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Incidence of Tardive Dyskinesia in Older Adult Patients Treated With Olanzapine or Conventional Antipsychotics

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Abstract

Background: The risk of *persistent* tardive dyskinesia (TD) was compared in patients with acute psychosis or agitation aged 55 years or older who were treated with olanzapine (OLZ) or conventional antipsychotic (CNV) drug therapy. **Methods:** Patients without TD were randomized to treatment with OLZ (2.5-20 mg/d; n = 150) or CNV (dosed per label; n = 143). Following a 6-week drug tapering/initiation period, patients without TD were treated with OLZ or CNV for up to 1 year. The a priori defined primary outcome end point was *persistent* TD defined as Abnormal Involuntary Movement Scale (AIMS) scores = 2 on at least 2 items or ≥3 on at least 1 item (items 1-7) lasting at least for 1 month (Criterion A). Post hoc analyses assessed *persistent* TD meeting the criterion of moderate severity defined as AIMS score ≥3 on at least 1 item persisting for 1 month (Criterion B) and *probable* TD defined as elevated AIMS scores (Criterion A or B) not persisting for 1 month. Treatment groups were compared using Kaplan-Meier curve with log-rank exact test. **Results:** On average, patients were 78 years of age; the predominant diagnosis was dementia (76.7% in the OLZ group and 82.5% in the CNV group). Approximately, 40.6% of patients in the CNV group received haloperidol. No significant difference in time to developing *persistent* TD was observed during treatment with OLZ or CNV (cumulative incidence: OLZ, 2.5% [95% confidence interval [95% CI]: 0.5-7.0]; CNV, 5.5% [95% CI: 2.1-11.6], $P = .193$). The exposure-adjusted event rates per 100 person-years were not significantly different between treatment groups: OLZ (2.7) and CNV (6.3; ratio: 0.420; 95% CI: 0.068-1.969). Post hoc analyses revealed a significantly lower risk of at least moderately severe *persistent* TD persisting for 1 month ($P = .012$) and *probable* TD not persisting for 1 month (Criterion A, $P = .030$; Criterion B, $P = .048$) in OLZ-treated patients. For those patients without significant extrapyramidal symptoms at baseline, significantly more patients in the CNV treatment group developed treatment-emergent parkinsonism than for patients in the OLZ treatment group (CNV: 70%, 35 of 50 patients; OLZ 44%, 25 of 57 patients; $P = .011$). No significant difference between the groups was observed for treatment-emergent akathisia (CNV: 6%, 7 of 117 patients; OLZ: 10%, 13 of 130 patients; $P = .351$). **Conclusion:** The cumulative incidence of *persistent* TD was low and the risk of *persistent* TD did not differ significantly among predominantly older adult patients having dementia with acute psychosis or agitation treated with OLZ or CNV.

Keywords

schizophrenia, tardive dyskinesia, olanzapine, conventional, atypical antipsychotics, extrapyramidal symptoms

Introduction

Although antipsychotic drugs are the treatment of choice in patients diagnosed with schizophrenia, these medications have been used much more broadly, especially in geriatric patients to treat the symptoms of agitation or psychosis that often accompany disease states such as dementia. The use of these medications in this population occurs, despite lack of approval by requisite regulatory bodies. Data from some clinical studies have suggested that older adult patients with dementia experiencing symptoms of agitation and psychosis may benefit from treatment with antipsychotics.[1,2] However, an increased incidence of mortality and cerebrovascular adverse events, including stroke, have been reported in older adult patients with dementia-related psychosis (reviewed in [3]). The atypical

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antipsychotic, olanzapine (OLZ), is not approved to treat such patients, and its label carries a black box warning regarding the increased incidence of mortality in elderly patients with dementia-related psychosis.[3]

Tardive dyskinesia (TD) is a significant and potentially disabling abnormal involuntary movement disorder that can develop in patients chronically treated with antipsychotic drugs. Among nonelderly adult patients receiving treatment with conventional or first-generation antipsychotic drugs, the incidence rate for the development of TD is approximately 5% per year.[4,5] In older adult patients, the risk of developing TD during conventional antipsychotic (CNV) drug therapy is significantly higher, with 1-year incidence rates reported at 25% to 30% or greater.[6-9]

Early studies of clozapine, the first atypical antipsychotic, suggested a lower risk for the development of TD in patients with schizophrenia.[10,11] Several studies followed reporting a significantly lower rate of TD in adult patients with schizophrenia receiving treatment with other atypical antipsychotic drugs including risperidone[12] and OLZ.[13] Early reports also suggested that the potential risk of TD was lower in older adult patients treated with atypical antipsychotics. Jeste and colleagues reported, in older adult patients with a primary diagnosis of schizophrenia, an approximate 3% to 4% cumulative incidence over a 1-year period for patients treated with risperidone that was significantly less than the rate of 30% for patients treated with haloperidol.[14] In elderly patients with dementia, an incidence rate of 2.6% for TD was observed following treatment with risperidone for 1 year.[15] In elderly patients with schizophrenia or other psychotic disorders, the incidence of assessed TD was 4.3% following risperidone treatment in a 12-month, open-label study.[16]

Correll and colleagues published 2 reviews of TD rates in patients treated with first-generation or second-generation antipsychotics first in 2004 (across 11 long-term studies)[17] and then in 2008 (across 12 studies).[18] In both reviews, a significantly lower risk of TD was observed in adult patients treated with atypical or second-generation antipsychotics (weighted mean annual incidence of TD: 0.8%[17] and annual TD incidence rate: 2.98%[18]) compared to adult patients treated with first-generation agents (weighted mean annual incidence of TD: 5.4%[17] and annual TD incidence rate: 7.7%[18]), although clear differences were not evident in the older adult to elderly patient populations.

Woerner and colleagues[19] assessed the incidence of TD in a prospective inception cohort study of antipsychotic-naive elderly patients who were treated with risperidone or OLZ. They reported cumulative TD rates that were comparable (risperidone: 5.3% at 1 year and 7.2% at 2 years; OLZ: 6.7% at 1 year and 11.1% at 2 years) and substantially lower than previously reported rates (20% at 1 year and 30% at 2 years)[8] for similar patients treated with first-generation antipsychotics. However, the incidence rates of TD were not compared concurrently in patients treated with first- or second-generation antipsychotics, although as noted by the authors the design and methodology for the 2 studies were identical.

In contrast, in a retrospective, population-based cohort study, Lee and colleagues reported no significant difference in the risk of developing TD or a drug-induced movement disorder other than parkinsonism in patients being treated with an atypical agent (risperidone, quetiapine, or OLZ) or with a typical antipsychotic (ie, 5.24 cases of TD or other drug-induced movement disorder per 100 person-years on therapy with a typical antipsychotic [3.0%] and 5.19 cases on therapy with an atypical agent [3.5%]).[20] While interpretation of these findings may be complicated by the inclusion of ''other drug-induced movement disorders,'' there are other studies assessing the risk of TD in patients treated with atypical and CNV medications that have not demonstrated a clear advantage for atypical antipsychotics.[21-23]

Given the disparate findings to date, additional research is warranted regarding TD risk associated with atypical and typical or CNVs. In this prospective clinical trial, the primary objective of this study was to evaluate time to *persistent* TD in older adult patients having acute psychosis or agitation treated with OLZ or CNV drug therapy. It was hypothesized that patients treated with OLZ would experience a significantly lower cumulative incidence of *persistent* TD compared to patients treated with CNVs. In addition, we also looked at the occurrence of moderately severe *persistent* TD and *probable* TD that did not persist over 2 consecutive visits. These post hoc analyses may be helpful in further assessing the overall potential risk of developing TD in these 2 treatment groups.

