# Correlates of Anticholinergic Activity in Patients With Dementia and Psychosis Treated With Risperidone or Olanzapine

Benoit H. Mulsant, M.D.; Georges M. Gharabawi, M.D.; Cynthia A. Bossie, Ph.D.; Lian Mao, M.S.; Rick A. Martinez, M.D.; Larry E. Tune, M.D.; Andrew J. Greenspan, M.D.; Jeni N. Bastean, Pharm.D.; and Bruce G. Pollock, M.D., Ph.D.

***Background:*** Older individuals with dementia are highly sensitive to the effects of muscarinic receptor blockade.

***Study Design:*** This was a 6-week multisite, randomized clinical trial. ***Subjects:*** Eighty-six patients with probable Alzheimer's disease, vascular dementia, or mixed-etiology dementia (DSM-IV criteria) were randomly assigned to treatment with olanzapine or risperidone. ***Assessments:*** Anticholinergic activity was measured with a radioreceptor assay, and plasma levels of antipsychotic medications were determined. Primary outcomes were assessed with the Udvalg for Kliniske Undersogelser (UKU) scale and somnolence adverse events; secondary outcome measures included scores on the Neuropsychiatric Inventory (NPI) and other scales.

***Results:*** There were no between-treatment differences in the UKU scale or in somnolence adverse events. Statistically significant improvements ($p < .001$) from baseline were found for the NPI measures, with no between–treatment group differences. Olanzapine was associated with significant increases from baseline in anticholinergic activity, while risperidone was not; the between–treatment group differences were not statistically significant. Increase in anticholinergic activity was associated with an increase in anticholinergic side effects and slower performance on the Trail Making Test Part A. Higher endpoint anticholinergic activity was associated with higher endpoint scores on several items from the NPI, including delusions, anxiety, and aberrant motor behavior.

***Implications:*** Efficacious doses of olanzapine increased anticholinergic activity in older patients with dementia, while similarly efficacious doses of risperidone did not. Patients whose anticholinergic activity increased were more likely to experience anticholinergic side effects and to have worsening in certain cognitive domains. These data suggest that certain patients may be vulnerable to the anticholinergic activity associated with antipsychotic treatment.

*(J Clin Psychiatry 2004;65:1708–1714)*

*Received May 19, 2004; accepted Sept. 14, 2004.* *From Western Psychiatric Institute and Clinic, Department of Psychiatry, Division of Geriatric Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pa. (Drs. Mulsant and Pollock); Janssen Medical Affairs, L.L.C., Titusville, N.J. (Drs. Gharabawi, Bossie, Greenspan, and Bastean and Mr. Mao); Geriatric Research, Education, and Clinical Center, Pittsburgh Veterans Administration Health System, Pittsburgh, Pa. (Dr. Mulsant); Janssen Research Foundation, Titusville, N.J. (Dr. Martinez); and Wesley Woods Health Center of Emory University, Atlanta, Ga. (Dr. Tune).*

*This research was funded by Janssen Medical Affairs, L.L.C.*

*Financial disclosure appears at the end of the article.*

*Corresponding author and reprints: Benoit H. Mulsant, M.D., Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213 (e-mail: mulsantbh@upmc.edu).*

Muscarinic acetylcholine receptors are distributed throughout the nervous system, both centrally and peripherally. Modulation of the activity levels of these transmitters has a variety of effects, including peripheral effects impacting on the gastrointestinal (i.e., nausea, constipation, and dry mouth) and cardiovascular (tachycardia and palpitation) systems.[1] The central acetylcholine receptor system is intrinsically involved in several cognitive domains, particularly attentional functions and episodic memory.[2] Thus, medications that interact with the muscarinic cholinergic system can have a variety of therapeutic or adverse effects. Multiple different compounds cause adverse anticholinergic effects, generally by antagonism at the muscarinic $M_1$ receptor.[3,4] It has been demonstrated that the effects of total anticholinergic activity are cumulative[5,6] and can be measured in vivo. This activity may be measured with radioreceptor binding and can be expressed in terms of atropine, the prototypical $M_1$ antagonist, equivalents.[7,8]

