

Letters to the Editor

Amitriptyline: Dual-Action Antidepressant?

Sir: The hypothesis that dual mechanisms of action on serotonin and norepinephrine reuptake confer superior efficacy for antidepressant action is of such importance that it is appropriate to subject the evidence for it to close and skeptical scrutiny.

Thase and Ninan^{1,2} have joined Freemantle and colleagues³ in suggesting that amitriptyline is of such superior efficacy and has dual action.

The spectrum concept of serotonin toxicity (serotonin syndrome) is derived from prospectively gathered clinical data and leads to a unifying interpretation of serotonin effects in 3 clinical situations: (1) side effects, (2) toxicity in overdose, and (3) fatalities from serotonergic toxicity caused by interactions with monoamine oxidase inhibitors (MAOIs).^{4,5} That interpretation, in turn, can be used to make deductions about the probable in vivo potency of a drug's serotonergic effects (i.e., a drug that possesses none of the above 3 properties may not have clinically significant serotonergic effects). Gillman⁵ and Whyte and Dawson⁶ have constructed a hierarchy for the likelihood of the development of serotonin toxicity for a range of drugs (for detailed explanation and further references, see Gillman⁵).

If we compare amitriptyline and clomipramine, we find the following characteristics: (1) serotonin side effects at therapeutic dose: amitriptyline, none; clomipramine, frequent; (2) serotonin toxicity in overdose (mild-to-moderate severity): amitriptyline, none; clomipramine, frequent; and (3) serious or fatal serotonin toxicity if mixed with MAOIs: amitriptyline, none; clomipramine, frequent.

These differences also match in vivo measures of serotonin reuptake inhibitor potency, e.g., platelet serotonin content, as well as receptor data⁷ (clomipramine, potent; amitriptyline, weak) and clinical effect (efficacy in obsessive-compulsive disorder: amitriptyline, none; clomipramine, excellent). On all of these indices, amitriptyline appears nonserotonergic in humans at any dose level (indeed, all the same arguments apply equally to another so-called dual-action drug, mirtazapine⁵).

It is challenging to match theory and practice in this area, and it may still be that amitriptyline has significant effects on serotonin when treating depression, but substantive evidence needs to be adduced for such a notion to remain convincing, or even sustainable.

Dr. Gillman reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Dr. Thase Replies

Sir: Dr. Gillman calls me to task for uncritically accepting the hypothesis that amitriptyline's antidepressant efficacy is linked, at least in part, to inhibition of reuptake of both serotonin and norepinephrine. I plead guilty to the charge, with mitigating circumstances. Twenty years ago, Baldessarini¹ concluded that clomipramine was 10 times more serotonergic than amitriptyline. As outlined by Dr. Gillman, differences in models of serotonergic toxicity clearly distinguish between clomipramine and the other tertiary amine tricyclic antidepressants (TCAs), especially the greater lethality of clomipramine when used in proximity to an irreversible, nonselective monoamine oxidase inhibitor. It is also true that clomipramine has established efficacy in obsessive-compulsive disorder, whereas amitriptyline and imipramine do not.

There is, however, no evidence that clomipramine is significantly more effective as an antidepressant than the other tertiary amine TCAs. Moreover, in Anderson's² meta-analysis of 25 inpatient studies, both amitriptyline and clomipramine were significantly more effective than selective serotonin reuptake inhibitors. Interestingly, Anderson's² results also suggested that the tertiary amine TCAs held a similar advantage over maprotiline, desipramine, and nortriptyline (i.e., drugs that are presumed to be almost exclusively noradrenergic) in studies of hospitalized patients. Lastly, the results of the recent meta-analysis by Barbui and Hotopf³ indicated that amitriptyline can still be considered to be the standard of efficacy against which other antidepressants can be tested.

It is possible that both positions are true: amitriptyline has efficacy advantages for severe depression, but this effect is not due to dual reuptake inhibition. Perhaps blockade of α_2 heteroreceptors, postsynaptic serotonin-2 receptors, or histamine receptors is implicated (in combination with potent inhibition of norepinephrine reuptake).