Patients and Methods

Patients

Patients who participated in this study (HGGE Study) were inpatients or outpatients, 55 years of age or older, who fulfilled the criteria for a psychotic disorder and/or dementia according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition; *DSM-IV*). This diagnostic group encompassed psychoses, disorders with psychotic features (including mood disorders and dementia), and nonpsychotic dementia with behavioral disturbances. Patients with a diagnosis of a psychotic disorder (demented or non-demented) had to have a rating of at least moderate ($\geq$4) on 1 of the Brief Psychiatric Rating Scale (BPRS1-7)[24] on psychosis items or documentation of treatment of an acute psychotic episode that was initiated within 1 year of Visit 1 and a clinical indication to maintain antipsychotic drug treatment. Patients with a diagnosis of dementia with agitation had to have a rating of at least moderate ($\geq$4) on the BPRS1-7 on either the ''excitement'' or the ''tension'' items or documentation of treatment of an acute episode of behavioral agitation that was initiated within 1 year of Visit 1 and a clinical indication to maintain antipsychotic drug treatment. Relevant exclusion criteria included a prior history of TD, current TD symptoms, comorbid neurological illnesses that might contribute to TD symptoms, treatment with an injectable depot neuroleptic within 12 weeks prior to study entry, treatment with OLZ or clozapine for >2 months

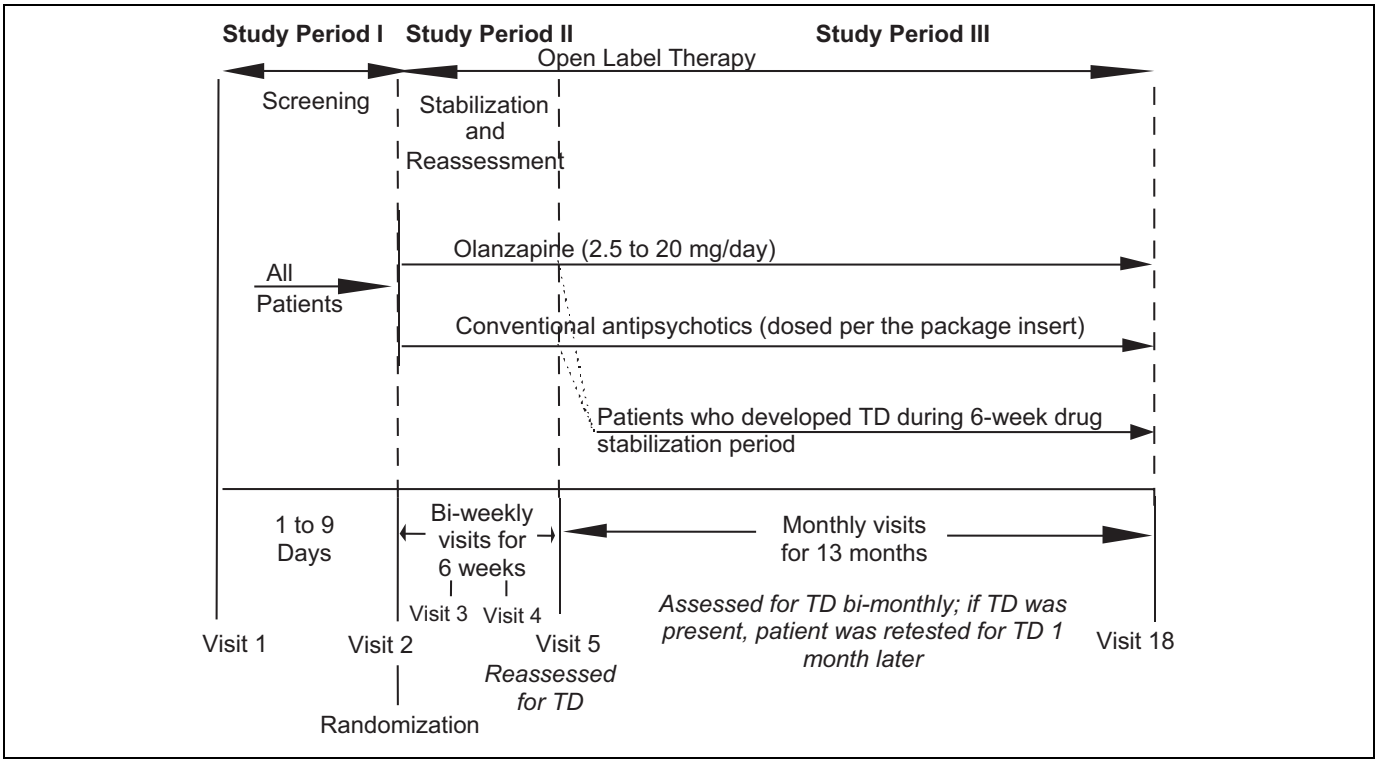

Figure 1. A summary of the overall design of this prospective clinical trial.

immediately prior to study entry, and greater than 5 years cumulative exposure to an antipsychotic medication within the last 10 years. All patients gave written informed consent prior to entering the study. The study protocol was approved by appropriate institutional review boards and conducted in accordance with the ethical principles stated in the Declaration of Helsinki. This study was conducted in the United States at 22 study centers, from December 1997 to August 2001. There were initially 29 investigators at 29 study centers; however, 7 sites did not enroll patients into the study.

Procedure

This was a randomized, open-label, parallel study of patients with a psychotic disorder or dementia who were treated with OLZ or CNVs to assess the potential risk of developing TD. The CNVs included in this study were haloperidol, thiothixene, fluphenazine, trifluopherazine, pimozide, loxapine, perphenazine, chlorpromazine (CPZ), thioridazine, and mesoridazine.

During Study Period I, patients were screened for enrollment, and those patients meeting inclusion criteria were randomized to 1 of 2 treatment groups: (1) OLZ (2.5-20 mg/d; n = 150) or (2) CNVs (dosed per label; n = 143; Figure 1). Patients randomized to the CNV group began therapy with a specific CNV based on the investigator's clinical decision.

During Study Period II, patients underwent an initial 6-week drug stabilization period. Patients on an antipsychotic drug at study entry either continued on that medicine (if allowed by the treatment assignment) or had it gradually withdrawn during initiation of treatment with OLZ or CNV so that all patients were on monotherapy by week 3. All patients were on a stable dose of medication beginning week 4. Patients were assessed clinically every 2 weeks and reassessed for TD after the initial 6-week treatment period to identify those patients showing newly developed dyskinetic symptoms. The development of TD during this 6-week drug stabilization period may have reflected an unmasking of TD already present in patients previously treated with antipsychotics. Therefore, patients who developed TD defined as patients fulfilling cross-sectional Schooler-Kane criteria for TD (ie, at least 1 item score ≥ 3 or 2 items ≥ 2) during this 6-week period were excluded from the primary analysis of time to *persistent* TD, although these individuals could remain in the study.

During Study Period III, patients who remained without TD after first 6 weeks were treated with OLZ or CNV for up to 1 year and were followed for the development of *persistent* TD. Patients received usual clinical care by nonblinded study clinicians who met with the patients at least monthly. Patients were also assessed for TD by blinded study raters every 2 months. Patients who demonstrated abnormal involuntary movements at Visit 5, 7, 9, 11, 13, 15, or 17 (*bimonthly plan*) were reevaluated in 1 month (Visit 6, 8, 10, 12, 14, 16, or 18) in order to determine whether symptoms had persisted and the protocol-defined threshold criteria for TD had been achieved. If TD was found at 1 visit (*bimonthly plan*) but not at the subsequent 1-month follow-up visit, then the patient was not ''labeled'' as having *persistent* TD and his or her dyskinetic symptoms were reassessed according to the *bimonthly plan*. If TD was found at

1 visit (*bimonthly plan*) and also at the 1-month follow-up visit, then the patient was ''labeled'' as having *persistent* TD. Following the designation of having *persistent* TD, his or her subsequent testing for TD occurred according to the *bimonthly plan*. Once *persistent* TD was confirmed, patients did not receive any further unscheduled visits.

