would be 30 ng/mL (Table 1).[2] This finding is consistent and may explain why the patients were not responding to sertraline at dosages (200 mg/day) that were 4 times higher than its minimum effective dose (50 mg/day). The plasma levels of desmethylsertraline, the primary metabolite of sertraline, were not measured; desmethylsertraline is 25 times less potent than the parent drug in blocking the serotonin uptake pump,[3] and therefore, even in the presence of 1.5 times higher levels than the parent drug,[4] desmethylsertraline will not be expected to block the serotonin uptake pump to any significant degree.

Table 1. Observed and Expected Plasma Drug Levels in 2 Patients Treated With Sertraline and Carbamazepine

Patient/Drug	Dose (mg/d)	Observed Levels (ng/mL) After 12 h	Expected Levels (ng/mL) After 24 h[a]
Case 1: (33-year-old woman)			
Carbamazepine	1000	8.0	NA
Sertraline	200	19.0	107
Sertraline	300	39.0	160
Case 2: (25-year-old man)			
Carbamazepine	400	9.3	NA
Sertraline	100	< 10	30

[a]Reference values based on Ronfeld et al.[2] Abbreviation: NA = not available.

While noncompliance should be considered as a possible explanation for unusually low plasma levels of sertraline, several observations make this explanation unlikely. For example, the first patient at a dose of 300 mg/day of sertraline achieved both therapeutic response and levels typically achieved at the usually effective minimum dose of 50 mg/day. In the second patient, the plasma sertraline level obtained at a dose of 100 mg/day suggests that he may have developed the same plasma level at a dose of 300 mg/day of sertraline as did the first patient at a similar dose while accounting for gender differences (Table 1). Both patients on direct questioning indicated that they had been taking their sertraline as directed. In addition, both patients were compliant with their carbamazepine as suggested by their therapeutic drug monitoring over a period of multiple years, which favors compliance with sertraline.

The lower-than-expected plasma levels of sertraline are consistent with a drug-drug interaction between carbamazepine and sertraline. Based on in vitro studies, sertraline is metabolized by several CYP enzymes including CYP2C9, CYP2C19,[5,6] and CYP3A4.[5,7] Under normal conditions, CYP3A4 may not contrib-

ute significantly to the metabolism of sertraline; however, with an increase in CYP3A4 activity, sertraline may be metabolized more rapidly. Therefore, concomitant use of carbamazepine, which increases the activity of CYP3A4 via enzyme induction,[8,9] would be expected to enhance the metabolism of sertraline, resulting in its subtherapeutic plasma levels and hence lack of efficacy as an antidepressant. Therefore, instead of using higher dosages of sertraline, it would be more cost effective to select an antidepressant that is not metabolized by CYP3A4 (e.g., paroxetine) to be used with carbamazepine.

Formal pharmacokinetic studies are required to confirm our findings in terms of sertraline; however, since all SSRIs are primarily metabolized by CYP enzymes, our case report suggests that therapeutic drug monitoring of SSRIs may be useful to detect (1) pharmacokinetic drug-drug interactions, which can result in lower-than-expected levels and hence lack of efficacy; and (2) lower than expected levels, which may be the reason for the lack of efficacy.

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Ahsan Khan, M.D.
Mujeeb U. Shad, M.D.
Sheldon H. Preskorn, M.D.
University of Kansas School of Medicine
Wichita, Kansas

Increased Lithium Concentrations Reported in Patients Treated With Sulindac

Sir: Lithium continues to be a primary treatment of choice in bipolar disorder; however, the use of this mood stabilizer requires close monitoring owing to a narrow therapeutic range. Equally important is the close monitoring of adverse drug reactions and toxicity resulting from concomitant medications. A specific association with increased lithium concentrations has been established for nonsteroidal anti-inflammatory drugs (NSAIDs). Several reports in the literature support the idea that concomitant NSAID administration raises lithium concentrations.[1–5] Alternatively, the NSAID sulindac and aspirin have been shown not to increase lithium concentrations significantly.[6,7]

The following case reports describe 2 patients who experienced an increase in lithium concentration while on concomitant sulindac therapy.

