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S Craig Risch
University of California, San Francisco

Michael D. Horner
Medical University of South Carolina

Susan R. McGurk
Dartmouth College

Simmy Palecko
University of California, San Francisco

John S. Markowitz
Medical University of South Carolina

See next page for additional authors

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BRIEF REPORT

Donepezil effects on mood in patients with schizophrenia and schizoaffective disorder

S. Craig Risch[1], Michael D. Horner[2], Susan R. McGurk[3], Simmy Palecko[1], John S. Markowitz[2], Ziad Nahas[2] and C. Lindsay DeVane[2]

[1] *University of California, San Francisco, CA, USA*
[2] *Medical University of South Carolina, Charleston, SC, USA*
[3] *Dartmouth Medical School, Hanover, NH, USA*

Abstract

Donepezil, 5 mg/d for 6 wk then 10 mg/d for 6 wk, and placebo daily for 12 wk in a double-blind cross-over paradigm, was added to the therapeutic regimen of 13 patients with schizophrenia or schizoaffective disorders, clinically stable on atypical antipsychotic medications. Patients had varying degrees of depressive symptoms, ranging from no depression to clinically significant depression. There was no worsening or induction of depression in individual patients or the group as a whole. In addition there was a statistically significant antidepressant effect in the group as a whole during the donepezil condition and a clinically significant antidepressant effect in the patients with clinically significant depressive symptoms, although there were not enough depressed patients in the group to conclude that donepezil may have antidepressant effects. Thus, in this study, donepezil did not induce or worsen depressive symptoms in schizophrenic and schizoaffective disorder patients.

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Key words: Acetylcholinesterase inhibitors, depression, donepezil, schizophrenia, schizoaffective disorder.

Introduction

Cummings (2000) has reviewed the demonstrated or potential clinical utility of cholinesterase inhibitors as 'cognitive enhancers' in a wide variety of neuropsychiatric illnesses. Studies of cholinesterase inhibitor augmentation of antipsychotics in schizophrenic patients have yielded mixed results. Two placebo-controlled studies (Friedman et al., 2002; Tugal et al., 2004) demonstrated no benefits, while other studies (Allen and McEvoy, 2002; Buchanan et al., 2003; Risch et al., 2001; Rosse and Deutsch, 2002) have demonstrated benefits in Positive and Negative Symptom Scale (PANSS) ratings and/or cognitive tests, at least in some patients. These studies suggest some heterogeneity in response among treatment-resistant patients, as is often seen with other augmentation agents in psychotic patients (Miller, 2004). In this regard, we (Nahas et al., 2003; Risch et al., 2001) have reported in double-blind placebo-controlled studies that donepezil, when added to the therapeutic regimen of patients treated for schizophrenia or schizoaffective disorder receiving a variety of atypical antipsychotics, may improve functional magnetic resonance imaging (fMRI) measurements of blood flow in the left frontal lobe and the medial frontal cingulate.

However, as reviewed by Janowsky and Overstreet (1995) a large literature also suggests that the administration of physostigmine, a reversible cholinesterase inhibitor, and other cholinomimetic agents may induce a syndrome similar to clinical depression in patients who have previously suffered from depressive disorders. Thus, there has been some concern about the relative safety of using cholinesterase inhibitor medications in patients who have previously had or currently have co-existing depressive symptoms.

We report preliminary results of the effects of donepezil on mood when used concurrently with atypical antipsychotics in an augmentation strategy for cognitive enhancement in patients with schizophrenia or schizoaffective disorder.

Address for correspondence: Dr S. Craig Risch, M.D., UCSF Department of Psychiatry, 401 Parnassus Avenue Box F-0984, San Francisco, CA 94143-0984, USA.
Tel.: (415) 476-7710 *Fax*: (415) 476-7320
E-mail: craigr@lppi.ucsf.edu

Methods

This was a Medical School Committee on Human Subjects approved protocol and was performed in

Table 1. Raw scores on the 31-item Hamilton Rating Scale for Depression (HAMD) for all subjects at baseline, on donepezil, and on placebo

Subject no.	HAMD baseline	Donepezil	Placebo
1	0	0	0
2	26	12	21
3	6	1	12
4	9	2	8
5	3	6	5
6	27	14	19
7	4	9	2
Subject no.	**HAMD baseline**	**Placebo**	**Donepezil**
8	18	6	2
9	5	1	2
10	10	5	8
11	9	22	16
12	26	21	12
13	12	11	0

Subjects 1–7 received donepezil before placebo and subjects 8–13 received placebo before donepezil.
Subject number does not reflect the actual sequence of patient order as this was a randomized, counterbalanced study. Rather, the table presents together the subjects who received donepezil first (top) and those who received placebo first (bottom).

accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects were legally competent and gave written informed consent.

