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The central cholinergic system profile of olanzapine compared with placebo in Alzheimer's disease

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SUMMARY

Objective The objective of this analysis was to compare the treatment-emergent central anticholinergic-like adverse events experienced during treatment with olanzapine versus placebo in patients with psychosis and/or agitation due to Alzheimer's disease (AD). In addition, changes in cognition were assessed in a subgroup of patients with mild to moderate cognitive impairment.

Methods Double-blind data were compared for placebo and three fixed olanzapine dosages (5 mg/day, 10 mg/day, and 15 mg/day) in 206 nursing home-residing patients with AD for five *a priori* selected central nervous system anticholinergic-like adverse events: confusion, delirium, delusions, hallucinations, abnormal thinking. Mean change from baseline to endpoint on the Alzheimer's Disease Assessment Scale—Cognitive (ADAS-Cog) was measured for a subgroup of 43 patients who had mild to moderate cognitive impairment at baseline.

Results There were no significant differences in central anticholinergic-like adverse events at any olanzapine dose compared to placebo. Additionally, in the 43-patient subgroup, there were no significant differences in mean change in ADAS-Cog scores between placebo and the three olanzapine dose subgroups.

Conclusion Olanzapine did not differ significantly from placebo for any of the five central nervous system anticholinergic events nor on the ADAS-Cog. Olanzapine's initially reported potent in vitro muscarinic receptor affinity is not consistent with this clinical study of central nervous system anticholinergic-like adverse events in patients with AD.

KEY WORDS — olanzapine; Alzheimer's disease

INTRODUCTION

Antipsychotic drugs are the treatment of choice for Alzheimer's disease (AD) patients with persistent hallucinations, delusions, and agitation/aggression. Although antipsychotic drugs do appear to help manage these components of the dementia patient's clinical presentation, patients may experience treatment-emergent adverse events, including anticholinergic-like ones. Such events are of special concern in AD patients who are particularly vulnerable to anticholinergic adverse events even at low doses of antimuscarinic drugs. Treatment-emergent or worsening adverse clinical events that can indicate centrally mediated anticholinergic activity include confusion, delirium, or impairment of cognition (Richardson *et al.*, 1985; Thienhaus *et al.*, 1990; Tollefson *et al.*, 1991; Flacker *et al.*, 1998), and peripherally mediated events such as dry mouth, severe constipation, blurred vision, and difficulties with urination (Lipowski, 1990; Kennedy *et al.*, 2000a).

In vitro methodologies are commonly used to predict a molecule's tendency to produce untoward events in vivo. Results from in vitro radioligand receptor binding predicted that olanzapine had potent and nonspecific muscarinic receptor antagonism where antagonism of the postsynaptic M_1 receptor would be associated with both central and peripheral anticholinergic side effects (Bymaster *et al.*, 1996). However, placebo-controlled trials of patients with

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schizophrenia (Beasley *et al.*, 1996) showed that rates of peripheral anticholinergic-like adverse events were relatively low. Similarly, relatively low rates of peripheral anticholinergic-like events reported in a placebo-controlled trial of AD patients taking olanzapine (Street *et al.*, 2000), as well as in double-blind olanzapine *vs* clozapine (Chengappa *et al.*, 2000) and olanzapine *vs* risperidone (Kennedy *et al.*, 2000a) comparator studies. These studies found that dry mouth, blurred vision, constipation, and micturition difficulties occurred with risperidone in vivo (Arnt and Skarsfeldt, 1998) at a rate that was not significantly different from that seen in patients treated with olanzapine (Kennedy *et al.*, 2000a) despite risperidone's low antimuscarinic affinity in vitro. Although olanzapine's peripheral anticholinergic-like events have been recently reviewed in the literature (Purdon *et al.*, 2000; Street *et al.*, 2000) the extent to which olanzapine has central anticholinergic activity in the elderly patient has not.

The purpose of this post-hoc study was to compare central anticholinergic-like adverse events and cognitive outcomes in patients with AD treated with olanzapine to those treated with placebo and to determine whether olanzapine's reported in vitro muscarinic receptor antagonism is predictive of the in vivo frequency of central anticholinergic-like adverse events.