Many previous studies have identified moderate (memory impairment)[9] to serious (significant delirium)[10] effects resulting from anticholinergic activity of medications. Many individuals are taking medications with "hidden" anticholinergic effects, including medications used to treat cardiac conditions, allergic rhinitis, and psychiatric conditions such as depression. Vulnerability to this effect is increased substantially with age[11] and in individu-

als whose cortical functioning is otherwise compromised, such as patients who have Alzheimer's disease,[12] late-life schizophrenia,[13] or traumatic brain injury.[14,15] Moreover, as individuals age, they are increasingly likely to be prescribed multiple medications resulting in additive total anticholinergic activity.[16]

Treatment of Alzheimer's disease and related conditions with medications that improve cholinergic functioning has been a recent therapeutic development.[17] The 4 medications (tacrine, donepezil, galantamine, and rivastigmine) currently approved by the U.S. Food and Drug Administration for the treatment of mild to moderate Alzheimer's disease are acetylcholinesterase inhibitors. These medications increase cholinergic functions by inhibiting the breakdown of endogenously produced acetylcholine. They apparently do not impact the production of acetylcholine or the sensitivity of acetylcholine receptors. Importantly, there are no human data to assess whether or not these medications reverse the effects of cholinergic receptor antagonism. Patients treated with acetylcholinesterase inhibitors who received medications with anticholinergic properties had a worse course of illness than those who did not receive this type of medication.[18] So, even in cases in which clinically effective doses of acetylcholinesterase inhibitors are administered, adverse effects can be caused by medications that block central cholinergic receptors.

The consequences of excessive anticholinergic activity in elderly individuals, especially those with dementia, can be substantial. One of the major potential causes of reversible cognitive impairment in older individuals is unintentional excessive treatment with anticholinergic medications, often through combinations of medications administered to treat other conditions.[19] As a result, avoidance of excessive administration of anticholinergic medications, particularly in vulnerable populations, is a clinical imperative.

Current treatment standards for first-line pharmacotherapy of agitation and psychosis in dementia typically include the use of antipsychotic medications. Due to concerns about the development of irreversible tardive dyskinesia,[20] a high risk even in the short term for the treatment of elderly individuals, most of these patients are treated with atypical antipsychotic medications. Double-blind studies have demonstrated the efficacy of both olanzapine and risperidone for these symptoms.[21–25] While these medications have been shown to be effective relative to placebo (at least at certain doses), there are essentially no published head-to-head randomized, prospective comparative studies of the relative safety and efficacy of atypical antipsychotic medications for the treatment of psychosis in dementia. Comparative information about different atypical medications would be helpful for clinicians treating this population.

This study addressed the relative efficacy and safety of 2 widely used atypical antipsychotic medications (risperidone and olanzapine) for the treatment of psychosis in dementia, assessed with several outcome measures. As previously reported, muscarinic $M_1$ receptor antagonism and the level of anticholinergic activity of olanzapine are both considerably less than those seen with clozapine[26,27] and considerably greater than those seen with risperidone treatment.[28] Thus, we also assessed anticholinergic activity and anticholinergic-related side effects.

## METHOD

### Subjects

This multisite clinical trial was conducted at 12 different study sites. Patients were entered into the study if they were over the age of 55 years, had probable Alzheimer's disease, probable vascular dementia, or probable dementia of mixed etiology. Male and female patients were recruited, and all subjects were required to meet several inclusion criteria. These patients had to meet DSM-IV criteria for 1 of the 3 dementia types described above, with a requirement that subjects had to have a duration of illness of at least 1 year. All were residents of long-term care facilities, with Mini-Mental State Examination[40] scores at study entry between 7 and 26. They also had to have definite psychotic symptoms, as defined by having a Neuropsychiatric Inventory (NPI)[29] frequency × severity score of greater than or equal to 4 on delusions, hallucinations, or both.

Exclusion criteria were the presence of delirium at the time of study entry as defined by the Confusion Assessment Method,[30] an inability to swallow oral medication, a probable or definite diagnosis of psychosis prior to the onset of dementia, and an inability to otherwise cooperate with the study procedures. The study was approved by an institutional review board at each of the 12 sites, and each patient or his or her legal representative signed an informed consent form. Descriptive characteristics of the patients, as a function of treatment condition, are presented in Table 1.