Thirteen psychiatrically stable patients (22–50 yr old) with schizophrenia or schizoaffective disorder, medicated with maintenance olanzapine, risperidone or clozapine, received 5 mg/d donepezil for 6 wk titrated to 10 mg/d for an additional 6 wk and placebo for 12 wk, administered in a double-blind, randomized, counterbalanced order. A trained clinician blinded to donepezil status administered the 31-item Hamilton Depression Rating Scale (HAMD) at baseline, at 12 wk (after either placebo or donepezil), and at 24 wk (after the other condition). HAMD scores at baseline ranged from 0 to 27.

Results

Scores on the 31-item HAMD during the three conditions, baseline, donepezil augmentation and placebo augmentation, are depicted in Table 1. Comparing the change in HAMD scores, baseline–donepezil (5.5 ± 7.9 S.D.) vs. baseline–placebo (1.7 ± 6.3), there was a significant overall group improvement in the HAMD scores during the donepezil treatment arm ($t = 2.38$, $p = 0.035$). Using repeated-measures ANOVA, with HAMD scores as the dependent variables and condition (baseline, donepezil, and placebo) as the within-subjects factor, the results were similarly significant ($F = 4.54$, $p = 0.026$) (Table 2).

Table 2. Repeated measures ANOVAs for each test separately (baseline vs. donepezil vs. placebo) ($n = 13$)

Cond	Mean	S.E.	95% CI Lower Bound	Responsive Upper Bound
1	12.024	2.688	6.109	17.939
2	6.476	1.658	2.827	10.125
3	10.286	2.342	5.131	15.440

Most of these patients had no or only mild depressive symptoms (HAMD scores <18) and no clinically significant induction or worsening of depressive symptoms occurred in any of these patients during the donepezil condition. However, four patients had HAMD scores $\geqslant 18$ (range 18–27) and all four of these patients had a clinically significant reduction of HAMD scores and depressive symptoms (reductions ranged from 13 to 17 points) during the donepezil condition.

Discussion

Our data are consistent with the report of Tugal et al. (2004) that donepezil augmentation of antipsychotic pharmacotherapy does not induce depressive symptoms in non-depressed schizophrenics. In their study 12 patients with schizophrenia on a stable dose of high-potency typical antipsychotics received 5 mg donepezil for 6 wk and placebo for 6 wk in a double-blind cross-over trial. In their study they reported no change relative to placebo in the PANSS, a variety of neurocognitive tests, and in the Calgary Depression Scale during the donepezil condition. Our study differs from that of Tugal et al. (2004) in that our patients received 10 mg donepezil (rather than 5 mg) for 6 wk then 10 mg for 12 wk (rather than 6 wk) and were on atypical antipsychotics (rather than high-potency typical neuroleptics). In the study of Tugal et al., 2004, patients with a Calgary Depression Scale (Addington et al., 1992) score >6 were excluded and thus the study was not designed or evaluable to determine the antidepressant effects of donepezil in depressed schizophrenics. In our

study there were no exclusion criteria for the presence of depressive symptoms and thus, as noted above, we found a clinically significant improvement in HAMD scores in schizophrenic and schizoaffective disorder patients with clinically significant depression.

These study results, although limited to 13 subjects, are also consistent with a report by Burt et al. (1999) in which a treatment-refractory depressed bipolar patient received a clinically significant antidepressant benefit from donepezil augmentation. Thus, our preliminary data suggest that the use of donepezil with atypical antipsychotics in schizophrenic and schizoaffective disorder patients neither induces or worsens depressive symptoms (as also previously reported by Tugal et al., 2004) and may even be associated with a reduction or remission of depressive symptoms ingin some subjects, as reported by Burt et al. (1999) in a bipolar patient. It is important to note that this study was not designed to test the antidepressant effects of donepezil, but rather its relative safety with respect to induction or worsening of depressive mood symptoms in schizophrenic and schizoaffective disorder subjects.

As detailed in Table 1, one of the four clinically depressed subjects (subject no. 2) had clinically significant improvement in mood symptoms on donepezil which relapsed when switched to placebo. Subject no. 6 had some improvement in mood on donepezil which worsened somewhat on placebo. Subject no. 12 had a slight improvement in mood on placebo which became clinically significant when switched to donepezil. Finally, subject no. 8 had clinically significant improvement in mood on placebo which further improved on donepezil. However, spontaneous remissions or 'time in study' effects cannot be ruled out in these subjects, and the sample size of clinically depressed subjects is small. Thus, we conclude that in this study donepezil did not induce or worsen depressive symptoms in schizophrenic or schizoaffective disorder subjects.

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Statement of Interest

Dr Risch is currently or has been in the past on the speakers' bureau, a consultant, or has received research funds from the following sources: Abbott, Astra-Zeneca, Bristol–Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Novartis, Pfizer, Smith Kline Beecham and the NIMH. Dr McGurk is on the speakers' bureau for Janssen and Pfizer. Dr DeVane is on the speakers' bureau, a consultant, or has received research funding from Theracos Inc., Novodel Inc., Quintiles Inc., GlaxoSmithKline, Janssen, Lilly, NIDA and NIMH.

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