Consistent with this notion, mirtazapine has been shown to facilitate serotonergic neurotransmission in studies measuring cell firing rates, even though it does not have meaningful inhibitory effects on serotonin reuptake.⁴

Table 1. Characteristics and Clinical Course of 6 Dementia Patients Treated With Donepezil^a

Case	Gender	Age (y)	Type of Dementia	HDS-R Score ^b	Visual Hallucinations	Clinical Course	
						HDS-R Score ^c	Visual Hallucinations
1	F	81	DLB	13	Ladies, children	Improved to 20	Disappeared within 2 days
2	F	82	Mixed	12	Dead husband	11	Disappeared within 3 weeks
3	F	73	Mixed	24	Grandchildren	24	Disappeared within a month
4	M	80	DLB	17	Scorpion, visitors, smoke, children, and other images	Fluctuated from 13 to 8	Decreased
5	M	79	Vascular	15/25	Dinner, faces, flowers, trees, animals, mosaic pavement	16/25	Decreased
6	F	77	Alzheimer's	13	Old friends, dead relatives, thieves, and other images	15	Were unchanged

^aAll patients received donepezil doses of 3 to 5 mg/day. Case 3 experienced mild light-headedness with a 5-mg/day dose; the side effect was lessened by a dose reduction to 3 mg/day.

^bHighest possible score on the HDS-R is 30; lower scores reflect poorer cognition. For case 5, the highest possible score was 25 because the patient was blind and could not perform items that required visual acuity.

^cRecorded after approximately 1 month of treatment.

Abbreviations: DLB = dementia with Lewy bodies, F = female, HDS-R = Hasegawa Dementia Scale Revised, M = male.

I agree that it is only a hypothesis that the greater treatment efficacy of amitriptyline, clomipramine, and venlafaxine⁵ is attributable to "dual" reuptake inhibition. Hopefully, methods to visualize norepinephrine transporter occupancy in the living brain will soon permit more definitive tests of this hypothesis.

Dr. Thase has financial associations with many companies that produce psychoactive agents. The associations include receipt of research support, consultancies, and participation in speakers bureaus and advisory boards.

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Can Donepezil Be Considered a Mild Antipsychotic in Dementia Treatment? A Report of Donepezil Use in 6 Patients

Sir: Elderly people often experience visual hallucinations in association with such conditions as dementia, Charles Bonnet syndrome, and delirium.¹ It is well known that elderly patients with dementia are sensitive to antipsychotic drugs. Several reports indicate that both typical antipsychotics² and atypical antipsychotics such as risperidone³ and olanzapine⁴ induce serious side effects in elderly psychiatric patients, particularly in dementia with Lewy bodies (DLB), which is often associated with

visual hallucinations. On the other hand, donepezil, a selective acetylcholinesterase inhibitor, has been reported to improve visual hallucinations in DLB⁵⁻⁷ and Parkinson's disease⁸ without severe side effects.

In the present study, 6 patients suffering from dementia with visual hallucinations are described to illustrate the effects of donepezil on visual hallucinations and to investigate the effects of donepezil on cognitive function.

Method. All 6 cases in this naturalistic clinical study were consecutively diagnosed and treated between November 2000 and March 2003 by one of the authors (T.T.). The patients' characteristics are summarized in Table 1. Clinical psychiatric diagnoses were made according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), and consensus guidelines for the clinical and pathologic diagnosis of DLB.⁹ Assessment of cognitive function was performed using the Hasegawa Dementia Scale Revised (HDS-R; measures orientation, memory, calculation, and other variables; highest possible score is 30, lower scores reflect poorer cognition),¹⁰ which is similar to the Mini-Mental State Examination (MMSE).¹¹

Results. The subjects' clinical courses are summarized in Table 1. Three of 6 cases (cases 1, 2, and 3) reported complete resolution of visual hallucinations within a month of beginning treatment with donepezil. Two cases (4 and 5) experienced partial response to donepezil, and 1 case (6) experienced no reduction in visual hallucinations. Thus, donepezil produced at least partial reduction of visual hallucinations in 5 of 6 cases. In addition, no side effects were associated with donepezil other than mild light-headedness in case 3, which occurred at a dose of 5 mg/day. In this instance, decreasing the patient's donepezil dose to 3 mg/day reduced the light-headedness.

