

Clozapine-Benzodiazepine Interactions

Sir: Clozapine is an atypical antipsychotic often used in the treatment of refractory schizophrenic patients. The manufacturer recommends caution when combining clozapine therapy with other CNS-active drugs, particularly benzodiazepines. Sassim and Grohmann¹ first reported two cases of severe collapse with this combination. The first patient was a 51-year-old man on diazepam 20 mg/day. He was placed on clozapine 25 mg because of nonresponse to other neuroleptics. On the first day of treatment with clozapine 25 mg, a severe collapse took place. The second patient was a 36-year-old man who was on diazepam 5 mg/day for 2 weeks and had received 30 mg of flurazepam the day before clozapine treatment was initiated. On the second day of treatment with clozapine 12.5 mg/day, the patient became delirious and collapsed, similar to the first patient. The authors then reviewed the charts of 39 patients at the psychiatric university hospital at Munich who had been exposed to this combination. They found that 3 patients (7.7%) had collapsed while undergoing treatment with clozapine plus benzodiazepine, versus only 1 patient (2.6%) treated with clozapine alone. Other side effects reported to be significantly increased with this combination were dizziness, sedation, and elevations of SGPT and GGT.

Grohmann et al.² reviewed data on 959 patients taking clozapine. Four cases of severe cardiovascular and respiratory dysregulation were observed with clozapine-benzodiazepine combinations. All cases occurred at the beginning of clozapine initiation; the common findings were unconsciousness, delirium, severe hypotension, and respiratory arrest; nevertheless, all patients recovered under intensive medical management. The investigators concluded that among the 189 patients exposed to the clozapine-benzodiazepine combination, there was a risk of 2.1% for these severe drug interactions.

Klimke and Klieser³ described the case of a 43-year-old refractory schizophrenic who was started on clozapine therapy and the dosage increased to 400 mg over 2 weeks. After 17 days of clozapine treatment, the patient refused clozapine, became agitated, and was given three doses of lorazepam 2 mg i.v. over 9 hours. The patient died in sleep that night, most probably due to respiratory arrest. Recently, Jackson et al.⁴ reported three cases of delirium on clozapine-benzodiazepine combinations. Interestingly, two of these patients were rechallenged with lorazepam and became delirious again; the third patient was not re-challenged. Bredbacka et al.⁵ described a case of severe orthostatic hypotension on treatment with clozapine-benzodiazepine combination and on clozapine alone.

According to unpublished data (data on file, Novartis Pharmaceuticals Corp.), 15,311 patients were treated with clozapine during the first 18 months of its reintroduction in the United States. About 11% of these patients received concomitant benzodiazepine therapy. Six cases of respiratory depression/arrest were reported, representing 0.31% of the clozapine-benzodiazepine group. Only two of these cases occurred in the context of beginning of treatment, while two cases involved deliberate overdose (one case of clozapine and one case of benzodiazepine overdose). In addition, two patients had prior history of myocardial infarction or "multiple cardiovascular risk fac-

tors." The Novartis data are somewhat different from those reported in the European literature insofar as most cases of severe adverse interactions did not occur at the start of treatment with clozapine; also, the incidence of respiratory arrest or cardiovascular collapse was much lower. Finally, all of these patients recovered with proper medical management. Of the more than 63,000 patients exposed to clozapine by September 1993, there were 10 reported instances of cardiorespiratory arrest within the first 3 days of clozapine therapy; "some" of the patients were taking concomitant benzodiazepines. Nonetheless, all of these patients also recovered.

