

Letters to the Editor

Augmentation of Risperidone With Valproic Acid

Sir: The response of psychotic symptoms following the addition of valproate to typical antipsychotic medications has shown conflicting results.¹ The combination of risperidone, lithium, and valproate has been reported to be efficacious in patients with bipolar disorder.^{2,3} We report a patient with schizophrenia for whom the addition of valproic acid to treatment with a typical antipsychotic had no effect on psychotic symptomatology but for whom marked improvement occurred when valproic acid was added to risperidone.

Case report. Ms. A, a 46-year-old Chinese woman, was diagnosed with schizophrenia at age 33 and had been chronically institutionalized for the past 3 years. Despite treatment with neuroleptics from several different classes (e.g., fluphenazine, chlorpromazine, pipotiazine palmitate, haloperidol) at daily doses ranging from 1200 mg to 1600 mg chlorpromazine equivalents for at least 8 weeks each, she continued to exhibit aggressive episodes, suicidal attempts, auditory hallucinations, thought disorder, and marked social impairment. Electroconvulsive therapy had been administered on several occasions without effect. A trial of adjunctive lithium therapy was terminated after Ms. A developed a generalized skin rash. Subsequently, valproic acid (at doses up to 800 mg/day) was added to therapy with various neuroleptics (i.e., haloperidol, flupentixol, and sulpiride) without resulting improvement. Each combination treatment extended for a minimum of 2 months. Monotherapy with risperidone was then tried. Doses were gradually increased to 7.5 mg/day over a period of 9 months. Ms. A showed no improvement after 4 months of risperidone treatment at 7.5 mg/day, and the dose was subsequently increased to 8 mg/day.

After Ms. A had received this dose for 10 weeks without any improvement, valproic acid was added at a starting dose of 400 mg/day. Dosage was increased to 800 mg/day in divided doses by week 2 and maintained at this dose thereafter. She was rated weekly with the Brief Psychiatric Rating Scale (BPRS) by a psychiatrist who was blind to her treatment. Ms. A's BPRS total score was 43 before valproic acid was added and showed a steady decrease over the next 5 weeks, after which it had dropped to 26, with a further decrease to 21 by week 8. Her auditory hallucinations disappeared, and her persecutory ideas lessened significantly. At this time, Ms. A is no longer aggressive and interacts more positively with the nursing staff and patients.

Although the clinical improvement seen might be due to a spontaneous waning of Ms. A's psychosis, the considerable length of her severe and persistent symptoms argues against this explanation. The duration of risperidone treatment (more than a year) and the dosage (maximum of 8 mg/day) prior to the addition of valproic acid make it unlikely that the improvement was due to a delayed response to risperidone. Pharmacokinetic and pharmacodynamic interactions may account for the noted

effect, although the former seems unlikely as valproic acid has no inhibitory or inducing effect on cytochrome P450 2D6, which is the main metabolic pathway of risperidone.⁴ The apparent efficacy of this augmentation strategy in patients with schizophrenia needs to be verified further in controlled studies.

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Risperidone-Carbamazepine Interactions: Is Cytochrome P450 3A Involved?

Sir: De Leon and Bork¹ recently highlighted potential pharmacokinetic interactions between risperidone and carbamazepine. They presented a patient in whom carbamazepine coadministration lowered plasma levels of risperidone greater than 2-fold. Earlier, Ereshefsky² indicated that carbamazepine can induce the activities of cytochrome P450 3A (CYP3A) and possibly CYP2B. Accordingly, de Leon and Bork¹ further suggested that risperidone metabolism, which is known to involve CYP2D6,² also involves CYP3A.