In comparison to the reduction of visual hallucinations observed in 5 cases, cognitive function as measured by the HDS-R remained almost unchanged in 4 of 6 cases (cases 2, 3, 5, and 6) and was exacerbated in 1 case (case 4). Only 1 case (case 1) showed cognitive improvement along with resolution of visual hallucinations, but during the subsequent 2½ years, the patient's cognitive function declined despite the remission of visual hallucinations. As such, a clear discrepancy between improvement in visual hallucinations and changes in cognitive function is apparent.

Discussion. It seems likely that the effects of donepezil on visual hallucinations are independent of its effects on cognition, which is in accordance with the recent study by Fabbri et al.⁸ showing that although donepezil improved hallucinations and

delusions in 8 patients with Parkinson's disease, their MMSE scores did not change.

In conclusion, the present preliminary findings suggest an effect of donepezil on visual hallucinations that may be independent of its action on cognitive function. As such, donepezil may be regarded as a mild antipsychotic drug—at least in dementia. Further controlled trials are required to confirm the unique action of donepezil in the elderly.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Mania From Dose-Related Ziprasidone Augmentation of an SSRI

Sir: Ziprasidone, a new atypical antipsychotic, is unique in its receptor affinities when compared with other atypical agents. Like its atypical predecessors, it antagonizes both 5-hydroxytryptamine (5-HT_{2A}) and dopamine (D₂) receptors. However, it is unique in that it possesses agonist activity at 5-HT_{1A} receptors and antagonist activity at 5-HT_{1D} receptors, as well as serotonin and norepinephrine reuptake inhibition of similar potency to imipramine and amitriptyline. This profile confers antidepressant and anxiolytic activity, respectively, and makes ziprasidone potentially beneficial in patients with major depression with anxiety who require antipsychotic augmenta-

tion.^{1,2} We present a case in which a patient with a clinical profile of depression and anxiety experienced mania despite receiving the low doses of 20 mg and 5 mg but not while receiving 2 or 3 mg of ziprasidone added to her antidepressant. Although the patient had taken numerous other medications, they were held stable during each atypical antipsychotic trial.

Successful selective serotonin reuptake inhibitor (SSRI) augmentation with atypical antipsychotics in nonpsychotic major depression^{3,4} as well as in severe mood disorders has been described.^{5,6} Ziprasidone augmentation was implemented in a patient with severe, refractory major depression and generalized anxiety disorder.

Case report. Ms. A is a 52-year-old, divorced, white, female mother of 3 with a history of DSM-IV major depressive disorder, generalized anxiety disorder, recurrent panic disorder without agoraphobia, alcohol dependence in remission, and severe asthma and chronic obstructive pulmonary disease (COPD). She denied any history of hypomania or mania, but her family history was positive for bipolar disorder in a female cousin. The symptoms of her panic disorder and COPD would often overlap and necessitated close coordination of her care among her treatment providers and the emergency department staff. As an illustration, she presented to the emergency room 10 times in a 2-week period. Since she had severe COPD and panic disorder, hypoxemia needed to be in her differential diagnosis. However, her pulmonologist and primary care physician deemed depression and anxiety to be the most frequent factors leading to emergency department visits.

