Donepezil for Psychotropic-Induced Memory Loss

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Background: Donepezil is an acetylcholinesterase inhibitor marketed for treatment of memory loss and behavioral deterioration associated with the acetylcholine deficit of Alzheimer's disease. We investigated the utility and tolerability of donepezil in nongeriatric affective illness for treatment of psychotropic-induced memory loss, dry mouth, and constipation.

Method: Nondemented outpatients with stabilized DSM-IV affective illness took 5 mg/day of donepezil for 3 weeks and then increased to 10 mg/day in open trials. Self-rating scales of target symptoms were completed by patients before and 3 to 4 weeks after starting each dose condition. Patients who chose to continue donepezil therapy returned for clinical monitoring every 4 to 8 weeks.

Results: Eleven women and 11 men (mean ± SD age = 45.4 ± 8.5 years) completed donepezil trials. Nineteen patients with memory loss rated improvement while taking 5 mg/day of donepezil ($p < .001$); subsequently, 6 rated further improvement with 10 mg/day ($p = .057$). Donepezil, 5 mg/day, also reduced ratings of dry mouth ($N = 16$; $p < .001$) and constipation ($N = 11$; $p < .05$). Side effects included insomnia, nausea, vomiting, and diarrhea; surprisingly, 2 bipolar patients became manic within hours of starting donepezil. Sixteen patients (72%) continued donepezil for an average of 7 months. Consideration of family histories suggested that donepezil response in affective illness may be an early indicator of vulnerability to dementia of the Alzheimer's type.

Conclusion: (1) Donepezil can reduce memory loss, dry mouth, and constipation in nongeriatric affective patients, but may trigger mania; and (2) long-term follow-up will reveal the predictive value for dementia of donepezil's memory restoration in nongeriatric subjects.

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Acetylcholine plays complex neurophysiologic roles in affective illness, memory disorders, and the regulation of sleep.[1–3] Blockade of acetylcholine can cause the side effects experienced by many individuals who take psychotropic medications. Short-term memory loss, dry mouth, and constipation are common and irksome anticholinergic side effects. Treatment of these side effects with cholinergic agents such as the cholinomimetic bethanechol[4] often provides inadequate relief or causes other side effects,[5] resulting in dissatisfaction for both patient and clinician.

The acetylcholinesterase inhibitor donepezil increases available acetylcholine by blocking its enzymatic degradation.[6–8] Donepezil is marketed for the treatment of Alzheimer's disease, specifically targeting the short-term memory loss and behavioral abnormalities associated with the progressive death of cholinergic neurons.[7–9] Donepezil has not previously been studied in nondemented, nongeriatric individuals, and its potential therapeutic benefits and risks beyond Alzheimer's patients remain to be determined.

In this uncontrolled pilot study, we investigated whether the use of donepezil could benefit patients with affective illness whose clinical stabilization with psychotropics was marred by persistent side effects including complaints of memory dysfunction, dry mouth, and constipation.

METHOD

Subjects were nondemented, nongeriatric, medically healthy outpatients in an office-based private practice who had major affective illnesses that had been successfully stabilized for 2 months or more with pharmacotherapy. Affective illness was defined as fulfilling DSM-IV criteria[10] for either bipolar disorder (I, II, or not otherwise specified [NOS]) or major depression (including comorbid obsessive-compulsive disorder) prior to stabilization with psychotropic agents. Patients were excluded from consideration for participation if they had suffered from the exacerbation of any previously stabilized medical condition or required any medication adjustment within 2 months prior to study entry. Stabilization of affective illness was defined as a clinician-rated nonblinded Clinical Global Impressions-Severity of Illness (CGI-S)[11] score of 1 (normal) or 2 (borderline mentally ill) prior to study entry. Written informed consent was required for participation in the donepezil study.

A 3 to 4 week trial of donepezil was offered to patients who complained of certain side effects associated with their psychotropic regimens that had failed to diminish, untreated, over time and that had failed, in most cases, to respond to other oral agents such as bethanechol,[4] phosphatidylcholine,[12] and ergoloid mesylates.[13] The target symptoms for prescription of donepezil were subjective short-term memory loss (N = 21) (e.g., difficulty with word retrieval or recalling recent events), dry mouth (N = 16), and/or constipation (N = 11) that began following the prescription of psychotropic medications. Patients were instructed to rate these target symptoms on a scale according to severity: 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = incapacitating. Self-ratings of target symptoms were repeated after 3 to 4 weeks on each dose of donepezil during a supervised office visit, and a clinician-rated CGI scale was repeated if any clinical change was reported or observed.