Blinded study raters who were blind to each patient's treatment group assignment assessed patients for *persistent* TD as rated by the Abnormal Involuntary Movement Scale (AIMS).[25] These individuals received group training initially on the AIMS at the study start-up meeting, followed by subsequent video training in which raters needed to rate correctly in order to be certified as a blinded study rater. However, the actual subject ratings were not done by video. Other clinicians who were not blind to the patient's treatment were involved in other clinical assessments.

In order to model actual clinical practice, flexibility in antipsychotic drug therapy was allowed such that the dose of drug could be increased or decreased within the dose range allowed per label or the drug could be withdrawn and/or restarted as clinically indicated. Patients randomized to OLZ could only receive OLZ. Patients randomized to CNV could be switched to another CNV drug as clinically indicated.

Assessments and Criteria for TD

The AIMS,[25] a 12-item scale designed to record the occurrence of dyskinetic movements, was used as the primary measure to assess the incidence of TD. Items 1 through 7 of the AIMS rate dyskinetic movements in 3 body regions on a 5-point scale (with 0 reflecting *no dyskinetic movements* and 4 reflecting *severe dyskinetic movements*) for a total score ranging from 0 to 28. *Persistent* TD was diagnosed according to modified Research Diagnostic criteria for TD[26]: the appearance of abnormal involuntary movements of at least moderate severity (AIMS score $\geq$3) in 1 or more body regions or mild severity (AIMS score = 2) in 2 or more body regions lasting at least 1 month (2 consecutive visits) during study evaluation in patients with no history or baseline evidence of TD and with a history of at least 1-month cumulative duration of prior antipsychotic drug therapy. Modifications to the Research Diagnostic criteria included 1 month prior exposure to neuroleptics rather than 3 months, and the persistence of TD for 1 month rather than 3 months. The *DSM-IV* criteria have specified the requirement of only 1 month prior exposure to neuroleptics in patients aged 60 years and older. Whether a shorter duration would also be appropriate for assessing persistence of TD in patients $\geq$55 years of age is not known. One of our authors (DJ) has reported emergent *persistent* TD as occurring on 2 or more consecutive visits, with visits being spaced out every 2 months in patients with dementia,[15] although our study may be the first to utilize a duration of only 1 month.

In addition to assessing the development of *persistent TD* as defined earlier (scores = 2 on 2 or more items or $\geq$3 on one or more items of the AIMS, Criterion A), post hoc analyses included assessing the development of *persistent* TD meeting moderate severity (score $\geq$3 on 1 item of the AIMS; Criterion B), and the development of *probable TD* defined as dyskinetic symptoms not persisting for 1 month, using Criteria A and B.

Additional measures of extrapyramidal symptoms (EPSs) included akathisia and parkinsonism. The Barnes Akathisia Scale[27] was used to assess akathisia at baseline and during treatment; clinically significant akathisia was defined categorically as Barnes Akathisia Global score $\geq$2. The modified Simpson-Angus Scale[28] was used to evaluate parkinsonian symptoms at baseline and during treatment; clinically significant parkinsonism was defined categorically as Simpson-Angus score >3.

Statistical Methods

The primary analysis specified in the protocol was evaluation of difference in time to *persistent* TD between OLZ and CNV by Cox regression with a single term for treatment and stratified by investigative site. Assuming 138 OLZ-treated patients and 138 CNV-treated patients were to contribute data to Study Period III, the study was estimated to have 85% power to detect a difference in the incidence of TD in Study Period III. Underlying this estimate was the assumption that the true incidences of TD for OLZ and CNV would be 5% and 13%, respectively.

After the study was completed, the low cumulative TD incidence observed rendered questionable the assumptions underlying intended semiparametric Cox model and the log-rank test. Therefore, the log-rank exact test was used to compare treatment groups and the Kaplan-Meier method to visually inspect the patterns of survival distributions for time to *persistent* TD (per protocol) as well as moderately severe *persistent* TD or *probable* TD not persisting over consecutive visits. The exposure-adjusted event rate was computed by dividing the number of observed events by the total exposure (eg, patient-years) in each treatment group. A 95% confidence interval (95% CI) of the ratio of event rates was constructed to compare the treatment groups (CI containing ''1'' precludes stating that the treatment groups are different). Patients who developed TD (based on Criteria A or B, depending on the event analyzed) during the first 6-week drug stabilization period after randomization were excluded. Patients were also excluded from these analyses if they discontinued from the study during the first 6-week period or did not have any AIMS score available after week 6.

Patients who discontinued early or completed the study without developing TD were right censored at the time of their last AIMS assessment. The time to development of TD was calculated by starting from randomization (Visit 2).

Time to treatment discontinuation was evaluated using Kaplan-Meier estimator of survival distribution for time to the last dose of study drug (this end point instead of conventional analysis of time to discontinuation from the study was selected because patients were allowed to stay in the study without taking any study medication). Treatment differences were evaluated with a log-rank test.

Table 1. Baseline Characteristics.

	All Randomized Patients			Analyzed Sample		
	OLZ (N = 150)[a]	CNV (N = 143)[a]	*P* Value	OLZ (N = 122)[a]	CNV (N = 109)[a]	*P* Value
Age, years, mean (SD)	78.0 (8.3)	78.9 (8.1)	.341	78.1 (7.8)	78.2 (8.2)	.930
Gender: female (%)	54%	51%	.641	57%	46%	.115
Ethnicity: caucasian (%)	83%	90%	.268	84%	88%	.690
Diagnosis (%)			.178			.494
Psychotic disorders (schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder NOS)	15%	8%	–	14%	10%	–
Mood disorders (major depressive disorder or bipolar I with psychotic features)	8%	9%	–	7%	11%	–
Dementia (Alzheimer's dementia late, Alzheimer's dementia early, vascular dementia, dementia NOS)[b]	77%	83%	–	79%	79%	–
Minimal exposure in the past 2 years, %[c]	57%	65%	.189	57%	67%	.136
Abnormal Involuntary Movement Scale (AIMS), mean (SD)	0.5 (1.1)	0.6 (1.1)	.500	0.5 (1.1)	0.6 (1.1)	.428
AIMS score = 2 on one item (%)	7%	6%	.810	7%	6%	1.00
AIMS score = 1 on one item (%)	31%	41%	.114	30%	38%	.210
Simpson Angus score, mean (SD)[d]	4.3 (4.2)	3.9 (3.8)	.408	3.9 (3.9)	3.6 (3.4)	.575
Parkinsonism (% meeting Simpson Angus score >3)[d]	53%	52%	.801	50%	49%	1.00
Barnes Akathisia Global score, mean (SD)[d]	0.3 (0.6)	0.4 (0.7)	.692	0.3 (0.6)	0.4 (0.7)	.260
Akathisia (% meeting Barnes Akathisia Global score $\geq$2)[d]	9%	10%	.846	7%	11%	.250
BPRS total (scored 1-7), mean (SD)	43.1 (11.7)	44.4 (14.0)	.402	43.2 (12.1)	44.0 (14.6)	.655

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; CNV, conventional antipsychotic; NOS, not otherwise specified; OLZ, olanzapine; SD, standard deviation.

[a]For some comparisons, the number of patients were less than the number of patients randomized to each treatment group.

[b]Percentage of patients with specific diagnosis: 51.2% Alzheimer's dementia late, 8.9% Alzheimer's dementia early, 11.6% vascular dementia, 7.8% dementia NOS.

