JAMDA 17 (2016) 142–147

JAMDA

journal homepage: www.jamda.com

Original Study

A Randomized Placebo-Controlled Discontinuation Study of Cholinesterase Inhibitors in Institutionalized Patients With Moderate to Severe Alzheimer Disease

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Keywords:
Cholinesterase inhibitors
randomized controlled trial
neuropsychiatric symptoms
Alzheimer disease
institutionalization

A B S T R A C T

Objectives: Cholinesterase inhibitors (ChEIs) offer modest benefits in Alzheimer disease (AD), which must be balanced against risks. Relatively few data delineate the benefits and risks of long-term ChEI administration in institutionalized patients with advanced AD. This study investigated the effects of ChEI discontinuation in institutionalized patients with AD.

Design: Institutionalized patients with moderate to severe AD (standardized Mini- Mental Status Examination $\leq$15) and treated with a ChEI for $\geq$2 years were randomized, double-blind, to ChEI continuation or placebo, with a 2-week tapering phase, for 8-weeks.

Measurements: The primary outcome of this pilot study was change on the Clinician's Global Impression of Change (CGI-C) scale. Secondary outcomes included safety, efficacy, and tolerability. Baseline (BL) predictors of clinical deterioration were also determined.

Results: Forty patients (mean $\pm$ standard deviation age = 89.3 $\pm$ 3.5 years, standardized Mini-Mental Status Examination = 8.1 $\pm$ 5.2, Neuropsychiatric Inventory–Nursing Home version total score = 21.1 $\pm$ 15.9, 80% male) were randomized to ChEI continuation (n = 21) or placebo (n = 19). There was no significant difference in clinical worsening in the ChEI continuation (28.6%) and placebo groups (36.8%) on CGI-C (odds ratio for worsening 1.58, 95% confidence interval .38–6.55, $P = .53$). The occurrence of adverse events was similar in both groups. There were no significant differences in any of the secondary outcome measures. In the placebo group, BL hallucinations predicted CGI-C worsening [$F(1,17) = 6.4$, $P = .02$], and there was a trend for BL delusions to predict CGI-C worsening [$F(1,15) = 3.5$, $P = .08$].

Conclusions: These results suggest that ChEI discontinuation is safe and well tolerated in the majority of institutionalized patients with moderate to severe AD. When discontinuing ChEI, the presence of hallucinations and delusions may predict clinical deterioration, suggesting the need for increased caution.

Alzheimer disease (AD) is the most prevalent form of dementia, occurring in 5%–7% of individuals aged 60 and over.[1] Patients with moderate to severe AD account for an estimated 50% of all AD cases, and it has been projected that in the future, those with moderate to severe AD will represent 90% of patients residing in long-term care (LTC).[2,3]

Currently approved treatments available for the symptomatic management of mild to moderate AD include cholinesterase inhibitors (ChEIs); donepezil, rivastigmine, and galantamine, and the N-methyl-

This study was funded by the Alzheimer's Society of Canada (#:12-74) and the Coleman Fund (internal funding). The research protocol for this study was approved by the research ethics boards at Sunnybrook Health Sciences Center and North York General Hospital. Written consent was obtained from the participant's substitute decision maker prior to study enrollment.

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http://dx.doi.org/10.1016/j.jamda.2015.08.019

D-aspartate receptor antagonist, memantine. Donepezil, the rivastigmine transdermal patch, and memantine are also approved for the treatment of severe AD.

Several clinical practice guidelines have proposed ChEIs for the treatment of all stages of AD, with some advocating ChEI discontinuation if tolerability issues arise, or if there is no longer a noticeable clinical benefit.[4–6] While ChEIs have demonstrated short-term stabilization on measures of cognition and global functioning in randomized controlled trials (RCTs) of community-dwelling patients with severe AD,[7–10] data with respect to ChEI use in institutionalized patients with AD are limited. Further studies in this setting are important because patients residing in LTC settings have increased AD severity,[11] are more functionally impaired,[12] present with more comorbid illnesses,[13] take more concomitant medications,[14,15] and are on ChEIs for a longer duration.[16] In addition, ChEIs, although generally well tolerated, have potential adverse events (AEs) including nausea, diarrhea, insomnia, vomiting, muscle cramping, fatigue, and weight loss.[17–19] As such, ChEI discontinuation in institutionalized patients with AD no longer displaying obvious clinical benefit may reduce the risk of AEs, minimize polypharmacy, and reduce cost of care.