After completion of the initial ratings, patients started taking donepezil, 5 mg p.o. each evening, per the manufacturer's recommendation.[7] After completion of the 5-mg/day trial, patients were given 3 options: to stop taking donepezil, to continue taking the 5-mg/day dose, or to increase the dose to 10 mg/day for an additional 3- to 4-week trial. After 10 patients had completed the initial 5-mg/day trial, the timing of donepezil administration was changed to the morning (generally with breakfast) to avoid insomnia, which most patients reported with the evening administration.

After completion of the trials, patients were allowed to continue taking donepezil as desired and were evaluated clinically every 4 to 8 weeks to monitor the emergence of side effects, such as tolerance. During each follow-up visit, patients were asked to report any physical, cognitive, or emotional changes that might signify long-term response characteristics to donepezil. One patient with a history of good compliance with pharmacotherapy was given the option of taking donepezil as needed (p.r.n.) for an exacerbation of the dry mouth she suffered with singing performances.

RESULTS

Twenty-four patients with psychotropic-stabilized affective illness (mean ± SD age = 45.7 ± 8.8 years) entered the donepezil trials. Demographic characteristics and raw data of the patients are presented in Table 1. Twelve patients were diagnosed with a bipolar spectrum disorder (I, II, or NOS), and 12 had suffered from a recurrent major unipolar depression, including 1 patient with comorbid obsessive-compulsive disorder. Seven patients had a parent who had suffered from diagnosed or probable Alzheimer's disease; 3 additional patients had a second-degree relative (grandparent, aunt, or uncle) who had suffered from dementia. Of the patients who completed a trial of donepezil, 17 were taking tricyclic antidepressants or bupropion as primary antidepressants, 4 were taking serotonin reuptake inhibitors, 3 were taking nefazodone, and 1 was taking tranylcypromine. Twelve patients were taking divalproex and/or lithium for mood stabilization and/or augmentation. Additionally, 10 patients were taking hormones or other medications for a variety of medical conditions (Table 1). Prior to starting the donepezil trial, 19 (79.2%) of 24 patients had undergone unsatisfactory trials of bethanechol, phosphatidylcholine, and/or ergoloid mesylates for relief of memory dysfunction, dry mouth, or constipation.

Twenty-two of 24 patients (10 Caucasian women, 1 African American woman, 11 Caucasian men, mean ± SD age = 45.4 ± 8.5 years) completed a 3-week trial of donepezil, 5 mg/day. Two patients stopped donepezil within a few days due to side effects. Ten patients (46%) who completed the 5-mg/day trial elected to try the 10-mg/day dose of donepezil, and 9 of these completed at least a 3-week trial of the higher dose.

Nineteen (90.5%) of 21 patients complaining of psychotropic-induced memory loss rated complete or partial improvement after 3 weeks of taking donepezil, 5 mg/day (paired $t = 6.55$, $df = 20$, $p < .0001$). Four of 6 patients who complained of residual memory loss after completing the 5-mg/day trial and then took 10 mg/day of donepezil for 3 weeks rated further improvement in memory (paired $t = 2.43$, $df = 5$, $p = .059$). Two subjects reported improvement in memory only after taking 10 mg/day of donepezil: both had mothers who had died of Alzheimer's disease (Table 1). Although there was no difference in baseline ratings of memory dysfunction between patients who reported a family dementia history and those without this history (unpaired $t = -1.55$, $df = 21$, p = N.S.), patients with a family dementia history rated significantly less improvement in memory after taking donepezil, 5 mg/day, than patients without a family dementia history (unpaired $t = -3.44$, $df = 19$, $p < .005$). When memory dysfunction ratings of patients taking tricyclic antidepressants were compared with those of patients taking other antidepressants, no baseline differences were seen (data not shown). However, there was a trend for greater memory improvement with donepezil, 5 mg/day, in the patients taking tricyclics as opposed to other antidepressants (unpaired $t = -1.86$, $df = 19$, $p = .078$).

