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Antipsychotic discontinuation after the initiation of selective serotonin reuptake inhibitors therapy for the treatment of behavioral and psychological symptoms associated with dementia

Monica Mathys, PharmD, BCGP, BCPP[1]; Steven Fang[2]; Jini John[3]; Jasmine Carter[4]

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Abstract

Introduction: Antipsychotics are used off label to treat behavioral and psychological symptoms of dementia (BPSD). Due to the emerging data of selective serotonin reuptake inhibitors (SSRIs) for treatment of BPSD, clinicians may choose to use this medication class instead of antipsychotics when pharmacologic therapy is necessary. The objective of this study was to evaluate the prevalence of antipsychotic discontinuation 6 months after SSRI initiation for the treatment of BPSD.

Methods: Patients with Alzheimer dementia who were prescribed an antipsychotic and later prescribed an SSRI for BPSD during January 1, 2009, through December 30, 2014, were studied. Exclusion criteria included (1) a dementia diagnosis besides Alzheimer; (2) scheduled benzodiazepines, mood stabilizers, or non-SSRI antidepressant use during the study period; (3) diagnoses of bipolar or psychotic disorders; and (4) diagnosis of delirium during the study period. Patients' age, sex, race, and functional assessment of staging for Alzheimer disease scores were collected. The names, doses, and stop dates of SSRIs and antipsychotics were also recorded.

Results: Thirty-six patients were included in the analyses. Overall, antipsychotic use was reduced in 11 patients (30.6%). Ten patients (27.8%) discontinued the antipsychotic, and 1 additional patient had a reduction in dose. When comparing specific SSRIs, 8 (72%) responders were prescribed citalopram, and 15 (60%) nonresponders were prescribed sertraline.

Discussion: Approximately 30% of patients with Alzheimer dementia who were prescribed antipsychotics for BPSD were able to discontinue the medication or had a dose reduction after starting SSRI therapy. Most SSRI responders were prescribed citalopram.

Keywords: dementia, psychological symptoms, behavioral symptoms, selective serotonin reuptake inhibitors, antipsychotics, use reduction

[1] (Corresponding author) Associate Professor of Pharmacy Practice, Clinical Pharmacy Specialist – Mental Health, Texas Tech University Health Sciences Center, Veterans Affairs North Texas Health Care System, Dallas, Texas, monica.mathys@ttuhsc.edu, ORCID: http://orcid.org/0000-0002-6907-1996; [2] PharmD Student, Texas Tech University Health Sciences Center, School of Pharmacy, Dallas, Texas, ORCID: http://orcid.org/0000-0001-5483-413X; [3] PharmD Student, Texas Tech University Health Sciences Center, School of Pharmacy, Dallas, Texas, ORCID: http://orcid.org/0000-0003-4290-4334; [4] PharmD Student, Texas Tech University Health Sciences Center, School of Pharmacy, Dallas, Texas, ORCID: http://orcid.org/0000-0003-0332-832X

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Introduction

Approximately 80% of individuals with major neurocognitive disorder (dementia) experience behavioral and psychological symptoms of dementia (BPSD).[1,2] These symptoms are divided into 4 syndromes, which include hyperactivity (agitation, aggression, euphoria, disinhibition, irritability, aberrant motor activity), psychosis (hallucinations and delusions), mood liability (depression and anxiety), and instinctual (appetite disturbance, sleep

disturbance, and apathy) clusters.[3] The cause of BPSD is not completely understood, but the widespread deficit of serotonin in patients with dementia may account for many of the symptoms.[4]

Antipsychotics are used off label for BPSD, especially when agitation, aggression, and psychotic symptoms are present. However, these agents carry a Food and Drug Administration boxed warning for increased mortality when used for dementia-related psychosis.[5-8] Additional antipsychotic adverse effects include extrapyramidal symptoms, metabolic changes, and faster cognitive decline.[9-13]

Due to the risks associated with antipsychotics, many clinicians search for other pharmacologic options for BPSD when nonpharmacologic therapies fail. Several studies show selective serotonin reuptake inhibitors (SSRIs) to be effective in treating BPSD. To date, citalopram, escitalopram, and sertraline are the most studied medications from this class.[14-19]

Because of the risks associated with antipsychotics and the literature supporting SSRI therapy for BPSD, clinicians may wish to use SSRIs over antipsychotics. The purpose of this study was to evaluate changes in antipsychotic use after SSRI therapy was added for BPSD treatment.