[c]Defined as <3 cumulative months exposure to antipsychotic drugs during preceding 2 years.

[d]Parkinsonism and akathisia measured at baseline presumably reflects drug-induced symptomatology associated with limited but prior neuroleptic exposure.

Antipsychotic drug exposure was summarized as mean modal dose and mean duration of treatment during the study and frequency of switching from previous antipsychotic medication at randomization. Chlorpromazine equivalencies were determined for the OLZ treatment group and collectively for the CNV treatment group. The CPZ dose equivalents were based on values published in the previous studies.[29-31]

Analysis of variance was used to test for treatment differences for continuous variables and Fisher exact test for categorical variables. All analyses were run by SAS, Version 8, except for log-rank exact tests that were implemented by StatExact, Version 5. All the tests of hypotheses were 2 sided with a significance level of 0.05.

Results

Patient Characteristics

Baseline demographics and clinical status are shown in Table 1. On average, patients were 78 years of age, 86% caucasian, with an approximately equal distribution of male and female patients in each group. The predominant diagnosis was dementia (76.7% in the OLZ group and 82.5% in the CNV group), although patients with a psychotic disorder or a mood disorder with psychotic features were also included. Approximately 57% to 65% of the patients had minimal prior exposure to antipsychotic medications within the past 2 years (<3 months cumulative antipsychotic drug exposure within the past 2 years). Scores from the Simpson-Angus scale administered at baseline indicated that approximately half of the patients in both treatment groups met criteria for parkinsonism—57% for patients in the OLZ treatment group and 65% in the CNV treatment group. Overall, patients were moderate to severely impaired clinically with relatively high levels of agitation. The only statistically significant difference noted between the treatment groups at baseline was the mean score on the Montgomery-Asberg Depression Rating Scale (MADRS) (OLZ, 13.2; CNV, 15.7; $P = .020$).

Patient Disposition

A summary of patient disposition is provided in Figure 2. Of the 150 patients randomized to OLZ treatment, 88% completed Study Period II and 53% completed Study Period III (the 1-year incidence phase). Of the 143 patients randomized to CNV treatment, 85% completed Study Period II and 43% completed Study Period III.

The reported reasons for early study discontinuation are summarized in Table 2. The only significant difference between treatment groups for reasons underlying early study discontinuation was noted for lack of efficacy reported in 3% of patients in the OLZ treatment group and 10% of patients in the CNV treatment group ($P = .014$).

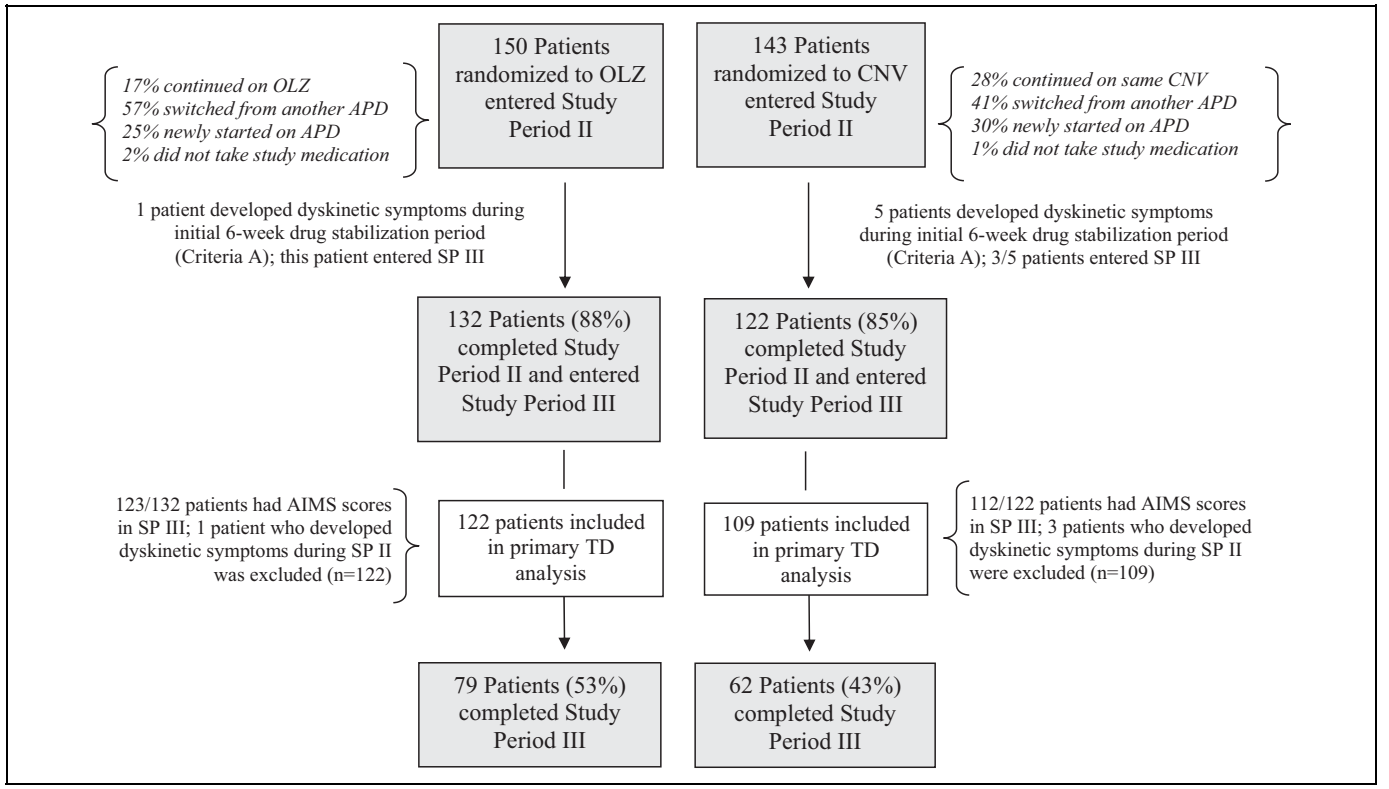

Figure 2. Drug history at the time of randomization and patient flow through study. The percentage of patients for drug history at the time of randomization is greater than 100% due to rounding up to the next whole number.

Table 2. Reasons for Early Study Discontinuation.

	OLZ (N = 150)	CNV (N = 143)
Completion rate, %	53	43
Reasons for early study discontinuation[a]		
Satisfactory response, %	–	1
Adverse event, %	17	20
Lack of efficacy, %	3	10
Lost to follow-up, %	1	1
Patient/physician/sponsor decision, %	20	22
Noncompliance, %	6	3
Discontinuation rate, %	47	57

Abbreviations: CNV, conventional antipsychotic; OLZ, olanzapine.
[a]Significant difference between treatment groups noted only for lack of efficacy ($P = .014$).

Antipsychotic Drug Exposure

Patients who entered the study could have been randomized to the same drug, switched from a different drug, or newly started on medication. The percentage of patients who met each condition is summarized in Figure 2.

After randomization, the mean modal dose (standard deviation) of OLZ was 5.9 (4.4) mg/d. The average dose of CNV varied according to drug (Figure 3). Mean duration of exposure to study medication was significantly longer for patients in the OLZ treatment group than for patients in the CNV treatment group (OLZ: 280 ± 158 days; CNV: 240 ± 155 days; $P = .032$). The CPZ equivalents for the 2 treatment groups were calculated. For the OLZ treatment group, the CPZ equivalence was 118 mg/d CPZ equivalents (5.9 mg/d × 20 = 118 mg/d). For the CNV treatment group, a weighted average of the CPZ equivalence of all of the listed drugs = 69.2 mg/d CPZ equivalents.

