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Double-blind donepezil–placebo crossover augmentation study of atypical antipsychotics in chronic, stable schizophrenia: A pilot study

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Abstract

Thirteen outpatients with chronic but stable schizophrenia received donepezil and placebo augmentation of their maintenance antipsychotic medication regimen. Each subject received in a randomized, counterbalanced order 1) donepezil 5 mg for 6 weeks then donepezil 10 mg for six weeks and 2) placebo donepezil for 12 weeks. Serial ratings of the Positive and Negative Symptom Scale (PANSS) [Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13(2): 261–276] were performed by a trained rater blind to the donepezil order and condition: at baseline, 12 weeks and 24 weeks. On donepezil as compared to baseline or placebo, there was a significant improvement in PANSS negative scores ($p = .018$, $n = 13$). These results are discussed with respect to other studies using cholinesterase inhibitors as an augmentation strategy in schizophrenia.

Keywords: Schizophrenia; Cholinesterase Inhibitors; Pharmacological Augmentation

1. Introduction

A number of marketed, centrally active cholinesterase inhibitor medications (donepezil, rivastigmine, galantamine) are currently approved by the Food and Drug Administration for the treatment of dementia of the Alzheimer's type (DAT). They are relatively well tolerated with few adverse effects. Preliminary clinical studies with these medications have demonstrated in a variety of other psychiatric disorders that the neuropathology of Alzheimer's dementia does not have to be present for cognitive enhancement with cholinesterase inhibitors to occur (Cummings, 2000).

Our initial rationale for the use of cholinesterase inhibitors to augment antipsychotic response in patients with schizophrenia was based on the well documented and multifaceted neurocognitive deficits frequent in

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schizophrenia, and on the accumulating data suggesting cholinesterase inhibitors may enhance cognition in many presumably "noncholinergic deficit" illnesses. In this regard, Cummings (Cummings, 2000) has reviewed evidence that cholinesterase inhibitors are useful in the treatment of a wide variety of neuropsychiatric conditions other than DAT, including dementia with Lewy bodies, Parkinson's disease with dementia, Pick's disease, olivopontocerebellar atrophy, progressive supranuclear palsy, the parkinsonism dementia complex of Guam, alcoholism with Wernicke's encephalopathy, Creutzfeld–Jakob disease, subacute sclerosing panencephalitis, dementia pugilistica, traumatic brain injury, vascular dementia, sleep disorders, autism, attention-deficit-hyperactivity disorder, bipolar disorder, and schizophrenia. In his review Cummings (Cummings, 2000) also notes, "Cholinergic agents affect many aspects of cognition, which suggests that the primary effect may be on an attentional or executive system with a secondary, pan-intellectual modulating influence on memory, language, and visuospatial skills (Lawrence and Sahakian, 1995)."

This concept is of particular relevance to cognitive enhancement in schizophrenia. Green et al. (2000) and Mohamed et al. (1999) have reviewed the nature and specificity of neurocognitive dysfunction in schizophrenia. They emphasize that there are no specific types of cognitive dysfunction common to all patients with schizophrenia. Rather, different patients have different types of cognitive impairments. Broad cognitive screens are necessary to determine the specific types of cognitive dysfunction, if any, that is present in a particular patient. Thus, broad based cognitive enhancers (for example, cholinesterase inhibitors which improve many types of cognitive impairments) may be necessary for use as general cognitive enhancers in this illness.

Cognitive impairments in schizophrenia may occur at a very early age, often before other overt symptoms (Hans et al., 1999). With the onset of obvious psychotic symptoms, cognitive impairments may worsen, sometimes to dementia levels (Davidson et al., 1996; Goldberg et al., 1987; Heaton et al., 1994). Patients with schizophrenia, even those meeting criteria for dementia, do not usually have the typical neuropathology of dementia of the Alzheimer's type (Powchick et al., 1998), and the incidence of DAT in elderly patients with schizophrenia is not different than that of the general elderly population (Davidson et al., 1996; Powchick et al., 1998). Nevertheless, within schizophrenia subjects, who on autopsy have brain cortical choline acetyltransferase levels no different than normal controls, premorbid Clinical Dementia Rating Scale Scores (Hughes et al., 1982) were significantly negatively correlated in patients with brain cortical choline acetyltransferase activity ($r=-0.29$, $p<0.005$) to a similar degree as in patients with DAT ($r=-0.36$, $p<0.0003$) (Powchick et al., 1998).