METHODS

Study group

Data from a 6-week, double-blind, placebo-controlled trial of three fixed doses of olanzapine (5 mg/day, 10 mg/day, and 15 mg/day) in 206 elderly patients with AD were retrospectively analyzed (Street *et al.*, 2000). This previously published study included only patients with possible or probable AD defined by stringent research criteria (Street *et al.*, 2000) and who had symptoms of agitation/aggression, hallucinations, or delusions as measured by the Neuropsychiatric Inventory—Nursing Home version (NPI/NH) (Wood *et al.*, 2000).

The majority of patients in this trial had severe to very severe cognitive impairment at baseline as measured by the Mini-Mental State Examination (MMSE) (Street *et al.*, 2000). There was no statistically significant difference in MMSE scores comparing any dose to placebo (Street *et al.*, 2000). Because the MMSE is insensitive to subtle cognitive deficits and the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) is neither reliable nor valid for use in very severely cognitively impaired patients, a subgroup of patients with mild to moderate cognitive impairment ($n = 43$) was identified from the total patient population for a subanalysis. This subgroup was defined using the cutoffs of a MMSE score > 7 and $\leqslant 23$ points and an ADAS-Cog score of < 46 points at baseline.

Assessments

All patient assessments were conducted at the nursing home facilities by health care professionals, including neurologists, psychiatrists, geriatricians, psychometrists, nurses, and other degreed individuals who received training for the study. To characterize the presence or absence of central anticholinergic treatment-emergent adverse events, five events were derived *a priori* by a content analysis of the standardized classification terms for adverse reactions used in the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). These events were confusion, delirium, delusions, hallucinations, and abnormal thinking. At each study visit, the investigator solicited the presence and severity for each of these events.

In addition to the baseline MMSE, cognitive function was assessed at the baseline randomization visit and at the last study visit (Week 6 or at early termination) using the ADAS-Cog. Psychosis and other behavioral features were assessed at weekly visits using the NPI-NH.

Statistical methods

All 206 patients from the study sample were included in the categorical analysis of the five central cholinergic system adverse events. The event rates were compared between the olanzapine and placebo treatment groups for each dose level of olanzapine as well as for all three dose levels combined. Because of the expected small cell counts, these analyses were conducted using Fisher's Exact test. In addition, the relationship between dose and each of the event rates was tested using the Mantel-Haenszel statistic.

The effect of olanzapine on cognition was explored in a subset of patients with mild to moderate cognitive impairment. In this subgroup, changes from baseline in the ADAS-Cog total were computed using the last observation carried forward (LOCF) for each patient. Within each treatment group, these changes were tested for significance with the Wilcoxon Signed Rank Test. An analysis of variance (ANOVA) was used to

Table 1. Frequency of central anticholinergic-like treatment-emergent adverse events in Alzheimer's patients ($n = 206$) on placebo *vs* daily olanzapine[1]

Event	Placebo ($n = 47$) % (n)	OLZ 5 mg ($n = 56$) % (n)	OLZ 10 mg ($n = 50$) % (n)	OLZ 15 mg ($n = 53$) % (n)	OLZ Total[3] ($n = 159$) % (n)
Confusion[2]	4.3(2)	3.6 (2)	10.0 (5)	5.7 (3)	6.3 (10)
Delirium[2]	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.06 (1)
Delusions[2]	6.4 (3)	1.8 (1)	6.0 (3)	0.0 (0)	2.5 (4)
Hallucinations[2]	4.3 (2)	7.1 (4)	4.0 (2)	5.7 (3)	5.7 (9)
Abnormal thinking[2]	0.0 (0)	5.4 (3)	8.0 (4)	0.0 (0)	4.4 (7)

[1]One or more individual events may have occurred in any single patient.
[2]No statistically significant differences among four treatment groups ($p \geqslant 0.100$).
[3]No statistically significant differences in total olanzapine events (pooled across dosage groups) compared with placebo ($p \geqslant 0.197$) among four treatment groups.

test for differences between the treatment groups. The relationship between changes in ADAS-Cog and changes in the NPI-NH core total (sum of delusions plus hallucinations plus agitation) was determined for each treatment group using Pearson's correlation coefficient. Mean changes from baseline to endpoint for each olanzapine dose are presented for each of 11 ADAS-Cog sub-domains with the corresponding sub-domain placebo mean change subtracted from it to show the component of the effect ascribable to olanzapine. All tests of statistical significance were conducted using two-tailed tests with $\alpha = 0.05$.