Time to last dose of study medication was also significantly longer for OLZ-treated patients compared to patients in the CNV treatment group (median days of treatment: OLZ, 387 days; CNV, 266 days; $P = .026$; Figure 4).

Tardive Dyskinesia Symptoms

During Study Period II, 1 patient in the OLZ treatment group and 5 patients in the CNV treatment group developed TD during the initial 6-week drug stabilization period (Criteria A) and were not included in assessment of the 1-year TD incidence rate. Figure 5 provides the Kaplan-Meier survival curve for time to *persistent* TD or development of dyskinetic symptoms for both treatment groups during Study Period III. The cumulative incidence of TD is shown for dyskinetic symptoms by increasing persistence (*probable TD → persistent TD*) and increasing severity (*Criterion A → Criterion B*).

Persistent TD. No significant difference in the time to *persistent* TD of 1-month duration or longer (*primary end point*) was

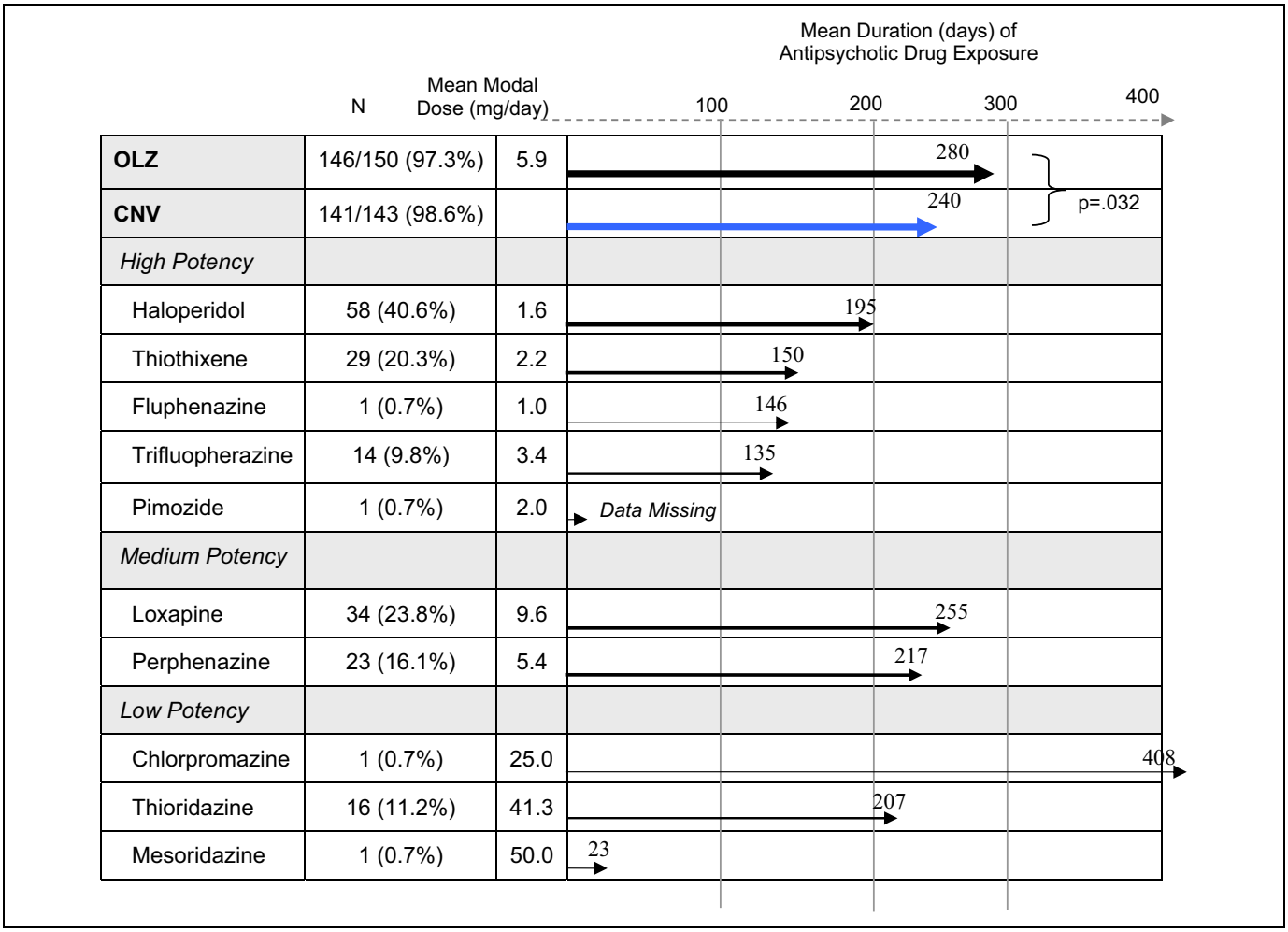

Figure 3. Duration of exposure to antipsychotic drugs any time after randomization. The number of patients prescribed the indicated antipsychotic drug during the study does not add up to the total number of patients randomized because of switching and compliance. Two patients were incorrectly prescribed quetiapine HCl; these patients were included as part of the intent-to-treat analyses. In all, 3 patients randomized to olanzapine (OLZ) did not take any study drug, and 1 patient randomized to OLZ had taken conventional antipsychotic.

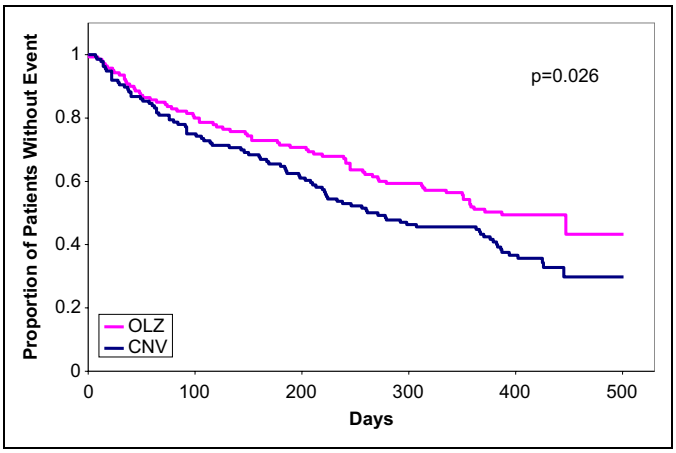

Figure 4. Time to last study dose for all randomized patients treated with olanzapine or a conventional antipsychotic (*P* value is from log-rank test).

observed during treatment with OLZ (2.5%, 95% CI: 0.5-7.0) or CNV (5.5%, 95% CI: 2.1-11.6; $P = .193$; *Criterion A*). The exposure-adjusted event rates were not significantly different between the treatment groups: OLZ (2.7) and CNV (6.3; ratio: 0.420; 95% CI: 0.068-1.969).

A significantly lower risk of at least moderately severe *persistent* TD persisting for at least 1 month was observed in patients treated with OLZ (0.0%) compared to those treated with CNV (2.7%, 95% CI: 0.6-7.8; $P = .012$; *Criterion B*). The exposure-adjusted event rates per 100 patient-years were not significantly different between the treatment groups: OLZ (0.0) and CNV (3.1; ratio: 0.000; 95% CI: 0.000-2.032).