More recently, alterations in cholinergic neurotransmission in schizophrenia have been demonstrated, including (1) a deficit in the regulation of the low affinity alpha-7 nicotinic receptor in a subgroup of schizophrenic patients with impaired sensory gating (Adler et al., 1998; Freedman et al., 1997); (2) altered high affinity nicotinic receptor binding in postmortem brain samples of schizophrenic patients (Breese et al., 2000); (3) decreased autopsied hippocampal muscarinic receptor binding in schizophrenic patients compared with matched normal controls (Crook et al., 2000) and (4) reduced density of cholinergic interneurons in the ventral striatum in schizophrenic patients (Holt et al., 2005). These findings, in addition to the documented presumably "nonspecific" benefits of cholinesterase inhibitors in a large number of illnesses, suggest that there may also be specific deficits in nicotinic and/or muscarinic cholinergic neuropharmacology in some patients with schizophrenia.

In this regard, a number of investigators (Allen and McEvoy, 2002; Buchanan et al., 2003; Erickson et al., 2005; Howard et al., 2002; Lenzi et al., 2003; MacEwan et al., 2001; Mendelsohn et al., 2004; Risch et al., 2001; Risch et al., 2005; Rosse and Deusch, 2002; Schubert et al., 2006; Stryjer et al., 2003) have preliminarily reported that the addition of cholinesterase inhibitors to schizophrenic patients antipsychotic regiments may improve some patients' symptoms and general functioning. However, these benefits, when they occurred were modest. Furthermore, one study of donepezil augmentation of typical antipsychotics (Tugal et al., 2004) and one study of donepezil augmentation of atypical antipsychotics (Friedman et al., 2002) were unable to demonstrate any benefits. Thus the role, if any, of cholinergic augmentation in schizophrenia awaits further study.

2. Experimental/materials and methods

Thirteen outpatients with schizophrenia ($N=11$) or schizo-affective disorder ($N=2$) (DSM IV) (mean age = 34.7 years, SD = 10.0; mean level of education = 11.9 years, SD = 1.7) were psychiatrically stable (i.e., not hospitalized within 1 year prior to entry into the study) and had been maintained on stable regimens of their atypical antipsychotic medication (olanzapine, risperidone, or clozapine) during this period. A within-subjects, double-blind, placebo-controlled, crossover design was used to test our hypothesis of improved symptoms during donepezil augmentation as compared to placebo augmentation.

Subjects were randomized to initially receive either donepezil or placebo based upon a random number table generated using SPSS software. Study medications were prepared by the research pharmacist in blue opaque "o" sized capsules (Gallipot® Inc., St. Paul, MN), packed with commercially obtained cornstarch as an excipient, and either 5 or 10 mg of donepezil (as Aricept® Pfizer, Inc., NY, NY) from a single lot source of each. Placebo capsules, likewise packed with cornstarch, were matched for color and appearance.

All patients received, in a randomized, counterbalanced order, (1) donepezil 5 mg for 6 weeks followed by donepezil 10 mg for 6 weeks, and (2) placebo donepezil for 12 weeks. They received serial ratings of the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) and extrapyramidal symptoms: Abnormal Involuntary Movement Scale AIMS; (Lane et al., 1985), Simpson–Angus Scale (Simpson and Angus, 1970), and Barnes Akathisia Rating Scale (Barnes, 1989). Patients were rated at baseline, at 12 weeks [after receiving either 12 weeks of placebo or 6 weeks of donepezil (5 mg/day) followed by 6 weeks of donepezil (10 mg/day),] and at 24 weeks on whichever condition they did not receive in the first 12 weeks of the study. All 13 subjects were successfully titrated to 10 mg of donepezil during the second six weeks of the donepezil condition. Thus, all donepezil ratings were done only after 12 weeks of donepezil [after the patients had received 6 weeks of donepezil (5 mg/day) followed by 6 weeks of donepezil (10 mg/day)].

Changes in PANSS scores were analyzed using a series of repeated-measures analyses of variance (ANOVAs), using scores on each PANSS rating as the dependent variables, and condition (baseline, donepezil, or placebo) as the within-subjects factor. In addition, *T* tests of difference scores between baseline-donepezil and baseline-placebo were also performed.