Fourteen of 16 patients complaining of dry mouth rated complete or partial improvement after taking donepezil, 5 mg/day (paired $t = 5.20$, $df = 15$, $p < .001$) (Table 1). Residual complaints of dry mouth improved further in 4 of 6 patients who increased donepezil to 10 mg/day (paired $t = 3.59$, $df = 5$, $p < .05$). No reports of hypersalivation were recorded.

Seven of 11 patients complaining of constipation rated complete or partial improvement after taking donepezil,

Table 1. Donepezil in Affective Illness

Primary DSM-IV Diagnosis[b]	Age (y)	Sex	Self-Ratings of Target Symptoms[a]: Memory Loss Bsl	Memory Loss mg/d[c] 5	Memory Loss mg/d[c] 10	Dry Mouth Bsl	Dry Mouth mg/d[c] 5	Dry Mouth mg/d[c] 10	Constipation Bsl	Constipation mg/d[c] 5	Constipation mg/d[c] 10	Side Effects	Weeks of Treatment	Family History of Dementia[d]	Concomitant Psychotropic Regimen, mg/d	Hormones, µg/d	Other Medications, mg/d	Past Treatment(s)
296.8	36	F	3	2	0.75	2	1	0	3.5	2	0.25	Insomnia	57	…	Clomipramine 25, fluoxetine 20, bupropion 200, buspirone 90, divalproex 100, gabapentin 1200, alprazolam 0.125			Bethanechol, ergoloid mesylates
296.5	36	M	3	2	…	3	1	…	0	0	…	Mania[e]	…	…	Piracetam 60, buspirone 60, olanzapine 10, lithium 1350			Bethanechol, ergoloid mesylates
296.3	46	F	0	0[f]	…	3	1	…	3	1.5	…	…	…	f	Sertraline 200, nortriptyline 50			Bethanechol, ergoloid mesylates
296.3	38	F	3	0	0	3	2	1	3	2	1	Insomnia	36	…	Clomipramine 50, bupropion-SR 150, buspirone 30	Ethinyl estradiol, norethindrone acetate		Bethanechol, ergoloid mesylates
296.3	45	M	3	1	…	2.5	1.5	…	2	2	…	…	quit Rx		Bupropion-SR 450, trazodone 50			Bethanechol, ergoloid mesylates
296.5	49	M	2.5	1	…	1	0	…	0	0	…	Diarrhea[e]	…	…	Nefazodone 450, lithium 900, gabapentin 800, clonazepam 0.5	Levothyroxine 50		Ergoloid mesylates
300.3	39	F	0.5	0	…	3	1	…	1	0	…	…	57/prn	…	Clomipramine 75, sertraline 200			Bethanechol, ergoloid mesylates
296.89	49	M	2.3	0.8	0.5	1.3	1.3	1	0.5	0.5	0.5[c]	Insomnia	27	…	Clomipramine 25, methylphenidate 20, buspirone 40	Testosterone transdermal system	Albuterol, cromolyn	Bethanechol, ergoloid mesylates
296.3	64	M	2	2	1	3	1	1	0	0	0	Insomnia	47	m	Bupropion-SR 300, divalproex 250, amantadine 100		Doxazosin 4	Ergoloid mesylates
296.89	28	F	3	2	0.5	0	0	…	0	0	…	…	24	…	Bupropion-SR 300, buspirone 60, divalproex 250	Ethinyl estradiol, mestranol, norethindrone acetate		
296.3	47	M	2	1	1	0	0	0	1	0	0	…	17	…	Bupropion 400, buspirone 40	Liothyronine 25		Ergoloid mesylates
296.3	46	M	3	2	…	0	0	…	1	0	…	Insomnia	35	…	Nefazodone 450, lithium 675, divalproex 500, gabapentin 1200	Levothyroxine 175 + liothyronine 25		Ergoloid mesylates
296.5	59	F	2	1	…	3	0	…	3	0	…	Mania	27	f, pgf?	Sertraline 75, clonazepam 3, trazodone 50			Bethanechol, ergoloid mesylates
296.89	54	M	1.5	1.5	…	1	0.8	…	0	0	…	Diarrhea[e]	13	f	Bupropion 500, divalproex 750, lithium 450, sertraline 50			
296.3	48	M	2.5	1.8[f]	…	0	0	…	0	0	…	…	…	…	Sertraline 200, clonazepam 1			Ergoloid mesylates
296.89	48	M	3	1	…	0	0	…	0	0	…	Loose stools	31	…	Bupropion-SR 450, buspirone 30, divalproex 1500, trazodone 50		Cimetidine 200	Ergoloid mesylates
296.3	48	F	3.5	1.3[f]	…	3.5	2.3	…	2.8	2.8	…	…	…	…	Bupropion 400, divalproex 1000			
296.3	49	M	2	1	…	0	0	…	0	0	…	…	21	m	Nefazodone 375, amantadine 200			Ergoloid mesylates, piracetam
296.3	51	F	2.5	2.3	0.5	2	0	0	0	1	1	…	11	pa	Bupropion-SR 300, clonazepam 1			
296.89	41	F	3	2	…	2	0.5	…	0	0	…	GI reflux	25	pgm	Bupropion-SR 400, buspirone 45, divalproex 1500		Cisapride 40, omeprazole 20	Ergoloid mesylates
296.89	37	F	2	1	1	3	2	2	1	2	0	…	13	…	Nortriptyline 100, divalproex 500, lithium 600, gabapentin 1600			Bethanechol
296.89	62	M	2[e]	…	…	0	…	…	2	…	…	Diarrhea[e]	…	?f Alz	Bupropion-SR 300 + bupropion 150, paroxetine 10			Bethanechol, phosphatidylcholine
296.3	43	M	2[e]	…	…	2	…	…	0	…	…	Dizzyness[e]	…	ma	Bupropion-SR 300, clonazepam 1			Bethanechol, ergoloid mesylates
296.89	33	F	2.5	2.5	1.5	1	2	1.5	0	0	0	…	13	m, 2ma, mu, mggf	Tranylcypromine 30, divalproex 500	Liothyronine 25		
Mean	45.7		2.3	1.4	0.8	1.7	0.9	0.8	1.1	0.8	0.5		28.4					
SD	8.8		0.8	0.7	0.4	1.2	0.7	0.7	1.3	1.0	1.0		14.9					