Case 1. Mr. A, a 23-year-old man with a history of bipolar disorder with psychotic features and polysubstance dependence, was admitted to our state psychiatric facility. Sulindac, 150 mg every 12 hours as needed for shoulder pain, was added to the current medications of lithium carbonate, 600 mg at noon and 900 mg at bedtime; divalproex sodium, 1500 mg at noon and 2000 mg at bedtime; olanzapine, 25 mg at bedtime; and tetracycline, 250 mg twice a day for acne. He had been receiving these concurrent medications for the past 4 months. Mr. A received sulindac for 21 days. His baseline serum creatinine, electrolytes, electrocardiogram, and thyroid functions were within normal limits. His serum lithium concentration the month prior to sulindac administration was 1.0 mEq/L. Subsequent lithium concentrations were as follows: 4 days after sulindac initiation, 1.3 mEq/L; 19 days after sulindac initiation, 2.0 mEq/L; 5 days after sulindac discontinuation, 0.8 mEq/L; 29 days after sulindac discontinuation, 0.8 mEq/L. According to his progress notes during the period of elevated lithium levels, Mr. A exhibited increased signs and symptoms of lithium toxicity such as hand tremors and restlessness.

Upon discontinuation of sulindac, lithium levels returned to normal baseline concentrations over the next 2 months. Mr. A continued on acetaminophen treatment as needed to relieve his shoulder pain. Importantly, although sulindac was prescribed on an as-needed basis, Mr. A took it on a routine basis except for 2 days, during which he took the medication only once per day.

Case 2. Ms. B, a 27-year-old woman with a history of schizoaffective disorder, polysubstance dependence, and antisocial personality disorder, was admitted to our state psychiatric facility. Sulindac, 150 mg twice a day for jaw pain, was started along with the current medications of lithium carbonate, 900 mg 2 times a day; nefazodone, 200 mg in the morning and 300 mg in the evening; fluphenazine decanoate, 37.5 mg i.m. every 2 weeks; lorazepam, 0.5 mg 3 times a day; and gemfibrozil, 600 mg twice a day. With the exception of gemfibrozil, which was started along with sulindac, she had been taking the other concurrent medications for the previous 5 months. She was given sulindac on a twice-a-day schedule for 100 days. Ms. B's lithium concentration the month prior to sulindac administration was 0.9 mEq/L, and 7 days after initiating sulindac, it had increased to 1.7 mEq/L. At this time, the clinician decreased her lithium dose by 300 mg per day to 600 mg in the morning and 900 mg at bedtime and opted to continue the sulindac since it effectively alleviated her jaw pain.

Despite elevated lithium concentrations, Ms. B did not exhibit signs and symptoms of lithium toxicity such as increased tremulousness, cognitive changes, delirium, or ataxia. Her lithium concentration 37 days after sulindac initiation was 1.2 mEq/L, and 70 days after sulindac administration, it was 1.0 mEq/L. Subsequently, sulindac and lithium therapies were discontinued, and a new approach to manage psychosis was implemented.

Both case reports indicate a marked rise in serum lithium concentrations after the administration of sulindac. In both cases, the patients were initially started with another NSAID (ibuprofen or naproxen), and the pharmacist intervened, recommending sulindac owing to the reported risk of elevating serum lithium concentrations and subsequent toxicity. It is interesting to note that in case 2, the lithium returned to normal concentrations after its dose was reduced (as opposed to discontinuing the

sulindac), but it was quite clear that the lithium concentrations rose initially when the sulindac was introduced. This raises an interesting point that more than one type of clinical intervention can be used to minimize the risk of or prevent lithium toxicity. Sulindac remains a choice for concomitant NSAID therapy when a patient is on lithium therapy, but it is not risk free. The clinician must carefully monitor clinical symptoms and laboratory values, since we highly suspect sulindac to have contributed to the elevated serum lithium concentrations in these 2 cases.