3. Results

On donepezil as compared to baseline or on placebo, there was a significant improvement in PANSS Negative Scores, $F(2, 22)=4.84$, $p=.018$ (Table 1). *T* tests of difference scores for each test separately (baseline-donepezil or baseline-placebo) showed significant improvement in both PANSS Negative ($p<.05$) and PANSS total ($p<.05$) (Table 2). There were no significant changes in PANSS positive scores either by ANOVA or *T* Tests.

There were no significant effects of order of drug condition (i.e., placebo followed by donepezil or vice versa). There were no differences between baseline, donepezil, and placebo conditions on extrapyramidal symptoms, except that Simpson–Angus ratings were better on donepezil or placebo than at baseline. In the donepezil condition in this pilot study, all patients were tested only on the 10 mg. dose, so that data on whether the observed effects are dose-related are currently unavailable. The sample size did not permit separate analyses for different subgroups based on age, education, medication, or any other variables.

Table 1
Mean (and SD) PANSS scores at baseline, on donepezil, and on placebo ($n=13$)

Test	Baseline		Donepezil		Placebo	
PANSS negative *	20.7	(5.5)	18.9	(5.6)	24.9	(8.2)

* $p=.018$.

Table 2
Mean (and SD) differences from baseline of PANSS scores in donepezil and placebo conditions ($n=13$)

	Mean difference	(SD)
PANSS negative *		
baseline-donepezil	1.9	(4.8)
baseline-placebo	−4.2	(8.0)
PANSS total *		
baseline-donepezil	5.7	(13.4)
baseline-placebo	−7.8	(21.4)

Comparing the mean PANSS Negative scores on donepezil versus placebo (Table 1) indicated an effect size (Cohen's *d)* of 0.85, which is generally considered a large effect (Cohen, 1988).

* $p<.05$.

4. Discussion

A review of the literature of other studies of cholinesterase inhibitor augmentation of antipsychotics in schizophrenic patients shows mixed results with respect to benefits. Two studies with donepezil (Friedman et al., 2002; Tugal et al., 2004) demonstrated no benefits. However, other studies with donepezil (Buchanan et al., 2003; Howard et al., 2002; MacEwan et al., 2001; Risch et al., 2001; Stryjer et al., 2003), and studies with galantamine, (Allen and McEvoy, 2002; Rosse and Deusch, 2002; Schubert et al.,2006) and rivastigmine (Lenzi et al., 2003; Mendelsohn et al., 2004; Stryjer et al., 2003) have demonstrated benefits in Positive and/or Negative Symptom Scale (PANSS) ratings and/or in various cognitive performance tests. To date, all of the augmentation studies with galantamine (Allen and

McEvoy, 2002; Rosse and Deusch, 2002; Schubert et al., 2006) have been consistently positive, perhaps reflecting its additional noncompetitive agonist/allosteric modulation of nicotinic cholinergic receptors (Maelicke and Albuquerque, 2000). Thus the current literature suggests some heterogeneity in response among patients to cholinesterase inhibitor augmentation of their antipsychotic regimen, as is often seen with other augmentation agents in psychotic patients (Miller, 2004). In summary, this pilot study supports some but not all case reports and studies suggesting that the addition of a cholinesterase inhibitor to their antipsychotic medication regimen may benefit some schizophrenic patients. However, all studies to date have had relatively small subject numbers. Thus, much larger, placebo-controlled, parallel design studies appear indicated.

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6. Contributors

All of the authors were investigators in the study. All participated in all aspects of the study including its 1) design 2) conductance 3) data analysis and interpretation and 4) manuscript preparation. All authors reviewed and approved the manuscript prior to its submission.

7. Conflict 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, 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, Eli Lilly, NIDA and NIMH. Dr. Markowitz is currently or has been in the past on the speakers' bureau, a consultant, or has received research funding from Novartis, Janssen, Eli Lilly, and NICHD. Dr. Nahas is currently or has been in the past on the speakers' bureau, a consultant, or has received research funds from the following sources: Neuronetics Inc, Cyberonics Inc, Medtronic Inc. Neuropace, Integra, Eli Lilly, Avenir Pharmaceutical, Aventis Pharmaceutical, Astra Zeneca in addition to funding from the NIMH and NARSAD.

References

Adler, L.E., Olincy, A., Waldo, M., Harris, J.G., Griffith, J., Stevens, K., Flach, K., Nagamoto, H., Bickford, P., Leonard, S., Freeman, R., 1998. Schizophrenia, sensory gating and nicotinic receptors. Schizophrenia Bulletin 24 (2), 189–202.