RESULTS

Study demographics

Patient demographics and illness characteristics were similar across all four treatment groups (Street *et al.*, 2000). Mean age was 82.8 years, 61.2% were female, mean time since the diagnosis of AD was 2.2 years, and mean baseline MMSE score was 6.9 points, indicating that the overall sample was moderately to severely cognitively impaired. The 43-patient subgroup had comparable demographic and illness characteristics to those for the four treatment groups ($p \geqslant 0.549$). The study subgroup had a mean age of 85.2 years, 62.8% were female, and patients overall had moderate cognitive impairment (mean entry MMSE and ADAS-Cog scores of 15.7 and 34.8 points, respectively).

Central anticholinergic-like treatment-emergent adverse events in the total patient population

Central anticholinergic-like treatment-emergent adverse events in the placebo and olanzapine 5 mg, 10 mg, and 15 mg groups are summarized in Table 1. There were no significant differences in the occurrence of any event for any olanzapine dose compared with placebo ($p \geqslant 0.100$). Additionally, the total rate of events pooled across all olanzapine dosages compared with placebo was not significantly different ($p \geqslant 0.197$). Further, there was no relationship with olanzapine dose for any of the five events (confusion: $p = 0.476$; delirium: $p = 0.670$; delusions: $p = 0.198$; hallucinations: $p = 0.960$; abnormal thinking: $p = 0.918$).

Mean change in ADAS-Cog scores in mild to moderately impaired patient subgroup

Mean baseline ($\pm$ s.d.) and change scores for total ADAS-Cog within each treatment group are presented in Table 2. There were no significant differences across or within treatment groups. The placebo group had a mean within-group ADAS-Cog reduction of 1.38 points from mean baseline (i.e., worsening of cognition), while the 5 mg/day olanzapine treatment group increased (improved) change scores from mean baseline by 0.94 points. The group receiving 10 mg/day olanzapine had a reduction from mean baseline of 4.0 ADAS-Cog points, while the 15 mg/day group had a decline of 1.83 points.

These ADAS-Cog mean change scores within each dose group were not significantly associated with the NPI-NH core total change scores ($|r| < 0.53$ and $p > 0.183$ for all treatment groups), suggesting that any improvements in agitation and psychotic symptoms were not related to changes in cognition. Figure 1 illustrates the NPI-NH core change as a function of change in ADAS-Cog scores in the olanzapine 5 mg/day group, previously reported to have the

Table 2. Mean baseline and change scores for ADAS-Cog total in subgroup of Alzheimer's patients with mild to moderate cognitive impairment[1]

Treatment	*n*	Mean baseline (SD)	Mean change (SD)	Pair-wise *p*-value compared to placebo	Across treatment groups *p*-value
Placebo	8	34.38 (±7.74)	1.38 (±6.23)	0.961	0.511
OLZ 5 mg	17	35.71 (±5.96)	−0.94 (±8.10)	0.703	
OLZ 10 mg	8	34.12 (±5.87)	4.00 (±7.03)	0.203	
OLZ 15 mg	10	34.00 (±8.21)	1.83 (±8.98)	0.695	

[1]Negative change denotes improvement in score.

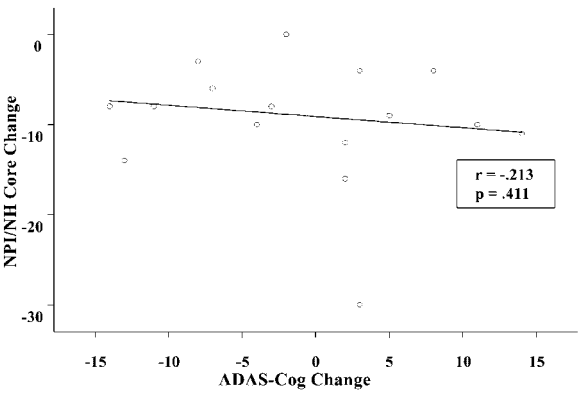

Figure 1. There is no significant relationship between changes in ADAS-Cog and changes in NPI-NH core total scores (sum of delusions plus hallucinations plus agitation) in a subgroup of AD patients ($n = 43$) with mild to moderate cognitive impairment on 5 mg olanzapine. Note: Lower change scores denote improvement

largest antipsychotic effect size (Street *et al.*, 2000), and there is also no significant relationship.