Currently, there are no double-blind RCTs addressing ChEI discontinuation in moderate to severe institutionalized patients with AD. The lack of data surrounding long-term ChEI use, coupled with the potential for AEs, make investigation of the effects of ChEI discontinuation in this population warranted.

Methods

Study Participants

All patients were institutionalized and resided in 1 of 2 LTC facilities. Informed consent was obtained from the patient's substitute decision maker and approved by the primary care physician. The Research Ethics Boards at both sites approved this study.

Eligible patients were ≥55 years, met the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria for probable AD, met Diagnostic and Statistical Manual of Mental Disorders-fourth edition criteria for primary degenerative dementia, had a score of ≤15 on the Standardized Mini-Mental State Examination (sMMSE), and had been treated with donepezil, galantamine, or rivastigmine (oral) for ≥2 years, with a stable dose for ≥3 months prior to study entry. Patients receiving a concomitant psychotropic had to be on a stable dose for ≥1 month prior to study entry.

Patients were excluded if they had dementia unrelated to AD, were treated with transdermal rivastigmine, had any uncontrolled medical illness that would interfere with their participation in the study, or had significant difficulty ingesting oral medication.

Study Procedures

This was an 8-week randomized, double-blind, placebo-controlled pilot trial. Following study entry, patients were randomized with a 1:1 balanced by ChEI to continue receiving their ChEI (continuation) at their current dose, or to receive an identical-looking placebo substitution. Patients randomized to placebo were tapered off their ChEI for the first 2 weeks and continued on placebo for the remaining 6 weeks. Randomization was completed independently by the pharmacy at Sunnybrook Health Sciences Center in permuted blocks using a computer-generated code. Patients, family members, nurses, clinicians, outcome assessors, and investigators were unaware of treatment group assignments or block size.

Following screening, patients were assessed at, 0 [baseline (BL)], 2, 4, and 8 (study endpoint) weeks. The study physician completed the Clinician's Global Impression (CGI) at 0, 4, and 8 weeks, and Clinician's Global Impression of Change (CGI-C) at 4 and 8 weeks. At 0, 4, and 8 weeks, patients completed 2 cognitive assessments, the sMMSE and Severe Impairment Battery. Primary nurses completed the Udvalg for Kliniske Undersogelser side effect rating scale, Neuropsychiatric Inventory-Nursing Home edition (NPI-NH), Cornell Depression Scale for Dementia, Apathy Evaluation Scale (AES), Cohen-Mansfield Agitation Inventory (CMAI), Alzheimer's disease Cooperative Study-Activities of Daily Living, modified for severe AD (ADCS-ADL-sev), and Quality of Life in Late Stage Dementia (QUALID). At 2 weeks, patients completed the sMMSE, and primary nursing staff completed the Udvalg for Kliniske Undersogelser side effect rating scale. Vital signs (blood pressure, pulse rate, and weight) were obtained at each study visit to monitor safety. Provided there was no substantial cognitive deterioration (sMMSE total decrease ≥3 points compared with BL)[20] or clinically significant increase in neuropsychiatric symptoms (NPS) (NPI-NH total increase ≥50% compared with BL),[21] the randomized treatment was continued.