Probable TD. A significantly lower risk of *probable* TD was observed for patients treated with OLZ (6.5%, 95% CI: 2.9-12.5) compared to those treated with CNV (14.7%, 95% CI: 8.6-22.7) ($P = .030$; *Criterion A*). The exposure-adjusted event

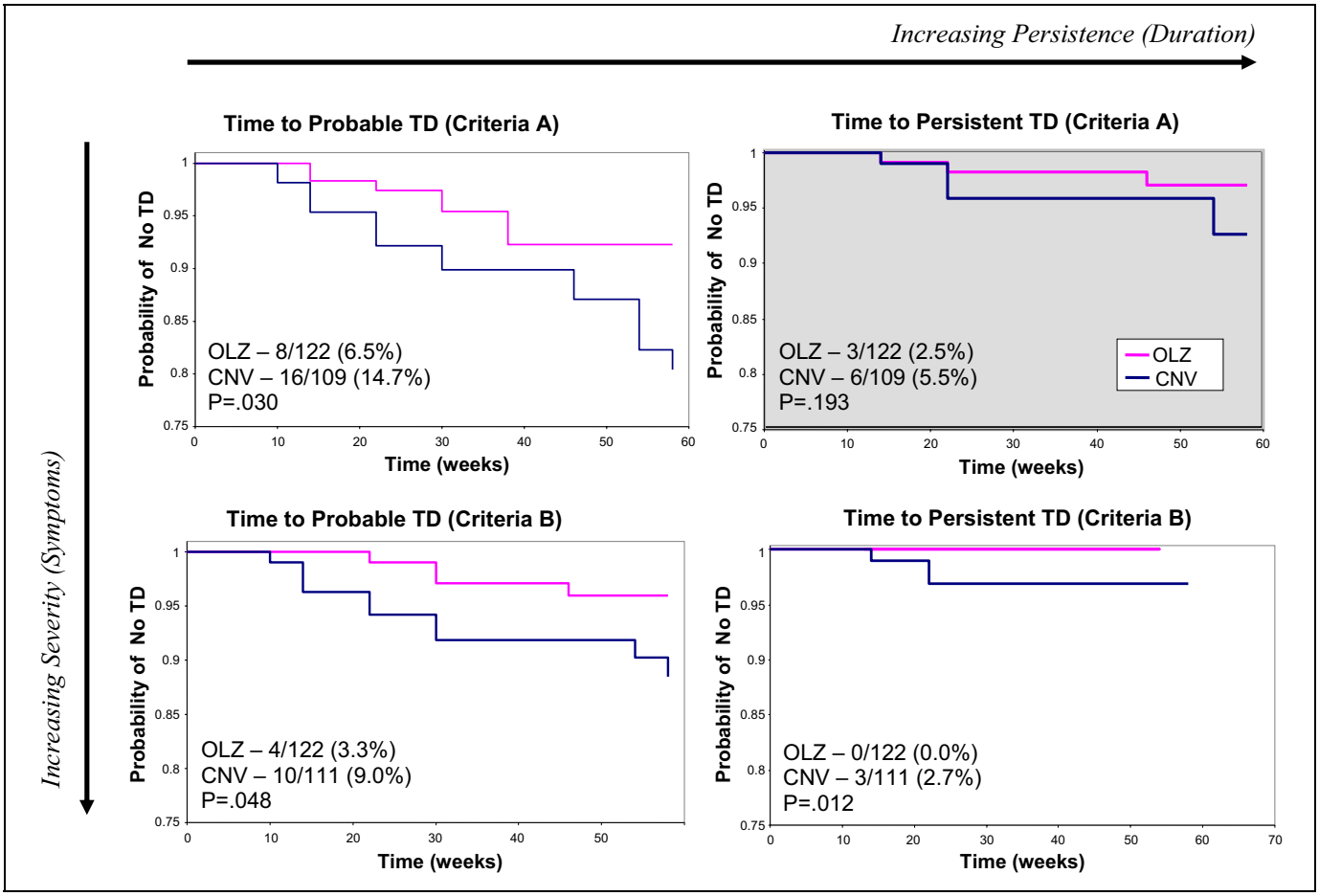

Figure 5. The Kaplan-Meier curves of time to tardive dyskinesia (TD) by varying degrees of dyskinesia severity and duration (*P* values are from log-rank exact test). The development of *persistent TD* was defined as Abnormal Involuntary Movement Scale (AIMS) scores = 2 on 2 or more items or ≥3 on 1 or more items (Criterion A). Post hoc analyses included assessing the development of *persistent* TD meeting only moderate severity defined as AIMS score ≥3 on 1 or more items (Criterion B), and the development of *probable TD* defined as dyskinetic symptoms not necessary persisting for 1 month, using Criterion A and Criterion B. The log-rank test *P* values and cumulative incidence rates are also provided within each Kaplan-Meier graph.

rates were not significantly different between the treatment groups: OLZ (7.2) and CNV (17.6; ratio: 0.411; 95% CI: 0.152-1.018).

A significantly lower risk of at least moderately severe *probable* TD was observed for patients treated with OLZ (3.3%, 95% CI: 0.9-8.2) compared to those treated with CNV (9.0%, 95% CI: 4.5-16.2; $P = .048$; *Criterion B*). The exposure-adjusted event rates were not significantly different between the treatment groups: OLZ (3.6) and CNV (10.9; ratio: 0.329; 95% CI: 0.075-1.139).

Other EPSs

For those patients without significant EPSs at baseline, significantly more patients in the CNV treatment group developed treatment-emergent parkinsonism than for patients in the OLZ treatment group (CNV: 70%, 35 of 50 patients; OLZ 44%, 25 of 57 patients; $P = .011$). No significant difference between groups was observed for treatment-emergent akathisia (CNV: 6%, 7 of 117 patients; OLZ: 10%, 13 of 130 patients; $P = .351$).

A significantly greater worsening in parkinsonian symptoms was observed in patients treated with CNV than those treated with OLZ with a mean change (± standard deviation [SD]) in Simpson-Angus total score of +1.12 (4.31) in OLZ-treated patients and +2.81 (4.20) in CNV-treated patients ($P = .001$). A significantly greater worsening in akathisia was observed in patients treated with OLZ than in patients treated with CNV with a mean change (±SD) in Barnes Akathisia Global score of +.05 (0.90) in the OLZ-treatment group and −.10 (0.74) in the CNV treatment group ($P = .003$).

Concomitant Medications

The percentage of patients taking at least 1 dose of the following concomitant drugs was similar between the OLZ and CNV groups: (1) cholinergic drugs: OLZ, 11.3% (17 of 150); CNV, 6.3% (9 of 143; $P = .153$); (2) anticholinergic drugs: OLZ,

11.3% (17 of 150); CNV, 18.2%, (26 of 143; $P = .102$, and (3) benzodiazepines: OLZ, 38.0% (57 of 150); CNV, 44.1% (63 of 143; $P = .342$).

Safety

The frequency of patients with at least 1 treatment-emergent adverse event was similar between the groups (OLZ, 94.0%; CNV, 94.4%). There were 47 treatment-emergent adverse events that reached a frequency of ≥10% in 1 or both treatment groups. Significant between-group differences were observed for 4 of the 47 events: weight loss (OLZ, 11.3%; CNV, 23.1%; $P = .008$), anemia (OLZ, 10.7%; CNV, 4.2%, $P = .045$), skin ulcer (OLZ, 3.3%; CNV, 11.9%; $P = .007$), and apathy (OLZ, 3.3%; CNV, 11.2%; $P = .012$).

As reported previously, the incidence of deaths and cerebrovascular adverse events were comparable between the 2 treatment groups: incidence of deaths (OLZ, 14.8%; CNV, 16.1%; $P = .871$) and cerebrovascular adverse events (OLZ, 3.4%; CNV, 4.3%; $P = .765$).[32]

In general, no significant changes occurred for any vital sign in patients treated with either OLZ or CNV. A significant difference in the mean change from baseline to end point was observed for weight with a mean (±SD) increase of 0.71 (±6.75) kg in patients treated with OLZ and a mean (±SD) decrease of −1.97 (±6.45) kg in patients treated with CNV ($P = .001$).