Table 3 lists mean differences between values of placebo and each olanzapine dose for each of the 11 ADAS-Cog items. Relative to the decline in the individual ADAS-Cog item scores associated with placebo treatment, olanzapine 5 mg/day and 15 mg/day groups improved on ten of 11 and on seven of 11 items, respectively, while the olanzapine 10 mg/day group improved on five of 11 items. Recall of test instructions was poor across all three olanzapine dosages. Five of 11 ADAS-Cog items demonstrated improvement across all olanzapine dose groups as follows: word recall, naming objects with fingers, following commands, ideational praxis, and language (Figure 2).

Table 3. Mean change scores for individual ADAS-Cog items in subgroup of Alzheimer's patients with mild to moderate cognitive impairment

Number	ADAS-Cog Item name	Mean change (OLZ Group—Placebo Group)[1,2]		
		OLZ 5 mg ($n = 17$)	OLZ 10 mg ($n = 8$)	OLZ 15 mg ($n = 10$)
1	Word recall	−0.257	−0.625	−0.575
2	Naming objects with fingers	−1.222	−0.556	−0.256
3	Following command	−0.654	−0.639	−0.789
4	Constructional praxis	−0.403	0.750	−0.225
5	Ideational praxis	−0.536	−1.139	−1.000
6	Orientation	−0.111	1.722	−0.078
7	Word recognition	−0.103	0.250	1.472
8	Language	−0.333	−0.319	−0.244
9	Spoken language comprehension	−0.111	0.486	0.311
10	Word—spontaneous speech	−0.056	0.361	0.611
11	Recall of test instructions	0.500	1.625	0.500
Number of test items improved relative to placebo		10/11	5/11	7/11

[1]Difference in mean change scores of each item of the ADAS-Cog for each dosage group of OLZ relative to the mean change in each item of the ADAS-Cog for the placebo group.
[2]Negative numbers indicate numerical differences indicating improvement in function.

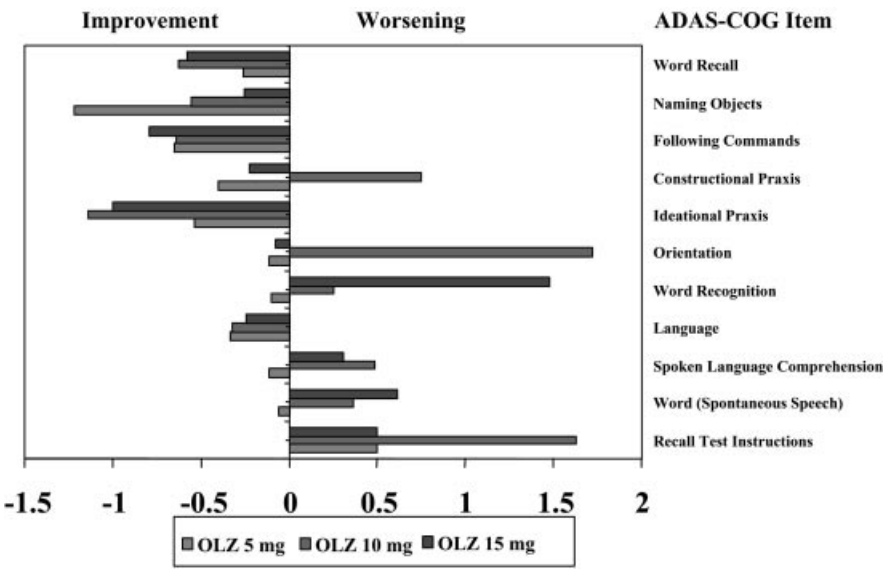

Figure 2. Baseline to endpoint change in ADAS-Cog items for placebo and olanzapine groups (5, 10, and 15 mg/day). Patients demonstrated significant improvement relative to placebo across all olanzapine dosages in the following items: word recall, naming objects with fingers, following commands, ideational praxis, and language

DISCUSSION

We describe clinical adverse events and cognitive tests for a cohort of AD patients participating in a double-blind placebo-controlled trial on three doses of daily olanzapine for agitation and/or psychotic symptoms. We found no significant differences between olanzapine and placebo groups for the occurrence of central anticholinergic-like adverse effects. These results are supported by recent in vivo binding and in vivo functional studies in normal animals and clinical populations who had relatively low levels of nonspecific anticholinergic-like activity for olanzapine (Schotte *et al.*, 1996; Zhang and Bymaster, 1999; Raedler *et al.*, 2000). Further, these data are consistent with the recently published data concerning olanzapine's relatively low occurrence of peripherally manifested anticholinergic-like events (Kennedy *et al.*, 2000a).