Outcome Measures

The primary efficacy outcome was CGI-C.[22] The CGI-C is a 7-point Likert scale (ranging from "marked improvement" to "marked worsening") that requires an experienced clinician to assess the degree to which a patient's illness has improved or worsened relative to a BL state. The CGI-C requires the clinician to consider changes in the cognitive, behavioral. and/or functional status of the patient. Given the nature of this population's significant cognitive and functional impairment necessitating full time institutional care, a global measure of clinical status was considered the most ecologically valid primary outcome measure, and the measure most clinicians and families would rely on when considering drug discontinuation.[23]

The secondary outcome measures were safety, efficacy, and tolerability. The safety outcome was determined by the number of individual and total AEs experienced. All emergent AEs were noted and followed up with until resolution. The efficacy and tolerability of ChEI discontinuation was determined by cognitive, functional, and behavioral outcomes. Cognitive outcomes were determined by total scores on the sMMSE and Severe Impairment Battery; the lower the score on either assessment, the greater the cognitive impairment. The behavioural outcomes were assessed by the NPI-NH (total score), CMAI, and AES; the greater the score on the NPI-NH, CMAI, and AES, the greater the overall behavioral disturbance, agitation, and apathy, respectively. The functional outcome was determined by the ADCS-ADL-sev; the lower the ADCS-ADL-sev score, the greater the functional impairment. Quality of life was measured by the QUALID; the lower the QUALID score, the lower the quality of life.

Sample Size

A sample size calculation was performed for the primary efficacy outcome described previously using a 2-tailed, 2-sample test of proportions estimation method. The proportion of ChEI continuation patients expected to deteriorate was based on Winblad et al,[24] which found that 18% of ChEI-treated patients showed clinically significant global deterioration (5, 6, or 7 on the CGI-C) over a similar time frame. A sample size of 20 patients per group would be sufficient to detect a 3.5-fold increase over the ChEI continuation group with 80% power and a 5% significance level as well as allow for 1 covariate.

Statistical Analysis

To compare BL characteristics between the treatment groups, independent *t*-tests (for parametric data) and Mann-Whitney U tests

(for nonparametric data) were computed for each medical, cognitive, behavioral, and functional measure.

The primary assessment of efficacy was based on an intention-to-treat comparison of the CGI-C ratings at week 8. The CGI-C ratings were grouped into clinical improvement/no change and clinical worsening. A logistic regression analysis, adjusting for BL sMMSE, was used to compare CGI-C ratings between the treatment groups. An observed case analysis with study completers and a subanalysis comparing antipsychotic users with nonusers was also completed.

To assess the safety of ChEI discontinuation, a χ^2 or Fisher exact test was used to determine the association between treatment group and AE occurrence and to determine if the proportion of participants with AEs was greater in those with CGI-C worsening at 8 weeks. To determine the efficacy and tolerability of ChEI discontinuation on cognition, behavior, function, and caregiver distress, a repeated measures analysis of covariance was used to compare groups over time (0, 4, and 8 weeks) for each cognitive, behavioral, and functional measure, and caregiver distress score on the NPI-NH, controlling for treatment group and BL sMMSE scores.

A linear regression model was run within each group to determine predictors of CGI-C worsening.

Results

Study Patient Characteristics

Forty institutionalized patients with moderate to severe AD were randomized to ChEI continuation (N = 21) or placebo (N = 19), and all were included in the analyses (Figure 1). All BL characteristics were comparable, except patients randomized to ChEI continuation had lower sMMSE scores (Table 1). Of the 40 randomized, 33 patients (82.5%) completed the study (85.7% continuation, N = 18; 78.9% placebo, N = 15;); 1 died prior to study completion (unrelated to study) (placebo), 1 was terminated early because of a serious AE (continuation), 1 was lost to follow-up (continuation), 1 had clinically significant cognitive decline (placebo), and 3 had clinically significant behavioral deterioration (2 placebo, 1 continuation). Number of early terminations [$\chi^2(1) = .316$, $P = .57$], time to early termination, as