[a]0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = incapacitating. [b]DSM-IV diagnostic codes: 296.3 = recurrent major depression; 296.5 = bipolar I, depressed; 296.8 = bipolar NOS; 296.89 = bipolar II; 300.3 = obsessive-compulsive disorder. [c]Some patients remain at 5mg/d. [d]Abbreviations: f = father, m = mother, ma = maternal aunt, mggf = maternal great grandfather, mu = maternal uncle, pa = paternal aunt, pgf = paternal grandfather, pgm = paternal grandmother. [e]Discontinued trial for side effects. [f]Discontinued trial for financial reasons.

5 mg/day (paired $t = 2.57$, $df = 10$, $p < .05$) (Table 1). In 5 patients who rated residual constipation while taking donepezil, 5 mg/day, and then took 10 mg/day, 3 rated further improvement (paired $t = 2.64$, $df = 4$, $p = .08$). In contrast, 4 patients reported loose stools or diarrhea while taking donepezil at either the 5- or 10-mg/day dose.

Side effects were reported by 11 (46%) of 24 patients who tried donepezil, 5 mg/day. Two patients (8%) stopped donepezil therapy within the first few days due to diarrhea or dizziness. Two additional patients (8%) developed side effects only when taking 10 mg/day of donepezil: 1 stopped the drug due to diarrhea (Table 1). The most common side effect of donepezil was insomnia: 7 (54%) of the first 13 patients who took donepezil, 5 mg/day, developed a sleep disturbance consisting of an initial and/or a middle insomnia. Two of the patients reporting donepezil-associated insomnia were stabilized bipolar patients who switched from euthymia to mania within hours of taking their first dose of donepezil. Both patients reported the abrupt onset of racing thoughts, very high energy, and strong impulsive urges that occurred hours before they attempted to go to sleep on their first evening of donepezil therapy. Based on the mania and insomnia produced by the evening dosing of donepezil, the study protocol was revised so that donepezil was thereafter taken in the morning, soon after waking. Following the change to morning dosing, the patients who had reported insomnia noted improved sleep. One of the patients with bipolar disorder who became manic with donepezil therapy quit the study, but after a brief period of restabilization to an apparent state of euthymia, the other patient with bipolar disorder resumed the study, taking the donepezil in the morning. After resuming donepezil, this bipolar patient went into a hypomanic state of variably mild-to-moderate intensity accompanied by an intermittent insomnia, largely controlled with clonazepam. This bipolar patient's father had been diagnosed with Alzheimer's disease; this patient's paternal grandfather had late-life dementia.