Cognitive effects as measured by the ADAS-Cog was not significantly different at olanzapine doses of 5, 10, or 15 mg/day versus placebo. These results are consistent with those previously reported for this same cohort where patients treated with olanzapine compared with placebo did not demonstrate any significant improvement nor worsening of MMSE total scores at any dose (Street *et al.*, 2000). The ADAS-Cog is more sensitive than the MMSE. To mitigate any potential floor changes using the ADAS-Cog in this specific study cohort that included severe patients, we analyzed a subgroup with mild to moderate cognitive impairment for changes on ADAS-Cog scores.

Additionally, as illustrated in Figure 1, the ability of olanzapine 5 mg to improve cognition appears to be unassociated with its potential ability to improve psychosis. This analysis supports the view that any observed change in ADAS-Cog performance with olanzapine 5 mg may be primarily a direct effect on cognition. This is consistent with the path analysis of olanzapine's effect on cognition in younger patients with schizophrenia as reported in the Purdon *et al*. study (2000).

In our subgroup, olanzapine demonstrated numerical improvement, relative to placebo, in five of the 11 elements of the ADAS-Cog (word recall, naming objects with fingers, following commands, ideational praxis, and language) across all dosages. Only recall of test instructions demonstrated non-dose-dependent worsening, which is also consistent with the literature (Purdon *et al.*, 2000). The absence of significant dose-related treatment-emergent adverse anticholinergic-like events, as well as the absence of significant adverse changes in cognition reported here, contrasts with previously published in vitro muscarinic equilibrium constants (K_i values) and raises serious

questions about their utility for predicting, at clinically effective doses, in vivo central and peripheral cholinergic profiles. In fact, the accumulating clinical literature suggests in vitro receptor binding data for olanzapine does not relate well to clinical practice.

Many possible explanations exist for the absence of dose-dependent anticholinergic-like adverse events observed in our analyses. Olanzapine has been characterized as a multiple-acting-receptor-targeted-antipsychotic (MARTA) (Kennedy, 2000), and as such, it is likely that a pharmacodynamic interplay occurs between the multiple receptors that are being antagonized in vivo by olanzapine. However, the relative infrequency of observed anticholinergic-like adverse events may be due to olanzapine's relatively low binding to human M_1 through M_5 receptors (Bymaster *et al.*, 1996; Bymaster and Falcone, 2000). Olanzapine is a weak functional muscarinic antagonist in vitro when compared with potent anticholinergic drugs like atropine and amitriptyline (Richardson *et al.*, 1985).

Furthermore, in AD at least some of the post-synaptic M_1 receptors are functionally de-coupled from part of the cholinergic neuron's internal transduction mechanisms. Thus, the M_1 system may be clinically sub-functional or nonfunctional in patients with this illness. Therefore, M_1 antagonism-associated worsening of cognitive function may only be evident when the antagonist is potent (Smith *et al.*, 1987; Flynn *et al.*, 1991) or post-synaptic neurons are still relatively functional, as may occur earlier in the disease progression.

Another possible explanation for the apparent infrequency of adverse central anticholinergic-like events relates to olanzapine's M_2 receptor (presynaptic auto-inhibitory receptor) binding, which demonstrates in vitro a K_i similar to the M_1 receptor (Bymaster and Falcone, 2000). In mild to moderately impaired AD patients with some degree of preservation of M_2 receptors, antagonism of the M_2 presynaptic inhibitory autoreceptors in theory could increase intersynaptic acetylcholine levels (Kennedy *et al.*, 1998). Therefore, selective M_2 receptor antagonists have been of considerable interest for drug development for the treatment of AD (Davis *et al.*, 1993). With respect to olanzapine, in vivo microdialysis in rats shows that olanzapine raises dopamine, norepinephrine, and acetylcholine extracellular levels, but not serotonin, in the prefrontal cortex (Meltzer *et al.*, 1999; Zhang and Bymaster, 1999). Further, olanzapine significantly raises rat hippocampal extracellular acetylcholine levels to about 1100 percent above baseline (Figure 3) (Shirazi *et al.*, 2000). In humans, recent PET data suggest that the M_2 antagonist property of olanzapine predominates at low (5 mg/day) and high (20 mg/day) dosages (Raedler *et al.*, 2000). Therefore, milder M_2 antagonism may be relevant to the absence of significant ADAS-Cog decline in the 10 and 15 mg groups, relative to placebo; our 5 mg dose group had numerically improved ADAS-Cog scores.