The pathophysiology of life-threatening clozapine-benzodiazepine interactions is not well understood. However, it seems to be relatively specific for this combination. Benzodiazepines have been used as adjuncts in the treatment of schizophrenia. The literature on benzodiazepines in schizophrenia is somewhat divided, but tends toward negative or null effects except when anxiety symptoms predominate.⁶ The combined use of a benzodiazepine and a typical antipsychotic can cause sedation, behavioral disinhibition, exacerbation of psychosis, increase in anxiety and depression, and, at high doses, cognitive impairment.⁷ Thus, it seems that the respiratory depression and cardiovascular complications, though uncommon, are specific for clozapine-benzodiazepine combinations. It is possible that the benzodiazepines act by increasing the blood clozapine level, as clozapine itself can cause collapse due to severe hypotension in rare cases.^{2,5} Therefore, we recommend close monitoring of clozapine levels if this combination is used. Blood benzodiazepine levels are not very useful principally because of a lack of data regarding concentration response relationships for benzodiazepines.⁸

Another relevant issue is the role of individual risk factors as it seems that patients with preexisting cardiovascular, liver, or organic brain disease may be more vulnerable to this adverse interaction (reference 3 and data on file, Novartis Pharmaceuticals Corp.). Also, individuals with obesity or heart failure are at an increased risk of adverse reactions with clozapine.⁹ Thus, in patients with these risk factors, appropriate investigations, e.g., ECG, liver function tests, and cardiology consultation, may be needed before starting treatment. During treatment, frequent—at least once weekly—monitoring of clozapine levels is in order.

Most authorities would discourage the combined use of clozapine and benzodiazepines especially—but not exclusively—with their concurrent initiation.^{7,10,11} Similarly, in view of the above case reports, it may be dangerous to start clozapine therapy in the context of established benzodiazepine treatment. This recommendation is based on the observation that most serious adverse interactions reported in the literature occurred at the start of this combination or when clozapine was added to an established benzodiazepine regimen. However, if a therapeutic dose (> 300 mg, as per manufacturer) of clozapine has been achieved with an acceptable plasma level, benzodiazepines can be cautiously added since this scenario has not been associated with respiratory depression or cardiovascular complications. Another approach can be to slowly taper the previous antipsychotic at the start of clozapine treatment or to combine clozapine with a small dose of a conventional neuroleptic at the initiation of treatment. The rationale here is that as clozapine is slowly in-

creased to a therapeutic level, this strategy may prevent the emergence of severe anxiety or agitation that may necessitate the addition of benzodiazepines. Obviously, future research will help to clarify these issues.

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Mania From Dexfenfluramine

Sir: A wide range of medications has been reported to induce manic episodes. These include stimulant drugs, such as dextroamphetamine. A drug recently approved for treatment of obesity, dexfenfluramine, is not reported to have adverse effects of mania, hypomania, psychosis, or other similar behavioral effects. A review of published literature yielded only one relevant clinical article that reported a study in which fenfluramine was used to augment the effects of desipramine in refractory patients. One patient with unipolar psychotic melancholia exhibited a clear worsening of her dysphoria, suicidal ruminations, hallucinations, and oppositional behavior, coupled with a refusal to eat or take fluids.¹ We report the case of a woman with bipolar disorder who developed mixed mania shortly after prescription of dexfenfluramine and the cessation of the mixed mania after discontinuation of dexfenfluramine.

Case report. Ms. A, a 56-year-old white woman, had had bipolar II disorder since age 18. She had been married and di-

vorced twice, the last time more than 20 years ago. She had worked as a librarian in the past but had been unable to for the last 10 years secondary to her illness. She had been living with her mother for many years. During the course of her illness, depressive episodes predominated, with over 10 severe major depressive episodes and nine suicide attempts, most by overdose. Depressive symptoms had included depressed mood, pessimism, guilt, waking during the night, and social withdrawal, with most episodes lasting less than a month, but several requiring hospitalization. Hypomanic episodes had been characterized by elated mood, speeded thoughts, impaired judgment, promiscuous sexuality, and reduced need for sleep. During a 6-year period of treatment with one of us (C.L.B.), after the retirement of her previous psychiatrist, her regimen was gradually evolved to a stable dosage of divalproex 1000 mg/day, carbamazepine 600 mg/day, molindone 50 mg/day, zolpidem 20 mg h.s., and occasional alprazolam 0.5 mg for anxiety. On this regimen, she had functioned well for 4 years, with only occasional increased sleep difficulty and increased symptomatology following efforts to reduce molindone (impaired judgment, tearfulness, fearfulness, and disturbed insight) or divalproex (mild rapid-cycling mood episodes, partial panic attacks, and migraine-type headaches).