Following completion of the study protocol, 15 patients (68.2%) continued treatment with donepezil for a mean ± SD duration of 28.4 ± 14.9 weeks. Several patients dropped out of treatment ($N = 2$) or were unable to obtain insurance coverage to pay for their donepezil prescriptions ($N = 3$), since they were not diagnosed as having Alzheimer's disease. One patient diagnosed with comorbid major depression and obsessive-compulsive disorder who complained that clomipramine-induced dry mouth interfered with singing successfully used donepezil on an as-needed (p.r.n.) basis for choral performances for over a year, taking a 5-mg dose several hours before each performance on a weekly or bimonthly basis. Debilitating mouth dryness recurred on 2 occasions when this patient forgot to premedicate with donepezil prior to a concert.

DISCUSSION

In this uncontrolled pilot study, a majority of patients with stabilized affective illness who complained of memory loss, dry mouth, or constipation caused by their psychotropic medications reported symptomatic relief from these side effects after adding donepezil to their pharmacologic regimens. Donepezil was generally well tolerated by these nongeriatric, nondemented patients, and most of them wanted to continue donepezil treatment after completing the study trials. While larger numbers of patients will need to be studied in placebo-controlled trials to precisely define the response parameters to donepezil in subtypes of affective illness, the current findings suggest that the enhancement of cholinergic function by donepezil can be a useful pharmacologic remedy for conditions associated with diminished cholinergic function in nongeriatric, nondemented subjects.

The improvement in memory reported with the administration of donepezil in the current series was dramatic: over 90% of the patients who complained of psychotropic-associated memory dysfunction rated improvement while taking donepezil, 5 mg/day. Since the trials of donepezil were uncontrolled, and the rating scales used were subjective, a placebo effect cannot be ruled out. However, a number of factors argue against a placebo effect. First, almost all patients who rated memory improvement with donepezil therapy had had previous unsatisfactory responses to trials of other agents (bethanechol, phosphatidylcholine, and/or ergoloid mesylates) prior to trying donepezil, suggesting that their memory dysfunction was not particularly placebo responsive. Second, several patients reported no benefit from taking 5 mg/day of donepezil for 3 weeks, but subsequently rated improvement while taking 10 mg/day of donepezil, and several other patients reported better responses when taking 10 mg/day than when taking 5 mg/day (see below). Third, in contrast with the tendency of inactive medication responses to fade, the memory improvement reported with donepezil was sustained for as long as patients continued to take the drug: after completing the initial trials, 16 patients continued donepezil for an average of 7 months without a reported diminution of effect. Finally, memory dysfunction was reported to recur soon after discontinuation of donepezil—often within 1 week—by patients who stopped the drug and was again diminished after donepezil was reinstated. Future investigation of the utility of donepezil in the treatment of nongeriatric memory dysfunction would be strengthened by double-blind methodology and standardized observer-rated memory testing. However, since subjective reports of memory dysfunction can be important signs of current and future cognitive deterioration,[14,15] and memory loss is often associated with diminished cholinergic transmission,[16–18] the subjective memory improvement rated by stabilized patients with affective illness taking donepezil in

the current series is a finding consistent with the drug's augmentation of brain cholinergic activity.[6–8]