Discussion

This study is the first prospective clinical trial to assess the incidence of TD in older adult patients treated with OLZ and to compare the incidence of TD in older adult patients during treatment with OLZ or CNV. In contrast to our hypothesis (primary objective), a low and nonsignificantly different incidence of *persistent* TD defined as AIMS scores = 2 on 2 or more items or ≥3 on 1 or more items (Criterion A) persisting for at least 1 month was observed in both treatment groups, and the risk to this primary end point event was not statistically different between treatment groups. In addition, post hoc analyses revealed that the risk of *persistent* TD meeting the criterion of at least moderate severity defined as AIMS score ≥3 on 1 or more items persisting for 1 month (Criterion B) and the incidence rate of *probable* TD defined as elevated AIMS scores (Criterion A or B) not persisting for 1 month were significantly lower in the OLZ treatment arm compared to the CNV treatment arm.

Our findings are consistent with other studies reporting relatively low rates of TD in older to elderly patients treated with atypical antipsychotics. Thus, the low cumulative incidence of *persistent* TD (2.5%) observed in OLZ-treated patients (77% who had a diagnosis of dementia) in the current study is consistent with the findings from Jeste and colleagues who reported a 2.6% cumulative incidence of TD in elderly patients with dementia who were treated with the atypical antipsychotic risperidone.[15] In older adult to elderly patients with a primary diagnosis of schizophrenia, an approximate 3% to 4% cumulative incidence over a 1-year period for patients treated with risperidone.[14,16] In elderly, antipsychotic-naive patients across a broader range of diagnoses, the cumulative TD rates were somewhat higher with a cumulative TD rate for risperidone that was 5.3% at 1 year and 7.2% at 2 years and a cumulative TD rate for OLZ that was 6.7% at 1 year and 11.1% at 2 years. Similarly, in recent reviews combining data across multiple clinical trials, incidence rates of 5.2%[18] and 5.3% to 6.8%[17] were reported for older adult to elderly patients treated with second-generation antipsychotics.

Our findings are also consistent with other recently published studies that have directly compared incidence rates of TD in patients treated with atypical and typical antipsychotics and found no significant differences. In a retrospective, population-based cohort study, Lee and colleagues reported no significant difference in the risk of developing TD or a drug-induced movement disorder other than parkinsonism in patients being treated with an atypical agent (risperidone, quetiapine, or OLZ; 3.5%) or with a typical antipsychotic (3.0%).[20] In patients with schizophrenia, Miller and colleagues reported no significant differences in the incidence or change in rating scales across several extrapyramidal adverse events including TD when comparing second-generation antipsychotics with the first-generation antipsychotic perphenazine (0.7%-2.2% for second-generation antipsychotics compared to 2.7% for perphenazine).[23] In a cohort study of TD incidence in a population of outpatients, Woods and colleagues reported no significant differences in the annualized TD incidence rates in patients who received second-generation antipsychotics (5.9%) compared to those receiving first-generation antipsychotics (5.6%).[21]

Our findings, though, do differ from other studies reporting significant differences in the risk of TD between atypical and typical antipsychotics. For example, Beasley and colleagues reported the 1-year risk of TD in adult patients with schizophrenia at 0.52% following treatment with OLZ compared to 7.45% following treatment with haloperidol.[13] In antipsychotic-naive elderly patients treated with risperidone or OLZ, Woerner and colleagues[19] reported *cumulative TD rates* that were comparable (risperidone: 5.3% at 1 year and 7.2% at 2 years; OLZ: 6.7% at 1 year and 11.1% at 2 years) in antipsychotic-naive elderly patients treated with risperidone or OLZ and substantially lower than previously reported rates (20% at 1 year and 30% at 2 years)[8] for similar patients treated with first-generation antipsychotics. However, as noted previously, the incidence rates of TD in patients treated with first- or second-generation antipsychotics were not compared concurrently. In 2 reviews of TD risk across multiple clinical trials, a significantly lower risk of TD was observed in adult patients treated with atypical or second-generation antipsychotics (weighted mean annual incidence of TD: 0.8%[17] and annual TD incidence rate: 2.98%[18]) compared to adult patients treated with first-generation agents (weighted mean annual incidence of TD: 5.4%[17] and annual TD incidence rate: 7.7%[18]), although significant differences were not evident in the older adult to

elderly patient populations (incidence rates of 5.2%[18] and 5.3%-6.8%[17] in patients treated with second-generation antipsychotics).

The observed cumulative incidence of *persistent* TD (5.5%) in older adult patients treated with CNV was lower than in previous studies. In a prospective, naturalistic study of 160 neuroleptic-naive patients older than 55 years of age, Saltz and colleagues reported preliminary findings of a 31% incidence rate of treatment-emergent TD only after 43 weeks of cumulative treatment with CNVs.[6] With the complete data set of 261 patients, the cumulative rates of TD were 25% after 1 year, 35% after 2 years, and 53% after 3 years of cumulative antipsychotic treatment.[8] Jeste and colleagues prospectively examined 266 middle-aged and older adult outpatients who were without TD at baseline and found the cumulative proportion of patients developing TD at the end of 1 year was 26%; by 2 years, it was 52%; and by 3 years, it was 60% following treatment with low doses of conventional agents.[7] In a subsequent study of older outpatients with psychiatric disorders (age >45 years) receiving low-dose typical neuroleptics, the 12-month cumulative incidence of TD was 22.3% for patients who were neuroleptic naive at baseline, 24.6% for patients receiving neuroleptics for 1 to 30 days prior to baseline, and 36.9% for patients who had received neuroleptics for more than 30 days prior to baseline.[9]

Several studies[16,19] reporting significant differences between atypical and typical antipsychotics have made indirect comparisons referencing data from these earlier studies (ie, 25%-30% incidence rates reported in older adult and elderly patients treated with typical antipsychotics[6-9]). In more recently published studies[20,21], and review articles,[17,18] the incidence rates of TD for older to elderly patients treated with typical antipsychotics for at least 1 year were in the range of 3% to 8%, values substantially less than the rates previously reported (and described earlier). Our findings of a cumulative incidence of *persistent* TD of 5.5% in older adult patients treated with CNV are consistent with these data. The reasons for the striking differences in TD incidence rates observed between early and more recently published studies have not been identified per se. Many of the early incidence studies used high doses of high-potency antipsychotics such as haloperidol, and there are studies implicating a history of greater cumulative exposure to antipsychotic drugs,[33] and the use of high doses of high-potency antipsychotic drugs[33,34] to a heightened risk of TD. Furthermore, many of the early incidence studies utilized patient populations with mixed diagnoses including those with affective disorders.[8,9,14] A recent article published by Woods and colleagues reported a higher risk of TD among affective patients exposed to CNVs compared to affective patients exposed to atypical antipsychotics.[21]

Several features of our study's design may have reduced the risk of the development of TD for patients in either treatment group. Patients could have experienced a decrease in dose or switch to a less potent CNV which could have decreased the incidence of TD by directly reducing drug exposure or indirectly reducing the extent of dopamine receptor antagonism, respectively. Patients also could have experienced an increase in dose which could have decreased the incidence of TD possibly by masking dyskinetic symptoms. In addition, patients in the CNV treatment arm also could have experienced a switch from one CNV drug to another, and depending on patients' genetic disposition and the conventional drug's potency and dosing, a switch in medication could have lessened the overall TD risk. Furthermore, the majority of patients in both treatment groups had minimal prior antipsychotic exposure during the past 2 years defined as having less than 3 cumulative months of antipsychotic drug exposure within the 2 years preceding study entry. Moreover, the mean modal dose for each antipsychotic drug used during this study was very low. Thus, it is possible that low doses of antipsychotic drugs, the use of low potency CNV, and/or limited prior exposure to antipsychotic medications may be associated with the low incidence of TD observed. However, it should be noted that other studies have reported high rates of TD in neuroleptic-naive patients treated with relatively low doses of CNV.[9]

Concomitant use of benzodiazepines (38%-44%) by patients in both groups was also quite high in this study. Several studies have reported a beneficial effect of benzodiazepines in reducing TD,[35-37]although the most recent review of the Cochrane database[38] provides only limited support for this class of medication to treat TD. Further study of the relationship between benzodiazepine use and the development of TD is warranted. Although other concomitant drugs allowed in this study such as cholinesterase inhibitors and anticholinergics might have altered the development and/or display of TD, the use of these latter agents was more limited and less likely to have appreciably affected the outcome.