However, because carbamazepine also alters the biotransformation of agents that might not be CYP3A substrates,³⁻⁵ it likely induces other enzymes. For example, carbamazepine has been reported to reduce the half-life of theophylline,⁶ which is catalyzed mainly by CYP1A2 and less by CYP2E1.⁷ Carbamazepine has also been noted to hasten nortriptyline metabolism in women.⁸ About 90% of nortriptyline disposition depends on CYP2D6, whereas the remaining 10% are mediated by CYP2C19 and CYP1A2.⁹ In addition, carbamazepine might accelerate the clearance of warfarin.^{4,5,10} When concomitant carbamazepine is withdrawn from warfarin therapy, prothrombin time may elevate, leading to clinically significant hemorrhage.^{4,5,10} The more active *S* enantiomer of warfarin is principally metabolized by CYP2C9,¹¹ which suggests that carbamazepine possibly induces CYP2C9 as well.⁴

The above suggestion that carbamazepine might possess nonspecific enzyme-induction properties should be examined further. A more thorough understanding of the enzymes induc-

ible by carbamazepine will allow better anticipation of its interactions with other drugs.⁴ Currently, whether CYP3A induction contributes to the probable interaction between risperidone and carbamazepine remains uncertain.

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Drs. de Leon and Bork Reply

Sir: We thank Drs. Lane and Chang for giving us an opportunity to clarify some concepts regarding the cytochrome P450 isoenzymes. To start, we recognize that the current knowledge in this field is far from being completely established. It is not certain which isoenzymes metabolize many drugs. Furthermore, it is not always known whether a specific isoenzyme or several isoenzymes explain a drug interaction. Carbamazepine clearly induces CYP3A, as is acknowledged by experts in the field such as Ereshefsky.¹ We are relatively familiar and have had personal clinical experience with interactions of some psychiatric drugs, but we are not as familiar with nonpsychiatric drugs. According to an extensive and recent review of pharmacokinetic interactions by Bertz and Granneman,² carbamazepine is an inducer of CYP3A and of glucuronyltransferase. Bertz and Granneman² do not affirm (or deny) that carbamazepine is an inducer of other isoenzymes, e.g., CYP1A2, CYP2C9, or CYP2C19.

Bertz and Granneman² also state that theophylline is metabolized mainly (> 70%) by CYP1A2 but that it is also metabolized by CYP2E1, CYP3A, and methyltransferase. *S*-warfarin is metabolized mainly by CYP2C9, but *R*-warfarin is metabolized by CYP1A2, CYP3A, and CYP2C9. We are more familiar with the literature on the metabolism of tricyclic

antidepressants, including nortriptyline. Researchers appear to agree that CYP2D6 hydroxylation is the main metabolic pathway for nortriptyline and other tricyclic antidepressants,^{3,4} because subjects deficient in CYP2D6 tend to develop side effects and high blood levels of tricyclic antidepressants. However, total agreement does not exist concerning the secondary metabolic pathways, including demethylation, for tricyclic antidepressants. The list described in the literature is more extensive than the one provided by Drs. Lane and Chang and includes CYP1A2, CYP2C19, and CYP3A.⁴ To summarize, CYP3A may play a role, although minor, in the metabolism of theophylline, warfarin, and nortriptyline. It is possible that the interactions of carbamazepine with these drugs may be explained by induction of CYP3A. Carbamazepine may induce other CYP isoenzymes, but we have not found specific statements in the literature describing the induction by carbamazepine of other isoenzymes, such as CYP1A2, CYP2C9, or CYP2C19.

Regarding the most important issue—whether or not risperidone is metabolized by CYP3A (in addition to CYP2D6)—we initially made our claim on the basis of the effects of carbamazepine on risperidone levels in 1 case. Currently, we have experience with 7 additional patients who are taking other CYP3A inducers or CYP3A inhibitors. These cases suggest that CYP3A is probably an important metabolic pathway for risperidone (J.B., unpublished data). It can not be completely ruled out that other CYP isoenzymes may affect risperidone metabolism since the inducers and inhibitors are not 100% pure.