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Michael T. Jones, M.S., Pharm.D.
Steven C. Stoner, Pharm.D., B.C.P.P.
NW Missouri Psychiatric Rehabilitation Center
St. Joseph, Missouri

Carbamazepine Augmentation of Clomipramine in the Treatment of Refractory Obsessive-Compulsive Disorder

Sir: The serotonin reuptake inhibitors (SRIs) are now considered first-choice agents for the pharmacologic treatment of obsessive-compulsive disorder (OCD).[1] However, many patients with OCD are nonresponders or partial responders to these agents. Although the augmentation therapy of these agents with neuroleptics, lithium, benzodiazepines, or buspirone is recommended to treat refractory OCD,[2] the efficacy of the augmentation strategy is still limited. The case presented here illustrates effective augmentation of clomipramine, an SRI, with carbamazepine in the treatment of a patient with OCD refractory to the previously recommended treatment strategies.

Case report. Ms. A, a 27-year-old married woman, had obsessive-compulsive symptoms that started at the age of 12 years. The symptoms comprised intrusion of ideas (for instance, an idea that she might have done injury to someone) and compulsive behavior such as repetitive checking and hand washing. Accordingly, she was diagnosed with OCD. No comorbid disorder was evident. Clomipramine monotherapy was initiated and maintained for a year, but did not improve the symptoms. Ms. A also could not tolerate subsequent clomipramine augmentation with haloperidol or thioridazine; thus, each combination was discontinued after 1 week of treatment. Bromazepam, a benzodiazepine-type anxiolytic recommended for the treatment of OCD in Japan before introduction of the SRI therapy for OCD, was then tried, but this agent was found to be ineffective. Although these pharmacotherapies were unsuccessful, Ms. A was able to cope with her daily activities, including those at school, while receiving supportive psychotherapy and support from family members. The OCD symptoms gradually waned and, after graduation from high school at the age of 18 years, she stopped seeking medical care, although the mild form of symptoms persisted.

Soon after marriage at age 23 years, however, Ms. A's OCD symptoms were exacerbated and hampered her everyday activities. Because of this exacerbation, she restarted medical care, but responded to neither clomipramine monotherapy (150–200 mg/day, 5 months) nor clomipramine combination therapy with agents such as sulpiride (300 mg/day, 4 weeks), a benzamide-type neuroleptic, or oxazolam (2.4 mg/day, 8 weeks), a benzodiazepine-type anxiolytic compound. In light of the refractory nature of her symptoms along with the exhaustion of her husband and parents from caring for her, she was referred to and admitted to our hospital at the age of 27 years.

On admission, Ms. A had little control over compulsive behavior and repetitive checking. She was markedly anxious and distressed. We started clomipramine (200 mg/day) combined with diazepam (30 mg/day), which was maintained for 6 weeks but did not ameliorate the symptoms. Further addition of risperidone (2–3 mg/day) for 4 weeks was also ineffective. Risperidone was then replaced with clonazepam. Because this augmentation therapy reduced her repetitive checking, the dose was increased gradually to 10 mg/day (plasma level = 84 ng/mL). However, the 12-week treatment of clomipramine and clonazepam eventually proved only partially effective. Thus, we switched clonazepam to carbamazepine. Carbamazepine was increased to 500 mg/day (plasma level = 6.1 mg/mL) while clomipramine was kept at the same dose (i.e., 200 mg/day), and this combination therapy dramatically alleviated the OCD symptoms. Within the following 2 weeks, Ms. A's anxiety and distress and repetitive checking almost disappeared. She was discharged and able to resume her daily activities. The efficacy of the treatment strategy of carbamazepine combined with clomipramine has been sustained for 5 months since discharge.

The augmentation of SRIs with either clonazepam or haloperidol has been shown to be effective in the treatment of SRI-refractory OCD,[1] and recently, the efficacy of augmentation of SRIs with risperidone has also been reported.[3] However, the patient in the present case resisted or was intolerant of either clomipramine monotherapy or these augmentation strategies, although she responded well to combination therapy with clomipramine and carbamazepine. Interestingly, clinical similarities have been described between patients with temporal lobe epilepsy and those with OCD,[4] and the possible efficacy of carbamazepine monotherapy in the treatment of OCD with the presence of coexistent or past epilepsy has been suggested.[5,6] It is also of interest to note that carbamazepine augmentation therapy with clomipramine alleviates major depression,[7,8] and a case report has shown that carbamazepine augmentation therapy with fluoxetine is effective in the treatment of a patient with OCD and aggressive behavior who was intolerant of clomipramine monotherapy.[9]