Allen, T.B., McEvoy, J.P., 2002. Galantamine for treatment-resistant schizophrenia. American Journal of Psychiatry 159, 1244–1245.

Barnes, T.R.E., 1989. A rating scale for drug-induced akathisia. British Journal of Psychiatry 154, 672–676.

Breese, C.R., Lee, M.J., Adams, C.E., Sullivan, B., Logel, Judy, Gillen, K.M., Marks, M.J., Collins, A.C., Leonard, S., 2000. Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. Neuropsychopharmacology 23 (4), 351–364.

Buchanan, R.W., Summerfelt, A., Tek, C., Gold, J., 2003. An open-labeled trial of adjunctive donepezil for cognitive impairments in patients with schizophrenia. Schizophrenia Research 59, 29–33.

Cohen, J., 1988. Statistical power analysis for the behavioral science, 2nd ed. Lawrence Earlbaum Associates, Hillsdale, NJ.

Crook, J.M., Tomaskovic-Crook, E., Copolov, D.L., Dean, B., 2000. Decreased muscarinic receptor binding in subjects with schizophrenia: a study of the human hippocampal formation. Biological Psychiatry 48 (5), 381–388.

Cummings, J.L., 2000. Cholinesterase inhibitors: a new class of psychotropic compounds. American Journal of Psychiatry 157 (1), 4–15.

Erickson, S.K., Schwarzkopf, S.B., Palumbo, D., Badgley-Fleeman, J., Smirnow, A.M., Light, G.A., 2005. Efficacy and tolerability of low-dose donepezil in schizophrenia. Clinical Neuropharmacology 28, 179–184.

Davidson, M., Harvey, P., Welsh, K.A., Powchick, P., Putnam, K.M., Mohs, R.C., 1996. Cognitive functioning in late-life schizophrenia: a comparison of elderly schizophrenias patients and patients with Alzheimer's disease. American Journal of Psychiatry 153, 1274–1279.

Freedman, R., Coon, H., Myles-Worsely, M, Orr-Urtreger, A., Olincy, A., Davis, A, Polymeropoulos, M., Holik, J., Hoff, M., Rosenthal, J., Waldo, M.C., Reimher, F., Wender, P., Yaw, J., Young, D.A., Greese, C.R., Adams, C., Paterson, D., Adler, L., Kruglyak, L., Leonard, S., Byerley, W., 1997. Linkage of a neuropysiological deficit in schizophrenia to a chromosome 15 locus. Proceedings of the National Academy of Sciences of the United States of America 94, 587–592.

Friedman, J.L., Adler, D.N., Howanitz, E., Harvey, P.D., Brenner, G., Temporini, H., White, L., Parrella, M., Davis, K.L., 2002. A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for the cognitive impairment of schizophrenia. Biological Psychiatry 51, 349–357.

Goldberg, T.E., Weinberger, D., Berman, K.E., Piskin, N.I.H., Podd, M.H., 1987. Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of the wisconsin card sorting test. Archives of General Psychiatry 44, 1008–1014.

Green, M.F., Kern, R.S., et al., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophrenia Bulletin 26, 119–136.

Hans, S.L., Marcus, J., Nuechterlein, K.H., Asarnow, R.F., Styr, B., Auerbach, J.G., 1999. Neurobehavioral deficits at adolescence in children at risk for schizophrenia. The Jerusalem Infant Development Study. Archives of General Psychiatry 56, 741–748.

Heaton, R., Paulsen, J.S., McAdams, L.A., Kuck, J., Zisook, S., Braff, D., Harris, M.J., Jeste, D.V., 1994. Neuropsychological deficits in schizophrenias: relationship to age, chronicity and dementia. Archives of General Psychiatry 51 (6), 469–476.

Holt, D.J., Bachus, S.E., Hyde, T.M., Wittie, M., Herman, M.M., Vangel, M., Saper, C.B., Kleinman, J.E., 2005. Reduced density of cholinergic interneurons in the ventral striatum in schizophrenia: an in situ hybridization study. Biological Psychiatry 58, 408–416.

Howard, A.K., Thornton, A.E., Altman, S., Honer, W.G., 2002. Donepezil for memory dysfunction in schizophrenia. Journal of Psychopharmacology 16, 267–270.

Hughes, C.P., Berg, L., Danziger, W.L., Coben, L.A., Martin, R.L., 1982. A new clinical scale for the staging of dementia. British Journal of Psychiatry 14, 566–572.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 13 (2), 261–276.