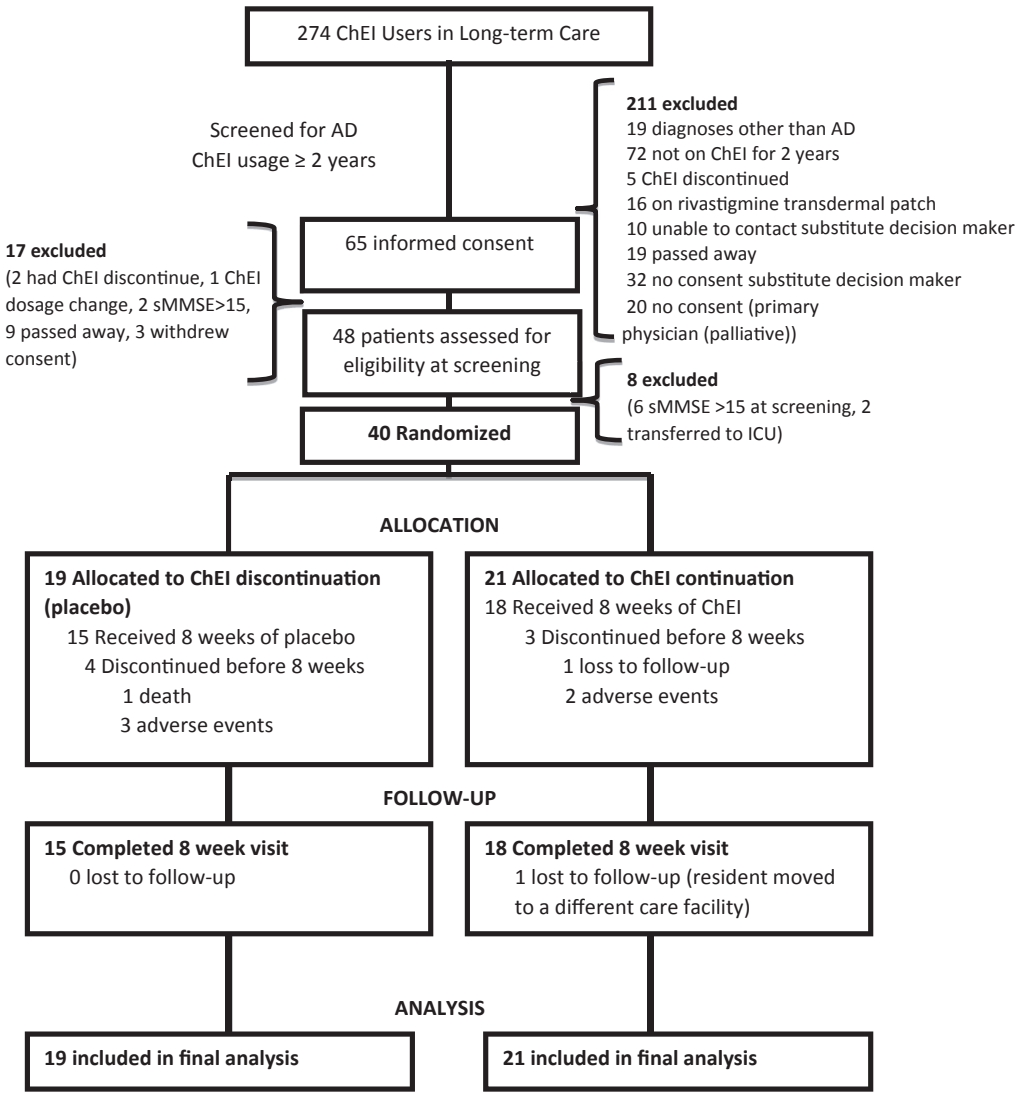

Fig. 1. Participant flow diagram.