In severely impaired AD patients, extensive degeneration of presynaptic nerve terminals containing M_2 autoreceptors (Kennedy *et al.*, 1998) makes it

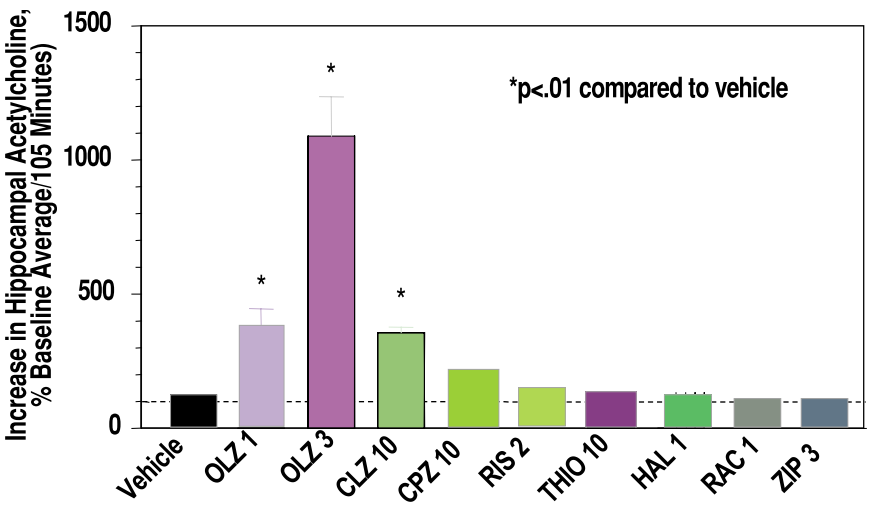

Figure 3. Effects of olanzapine and other antipsychotic drugs on extracellular levels of acetylcholine in the rat hippocampus: *in vivo* microdialysis (Shirazi *et al.*, 2000)

unlikely that M_2 antagonism is active, therefore rendering it an unlikely sole explanation for the finding that no central cholinergic-like treatment-emergent adverse event at any olanzapine dose was different from placebo, as demonstrated in this study ($p \geqslant 0.100$).

An alternate possible mechanistic account for the changes in ADAS-Cog performance in patients treated with olanzapine involves a recently hypothesized in vivo set of olanzapine antagonist functional interactions with serotonin receptor subtypes presumed to be present on cholinergic neurons (Kennedy *et al.*, 1998; Kennedy *et al.*, 2000b). This hypothesis is summarized pictorially in Figure 4. Panel A shows the usual condition where certain 5-HT receptor subtypes, when stimulated, either enhance or reduce the release of acetylcholine. Panel B shows how olanzapine's antagonistic effects on presynaptic M_2, 5-HT_3, and 5-HT_6 receptors could increase acetylcholine release. Olanzapine has been shown to be a functional 5-HT_3 and 5-HT_6 receptor antagonist (Eli Lilly and Company, data on file). Five independent investigations of the functional consequences of antagonizing the 5-HT_6 receptor [antisense (Bourson *et al.*, 1995), drug antagonism (Sleight *et al.*, 1998; Rogers *et al.*, 1999), knockout mice (Tecott *et al.*, 1998; Kennedy *et al.*, 2000b)] strongly suggest that the 5-HT_6 receptor resides on cholinergic neurons and plays an important role in regulating acetylcholine release (Branchek and Blackburn, 2000). Two preclinical studies found significant cognitive improvement in the presence of 5-HT_6 receptor blockade (Tecott *et al.*, 1998; Rogers *et al.*, 1999).