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Treatment of Disequilibrium and Nausea in the SRI Discontinuation Syndrome

Sir: Serotonin reuptake inhibitors (SRIs) and venlafaxine continue to play a prominent role in the treatment of depression. Utilization of these agents, however, has been complicated by the now well-described serotonin discontinuation syndrome.^{1,2}

The manifestations of the discontinuation syndrome have been clearly outlined.^{3–10} They emerge upon abrupt discontinuation or intermittent noncompliance with an SRI. The symptoms are distressful to patients but eventually remit in 1 to 2 weeks. The reaction can be mitigated by slow tapering of the SRI or by substitution with an SRI that has a longer half-life.¹¹ If the original SRI is restarted, the discontinuation syndrome will remit.

Discontinuation symptoms are varied and include disequilibrium, gastrointestinal distress, flu-like symptoms, sleep

disruption, and sensory symptoms. Patients with the discontinuation syndrome describe a sensation of dizziness, vertigo, and ataxia and feeling "spaced out."¹² Various biological mechanisms have been postulated as factors in the SRI discontinuation syndrome.^{8,12} These include a decrease in available synaptic serotonin because of down-regulated serotonin receptors and cholinergic rebound associated with paroxetine discontinuation.

Clinically, the discontinuation syndrome can have a significant adverse effect on patient management. Patients may confuse discontinuation symptoms after an appropriate SRI trial with reemergence of depressive symptoms and thus continue medication longer than necessary. Those taking SRIs with short half-lives may prematurely stop their medication if they accidentally skip a dose, mistaking discontinuation effects for side effects.

No agents to date have been identified that can directly mitigate the discontinuation effect. The following case describes the use of ginger root in successfully alleviating disequilibrium and nausea associated with the syndrome.

Case report. Ms. A, a married white woman who worked as a travel agent, experienced an onset of major depression secondary to significant financial and family legal stress. At presentation, Ms. A described symptoms of irritability, dysphoria, fearfulness, hopelessness, and awakening during the middle of the night. She was engaged in a course of psychotherapy to deal with her stressors. The persistence of her symptoms necessitated the use of an SRI antidepressant. She was begun on sertraline, 50 mg daily, and the dose was gradually titrated to 150 mg daily. Ms. A's symptoms responded well to this regimen. An attempt to taper and discontinue sertraline after 22 months of treatment resulted in discontinuation symptoms of dizziness, irritability, and depressed mood. Ms. A was particularly troubled by dizziness and ataxia. At this time, she remembered recommending to her clients with motion sickness the use of ginger root when traveling. After sertraline was discontinued, Ms. A added ginger root, one or two 550-mg capsules t.i.d., to her regimen and reported significant amelioration of disequilibrium and nausea.

Ginger root has been widely used as an alternative agent in the disequilibrium associated with motion. The sites of action are presumed to be autonomic centers of the CNS.¹³ A local effect on the gastrointestinal tract blocking nausea feedback has also been proposed.¹⁴ Its use in seasickness and vertigo has been established.¹⁵ Since the successful treatment of disequilibrium and nausea due to SRI discontinuation with ginger root in Ms. A, I have utilized ginger root 1100 mg t.i.d. in over 20 patients at the onset of serotonin discontinuation-induced disequilibrium and nausea. All patients reported partial to complete amelioration of the symptoms within 24 to 48 hours without ginger root side effects. Treatment with ginger root should be continued for approximately 2 weeks after SRI discontinuation.

The high incidence of SRI discontinuation syndrome¹ compels clinicians to look for alternative remedies to minimize the complications associated with this useful class of antidepressants. Ginger root appears to be such a remedy.

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Irradiation Therapy Prevents Gynecomastia in Sex Offenders Treated With Antiandrogens

Sir: The only therapy that has so far been shown to be effective in the treatment of male sex offenders is long-term administration of antiandrogens.¹ Cyproterone acetate and medroxyprogesterone acetate are the most widely used substances in this context. Although this therapy seems to be an effective method in reducing the relapse rate in sex offenders, it has yet come to only limited use. The frequent development of gynecomastia, seen after long-term treatment with antiandrogens, is a probable hindrance to the more widespread use of this treatment strategy.