Table 1
Baseline Characteristics

Demographics/ Baseline characteristics	Total (N = 40)	Placebo (ChEI Disc.) (N = 19)	ChEI Cont. (N = 21)	*P* Value
Age (years)	89.2 (± 3.5)	89.7 (± 3.8)	88.9 (± 3.3)	.46
Sex (%M)	80	73.7	85.7	.34
Number of concomitant illnesses	6.4 (± 2.43)	6.5 (± 2.8)	6.29 (± 2.1)	.62
Number of concomitant meds	12.3 (± 5.5)	11.3 (± 5.2)	13.2 (± 5.7)	.23
ChEIs				
Donepezil	17	7	10	.49
Galantamine	16	8	8	.80
Rivastigmine	7	4	3	.57
Psychotropics				
Memantine	37.5	31.6	42.9	.46
Antidepressants	45	42.1	47.6	.73
Antipsychotics	32.5	26.3	38.1	.39
Baseline Parameters				
CGI	3.7 (± 0.7)	3.5 (± 0.7)	3.8 (± 0.6)	.20
Weight (kg)	71.1 (± 14.5)	67.1 (± 14.9)	74.9 (± 13.4)	.15
sMMSE	8.1 (± 5.2)	10.0 (± 5.1)	6.4 (± 4.8)	.03
SIB Total	56.9 (± 31.1)	63.7 (± 28.0)	50.8 (± 33.1)	.20
NPI-NH Total	21.1 (± 15.9)	20.3 (± 18.0)	21.9 (± 14.0)	.52
Delusions (NPI-NH)	1.15 (± 2.95)	1.95 (± 4.02)	.43 (± 1.12)	.13
Hallucinations (NPI-NH)	.37 (± 1.35)	.47 (± 1.43)	.29 (± 1.31)	.67
NPI-NH disruption total	7.9 (± 6.4)	7.8 (± 7.3)	8.0 (± 5.7)	.94
CMAI	46.9 (± 13.7)	44.1 (± 12.4)	49.6 (± 14.6)	.26
AES	55.9 (± 11.2)	52.4 (± 12.7)	59.0 (± 8.7)	.08
ADCS-ADL-sev	12.7 (± 10.0)	14.2 (± 10.9)	11.3 (± 9.1)	.50
QUALID	21.6 (± 7.2)	20.1 (± 6.6)	23.0 (± 7.7)	.15

ChEI, cholinesterase inhibitor; Disc, discontinuation; Cont, continuation; sMMSE, Standardized Mini Mental State Examination; SIB, Severe Impairment Battery; CGI, Clinician's Global Impression Scale; NPI-NH, Neuropsychiatric Inventory - Nursing Home version; CMAI, Cohen-Mansfield Agitation Inventory; AES, Apathy Evaluation Scale; ADCD-ADL-sev, Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory, modified for severe AD; QUALID, Quality of Life in Late-Stage Dementia scale.

measured by the number of weeks actively participating in the study [t(5) = .48, P = .65] and percent drug compliance (97.3% placebo; 96.6% continuation, U = 162, P = .30) did not significantly differ between groups.

Table 2
Frequency of AEs

AE	Placebo (N = 19)	ChEI Continuation (N = 21)	Total (N = 40)
Unintentional weight loss (<1.66%)	5	3	8
Fall	3	3	6
Loss of consciousness	0	1	1
Vomiting	0	2	2
Perineum wound	0	1	1
Oral thrush	1	0	1
IV due to poor appetite	1	0	1
Respiratory tract infection	1	1	2
Conjunctivitis	0	1	1
Dizziness	0	1	1
Rash	0	1	1
Cognitive decline/confusion	1	0	1
Acute/unproductive cough	0	1	1
Deterioration in behavior	3	2	5
Bradycardia	0	1	1
Serious AEs	1	2	3
Bowel obstruction	1	0	1
Seizure	0	1	1
Atrial fibrillation	0	1	1

Study Outcomes

Minimal to marked worsening over 8 weeks on the CGI-C occurred in 6 continuation (28.6%) vs 7 placebo-treated (36.8%) participants. When adjusting for BL sMMSE, treatment group was a nonsignificant predictor of CGI-C worsening at 8 weeks [odds ratio (OR) for worsening 1.58, 95% confidence interval (CI) .38–6.55, P = .53]. In a post-hoc analysis adjusting for BL sMMSE and for antipsychotic use, to account for frequent antipsychotic use in this study population, treatment group remained a nonsignificant predictor of CGI-C worsening (OR for worsening 1.67, 95% CI .40–7.10, P = .49). In a subanalysis of study completers (n = 33), when adjusting for BL sMMSE, treatment group was a nonsignificant predictor of CGI-C worsening (OR for worsening 1.95, 95% CI .31–12.17, P = .48).