### Study Design

This was a 6-week, double-blind, randomized clinical trial preceded by a 7-day single-blind placebo period. Any subject who experienced a significant exacerbation of his or her psychosis could be entered into double-blind therapy after 3 days of washout. Following the washout, subjects were treated with either risperidone or olanzapine, 2 capsules per day at bedtime. The titration schedule for risperidone was 0.25 mg/day for the first 3 days, followed by an increase to 0.5 mg/day for days 3 through 6. Starting at day 7, the risperidone dose was increased to 0.75 mg/day until day 10, after which the investigator could increase the dose by 0.25 mg/day every 4 days if there was an insufficient clinical response. The total allowable risperidone dose was 1.5 mg/day. For olanzapine,

Table 1. Demographic and Baseline Characteristics of the Intent-to-Treat Population[a]

| Variable | Risperidone (N = 42) | Olanzapine (N = 43) |
|---|---|---|
| Gender, % female | 71 | 84 |
| Age, mean ± SD, y | 84.7 ± 7.32 (range, 63–96) | 83.0 ± 6.89 (range, 63–95) |
| Baseline MMSE score, mean ± SD | 13.7 ± 5.05 (range, 7–25) | 13.2 ± 4.79 (range, 7–25) |
| Race, % | | |
| White | 76 | 79 |
| Hispanic | 19 | 16 |
| Black | 5 | 5 |
| Weight, mean ± SD, kg | 60.6 ± 11.82 | 62.4 ± 13.86 |
| Dementia type, % | | |
| Alzheimer's disease | 76 | 86 |
| Vascular dementia | 12 | 2 |
| Mixed | 12 | 12 |
| Length of institutionalization, mean ± SD, mo | 11.9 ± 13.5 (median = 7; range, 1–54) | 27.1 ± 34.6 (median = 12; range, 1–156) |

[a]Includes all treated patients who had baseline and at least 1 postbaseline assessment. One 92-year-old white female olanzapine-treated patient did not have postbaseline assessment and was excluded from the intent-to-treat analysis.
Abbreviation: MMSE = Mini-Mental State Examination.

the starting dose was 2.5 mg/day and the same titration schedule was employed, with a maximum possible dose of 10.0 mg/day. No dose adjustments were allowed in the 4 days prior to any blood sample collection. These maximum doses and titrations were selected based upon previously published double-blind studies of risperidone[22] and olanzapine[23] in patients with dementia.

Lorazepam was allowed for 4 days in any 7-day period for the treatment of agitation, at a maximum dose of 3.0 mg/day. Any subject who had been receiving daily benzodiazepines for sleep disturbances for at least 2 weeks at baseline was allowed to continue; chloral hydrate or zolpidem was allowed to be instituted if new sleep problems emerged. No other antipsychotic, antidepressant, or mood stabilizer treatment was permitted in the double-blind period. Cholinesterase inhibitor treatments were allowed to continue during the double-blind period, provided that they had been in effect for at least 3 months at study entry. Four olanzapine patients (10 mg, 10 mg, 10 mg, and 20 mg q.d.) and 2 risperidone patients (both 10 mg q.d.) received donepezil pretrial and continued the treatment. Two olanzapine patients (8 mg and 12 mg b.i.d.) and 1 risperidone patient (8 mg b.i.d.) received galantamine pretrial and continued treatment. One risperidone patient took rivastigmine (3 mg b.i.d.) pretrial and continued the treatment.

Assessments of the primary and secondary outcome measures described below occurred at screening, baseline, and then at weekly periods for the duration of the trial. Cognitive assessments occurred at baseline and weeks 3 and 6 (or early termination).

## Assessments

The primary outcome measures were the Udvalg for Kliniske Undersogelser (UKU)[31] rating scale measuring peripheral anticholinergic effects (including visual accommodation disturbances, dry mouth, constipation, micturition disturbances, and palpitations) or a site report of a somnolence adverse event. Secondary outcome measures included clinical efficacy measures from the NPI,[29] including the target symptoms of hallucinations and delusions, as well as other symptom scores. The NPI has a total of 12 different items that were assessed, with these symptoms rated in terms of severity (1 = mild to 3 = severe) and frequency (1 = less than once per week to 4 = greater than once per day or continuously). Total scores include frequency × severity and impact on occupational adjustment.