Ms. A's nonpsychiatric medications included vitamins C and D, calcium, estradiol, prednisone, ipratropium bromide inhaler, albuterol, and ipratropium bromide nebulizer. She frequently displayed somatization and was highly fearful of the risk of side effects of medications. During the most recent year, Ms. A received, in varying combinations and therapeutic doses, fluoxetine, alprazolam, hydroxyzine, risperidone, gabapentin, valproic acid, paroxetine, quetiapine, and nefazodone. The combination of quetiapine, nefazodone (a 5-HT₂ antagonist with serotonin reuptake inhibition properties), and alprazolam did not ameliorate her anxiety with insomnia and was self terminated after a 3-day trial. Alprazolam was continued with fluoxetine, 20 mg daily. Risperidone augmentation was attempted at 0.25 mg b.i.d. for 4 days, then 0.5 mg b.i.d. Within a few days, Ms. A became manic with enormous energy, grandiosity, racing positive thoughts, excessive mood elevation, disinhibition, and talkativeness. She spent \$250 impulsively when she could ill afford it. Her mania resolved within days after the risperidone dose was eliminated.

Approximately 2 months later, ziprasidone, 20 mg, was added to her existing alprazolam, 4 mg, and paroxetine, 20 mg. Within a few days she experienced more severe mania than she had with risperidone. She hammered nails into her walls excessively and for irrational reasons, planted several plants (both behaviors thought to be excessive and bizarre by her family), with generally increased goal-directed activities. She spent more money than she did previously, had an elevated mood, racing thoughts, talkativeness, grandiosity, and impaired judgment. Ziprasidone was discontinued and her mood returned to baseline within a few days. Paroxetine was subsequently reduced to 10 mg, and she was rechallenged with ziprasidone lowered to 5 mg (estimated by pouring off 75% of the contents of the 20-mg capsule). She quickly experienced a recurrence of manic symptoms similar to her previous exposure to ziprasidone. She described herself as "flying." She began smoking 40 cigarettes per day despite her COPD and contrary to medical advice. Ziprasidone was discontinued with subsequent exacerbation of depression and anxiety within days. After discontinuing paroxetine,

ziprasidone, 5 mg q.d., alone was begun. No mania occurred with ziprasidone, 5 mg, alone; however, panic attacks returned, so ziprasidone was discontinued, and paroxetine was resumed at 10 mg daily. Because of the patient's early experience of relief of her depression and anxiety with ziprasidone before evolving into mania, lower doses of ziprasidone were added to 10 mg of paroxetine using specially compounded 1-mg capsules of ziprasidone in an attempt to provide symptom relief without exacerbation of mania. Ziprasidone, 2 to 3 mg, plus paroxetine, 10 mg, provided modest but substantial improvement of her depression and anxiety symptoms without causing mania. This improvement on ultra-low-dose ziprasidone augmentation of her SSRI persisted for weeks, giving her substantial relief and improved quality of life until her pulmonary condition irreversibly deteriorated. Therefore, the ultimate long-term stabilizing nature of this approach is not known.

This case provides evidence for induction of mania by dose-related ziprasidone augmentation of an SSRI, which also occurred in this patient with risperidone but not with quetiapine. The very-high to high binding affinity for the 5-HT_{2A} receptor as well as the 5-HT_{2C} receptor antagonism that is common with ziprasidone and risperidone, but not quetiapine, could be considered as a possible mechanism for causing mania in this patient. Ziprasidone additionally has serotonin and norepinephrine reuptake inhibition potency similar to imipramine and amitriptyline. Although the ratio of 5-HT₂ receptor to D₂ receptor hypothesis has been suggested to influence mood state,⁷ this ratio of antagonism only partially explains dose-related effects on mood. As in the case we have reported, ultra-low doses of ziprasidone augmentation relieved depression without causing mania. We would suspect that within the low-dose ziprasidone range that effects a larger 5-HT₂:D₂ ratio than the ultra-low dose, the amount of drug used would influence the degree of antidepressant effect, as is the case with other drugs with antidepressant properties. In this patient's case, too much ziprasidone (although in the low-dose range) caused the patient to cross the line into mania.