Lane, R.D., Glazer, W.M., Hansen, T.E., Berman, W.H., Kramer, S.L., 1985. Assessment of tardive dyskinesia using the abnormal involuntary movements scale. The Journal of Nervous and Mental Disease 173, 353–357.

Lawrence, A.D., Sahakian, B.J., 1995. Alzheimer disease, attention, and the cholinergic system. Alzheimer Disease and Associated Disorders 9 (Supplement 2), 43–49.

Lenzi, A., Maltinti, E., Poggi, E., Fabrizio, L., Coli, E., 2003. Effects of rivastigmine of cognitive function and quality of life in patients with schizophrenia. Clinical Neuropharmacology 26, 317–321.

MacEwan, G.W., Ehmann, T.S., Khanbhai, I., Wrixon, C., 2001. Donepezil in schizophrenia—is it helpful? An experimental design case study. Acta Psychiatrica Scandinavica 104 (6), 469–472.

Maelicke, A., Albuquerque, E.X., 2000. Allosteric modulation of nicotinic acetylcholine receptors as a treatment strategy for Alzheimer's disease. European Journal of Pharmacology 393, 165–170.

Mendelsohn, E., Rosenthal, M., Bohiri, Y., Weber, E., Kotle, M., Strous, R.D., 2004. Rivastigmine augmentation in the management of chronic schizophrenia with comorbid dementia: an open-label study investigating effects on cognition, behaviour and activities of daily living. International Clinical Psychopharmacology 19, 319–324.

Miller, A.L., 2004. Combination treatments for schizophrenia. CNS Spectrums 9 (9), 19–23.

Mohamed, S., Paulsen, J.S., O'Leary, D., Arndt, S., Andreasen, N., 1999. Generalized cognitive deficits in schizophrenia. Archives of General Psychiatry 56, 749–754.

Powchick, P., Davidson, M., Haroutunian, V., Gabriel, S.M., Purohit, P., Perl, D.P., Harvey, P.D., Davis, K.L., 1998. Postmortem studies in schizophrenia. Schizophrenia Bulletin 24 (3), 325–341.

Risch, S.C., McGurk, S., Horner, M.D., Nahas, Z., Owens, S.D., Molloy, M., Gilliard, C.E., Christie, S., Markowitz, J.S., DeVane, C.L., Mintzer, J., George, M.S., 2001. A double-blind placebo controlled case study of the use of donepezil to improve cognition in a schizoaffective disorder patient: fMRI correlates. Neurocase 7, 105–110.

Risch, S.C., Horner, M.D., McGurk, S., Palecko, S., Markowitz, J.S., Nahas, Z., DeVane, C.L., 2005. Donepezil effects on mood in patients with schizophrenia and schizoaffective disorder. International Journal of Neuropsychopharmacology 9, 1–3.

Rosse, R.B., Deusch, S.I., 2002. Adjuvant galantamine administration improves negative symptoms in a patient with treatment-refractory schizophrenia. Clinical Neuropharmacology 25, 272–275.

Schubert, Max H., Young, Keith, Hicks, Paul B., 2006. Galantamine improves cognition in schizophrenic patients stabilized on risperidone. Biological Psychiatry 60 (6), 530–533.

Simpson, G.N., Angus, J.W.S., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 212 (suppl 44), 11–19.

Stryjer, R., Strous, R.D., Bar, F., Werber, E., Shaked, G., Buhiri, Y., Kotler, M., Weizman, A., Rabey, J.M., 2003. Beneficial effects of donepezil augmentation for the management of comorbid schizophrenia and dementia. Clinical Neuropharmacology 26, 12–17.

Tugal, O., Yazici, K.M., Yagiociglu, E.A., 2004. A double-blind, placebo controlled, cross-over trial of adjunctive donepezil for cognitive impairment in schizophrenia. International Journal of Neuropsychopharmacology 7, 117–123.

Further reading

Benton, A.L., Hamsher, K., Sivan, A.B., 1994. Multilingual Aphasia Examination. AJA Associates, Iowa City.

Saykin, A., Shtasel, D.I., Gur, R.E., Kester, D.B., Moxley, L.H., Stafaniak, P., Gur, R.C., 1994. Neuropsychological deficits in neuroleptic naïve patients with first-episode schizophrenia. Archives of General Psychiatry 51 (2), 124–131.