An abbreviated cognitive assessment was also performed, which included measures of working memory and visuomotor speed. Working memory was measured by the Wechsler Memory Scale, Third Edition,[32] digit span subtest, while visuomotor speed was measured with the Trail Making Test Parts A and B.[33] These cognitive data are to be reported elsewhere in detail and will be used primarily for exploratory analyses of possible central anticholinergic effects. Additional safety information was collected with the Extrapyramidal Symptom Rating Scale (ESRS).[34] The ESRS was used to rate parkinsonism, dystonia, and dyskinesia at each assessment. In addition, Clinical Global Impressions (CGI) scores of the severity of parkinsonism, dystonia, and dyskinesia were also collected. Scores on the CGI range from 1 to 9.

## Assay Procedures

Assays of plasma blood samples were performed at baseline, week 3, and week 6 or endpoint to examine levels of both antipsychotic and anticholinergic activity. Drug levels were measured by radioimmunoassay as previously described by Woestenborghs et al.[35] Anticholinergic activity was measured in the laboratory of the Geriatric Psychopharmacology Program at the University of Pittsburgh using the radioreceptor assay developed by Tune and Coyle.[7,19] In this assay, anticholinergic displacement of titrated quinuclidinyl benzilate is examined in a homogenate of rat forebrain. Level of displacement is

compared to atropine as a standard and is expressed in pmol/mL of plasma. Previous results in our laboratory have suggested an intra-assay coefficient of variation of less than 12%.

### Statistical Analyses

For the primary and secondary variables, analyses included all treated patients who had baseline and at least 1 postbaseline assessment. A last-observation-carried-forward (LOCF) method was used to define endpoint value of each variable. In addition, plasma samples were not available on all patients, and analyses of those samples are based on those cases who had samples available at baseline and at least 1 postbaseline visit.

The primary efficacy analyses examined UKU peripheral anticholinergic effects and site reports of somnolence adverse events with the $\chi^2$ test and the Cochran-Mantel-Haenszel test to examine if these differences were consistent across investigators. Secondary efficacy variables were examined with 2-way analysis of covariance, with treatment and investigator as the factors and baseline as the covariate.

Exploratory analyses based on changes in anticholinergic activity were also performed. We used Pearson correlations to examine the relationship between antipsychotic dosage and anticholinergic activity in each treatment condition separately. Cases were subdivided into those whose anticholinergic activity increased versus those whose activity was stable or decreased. The NPI and cognitive correlates of those changes in anticholinergic activity were examined with t tests.

## RESULTS

### Completion

Eighty-six patients were randomized into the study, with 69 (80.2%) completing and 17 (19.8%) discontinuing. One olanzapine patient did not have a postbaseline assessment and was excluded from the intent-to-treat analysis. The most common reason for discontinuation from the study was an adverse event, occurring in 4 of the risperidone subjects and 2 of the olanzapine subjects ($p = .428$, Fisher exact test). The mean modal dose of risperidone was $0.81 \pm 0.04$ mg/day (average daily dose was 0.76 mg), while the mean modal dose of olanzapine was $5.56 \pm 0.19$ mg/day (average daily dose was 5.22 mg). Concurrent lorazepam usage was 40% in the risperidone group and 19% in the olanzapine group ($p = .034$, Fisher exact test).

### Primary Efficacy Measures

Twelve risperidone patients and 12 olanzapine patients had UKU-based anticholinergic events ($p = .95$, $\chi^2$ test). Six of the olanzapine patients and 2 of the risperidone patients had somnolence adverse events ($p = .27$, Fisher exact test).