In the retrospective, population-based cohort study by Lee and colleagues,[20] their study population consisted entirely of older adults with a diagnosis of dementia which was similar to our patient population (77%-83% of patients diagnosed with dementia), whereas most other incidence studies have utilized patient populations with mixed diagnoses and significantly fewer patients with dementia (range: 20%-30%).[8,9,14] There is some evidence to suggest that the incidence of TD in patients with dementia (when parceled out in some of the earlier studies) is somewhat less than that reported for patients without dementia,[8,9] although the previously reported rates (15%-25% in patients with dementia) are significantly higher than the rates presently observed. Furthermore, concomitant use of benzodiazepines reported at the start of antipsychotic drug use in the Lee study was also high (48%) in both treatment groups. Thus, a diagnosis of dementia reflecting neuropathological changes that differ from those occurring in schizophrenia possibly combined with relatively high levels of concomitant benzodiazepine use may potentially lessen or delay the development of abnormal involuntary movements during antipsychotic drug therapy.

Although no significant group difference was observed in the risk of *persistent* TD, patients treated with CNV had a significantly higher risk of moderately severe *persistent* TD persisting for at least 1 month and of *probable* TD defined as

dyskinetic symptoms that did not persist over 2 consecutive visits. Also, more patients in the CNV treatment group showed TD during the initial 6-week drug titration and TD reassessment period. These findings may be suggestive of a greater relative risk for the development of TD in patients exposed to CNV drugs. In addition, patients treated with CNV showed greater worsening in parkinsonian symptoms, and more patients developed treatment-emergent parkinsonism compared to patients treated with OLZ. The presence of parkinsonism at baseline and/or the development of treatment-emergent parkinsonian symptoms early in treatment has been identified as risk factors for TD.[39,40] The development of treatment-emergent parkinsonian symptoms may also have contributed to the partial masking of new-onset TD.

An Integrated Safety Summary of data from 5 double-blind, placebo-controlled dementia studies (integrated database) revealed that the incidence of mortality was significantly greater among OLZ- than placebo-treated patients (3.5% vs 1.5%, $P = .024$), while the incidence of CVAEs was approximately 3 times higher in OLZ- than in placebo-treated patients (1.3% vs 0.4%, $P = .177$), although the difference was not significant for pooled data.[32] Additional comparisons revealed no significant difference in mortality rates or cardiovascular adverse events (CVAEs) between OLZ- and risperidone-treated patients (mortality: OLZ, 2.9%, risperidone, 2.0%, $P = .751$; CVAEs: OLZ, 2.5%, risperidone, 2.0%, $P = 1.0$).[32] For patients in the current study (HGGE), no significant difference had been observed between OLZ- and CNV-treated patients (mortality: OLZ, 14.8%, conventionals, 16.1%, $P = .871$; CVAEs: OLZ, 3.4%, conventionals, 4.3%, $P = .765$).[32] It is unclear why the incidence of death was greater in the current study, given that the majority of patients enrolled in this study were older adult patients having dementia within a similar age range (76-83 years) as reported in the other dementia studies. For older adult patients, a number of factors may potentially increase the risk of treatment-emergent adverse events and/or death including comorbid illnesses, polypharmacy, and age-related changes in pharmacokinetics and pharmacodynamics including changes in drug responses and the ability to metabolize drugs.[32] In addition, the current study allowed a wide range of CNVs to be used including some that are restricted because of CVAEs (ie, thioridazine and pimozide).[41]

This study had been conducted from December 1997 to August 2001 to assess the potential risk of developing TD in older adult patients treated with OLZ or CNVs, prior to the label change reflecting an increased incidence of mortality in this population. Consistent with these findings and as stated in the boxed warning in the label for OLZ (Zyprexa, Eli Lilly & Company), older adult patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of older adult patients with dementia-related psychosis. Clinicians should be aware of the increased risk of death during treatment with antipsychotic drugs in this patient population.

Limitations

The study was not double blinded, although TD raters were blind to each patient's treatment assignment. In addition, this study was only 1 year in duration and, therefore, cannot judge potential outcomes of treatment for greater than 1 year. The observed difference between OLZ and CNV treatment groups for the cumulative incidence of *persistent* TD was smaller than initially hypothesized; therefore, the size of the current study would have low power to detect a small difference between treatment groups. It is worthwhile to note that patients in the OLZ treatment group were treated for a longer period of time compared to patients in the CNV treatment group.

In patients who develop dyskinetic symptoms, the pattern of severity in symptoms can fluctuate over time, and not all patients who show signs of TD go on to develop *persistent* TD. Indeed, a number of variables can affect the likelihood that a given patient will develop TD including the patient's genetic predisposition, age, gender, ethnicity, diagnosis, prior antipsychotic drug exposure, current antipsychotic drug regimen (ie, flexible dosing, duration of exposure, and potency), concomitant medications, substance abuse, and comorbid conditions (ie, parkinsonism). It is likely that many of these variables interacted to play a role in the low rates of *persistent* TD observed in this study. In addition, the lower than expected rates of TD made it difficult to evaluate possible treatment differences. Although the low cumulative incidence of *persistent* TD observed in the older adult patients was a favorable outcome, the potential risk of TD and other EPSs during treatment with antipsychotics warrants careful consideration.

The design of the HGGE study, in part, was to capture the tendency of physicians to either maintain patients on a given medication, to make changes in dosing or the decision to keep patients on a given medication or not, or to make a switch between medications (CNV group only). Presumably, these tendencies would most closely mirror treatment decisions occurring in the community. Therefore, if switching patients on or off a given antipsychotic drug (either treatment group) or between different drugs (CNV group) had occurred substantially more in the CNV group, this would be important to know and could be associated with a greater risk of developing TD in the CNV group. However, the results of the current study did not show a substantially greater risk for the development of the *persistent* TD in patients treated with CNVs.

Finally, we made the a priori decision to exclude those patients who developed *probable* TD during the first 6 weeks of treatment. This methodology was similar to that employed previously by Beasley et al (see Stratum 2).[13] We had postulated that TD development during this initial acute phase could reflect withdrawal TD from previous medication or the unmasking of preexistent TD. However, the number of patients who developed TD during this time frame was different between the 2 treatment groups (1 patient in the OLZ treatment group and 5 patients in the CNV treatment group), a finding suggestive of a possible treatment effect. Older adult patients can develop TD as early as 4 weeks during antipsychotic drug therapy, and therefore, it is possible that

the current study design potentially excluded the most sensitive patients who developed TD rapidly. One study has suggested that OLZ may have an ameliorative effect on preexisting TD,[42] a finding that might offer another explanation for why only 1 patient in the OLZ treatment group displayed TD symptoms during the first 6 weeks of treatment compared to 5 patients in the CNV treatment group.

Conclusion

The cumulative incidence of *persistent* TD was low and the risk to *persistent* TD did not differ significantly among predominantly older adult patients having dementia with acute psychosis or agitation treated with OLZ or CNV.

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