In some patients in the current series, the improvement in memory associated with donepezil appeared to be dose related, such that 4 of 6 patients who tried the 10-mg/day dose of donepezil rated further improvement compared with their memory ratings when taking 5 mg/day. This dose-response relationship may be clinically analogous to the greater cognitive improvement reported in some patients with dementia of the Alzheimer's type when taking 10 mg/day as compared with 5 mg/day of donepezil,[9] presumably relating to the relative amount of cholinergic deficit that is restored. It is intriguing in this regard that patients in the current series with positive family histories of dementia appeared less responsive to donepezil than patients without demented relatives, since they rated less improvement in memory while taking 5 mg/day of donepezil. Although this difference could be due to diminished expectations in the patients with a family history of dementia, their baseline ratings of memory dysfunction were similar to those of the patients who denied family histories of dementia. It is intriguing to speculate that this difference in response to donepezil might indicate diminished cholinergic function in the patients with family histories of dementia. Interestingly, the 2 patients who rated memory improvement only on the high dose of donepezil both had mothers who had died of dementia of the Alzheimer's type, thereby raising the possibility of an inherited vulnerability to anticholinergic memory dysfunction with a diminished responsiveness to cholinergic augmentation.[19]

Nearly half the patients who complained of memory dysfunction following psychotropic treatment of their affective illness gave family histories of first- or second-degree relatives who had been diagnosed with presumptive Alzheimer's disease or who had manifested significant memory impairment. Although the majority of Alzheimer's disease may be spontaneous rather than inherited,[20] and the memory dysfunction in patients suffering from depressive illness is often characterized as a pseudodementia,[21] episodes of major depression in midlife and late life can be premonitory signs for the subsequent development of Alzheimer's disease.[22–24] Moreover, since recent data suggest that the degenerative processes of Alzheimer's disease may begin at a much earlier age than previously recognized—between the ages of 20 to 30[25]—potential new disease markers are urgently needed to facilitate prophylaxis and earlier treatment intervention.

Alzheimer's patients have been shown to have a lower threshold for cognitive impairment in response to cholinergic blockade than age-matched controls.[18] Memory dysfunction as a symptom of anticholinergic hypersensitivity may also occur in the healthy elderly population to a greater extent than in younger healthy individuals.[26–28] The findings from the current series suggest that anticholinergic hypersensitivity manifested by persistent memory dysfunction (or excessive dry mouth or constipation) may also occur in nonelderly affectively ill individuals as a side effect of psychotropic treatment. Longitudinal monitoring of such affectively ill individuals who report memory improvement with donepezil should be conducted in order to assess whether this response may be correlated with the eventual development of Alzheimer's disease.[19] The memory improvement reported in the current series may be indicative of a relatively mild decrease in cholinergic function compared with that in Alzheimer's disease. A differential response to the relative severity of functional cholinergic deficit is supported by the finding that most patients in the current series who elected to try the higher dose of donepezil for the treatment of memory dysfunction were taking tertiary amine antidepressants, which block muscarinic receptors, or were taking bupropion. Although bupropion is reported to lack cholinergic receptor blocking activity,[29] in a series of over 60 bupropion-treated patients we have found that nearly all report side effects typical of anticholinergic activity (short-term memory loss, dry mouth, and/or constipation) (F.M.J., unpublished data, 1997), perhaps associated with a central mechanism. Memory improvement in the current series was somewhat greater in patients who were taking tricyclic antidepressants as compared with other antidepressants, but was also reported by patients who were taking antidepressants that lack cholinergic receptor blocking activity (e.g., sertraline, fluoxetine). This is perhaps not surprising, given that anticholinergic effects on cognition and behavior have been shown to be modulated by other neurotransmitters such as serotonin[30] and that all of the current patients were taking multidrug psychotropic regimens.

In the majority of patients studied, donepezil caused insomnia when it was taken in the evening. While insomnia is reported to occur in only 9% of Alzheimer's patients who receive donepezil in placebo-controlled trials[8,9] and is most problematic at the 10-mg/day dose,[31] the very high incidence of insomnia that occurred with evening dosing of donepezil suggests that affectively ill nongeriatric patients may be very sensitive to the sleep-altering effects of donepezil. This conclusion appears congruent with past reports that acetylcholinesterases cause more sleep disruption in affectively ill individuals than in normal controls.[32,33] This increased vulnerability to sleep disruption may relate to the well-documented cholinergic supersensitivity for rapid induction of REM sleep in patients with current, past, or family histories of affective illness.[33,34] Based on the findings of the current series of subjects with affective illness, evening dosing of donepezil for individuals who are not diagnosed with Alzheimer's disease may not be advisable.