Ms. A was mildly overweight and had been unsuccessful at reducing her weight by diet and exercise. With the introduction of dexfenfluramine, she asked that she be prescribed the drug. The psychiatrist explained the general experience of anorectic agents as historically associated with precipitation of mania and mood destabilization, but that no evidence of such disturbances with dexfenfluramine had been published. Despite his general discouragement of the trial and explanation of possible risks, Ms. A wished to try dexfenfluramine. She commenced treatment with 15 mg daily, which was increased after about 10 days to 15 mg b.i.d. Within 2 weeks of commencing treatment, she began to have distinct mood cycles, usually of less than a day's duration, often somewhat provoked by perceived criticism from her mother. Her symptoms included rapid onset and escalation of anger, rageful and even homicidal thoughts toward her mother, verbally but not physically expressed anger, racing thoughts, severely impaired concentration, and labile mood with easy shifts into tearfulness. She was unable to restrain her escalated, out-of-control mood and affect, which heretofore she had done readily. Her sleep changed minimally with continued use of zolpidem. She became more anxious and mildly agitated. She recognized the inappropriateness of her rapid mood shifts and hostility, and felt increasingly guilty about these. On several occasions, she reverted to a long quiescent pattern of alcohol abuse, once drinking over 500 mL of spirits in an effort to quiet her out-of-control temper. The patient, who was usually fully adherent and cooperative with the overall treatment plan, uncharacteristically did not inform the psychiatrist of the disturbance for 6 weeks, at least in part because she anticipated that the dexfenfluramine would be discontinued, which she felt was contributing to a 7-lb (3-kg) weight loss during the period. On examination, her speech was rapid, her motor behavior agitated, and her mood distraught with frequent tearfulness, and she was feeling quite guilty. Cognition was not impaired. The dexfenfluramine was discontinued, after discussion regarding its likely role in her symptomatology. Alprazolam dosage was increased to 2 mg b.i.d., but other medications were unchanged. Within 3 days, her mixed manic, rapid-cycling state had improved, and within 2 weeks, she was fully back to her baseline status. Following the episode, her recollection of the period was faulty. She was unable to recognize the severity of her impairment during the time.

In conclusion, psychiatrists and other physicians treating patients with dexfenfluramine should be aware of the possible, albeit not conclusively established, risk of worsening the course of bipolar disorder with this drug.

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Effects of Olanzapine on Polydipsia and Intermittent Hyponatremia

Sir: The syndrome of polydipsia and intermittent hyponatremia is a well-documented problem affecting psychotic patients. Recent studies, however, indicate the treatment with atypical antipsychotic agents is associated with decreased water consumption and normalization of serum sodium levels.¹⁻⁴ Olanzapine recently became available in the United States and is characterized as a selective monoaminergic antagonist with high affinity binding to serotonin, dopamine, muscarinic, histamine, and adrenergic receptors (package insert, 1996). Presented is a single case, included in a 12-month open-label study, demonstrating improvement in polydipsia and serum sodium levels with olanzapine at therapeutic dosage levels.

Case report. Ms. A is a 44-year-old woman with a 25-year history of schizophrenia, paranoid type and 32 hospitalizations. Ms. A's past medical records documented a positive history for polydipsia with intermittent hyponatremia during treatment with conventional antipsychotic agents. Abnormalities in serum sodium levels (ranging from 129 to 133 mEq/L) were documented, beginning approximately 5 years after her first acute episode. Her polydipsia had been controlled during inpatient stays with behavioral measures and restriction of fluid intake. Despite encouragement, she had not maintained normal sodium levels for more than 4 months continuously. Records showed numerous trials of conventional antipsychotics, including chlorpromazine, thioridazine, thiothixene, perphenazine, haloperidol, and trifluoperazine, as well as a confirmed history of medication noncompliance. Previous pharmacotherapy displayed limited effect on positive and negative symptoms. The patient never received a trial of clozapine despite her refractory psychosis and positive history for polydipsia. Ms. A was receiving haloperidol decanoate 50 mg i.m. q 1 week at the time of our initial contact.