The frequency of AEs is presented in Table 2. Unintentional weight loss (20% of total) and falls (15% of total) were the most common AEs experienced by study participants. However, treatment allocation did not have a significant effect on AE occurrence [$\chi^2(1) = 2.41$, P = .12], clinically significant weight loss (P = .44, Fisher exact test), or the occurrence of falls (P = 1.0, Fisher exact test). In addition, AE occurrence did not have a significant effect on CGI-C worsening in the whole group (P = .50, Fisher exact test), the continuation group (P = .12, Fisher exact test), or the placebo group (P = 1.0, Fisher exact test).

Mean change scores on all BL parameters are shown in Table 3. When controlling for BL sMMSE scores and treatment group, there was no significant effect of time on any cognitive, behavioral, and functional measures, or caregiver distress score on the NPI-NH.

In the placebo group, hallucinations at BL (NPI-NH) significantly predicted CGI-C worsening at study endpoint [F (1,17) = 6.39, P = .02] while delusions at BL (NPI-NH) approached significance [F(1,15) = 3.45, P = .08]. Hallucinations and delusions accounted for 27.3% and 13.3% of the explained variance in CGI-C worsening, respectively. In the placebo group, 31.6% of the patients who experienced delusions and/or hallucinations at BL, also experienced minimal to marked worsening (Figure 2).

Discussion

This study suggests that ChEI discontinuation is safe and well tolerated in institutionalized patients with moderate to severe AD who have been treated for at least 2 years. ChEI discontinuation was not associated with CGI-C worsening, increased AE occurrence, clinically significant weight change, falls, or changes in caregiver distress. However, the presence of hallucinations and delusions in the placebo group at BL suggested that those NPS may predict clinical deterioration when discontinued from ChEI treatment.

Currently, ChEIs are recommended for the treatment of moderate to severe AD, however, the American Geriatrics Society Choosing Wisely Workgroup suggests that clinicians should consider discontinuation if the cognitive, behavioral, and functional goals of the patient's treatment plan are not met.[25] A meta-analysis of 5 ChEI discontinuation, double-blind RCTs reported that ChEI discontinuation increases the rate of cognitive and behavioral deterioration.[26] However, of those studies, only the Donepezil and Memantine for Moderate to Severe Alzheimer Disease trial specifically included patients with moderate to severe AD, and that study excluded institutionalized patients. The Donepezil and Memantine for Moderate to Severe Alzheimer Disease trial demonstrated that ChEI discontinuation may lead to cognitive and functional deterioration, while having no significant effect on NPS.[7] Though the results of our study also indicated that treatment allocation did not have a significant effect on NPS, it did not replicate the findings of the other studies, as we found that treatment allocation did not have a significant effect on the change of cognition, function, or global ratings over 8 weeks. In addition to differences in setting, those studies involved participants

Table 3
Change Scores (Baseline to 8 Weeks)

