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Effect of Sertraline on Risk of Falling in Older Adults with Psychotic Depression on Olanzapine: Results of a Randomized Placebo-Controlled Trial

Alastair J. Flint, M.B., Andrea Iaboni, M.D., D.Phil., Benoit H. Mulsant, M.D., Anthony J. Rothschild, M.D., Ellen M. Whyte, M.D., and Barnett S. Meyers, M.D. on behalf of the STOP-PD Study Group

Department of Psychiatry, University of Toronto (AJF, AI, BHM); Department of Psychiatry, University Health Network, Toronto (AJF, AI); Toronto General and Toronto Rehab Research Institutes, Toronto (AJF); Centre for Addiction and Mental Health, Toronto (BHM), University of Massachusetts Medical School and UMass Memorial Health Care (AJR); Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine (EW, BHM); Department of Psychiatry Weill Medical College of Cornell University and New York Presbyterian Hospital–Westchester Division (BSM)

Abstract

Objective—Observational studies report that selective serotonin reuptake inhibitor (SSRI) antidepressants are associated with an increased risk of falls in the elderly, but these studies may over-estimate drug-specific risk because of confounding. A randomized controlled trial (RCT) is the optimal way to assess the causal relationship between use of an SSRI and falls. We therefore analyzed data from a RCT of the treatment of psychotic depression, to examine whether combined olanzapine and sertraline interacted with older age to increase the risk of falling compared with olanzapine plus placebo.

Design—Double-blind placebo-controlled RCT.

Setting—Four academic medical centers.

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Address for Correspondence: Dr. Alastair Flint, Toronto General Hospital, 200 Elizabeth St., 8 Eaton North–Room 238, Toronto, Ontario, M5G 2C4, Canada, Phone: (416) 340-4788; Fax (416) 340-4198; alastair.flint@uhn.on.ca.

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Conflicts of Interest:

AJF has received grant support from the NIMH, the Canadian Institutes of Health Research, and Lundbeck and has received honoraria from Janssen-Ortho, Lundbeck Canada, and Pfizer Canada. **BHM** currently receives research support from the Canadian Institutes of Health Research (CIHR), the US National Institute of Health (NIH), Bristol-Myers Squibb (medications for a NIH-funded clinical trial), and Pfizer (medications for a NIH-funded clinical trial). He directly owns stocks of General Electric (less than \$5,000). Within the past three years, he has also received some travel support from Roche. In the more distant past he has received honorarium and consulting fees from Pfizer. **AJR** has received grant support from the National Institute of Mental Health (NIMH), Cyberonics, Takeda, and St. Jude Medical and has served as a consultant to Allergan, GlaxoSmithKline, Eli Lilly, Noven Pharmaceuticals, Pfizer, Shire Pharmaceuticals, and Sunovion. **BSM** receives research support from the NIMH. He is receiving medication donated by Pfizer and Eli Lilly for his NIMH trial. During the last three years he has provided legal consultation to AstraZeneca and research consultation for Forest Laboratories. **EMW** has received research support from the NIMH, the National Institute of Child Health and Human Development (NICHD), the Department of Defense (DOD) and through a Small Business Innovation Research (SBIR) grant from Fox Learning Systems / National Institute of Neurological Disorders and Stroke (NINDS). **AI** has no conflicts to report.

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Participants—Two hundred and fifty nine patients with major depressive disorder with psychotic features (n=117 aged 18–59 years and n=142 aged 60 years or older).

Intervention—Twelve weeks of randomized double-blind treatment with olanzapine plus sertraline or olanzapine plus placebo.

Measurements—Proportion of participants who fell at least once.

Results—Older participants were significantly more likely than younger participants to fall. Among older participants, the odds ratio of falling with olanzapine plus sertraline versus olanzapine plus placebo was 1.56 (95% CI 0.63–3.83). There was not a statistically significant treatment effect or treatment × age interaction with respect to the proportion of participants falling. These negative results may have been due to low statistical power.

Conclusion—Evaluating the association between SSRIs and falls in a RCT is limited by the large sample size that is required. An alternative approach is to examine the effect of an SSRI on measures of postural stability and gait that are valid markers of risk of falling.

Keywords

Selective serotonin reuptake inhibitor; Falls; Depression; Randomized controlled trial; Aged

INTRODUCTION

Falls are common in late life, occurring annually in approximately one-third of persons age 65 years or older.¹ Ten percent of falls result in serious injury, which can lead to institutionalization or death.¹ Falls frequently result in a fear of future falls, which can result in fear-related restriction of activities and consequent physical and functional decline, social isolation, and impaired quality of life.²

Observational studies have reported that selective serotonin reuptake inhibitors (SSRIs) are associated with an increased risk of falls in the elderly, with the highest risk of falls in the first few weeks after initiation of the antidepressant.^{3,4} While these studies attempt to control for confounding variables, the quality of data pertaining to psychiatric disorders is usually poor, because the data are typically derived from an administrative database. These studies are subject to both ‘confounding by indication’ (i.e., the disorder for which the SSRI is prescribed may in fact contribute to or explain the observed association) and ‘confounding by contraindication’ (i.e., persons felt to be at high risk of falls may be prescribed an SSRI because the medication is believed to be safer than another antidepressant). Observational studies have found that depression is an independent risk for falls and fractures.⁵ A randomized controlled trial (RCT) is therefore the optimal way to assess the causal relationship between use of an SSRI and fall risk.