Polymorphism of the 5-HT_6 receptor may be a susceptibility factor for AD (Tsai *et al.*, 1999). However, whether or not 5-HT_6 receptors are increased, decreased, or functional in AD has not been reported in the peer-reviewed literature. There are also no data

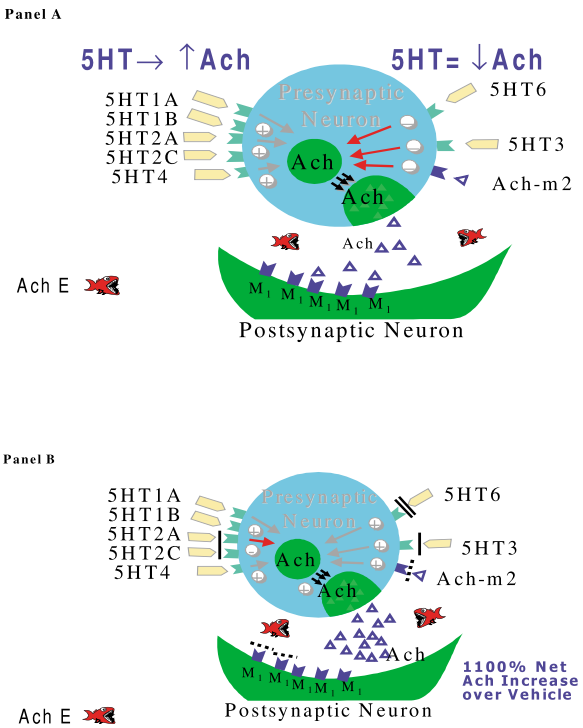

Figure 4. Panel A. Summary of hypothesized interactions between the serotonin and cholinergic systems. Presynaptic serotonin (5-HT) receptors located on the left side of the figure (5-HT1A, 2A, 2C, and 4), when stimulated by serotonin (▨), are reported to enhance the release of acetylcholine (△). Serotonin receptors located on the right side of the figure, when stimulated by serotonin, are proposed to suppress release of acetylcholine. The acetylcholine M_2 receptor, when stimulated by acetylcholine, suppresses acetylcholine release. Panel B. Summary of hypothesized interactions in the presence of olanzapine. Antagonism of presynaptic M_2, 5-HT_3, and 5-HT_6 receptors could enhance release of acetylcholine. In ambulatory rats in vivo microdialysis shows that olanzapine increases the release of acetylcholine in the prefrontal cortex (Meltzer *et al.*, 1999) and in the hippocampus (Shirazi *et al.*, 2000)

from normal healthy or patient populations to provide guidance as to the relevance of 5-HT_6 agonism or antagonism in treatment of any clinical disorder, being largely dependent upon generalizing from rat studies.

In this study, the trial investigators were aware that olanzapine had been reported to be potently anticholinergic in vitro and therefore were guided to solicit from direct observation of the patient and also the caregiver the presence or absence of anticholinergic-like treatment-emergent adverse events. Also, the treatment-emergent events examined herein were specified *a priori* as a safety focus in the statistical analysis reported in the primary analysis of the Street *et al*. study (2000). Nevertheless, the paucity of literature regarding untreated or placebo-treated 6-week incidence rates in AD for the five events examined leaves unclear whether the lack of significance found in this study is attributable to the placebo group experiencing more events than would be typically expected in a 6-week study in AD or if the study was underpowered to detect differences.

This present study has many other limitations, including the lack of a primary analysis focused on *a priori* defined cognitive analyses, and the small number of mild to moderate AD patients analyzed using the ADAS-Cog. It is important to note that the primary objective of this study was to investigate olanzapine *vs* placebo in the treatment of psychosis and behavioral disturbances associated with AD and therefore, the study was powered to effectively test that hypothesis. Since the hypotheses explored in this report are secondary in nature, the sample size may not have been sufficient to demonstrate statistically significant differences. Therefore, replication is needed using a prospective randomized, double-blind, placebo-controlled design conducted in patients with AD who are early in the course of the illness and relatively unaffected by non-cognitive behavioral symptoms. Such studies are currently underway in the United States.

CONCLUSION

This placebo-controlled study of 5 mg, 10 mg, and 15 mg of olanzapine in patients with AD found no statistically significant occurrences of adverse central anticholinergic-like symptoms and no statistically significant effects on cognition as measured by the ADAS-Cog in a subgroup of mild to moderately cognitively impaired AD patients. The non-significant numerical improvement in ADAS-Cog performance seen with the 5 mg dose was not attributable to reduction in psychosis and requires further prospective study with a larger sample to determine if statistically and clinically significant cognitive benefit is produced by olanzapine treatment of patients who have AD without psychotic symptoms.

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