After one dosing cycle of haloperidol decanoate (1 week) was withheld, Ms. A was seen for her first study visit. Results of a physical examination and ECG were normal, and all laboratory findings were within normal limits, including serum sodium level of 136 mEq/L and urine specific gravity of 1.010. The baseline Positive and Negative Syndrome Scale (PANSS) score was 125, and the baseline Abnormal Involuntary Movement Scale (AIMS) score was 21. On Visit 2, Ms. A was started on olanzapine 10 mg at bedtime (48 hours later). She was scheduled for subsequent visits every 7 days for the next 6 weeks, as indicated by the study design. On Visit 3, olanzapine was increased by 5 mg/day (15 mg q.h.s.) due to persistent psy-

chotic symptoms. On Visit 4, the family reported that Ms. A had again begun to drink water and iced tea excessively. They reported increased fluid intake (>5 liters per day), irritability at home, and nocturnal enuresis. Ms. A admitted to increased fluids and feelings of nausea, stating that she felt "sick to her stomach" and that the increased fluids "helped to settle her stomach." Laboratory findings revealed a sodium level of 131 mEq/L (normal, 135-147) with a urine specific gravity of 1.002. Olanzapine was increased to 20 mg at bedtime. Within 5 days, the family reported a decrease in water intake, improvement in mood, and cessation of enuresis. Laboratory findings from Visits 5, 6, and 7 were within normal limits, with sodium levels of 138, 139, and 135 mEq/L, respectively. Results of 6-month follow-up laboratory work, including Visits 8 through 13, confirmed stabilization of serum sodium between 135 and 139 mEq/L and urine specific gravity between 1.010 and 1.020.

The PANSS also showed a marked reduction from 125 to 44 over the 6-month period. AIMS scores decreased from 21 to 5 during the same period. Subsequently, the patient and her family have reported a continuing reduction of fluids and elimination of enuresis and nausea. According to the family, 6 months is the longest time that Ms. A has gone without water loading.

In this case, unlike conventional medications, olanzapine appears to have substantially reduced psychotic symptoms and prevented the recurrence of polydipsia and intermittent hyponatremia. Further studies of the use of olanzapine for polydipsia and hyponatremia will be important in determining the relative efficacy and safety in the treatment of this syndrome.

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A Possible Pharmacokinetic Interaction Between Fluoxetine and Acetylsalicylic Acid

Sir: In rare instances, fluoxetine has been shown to cause skin rashes.¹ During fluoxetine treatment, our patient experienced hives that resolved after antidepressant discontinuation, only to recur when the patient took acetylsalicylic acid (ASA, aspirin) for pain relief.

Case report. A 44-year-old healthy, physically active, white man developed major depressive disorder after a period of extreme stress. He was started on an oral dose of 20 mg of fluoxetine per day. Early during the treatment, the patient complained of transient diarrhea and headache. On the 23rd day of treat-

ment, the patient developed hives believed to be due to fluoxetine, which was discontinued. The patient was given an oral dose of 25 mg of diphenhydramine as needed. The hives persisted for 11 days after the discontinuation of fluoxetine.

The treatment plan was to wait for at least 48 hours after the disappearance of all hives and then to start a structurally dissimilar serotonin selective reuptake inhibitor (SSRI) such as sertraline. However, 36 hours into the hive-free period, the patient took an oral dose of two tablets (650 mg) of acetylsalicylic acid for an unrelated painful joint condition, and the hives reappeared. Despite the recurrence of hives, he continued to take two tablets of ASA every 6 hours. The hives eventually resolved. At that point, sertraline was started after a 48-hour hive-free period without subsequent problems.