Parameter	Placebo			Cholinesterase Cont.			*P* Value
	BL (Mean ± SD)	Endpoint (Mean ± SD)	Change (Mean ± SD)	BL (Mean ± SD)	Endpoint (Mean ± SD)	Change (Mean ± SD)	
CGI	3.5 ± 0.7	3.6 ± 0.4	−0.1 ± 0.5	3.8 ± 0.6	3.8 ± 0.8	0.0 ± 0.4	.64
CGI-C*	n/a	n/a	3.6 ± 1.1*	n/a	n/a	3.4 ± 1.2*	.55
Weight (kg)	67.1 ± 14.9	66.9 ± 15.2	−0.4 ± 2.2	74.8 ± 13.4	74.4 ± 12.5	−0.4 ± 4.1	.84
sMMSE	10 ± 5.1	8.8 ± 5.6	−1.0 ± 4.0	6.4 ± 4.8	7.1 ± 5.8	0.7 ± 3.1	.19
SIB	63.7 ± 28.0	57.2 ± 34.7	−6.5 ± 21.3	50.8 ± 3.1	49.5 ± 35	−1.3 ± 14.6	.25
NPI-NH	20.3 ± 18	23.8 ± 3.6	3.6 ± 12.6	21.9 ± 14	20.9 ± 18.4	−1.1 ± 8.9	.24
NPI-disruption	7.8 ± 7.3	8.8 ± 9.8	1.0 ± 4.2	8.0 ± 5.7	7.8 ± 7.0	−0.2 ± 6.3	.28
CMAI	44.1 ± 12.4	43.8 ± 9.1	−0.3 ± 7.3	49.6 ± 4.6	52.3 ± 19.3	2.5 ± 11.2	.90
AES	52.4 ± 12.7	54.2 ± 12.5	1.8 ± 7.6	59 ± 8.7	62.3 ± 5.9	3.3 ± 5.5	.32
ADCS-ADL-sev	14.2 ± 10.9	14.1 ± 11.1	−0.1 ± 3.8	11.3 ± 9.1	11.3 ± 9.1	0.0 ± 3.4	.54
QUALID	20.1 ± 6.6	20.4 ± 7.2	0.3 ± 3.1	23.0 ± 7.7	22.9 ± 8.5	−0.1 ± 4.8	.92

ANCOVA, analysis of covariance; cont, continuation; n/a, not applicable (change score only); sMMSE, Standardized Mini-Mental State Examination; SD, standard deviation; SIB, Severe Impairment Battery.
Asterisk (*) denotes that the reported CGI-C score is reported as the score provided by the study physician at study endpoint. This score represents how the patient has improved or worsened clinically, from baseline. Because this score was taken from a single point in time, a Mann-Whitney U test was used to compute the *P* value. For all other measures, a repeated measures ANCOVA, controlling for BL MMSE scores, was used to compute the *P* values.

who were younger, with similar or lower NPI scores, and higher sMMSE scores.[26] As such, these differences suggest that previous findings may not apply to institutionalized, more elderly populations, who often reach the stage where discontinuation of medications may be considered.

ChEI treatment has been associated with an increased risk of nausea, vomiting, weight loss, syncope, and bradycardia.[17–19] Those AEs must be taken into consideration during ChEI discontinuation as the patient group is both frail and elderly, and there may not be sufficient benefit from the treatment to justify such AEs. Furthermore, polypharmacy is a worrisome issue because swallowing medications, and the occurrence of drug-related AEs are common in institutionalized patients with advanced dementia.[27,28] Though the results of our study suggest that there was no significant effect of treatment allocation on early terminations or AE occurrence, 60% of participants (N = 24) experienced 1 or more AEs during the study. There was no significant association between AE occurrence and clinical deterioration (CGI-C) within the study group, and within each treatment allocation. While this study suggests that ChEIs can be safely discontinued in many institutionalized, patients with moderate to severe treated for ≥2 years, of particular clinical relevance was the finding that BL scores of psychosis (hallucinations and delusions) correlated with worsening following discontinuation. We, therefore, suggest clinicians closely monitor patients with psychotic symptoms if discontinuation is attempted.