Gynecomastia is a well-known side effect seen in about 70% of patients receiving estrogen treatment for carcinoma of the prostate.² This side effect has been shown to be effectively prevented by pretreatment with irradiation therapy.²⁻⁴ Such pretreatment is well established and could be given without serious side effects. Since this approach is based on the assumption that the mammalian glands are sensitive to irradiation, a similar preventive effect could be expected to be obtained by irradiation therapy in sex offenders on long-term therapy with antiandrogens.

Two of our patients were on antiandrogen treatment with cyproterone acetate (275 and 300 mg, respectively, given every 14 days as a deep intramuscular injection) because of severe problems with various forms of deviant sexual behavior. They both developed, within a few months after the commencement of the treatment, slight gynecomastia. They also complained about pain and tenderness in the breasts. Both were given irradiation therapy with a single dose of 1500 cGy on each mamillary region (195 kV, 20 mA, source-skin distance = 40 cm, 0.5-mm copper filter). Three and 6 years, respectively, after

the irradiation treatment, no further development of the gynecomastia has been seen, and the pain and tenderness have been reduced to a minimum.

Gynecomastia and pain and tenderness in the breasts can cause great distress. Therefore, effective prevention of these symptoms is warranted for successful treatment with antiandrogens. Pretreatment with irradiation of the breasts is thus recommended when antiandrogens are considered in the treatment of sex offenders.

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**Safety in Overdose of Quetiapine:
 A Case Report**

Sir: Quetiapine (Seroquel) is a new atypical antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. It is a serotonin and dopamine receptor antagonist, which also has antagonistic activity at α -adrenergic and histamine receptor sites.¹ A MEDLINE review of the literature yielded no prior published reports of quetiapine overdose. Therefore, we report the case of a patient who intentionally ingested a large quantity of quetiapine.

Case report. Mr. A, a 21-year-old physically healthy African American man with a 3-year history of schizoaffective disorder, was being treated at our day program. His medications were quetiapine, 250 mg p.o. b.i.d., and fluoxetine, 60 mg p.o. q.d. Mr. A ingested 4700 mg of quetiapine and 600 mg of fluoxetine in a suicide attempt. He was brought to the emergency room, where gastric lavage was performed and activated charcoal administered approximately 4 hours after drug ingestion. Lavage returned some white pasty material, but no intact pills. Mr. A had no loss of consciousness, but became drowsy and disori-

ented to place and time. He became agitated intermittently, requiring restraints and 4 mg of lorazepam intramuscularly. Continuous cardiac monitoring for 24 hours revealed only a sinus tachycardia, with a maximum rate of 128 b.p.m. Mr. A experienced no cardiac conduction abnormalities, appreciable changes in blood pressure, respiratory depression, seizures, or extrapyramidal symptoms. Results of all blood chemistries were within normal limits; findings of serum toxicology for alcohol and illicit drugs were negative.

Eighteen hours after the overdose, Mr. A's mental status returned to a fully alert and oriented state. However, his heart rate remained elevated for 48 hours after ingestion. A plasma level of quetiapine, obtained at 60 hours postingestion, was 180 ng/mL.

Mean steady-state plasma quetiapine levels associated with typical therapeutic dosages of 300 mg or 600 mg daily have been reported as 43.9 ng/mL and 91.1 ng/mL, respectively.² Mr. A's plasma quetiapine level was higher than would be expected. Based upon an elimination half-life of 6 hours and linear pharmacokinetics, one would expect that a plasma quetiapine level at 60 hours should be approaching zero. One possible explanation is metabolic inhibition by fluoxetine, an inhibitor of CYP2D6 and CYP2C9 at therapeutic concentrations and potentially a significant inhibitor of CYP3A4 at toxic concentrations.³ Quetiapine is metabolized primarily via CYP3A4. Another possibility is that nonlinear or saturation kinetics develop when quetiapine reaches higher plasma levels. Although the patient's development of sinus tachycardia suggests a need for cardiac monitoring, the overall course and outcome of this case indicate that an overdose of quetiapine may not be highly toxic. Additional reports are needed to confirm these preliminary observations.

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