The rapid switch from euthymia into mania in 2 previously stabilized bipolar patients was unexpected. These patients reported that racing thoughts, increased energy, and impulsive urges suddenly developed within 1 to 2

hours after taking their first dose of donepezil and subsequently prevented them from falling asleep. (A patient paged one of us [F.M.J.] at 2 a.m. after having taken the first dose of donepezil.) The paradoxical triggering of mania by donepezil in these previously euthymic bipolar patients provides partial support for the hypothesis of a cholinergic mechanism in the switch process in bipolar illness, although increased depression rather than mania would have been predicted.[1] Moreover, persistent elevation of mood to levels reaching hypomania has been observed both in the longitudinal follow-up of several bipolar patients in the current series and also in several rapid-cycling and mixed-state bipolar patients (data not included in the current series) who subsequently took donepezil as a morning dose under open-label conditions. While these observations may appear to contradict past reports in which increasing central cholinergic tone with anticholinesterases such as physostigmine reduces mania and induces depression in bipolar patients,[1,35] they are congruent with studies reporting more variable and complex effects of cholinergic agonists, including behavioral activation and mood elevation, in depressive and bipolar patients[18] and with the hypothesis of mania induction by cholinergic overdrive.[36] The donepezil-induced switch into mania/hypomania observed in the current series supports the need for further study of this long-acting anticholinesterase's effects in affective illness.

Dry mouth and constipation were diminished or eliminated in most patients who added donepezil to their psychotropic regimens, suggesting that this treatment may be a useful therapeutic option in patients with severe dry or slow gastrointestinal function unresponsive to other measures such as trials of bethanechol and phosphatidylcholine. Although the current findings are uncontrolled, a recent study found that patients' subjective ratings of oral dryness associated with antidepressant treatment correspond well to laboratory measures of their parotid salivary secretions.[37] Some caution in initiating donepezil for the treatment of dry mouth or constipation is indicated, however, since the potent intestinal-stimulating effects of donepezil may cause loose stools, diarrhea, or even gastrointestinal reflux, as reported by several patients in the current series. It may be advisable to use a lower initial dose of donepezil (2.5 mg/day) for patients with histories of colonic hypermotility or gastroesophageal reflux.

In patients whose dryness of mouth may be event related, such as singers, orators, or wind or brass musicians, donepezil can also be used intermittently or p.r.n. rather than continuously. The case of the church choir soprano who takes 5 mg of donepezil to relieve event-specific mouth dryness only on the days of concerts also suggests a potential role for donepezil in the treatment of dry mouth accompanying performance anxiety or stage fright.

In conclusion, the current findings suggest that the use of donepezil may have a variety of possible benefits in nondemented, nonelderly affectively ill patients, including the reversal of common anticholinergic side effects such as memory loss, dry mouth, and constipation. The current findings also raise the question of whether memory enhancement with donepezil in nondemented affectively ill individuals might have predictive value for the development of Alzheimer's disease as an early manifestation of anticholinergic hypersensitivity. However, the unexpected triggering of mania in several previously stabilized bipolar patients raises a cautionary note for clinicians and suggests that the effects of donepezil in affective illness and the nonelderly merit further investigation.

Drug names: albuterol (Proventil and others), alprazolam (Xanax and others), amantadine (Symmetrel and others), bethanechol (Urecholine and others), bupropion (Wellbutrin), buspirone (BuSpar), cimetidine (Tagamet and others), clomipramine (Anafranil and others), cisapride (Propulsid), clonazepam (Klonopin and others), cromolyn (Gastrocrom and others), divalproex (Depakote), donepezil (Aricept), doxazosin (Cardura), ergoloid mesylates (Hydergine), fluoxetine (Prozac), gabapentin (Neurontin), levothyroxine (Synthroid and others), liothyronine (Cytomel), methylphenidate (Ritalin), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), omeprazole (Prilosec), paroxetine (Paxil), phosphatidylcholine (PhosChol), sertraline (Zoloft), testosterone transdermal system (Androderm), tranylcypromine (Parnate), trazodone (Desyrel and others).

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