To our knowledge, ours is the first report of effective carbamazepine augmentation therapy with clomipramine for treatment-refractory OCD. The precise mechanism for the efficacy in this case is unclear. Since carbamazepine reportedly reduces the blood level of clomipramine,[7] it is unlikely that the significant improvement in the present case is attributable to the increased clomipramine blood level caused by addition of carbamazepine. The evidence that carbamazepine can release serotonin provides one possible explanation for the effectiveness of carbamazepine augmentation therapy for OCD.[7,10] In conclusion, the present report suggests that the efficacy of this augmentation strategy may be useful in SRI-refractory OCD, although controlled studies are needed to confirm the effectiveness of carbamazepine-clomipramine combination therapy in the treatment of refractory OCD.

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Yasuhide Iwata, M.D.
Yuzo Kotani, M.D.
Ryoichi Hoshino, Ph.D.
Noriyoshi Takei, M.D.
Masaomi Iyo, M.D.
Norio Mori, M.D.
Hamamatsu University School of Medicine
Shizuoka, Japan

SSRI-TCA Combination in the Treatment of Resistant Depression

Sir: We read with interest the article by Levitt et al.[1] that showed the effect of combining the selective serotonin reuptake inhibitor (SSRI) fluoxetine and a tricyclic antidepressant (TCA) in resistant depression. Seth et al.[2] also showed that 8 cases of resistant recurrent depression were successfully treated with a combination of nortriptyline and an SSRI, although Levitt et al.[1] did not cite their article.

Levitt et al.[1] addressed an interesting question as to whether there is a specific effect of the combination in subjects who failed to respond to desipramine or imipramine and failed to respond to fluoxetine. Their conclusion was, however, that the positive clinical effect of combining fluoxetine and a TCA may be related to the plasma levels of the tricyclic compound because their responders had significantly higher tricyclic levels than nonresponders (i.e., pharmacokinetic interaction). This means that their patients did not fail to respond to desipramine or imipramine, but they received insufficient doses and/or insufficient plasma levels of these drugs for their depression.

Therefore, Levitt et al.[1] could not have answered their question as to the specific effect of the combination because their patients did not receive an adequate treatment of either desipramine or imipramine. If they attribute the specific effect of the combination to the inhibition of tricyclic metabolism by fluoxetine, resistant depression could be improved by merely increasing TCAs, without fluoxetine combination.

Thus, we believe that Levitt and colleagues should have addressed another possibility: that a sufficient combination of both serotonergic and noradrenergic reuptake inhibitors may be necessary in the successful treatment of resistant depression, which was probably brought about by the combination of desipramine or imipramine and fluoxetine (i.e., pharmacodynamic interaction) in their patients. Although no direct evidence supported this possibility in their article, recent studies[3,4] investigating the effect of venlafaxine (one of the dual inhibitors or serotonin-norepinephrine reuptake inhibitors) demonstrated the positive effect on resistant depression. Moreover, Poirier and Boyer[5] have reported some evidence of venlafaxine's superiority to paroxetine in resistant depression. These findings support this possibility.

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Takeshi Terao, M.D., Ph.D.
Warneford Hospital, University of Oxford
Oxford, United Kingdom
Naomi Ikemura, M.D.
Maudsley Hospital, University of London
London, United Kingdom

Correction

In the article "Twelve-Month Outcome in Bipolar Patients With and Without Personality Disorders" by Eduardo Dunayevich, M.D., et al. (February 2000 issue, pp. 134–139), the data in the "mood stabilizer and antipsychotic" and "mood stabilizer and antidepressant" rows in Table 3 were transposed. The corrected table is presented below. The staff regrets the error.

Table 3. Discharge Medications of 56 Subjects With and Without Personality Disorder

Medication	No Personality Disorder (N = 29)	Personality Disorder Present (N = 27)
Mood stabilizer	9	8
Antipsychotic	2	0
Antidepressant	2	0
Mood stabilizer and antipsychotic	16	15
Mood stabilizer and antidepressant	0	1
Antipsychotic and antidepressant	0	0
Combined treatment	0	1
No medications	0	2