Methods

Study Design

The study was a retrospective chart review conducted at the Veterans Affairs North Texas Health Care System (VANTHCS) and was approved by the VANTHCS Institutional Review Board. Patients were included in the study if they had a diagnosis of Alzheimer dementia; an antipsychotic prescription for BPSD during January 1, 2009, through December 30, 2014; and a prescription for an SSRI for BPSD on or after the date of when the antipsychotic was prescribed. The study period was defined as the initial start date of the prescribed SSRI to an end date of 6 months after SSRI initiation.

Patients were excluded if they were diagnosed with a dementia other than Alzheimer; prescribed scheduled doses of benzodiazepines, mood stabilizers, or non-SSRI antidepressants; or diagnosed with delirium during the study period. In addition, those with bipolar or psychotic disorders were excluded. Patients who died before the end of the 6-month study period were also excluded from the data analyses.

To identify patients for the study, a list was generated for all those prescribed a cognitive enhancer (acetylcholinesterase inhibitor or memantine), antipsychotic, and an SSRI during January 1, 2009, through December 30, 2014. Additional patients were found by reviewing charts of those enrolled in the VANTHCS geriatric psychiatry clinic during this same time frame. Patient information was reviewed and obtained through computerized patient record systems.

Collected data included patient age, sex, race, and functional assessment of staging for Alzheimer disease scores. The names, doses, and start and stop dates for antipsychotics and SSRIs were recorded throughout the study period. Prescription refill history and any chart documentation of SSRI intolerability were also noted.

Outcome Measures

The primary objectives of the study were to evaluate the prevalence of antipsychotic discontinuation or dose reductions 6 months after an SSRI was initiated for the treatment of BPSD. Antipsychotic discontinuation was defined as the following: (1) The antipsychotic prescription was completely discontinued by the provider and not changed to another antipsychotic or (2) the patient had not refilled the antipsychotic prescription for more than 60 days past the next appropriate refill date while still refilling other maintenance medications.

Patients who discontinued the antipsychotic or had a dose reduction after 6 months of SSRI therapy were labeled as responders. Nonresponders were defined as those who (1) continued to fill the antipsychotic prescription at the same dose, (2) were switched to another antipsychotic, or (3) had an antipsychotic dose increase by the 6-month follow-up period. Antidepressant tolerability and whether a specific type of SSRI was correlated with antipsychotic discontinuation were secondary outcomes of the study.

Statistical Analysis

Descriptive statistics were used to report primary and secondary outcomes. The association between specific SSRIs and antipsychotic discontinuation was analyzed with the Fisher exact test. Baseline characteristics were compared by using the Fisher exact, Student *t* test (when comparing age), and Mann-Whitney *U* test (when comparing SSRI doses).

Results

Two hundred six patients with dementia and concurrent prescriptions for an antipsychotic and SSRI were identified. After reviewing the patients' charts, 166 were excluded from the study. The most common reasons for exclusion were (1) a dementia diagnosis other than

Alzheimer or (2) the SSRI prescription was started before the antipsychotic therapy. An additional 4 patients were excluded from analyses because they died during the study period.

Of the 36 patients included in the analyses, the mean age was 81 years, and most were white males. The majority of patients were prescribed second generation (n = 30, 83.3%) versus first-generation antipsychotics (Table 1). Citalopram and sertraline were the most prescribed SSRIs, and the median doses at the 6-month end point were 20 mg and 50 mg, respectively (Table 2). Half the study population (n = 18) was maintained on the same SSRI dose from baseline throughout the 6-month study period. Antidepressant dose increases occurred in 3 (27.2%) of the responders and 11 (44.0%) of the nonresponders.

Overall, 11 patients (30.6%) responded (able to reduce antipsychotic use). Antipsychotic therapy was discontinued in 10 patients (27.8%), and the dose was reduced in 1 patient. The majority of nonresponders continued the same antipsychotic dose from baseline to the 6-month follow-up period (n = 16, 44.4%; Table 3).