### Secondary Outcome Measures

***NPI scores.*** For risperidone patients, there was a statistically significant and substantial improvement in overall NPI frequency × severity scores ($p < .001$, paired t test). A similar improvement was detected for the olanzapine patients ($p < .001$). There were no between-group differences in the extent to which risperidone or olanzapine improved NPI frequency × severity scores. Both of the target symptoms required for entry into the study were also improved by risperidone (delusions: $p < .001$; hallucinations: $p = .007$) and olanzapine (delusions: $p < .001$; hallucinations: $p = .007$). Again, there were no between-group differences in the extent to which either of these medications improved these psychotic symptoms of delusions and hallucinations. Likewise, there were no group differences in any of the other individual NPI items across the 2 treatment groups. Similar results were found for occupational disruption items on the NPI, for which there was a statistically significant overall change from baseline ($p < .001$, paired t test) and no treatment-associated differences in any of the subscales.

***ESRS scores.*** For total ESRS scores, there were no statistically significant changes with either risperidone or olanzapine and no statistically significant differences between the 2 treatments. The results for the individual subscales were equivalent to the overall analyses.

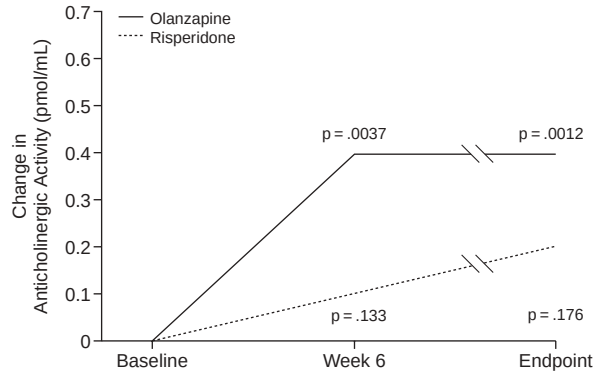
***CGI scores.*** CGI scores of parkinsonism were found to be significantly worse at endpoint than at baseline for the olanzapine-treated patients ($p = .008$, paired t test), while no significant changes were found for the risperidone patients ($p = .39$). The between-group differences on this variable did not reach statistical significance.

### Anticholinergic Activity

For these analyses, there were 23 risperidone and 25 olanzapine patients available. The demographic and baseline variables of those patients were similar to those of all randomized patients. Figure 1 shows the changes from baseline in anticholinergic activity expressed in pmol/mL atropine equivalents. As can be seen in Figure 1, olanzapine patients had an increase in anticholinergic activity from baseline that was statistically significant at week 3 ($p = .0001$, paired t test), with this increase sustained through endpoint ($p = .0012$). Risperidone-treated patients had no such increase in their anticholinergic activity. There were no statistically significant differences between the medications in their changes from baseline to endpoint.

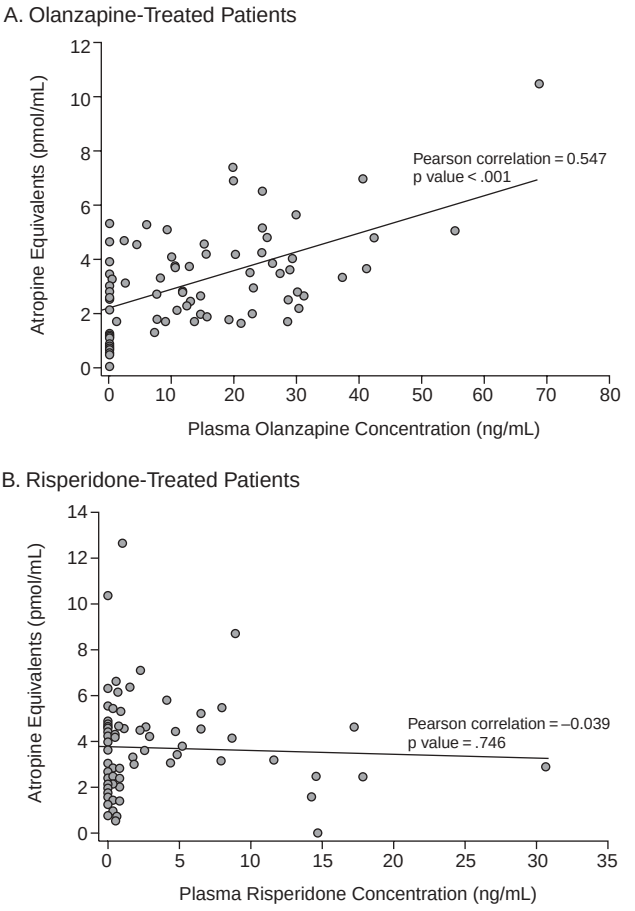
The correlation of plasma antipsychotic concentrations and anticholinergic activity was also assessed. There was a statistically significant Pearson product moment correlation between olanzapine levels and anticholinergic activity ($r = 0.55$, $p < .001$) while the correlation for the risperidone patients was essentially 0 ($r = –0.04$, $p = .75$). The distribution of these scores is presented in Figure 2.