According to the *Physicians' Desk Reference* (PDR),¹ skin rash was reported by 2.7% of the patients using fluoxetine and 1.8% of the patients taking placebo in clinical trials. The appearance of hives in our patient on the 23rd day of treatment and persistence of hives for 11 days after the discontinuation of fluoxetine are consistent with a causal role for fluoxetine and/or its metabolite norfluoxetine because of their long half-lives (3–5 and 7–15 days, respectively). Further, ASA and its metabolite salicylic acid may have altered the protein binding of fluoxetine and/or norfluoxetine, resulting in higher free plasma levels of fluoxetine and/or norfluoxetine sufficient to trigger a recurrence of the hives.

ASA may alter protein binding by two mechanisms. First, ASA itself acetylates serum albumin, which alters binding of other drugs to the protein.² Second, the deacetylated ASA, i.e., salicylic acid, is bound strongly to serum albumin³ and can displace other drugs from their protein binding sites. Chronic salicylate use has been shown to significantly reduce the plasma protein binding of acetazolamide in four volunteers via competitive inhibition of protein binding by salicylates.² ASA also increased the plasma levels of unbound valproic acid.³ Fluoxetine is strongly bound to plasma proteins,⁴ including albumin and α_1 -acid glycoprotein, and the extent of protein binding appears to be independent of plasma concentrations of fluoxetine.⁵

A careful literature search produced no reports in which one drug worsened an allergic response to another drug. However, a case report documents a severe allergic reaction and shock resulting from coadministration of ASA and sunflower seeds in a patient who had no allergic reaction with ASA and developed only oral paresthesia with sunflower seeds when the two agents were administered separately.⁶ Based on this case report, there is a possibility that a pharmacodynamic interaction occurred between ASA and fluoxetine, in which ASA may have sensitized the patient to develop hives during the falling plasma levels of fluoxetine after it was discontinued. However, the similarities in appearance and distribution of the hives with fluoxetine and then with ASA suggest a pharmacokinetic interaction as explained above.

The rarity of this phenomenon in clinical practice may be due to the fact that the incidence of skin rash among patients taking fluoxetine is 2.7%, which is only 0.9% greater than the incidence with placebo according to the PDR.

Levels of acute phase proteins (e.g., α_1 -acid glycoproteins and serum albumin) change in stressful situations,^{3,7} which may result in an increased protein binding and decreased free fraction of protein bound drugs like fluoxetine. Similarly, a decrease in the level of stress may decrease the protein binding and increase the free fraction of fluoxetine. However, the patient continued to suffer from considerable stress during fluoxetine treatment and after it was discontinued. Thus, it is unlikely

that the hives developed secondary to changes in the plasma protein levels due to altered stress.

If another highly protein bound drug had been given instead of ASA, as was the plan, the hives might have recurred for the same reason (e.g., displacement of fluoxetine and/or norfluoxetine). However, the conclusion might have been that the patient was allergic to the new SSRI as well as fluoxetine, resulting in an unnecessary switch to another class of antidepressants. This case report suggests that caution is needed whenever highly protein bound drugs are used together. It may be better to wait longer than the usual 48 hours after the resolution of an allergic reaction before switching to another drug, especially if it is highly protein bound and has a long plasma half-life.

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Asystole in ECT

Sir: In an excellent discussion of asystole in electroconvulsive therapy,¹ Dr. McCall makes a number of useful suggestions to minimize the likelihood that asystole will occur. I would like to amplify his treatment recommendation of intravenous atropine injection. Without cardiac function during asystole, atropine administered through a peripheral vein will not reach the heart unless “pushed” by a 20- to 30-mL fluid bolus followed by elevation of the arm. However, there is no certainty that the atropine will reach the heart even with this maneuver in the absence of circulation. External cardiac massage should also be initiated to assist the atropine in reaching its intended site of action. If intravenous access is compromised, endotracheal administration of atropine can be used. Transcutaneous cardiac pacing should be performed immediately if atropine does not overcome the asystole.

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