In a search of the literature, we identified 10 randomized placebo-controlled trials of SSRIs in late-life depression (list available on request). None of these studies reported data on falls. The Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) is a 12-week double-blind RCT that compared the efficacy and safety of olanzapine plus sertraline with olanzapine plus placebo in the treatment of younger and older adults with psychotic depression.⁶ STOP-PD systematically collected data on the incidence of participants falling during randomized treatment. Given the public health significance of falls and the absence of RCT data on the risk of falls with SSRIs in depression, we analyzed STOP-PD data to explore whether combined olanzapine-sertraline treatment in STOP-PD interacted with older age to increase the risk of experiencing a fall compared with olanzapine plus placebo.

METHODS

The design, methods, and main findings of STOP-PD have been reported elsewhere.⁶ One of the aims of STOP-PD was to compare outcomes in younger and older adults; as a result randomization to study medications was stratified by age group (18–59 years versus 60 years). On hundred and seventeen participants aged 18–59 years and 142 participants aged 60 years with non-bipolar major depression and at least one associated delusion and a 17-item HAM-D⁷ total score ≥ 21 were randomized to 12 weeks of double-blind treatment with either olanzapine plus sertraline or olanzapine plus placebo. Among the exclusion criteria were another Axis I mood disorder or psychotic disorder; DSM-IV⁸ defined dementia preceding the index episode of depression; substance abuse or dependence within the preceding 3 months; neurologic disease that might affect neuromuscular function such as Parkinson's disease; and acute medical illness, although many of the study participants had stable chronic medical problems. A history of falls during the study was systematically assessed at each study visit. Falls were defined as 'unintentionally coming to rest on the ground, floor or other lower level'. Written informed consent was obtained from participants, using procedures approved by local institutional review boards, prior to the initiation of any research assessments or treatment.

With respect to protocolized treatment, participants started taking 5mg/day of open-label olanzapine and 50mg/day of blinded sertraline/placebo. The dosages of these drugs were increased by increments of 5mg and 50 mg, respectively, every 3–4 days as tolerated, with the goal of reaching target doses of 15mg/day of olanzapine and 150mg/day of sertraline/placebo by the second week of the study. If necessary, the dosages could be increased in Week 3 to a maximum of 20mg/day of olanzapine and 200 mg/day of sertraline/placebo, based on efficacy and tolerability. Apart from 'as needed' lorazepam (up to a maximum of 4mg/day) and 'as needed' benztropine (up to a maximum of 2mg/day), no other psychotropic drugs were permitted.

Data Analysis

Logistic regression analysis was used to test for the effect of treatment, effect of age group (18–59 years versus 60 years or older), and a treatment by age interaction with respect to the proportion of participants who experienced at least one fall during the RCT, controlling for number of weeks in the trial. Analyses were performed with two-tailed alpha set at 0.05.

RESULTS

Table 1 presents the baseline characteristics of the study group based on randomized treatment assignment. The mean (SD) age of participants in the 18–59 year group was 41.3 (10.8) years and the mean (SD) age of participants in the 60 year group was 71.7 (7.8) years (range 60–93 years).

For data analytic purposes in STOP-PD, study medication dose was considered the last dose taken for a minimum of 7 days. Table 2 presents the mean daily dosages of olanzapine and sertraline, as well as the proportion of participants prescribed lorazepam, based on treatment group and age group. Groups were comparable on these variables, with the exception that older subjects took a lower dose of olanzapine than younger subjects (13.5 [SD 5.1] mg/day versus 15.7 [SD 4.7] mg/day, respectively; $t=3.45$, $df=234$, $p=0.0007$). Only 4 participants (2 in each treatment arm) received benztropine.

With respect to the number of participants who fell (Table 3), there was a significant age effect, with older participants more likely to fall ($\chi^2=4.29$, $df=1$, $p=0.038$; OR=2.47, 95% CI 1.08–5.65). However, there was not a statistically significant treatment effect ($\chi^2=0.001$,

df=1, p=0.973) or treatment $\times$ age interaction ($\chi^2=0.99$, df=1, p=0.319). With respect to the older participants, the odds ratio of incidence of falling for those treated with olanzapine and sertraline compared to those treated with olanzapine and placebo was 1.56 (95% CI 0.63–3.83). Finally, because the study was not *a priori* designed to examine the risk of falling, we calculated the sample size that would have been required to detect a statistically significant difference between the two treatment groups in the proportion of persons falling: given a two-tailed alpha of 0.05 and statistical power of 0.8, a sample size of 3,361 would have been required for analyses that included both age groups and a sample size of 858 would have been required for analyses confined to the older age group.