**Figure 1. Change in Anticholinergic Activity From Baseline for Dementia Patients Treated With Risperidone Versus Olanzapine[a]**




[a]Change = log (1 + EP)–log (1 + BL). Transformation was applied to correct the skewness of distribution in atropine-equivalent scores.
Abbreviations: BL = baseline, EP = endpoint.

**Figure 2. Correlations of Anticholinergic Activity and Medication Dose**




The correlation between antipsychotic levels and anticholinergic activity was significantly greater for the olanzapine-treated patients (Fisher z = 3.875, p < .001).

***Case-by-case changes in anticholinergic activity.*** In the next analyses, the sample was split into those cases in which anticholinergic activity was found to increase (N = 34) and to decrease (N = 14). These groups were compared on several outcome measures. Twelve of the 34 patients with increases in anticholinergic activity had at least 1 anticholinergic event, while none of the 14 patients with decreases in their anticholinergic activity had an event (35.3% vs. 0%, p = .024, Fisher exact test). In terms of cognitive performance, there was a statistically significant increase (+67.8 seconds) in Trail Making Part A time in patients whose anticholinergic activity increased, compared with those whose anticholinergic activity decreased, for whom an improvement in performance (–32 seconds) was detected (p < .05, analysis of variance). There was no statistically significant association between changes in digit span performance and changes in anticholinergic activity. Trail Making Test Part B could not be analyzed because so few patients received valid scores on this test at baseline (N = 9).

The final analyses examined NPI endpoint scores and endpoint anticholinergic activity, using Pearson product moment correlations. NPI overall frequency × severity scores were higher in those patients with higher anticholinergic activity (r = 0.28, p = .04), as were scores on overall occupational disruption (r = 0.42, p = .001). The severity of delusions, in terms of both frequency × severity (r = 0.35, p = .008) and occupational disruption (r = 0.45, p < .001), was also higher in patients with higher endpoint anticholinergic activity. Similar results were found for anxiety, in terms of both frequency × severity (r = 0.38, p = .004) and occupational disruption (r = 0.42, p = .002). Finally, in terms of occupational disruption, higher endpoint scores on both agitation/aggression (r = 0.29, p = .034) and aberrant motor behavior (r = 0.34, p = .012) were associated with higher anticholinergic activity.

## DISCUSSION

In terms of overall efficacy, both risperidone and olanzapine led to substantial and statistically significant improvements in psychotic symptoms in dementia. The fact that more than a quarter of the patients were treated with benzodiazepines suggests that the beneficial effects on cognition detected in patients with reduced anticholinergic activity may be an underestimate of the true benefit, because of the adverse effects of benzodiazepines on cognition in elderly patients. Consistent with earlier reports on the treatment of agitation in dementia,[21–25] both of these atypical antipsychotic medications improved psychosis

within a relatively brief treatment trial. Overall safety parameters were largely similar as well, with no treatment-associated differences between the 2 medications in terms of UKU and somnolence. ESRS scores were largely the same as well, with the only difference being a significant increase in CGI parkinsonism scores for olanzapine-treated patients. This finding may be consistent with earlier work indicating that olanzapine has the potential for increasing extrapyramidal symptoms in patients with Parkinson's disease and related conditions.[36]

There were considerable differences between these medications in terms of their impact on anticholinergic activity. Consistent with previous reports, olanzapine was associated with a dose-dependent increase in anticholinergic activity.[26,27] In contrast, risperidone induced no such change in anticholinergic activity and there was no anticholinergic dose response. A number of correlates of anticholinergic activity were detected as well. Patients whose anticholinergic activity was higher at endpoint were likely to have greater levels of certain behavioral or psychological symptoms. In addition, increased anticholinergic activity was associated with reduced motor speed and an increased risk of clinically detectable anticholinergic side effects and somnolence.