Further reports would be useful to determine if the new atypical antipsychotics have different risks of treatment-emergent mania. All 3 atypical antipsychotics mentioned in this report have been shown with hundreds of patients to be superior to placebo in the treatment of mania. In these mania treatment studies, standard doses, not ultra-low doses, were used. In standard doses, the 5-HT₂:D₂ ratio would have more D₂ antagonism than in the ultra-low doses. Therefore, understanding the induction of mania as a function of the pharmacodynamic properties of a drug that may differ at various doses or as a function of interaction with other drugs would be important. Other case reports have suggested that ziprasidone causes mania or hypomania: (1) causes hypomania as monotherapy in depression,⁸ (2) causes mania despite combination with divalproex in a patient with schizoaffective disorder, bipolar type,⁹ and (3) causes mania as monotherapy in a schizophrenic patient.¹⁰ Ours is the first report of mania with ziprasidone as an augmentation to an SSRI antidepressant in a patient with depression, generalized anxiety disorder, and panic disorder and with an apparent dose relationship to the manic effect. It also would be useful to have more systematic study of the benefit of ziprasidone augmentation in nonpsychotic major depression and to determine optimum doses for this strategy, as ziprasidone appears to exhibit many properties that are known to be effective in the treatment of depression and anxiety.

The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Successful Treatment With Clozapine at Higher Doses After Clozapine-Induced Priapism

Sir: It has been estimated that 15% to 45% of all priapism cases are caused by medications, with psychotropic drugs being commonly implicated.¹ Psychotropic-induced priapism is believed to be caused by the central α_1 -adrenergic antagonism of these medications.² Recent reports have documented priapism in patients treated with olanzapine,³ risperidone,⁴ ziprasidone,⁵ and clozapine.⁶⁻⁸

There is a reluctance to reinstate clozapine treatment in patients who develop priapism while on treatment with that agent. However, in treating severely and chronically mentally ill individuals, clozapine is seen as a last resort in alleviating psychotic symptoms.

A review of the literature on clozapine (a MEDLINE search using the keywords *clozapine* and *priapism* with no year or language limits) shows 3 reports of retreatment with clozapine after occurrence of priapism.⁶⁻⁸ One patient had 2 episodes of priapism when retreatment at lower clozapine doses was attempted.⁷ Another patient became noncompliant with complete blood count monitoring after retreatment, and clozapine was discontinued.⁸ The final patient was successfully reexposed to clozapine without a recurrence of priapism. His final clozapine dose was one half his original dose, and there was no discussion in the report as to whether his priapism had led to irreversible impotence.⁶

To the author's knowledge, this is the first report of successful retreatment of a patient with clozapine at doses higher than the dose that originally led to priapism, after determination that the patient's priapism had not caused irreversible impotence.

Case report. Mr. A is a 40-year-old man meeting DSM-IV diagnostic criteria for schizoaffective disorder who had recurrent symptoms of paranoia, auditory hallucinations, and delusions. Multiple trials of traditional neuroleptics, risperidone, and olanzapine, in combination with mood stabilizers, did not alleviate his symptoms. A clozapine trial was initiated, and the patient's dose was gradually increased to 300 mg/day. His psychotic symptoms abated, but unfortunately he developed priapism 2 months after initiation of clozapine, with a sustained erection lasting approximately 20 hours. Nonsurgical intervention led to the alleviation of priapism, and a follow-up evaluation with a urologist confirmed that Mr. A was not impotent. Clozapine was discontinued, and the patient's psychotic symptoms returned. Mr. A was treated with quetiapine (doses of up to 800 mg/day) for 5 weeks, with no resolution of his psychosis.

Mr. A frequently requested to be placed back on clozapine treatment, and after consultations and discussion of risks and benefits, treatment with clozapine was reinitiated. Mr. A's dose was slowly increased back to 300 mg/day over a 3-month period, with no recurrence of priapism. However, his psychosis did not adequately resolve with 1 month of treatment at that dose, so the dose was increased further to 400 mg/day over a 1-month period, with adequate resolution of his psychotic symptoms and no recurrence of priapism. He was successfully discharged from the hospital after being continually hospitalized for 18 months.

This case report describes successful treatment of an individual's severe psychotic symptoms with a clozapine dose that was higher than the dose that originally caused priapism.

With careful risk-benefit analysis and informed consent, this option should be considered for patients with refractory psychosis who have experienced clozapine-induced priapism.

Dr. de Nesnera reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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