DISCUSSION

Falls and their prevention are of great public health importance. Given the potential biases of observational studies reporting the risk of falls with SSRIs, and the absence of RCT data pertaining to this question, we performed this exploratory analysis in an attempt to move the field forward. Strengths of this study include its 12-week duration that allows for a longer period of observation of falling than the more traditional 6–8 week antidepressant RCT, the double-blind randomized design, the adult lifespan approach that allows for a comparison of younger and older adults, the inclusion of persons with chronic medical conditions who are more representative of ‘real world’ older patients than more physically healthy patients typically selected for regulatory studies of antidepressants, the standardized approach to the dosing of sertraline and olanzapine, and the prospective and systematic collection of falls data on all participants. Conversely, limitations of the study include the absence of sertraline and placebo monotherapies, the fact that the study was not *a priori* designed to examine risk of falls, and the focus on individuals with psychotic depression which potentially limits generalizability of the findings.

We found that the study was not sufficiently powered to detect a statistically significant difference between the two treatment arms in the proportion of participants falling, either for the study group as a whole or for older participants only. Therefore, the negative statistical findings pertaining to the treatment effect and the treatment $\times$ age interaction do not necessarily mean that the addition of sertraline to olanzapine was not associated with an increased risk of falls. In fact, notwithstanding the relatively wide confidence interval, the odds ratio of older participants falling when treated with olanzapine and sertraline versus olanzapine plus placebo is comparable to odds ratios reported by observational studies for the association of SSRIs and falls.³

This study demonstrates the limitation of trying to assess falls in association with an SSRI in a placebo-controlled RCT that is primarily designed and powered to evaluate treatment efficacy. It is unlikely that a placebo-controlled RCT of sufficient duration and power will be conducted to definitively address the question of whether SSRIs increase the risk of falls. A meta-analysis of several RCTs could address this question but unfortunately published SSRI trials have not reported falls data. An alternative line of research is to examine the effect of antidepressants on measures of postural stability and gait that are valid markers of increased risk of falls.^{9,10} These RCTs would not only account for potential confounding variables (such as vascular changes in the brain and executive dysfunction¹¹), but would also explore the interaction between the antidepressant and these variables.

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Table 1

Baseline Characteristics of Participants in STOP-PD

Characteristic ^a	Treatment with Olanzapine+Placebo (n=130)	Treatment with Olanzapine+Sertraline (n=129)	
	n (%)	n (%)	χ^2 , df, p
Age 60years	71 (54.6)	71 (55.0)	0.005, 1, 0.95
Female gender	83 (63.8)	83 (64.3)	0.007, 1, 0.93
	Mean (SD)	Mean (SD)	t, df, p
Age (years)	58.5 (17.5)	57.4 (18.0)	0.51, 257, 0.61
HAM-D total score	29.8 (5.5)	29.7 (5.0)	0.10, 257, 0.92
MMSE total score	26.9 (3.2)	27.0 (2.9)	-0.27, 251, 0.79
CIRS-G total score	5.2 (4.1)	4.8 (3.9)	0.75, 255, 0.46

^aHAM-D= 17-item Hamilton Depression Rating Scale;⁷ MMSE= Mini Mental State Examination;¹² CIRS-G= Cumulative Illness Rating Scale-Geriatric¹³

Table 2

Mean Daily Dosages of Olanzapine and Sertraline/Placebo and the Frequency of Use of Lorazepam in STOP-PD, Based on Treatment Group and Age Group

	Treatment with Olanzapine +Placebo (n=130)	Treatment with Olanzapine +Sertraline (n=129)	
	Mean (SD)	Mean (SD)	t, df, p
Olanzapine dose (mg/day)	14.3 (5.3)	14.7 (4.7)	-0.55, 234, 0.59
Sertraline/Placebo dose (mg/day)	168.9 (44.1)	169.7 (35.0)	-0.15, 234, 0.89
	n (%)	n (%)	χ^2 , df, p
Lorazepam (one or more doses during study)	62 (47.6)	51 (39.5)	1.44, 1, 0.23
Lorazepam (continuous use during study) ^a	33 (25.4)	32 (25.6)	0.001, 1, 0.98
	Younger Age (n=117)	Older Age (n=142)	
	Mean (SD)	Mean (SD)	t, df, p
Olanzapine dose (mg/day)	15.7 (4.7)	13.5 (5.1)	3.45, 234, 0.0007
Sertraline/Placebo dose (mg/day)	174.3 (34.1)	165.3 (43.7)	1.78, 234, 0.08
	n (%)	n (%)	χ^2 , df, p
Lorazepam (one or more doses during study)	49 (41.9)	64 (45.1)	0.27, 1, 0.61
Lorazepam (continuous use during study) ^a	28 (23.9)	37 (26.1)	0.15, 1, 0.69

^a Persons taking Lorazepam on a continuous basis during the study also contribute to the count of persons taking one of more doses of Lorazepam.

Table 3

Number and Percentage of Participants Who Fell in STOP-PD

	Treatment with Olanzapine+Placebo	Treatment with Olanzapine+Sertraline
18–59 years	N=59	N=58
n (%) participants falling	5 (8.5)	4 (6.9)
60 years or older	N= 71	N=71
n (%) participants falling	9 (12.7)	14 (19.7)
All Participants	N=130	N=129
n (%) participants falling	14 (10.8)	18 (14.0)