Before the implications of these findings are discussed, the limitations of the study should be delineated. Not all patients had plasma samples available for analysis, and, while there were no differences between those patients with available plasma samples and those without, the possibility that this factor influenced the results cannot be entirely ruled out. The baseline differences in anticholinergic activity in the risperidone- and olanzapine-treated patients reduced the ability to find differences in changes in anticholinergic activity. Despite criteria that tried to include as many patients as possible with higher levels of cognitive functioning, many of the patients were unable to be tested even on Trail Making Part B. Thus, many other important anticholinergic cognitive effects could not be examined in this sample and assessment of episodic memory was not possible.

Since there were no treatment-group differences in anticholinergic side effects but there were correlations between increased anticholinergic load and adverse clinical, cognitive, and safety variables, there may be individual differences in sensitivity to olanzapine-associated anticholinergic effects. These individual differences have been found in the general population, in that even some individuals who are known to be taking drugs with anticholinergic effects have low levels of measured anticholinergic activity.[19] The number of potentially anticholinergic medications taken does not necessarily correlate with measured anticholinergic activity. There are also likely to be individual differences in susceptibility to anticholinergic effects given a specific anticholinergic activity. For instance, some individuals with high levels of measured anticholinergic activity do not show demonstrable cognitive adverse consequences. It is clear, however, that in individuals with conditions that compromise the functioning of the central cholinergic system, susceptibility to anticholinergic effects is greater.[37]

Another issue is that of the magnitude and assessment of expected anticholinergic adverse effects. Subtle cognitive and clinical changes were much more likely than gross indicators of delirium or peripheral anticholinergic effects to be associated with increased anticholinergic activity. These data indicate that case-by-case examination of possible cognitive adverse effects may be important in older individuals treated with medications that have anticholinergic effects.

A final, albeit speculative, interpretation of these findings may be of interest as well. Previous studies of olanzapine treatment for agitation and psychosis in dementia have found a curvilinear dose-response curve, with 15-mg daily doses less effective than lower doses.[23] The data from the current study found an anticholinergic activity dose-response relationship with olanzapine and a correlation with higher levels of anticholinergic activity and greater symptoms at endpoint. Thus, these data indicate that one possible reason for the lack of efficacy of olanzapine at higher doses in dementia may be its potential for increased anticholinergic activity. This possibility should be considered in other populations such as older patients with schizophrenia, as higher doses of olanzapine are being investigated as possible treatments for schizophrenia.[38,39]

*Drug names:* atropine (Atropen), clozapine (Fazaclo, Clozaril, and others), donepezil (Aricept), galantamine (Reminyl), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal), rivastigmine (Exelon), tacrine (Cognex), zolpidem (Ambien).

*Financial Disclosure:* Dr. Mulsant has received grant/research support from the National Institutes of Health, AstraZeneca, Corcept, Eli Lilly, Forest, GlaxoSmithKline, Janssen, and Pfizer/Eisai; has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, Fox Learning System, GlaxoSmithKline, Janssen, and Pfizer; has served on the speakers bureau of AstraZeneca, Forest, GlaxoSmithKline, Janssen, and Pfizer/Eisai; and has received honoraria from AstraZeneca, Forest, Janssen, Lundbeck, GlaxoSmithKline, and Pfizer/Eisai. Drs. Gharabawi, Bossie, Greenspan, and Bastean and Mr. Mao are employees of Janssen Medical Affairs, L.L.C. Dr. Martinez is an employee of Johnson & Johnson. Dr. Tune serves as a consultant for and has received grant/research support from Janssen Pharmaceuticals. Dr. Pollock has received grant/research support from the National Institute of Mental Health, Janssen Pharmaceutica, Forest, and GlaxoSmithKline; has served as a consultant for Forest, Janssen Pharmaceutica, Organon, GlaxoSmithKline, AstraZeneca, Alexza Molecular Delivery, and Warner Chilcott; and has served on the speakers bureau of Forest and GlaxoSmithKline.

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