It is interesting to speculate on why NPS like hallucinations and delusions were associated with clinical worsening following ChEI discontinuation. Studies have shown that cholinergic deficiency may contribute to the development of NPS in moderate to severe AD, and that these NPS may improve after ChEI use, and worsen with anticholinergic medications.[29] Three RCTs of patients with AD reported NPS worsening in those randomized to placebo when compared with

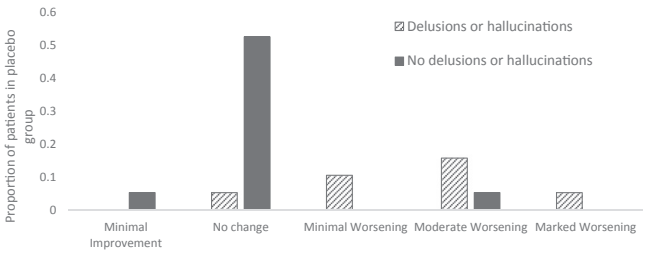

Fig. 2. Proportion of ChEI discontinued patients with and without delusions and hallucinations (NPI-NH).

ChEI treatment.[30–32] An open label study with donepezil in 120 patients with AD, with a mean NPI total score of 30 at BL, reported that after 20 weeks of ChEI use, there was a ≥30% reduction in the NPI total score in 62% of patients, with a 27% reduction in delusions, hallucinations, and sleep domains from BL.[33] In a post hoc analysis of 2033 patients with AD (double blind RCT with galantamine), in 57% of patients treated with galantamine, there was ≥30% reduction in the hallucination and delusions NPI score, with 72% of patients treated with galantamine having a 30% reduction in hallucinations.[34] It is, thus, possible to explain the worsening of hallucinations and delusions through discontinued ChEI use, its consequent increase in cholinergic deficiency,[35] and its subsequent contribution to clinical deterioration in the study group.

Study strengths included randomization, double-blinding, use of placebo control using an identical appearing capsule, and careful assessment of AEs, cognition, function, and behavior using scales appropriate to the population and setting. Nevertheless, there are certain limitations that should be taken into consideration. Patients from the Sunnybrook Veterans' Center are predominantly male, introducing sampling bias, because males are overrepresented at this site. Observational[36] and retrospective[37] studies suggest that being male is significantly associated with psychosis in AD. Although another cross-sectional study did not replicate those findings, they did find that male sex was significantly associated with agitation at the moderate and severe stages of AD.[38] This study also allowed concomitant use of antipsychotics as antipsychotics are commonly used in long-term care in patients with moderate to severe AD and behavioral disturbances. Even though this could mask medication effects, there were no significant differences between treatment groups in the number of individuals taking psychotropics. In addition, when controlling for antipsychotic use, treatment group was not a significant predictor of clinical deterioration (CGI-C). It should also be noted that patients on the rivastigmine patch were excluded. This exclusion criterion was necessary as study participants were required to take study medication in capsule form, but limits generalizability to that group. Similarly, patients who were not medically stable, or were in palliative care were excluded. As a result, patients included in the study may have been healthier and have had a better response to pharmacologic intervention. This study may also be considered to have a short duration of follow-up. However, we have demonstrated in a meta-analysis of previous ChEI discontinuation RCTs that most of the deterioration occurs within the first 6 weeks of discontinuation.[26]

Finally, this study also had a small sample size, which should be considered when interpreting results. Though not statistically significant, clinical deterioration in the placebo group was numerically

greater than that in the ChEI continuation group. A post hoc analysis of the mean of change scores between the treatment groups indicated that in order to obtain results with an analytical power of 80%, the sample size required is 520 participants for the CGI-C. Although statistically significant differences might have been detected with this large sample size, differences may not have been clinically relevant when balanced against risks in this population. At the very least, the results of this study provide necessary pilot data on the safety and tolerability of ChEI discontinuation, as well as some potential indicators of clinical factors that make discontinuation riskier.

Conclusions

This study of the safety and tolerability of ChEI discontinuation in institutionalized patients with moderate to severe AD provides the first evidence in this setting and adds to the limited evidence in those with advanced AD. These results contrast with previous studies in community-dwelling participants, which found continued efficacy.[7,30,32] This discrepancy calls for future ChEI discontinuation trials in institutionalized patients with more advanced AD. Further study may provide insight into those who should, and should not continue ChEI treatment, and may support a broader literature dealing with discontinuing medications of questionable benefit in the frail and elderly.

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