When comparing specific SSRIs, 72.7% of responders were prescribed citalopram compared to only 32% of nonresponders ($P = .034$). Adverse effects that led to SSRI discontinuation occurred in 8.3% of the study population, and all these patients belonged to the nonresponder group (Table 2).

Discussion

Several prospective studies found SSRIs to be effective for the treatment of BPSD. Gaber and colleagues[14] evaluated the efficacy of sertraline versus haloperidol for treatment of agitated behavior due to dementia. Both sertraline (25-50 mg/d) and haloperidol (1-2 mg/d) showed a significant reduction in agitation based on the Cohen-Mansfield agitation inventory scores, and patients treated with sertraline showed less extrapyramidal symptoms compared to the haloperidol group. Sertraline was later studied in another trial to determine its efficacy in the treatment of BPSD in patients treated with donepezil.[15] Participants received donepezil (5-10 mg) for 8 weeks and were then randomly assigned 12 weeks of adjunct sertraline (50-200 mg) or placebo. No statistical differences were seen between the two groups in regards to total neuropsychiatric inventory or clinical global impression scales. However, post hoc analyses of patients with moderate-to-severe BPSD found sertraline was associated with a greater improvement in the neuropsychiatric inventory behavioral and psychological symptom subscale compared to placebo ($P = .04$).[15]

Two studies led by Pollock and colleagues[16,17] compared citalopram to antipsychotic therapy for treatment of dementia-related psychosis and behavioral disturbances. The first study[16] had a placebo arm in addition to comparing citalopram to perphenazine. Eighty-five hospitalized patients were included in this 17-day study. Patients treated with citalopram and perphenazine showed significant improvement on several neurobehavioral rating scale subscores, and citalopram users showed significantly more improvement on the total neurobehavioral rating scale compared to placebo.[16] A second study[17] published later compared citalopram to risperidone. Agitation and psychosis scores improved in both treatment groups by the end of the 9-week trial although there were no statistical differences between the two groups. Significant improvement in agitation scores was observed with citalopram treatment (–12.5%) compared to baseline. Psychosis scores improved significantly with both citalopram (–32.3%) and risperidone (–35.2%) compared to baseline.[17]

The CitAD randomized clinical trial found citalopram 30 mg daily to be more effective than placebo in improving agitation at 9 weeks based on the neurobehavioral rating scale agitation subscale ($P = .04$) and the Cohen-Mansfield agitation inventory ($P = .008$). However, concerning effects, such as worsening cognition (decline of –1.05 on the mini mental status examination) and prolonged QTc interval were also observed in the citalopram group.[18]

Last, escitalopram was studied in a randomized, double-blind, comparison trial with risperidone. Neuropsychiatric scores improved significantly at 6 weeks with both risperidone 1 mg/d and escitalopram 10 mg/d. There were no statistical differences in regards to efficacy between the 2 groups. While risperidone appeared to have a quicker onset of symptom relief, escitalopram patients were more likely to complete the study due to fewer adverse effects.[19]

To the authors' knowledge, this was the first study to observe antipsychotic discontinuation rates when SSRIs were prescribed for BPSD. Study results showed antipsychotic use decreased in 30% of patients who were prescribed an SSRI. When comparing individual SSRIs, more responders were prescribed citalopram (72.7%). In clinical practice, the use of citalopram may be limited due to a recommend maximum daily dose of 20 mg in those over 60 years due to risk of prolonged QTc interval. However, 7 of 8 citalopram responders in this study were prescribed no more than 20 mg daily, and none of the patients prescribed citalopram discontinued the medication, which suggests the drug was well tolerated.

Sixteen patients (44.4%) in this study were continued on the same antipsychotic dose during the 6-month period. It

TABLE 1: Baseline characteristics

Baseline Characteristics	Responders to SSRI (N = 11)	Nonresponders to SSRI (N = 25)	*P* Value
Age, y	80.9 ± 8	81.0 ± 8	.74
Male (%)	11 (100)	22 (88)	.54
Race (%)			
White	10 (91.0)	17 (68.0)	.22
African American	1 (9.0)	8 (32.0)	
Antipsychotic prescribed (%)			
Aripiprazole	1 (9.0)	1 (4.0)	.52
Median dose	2.5 mg	5 mg	
Haloperidol	3 (27.3)	3 (12.0)	.34
Median dose	2 mg	0.5 mg	
Olanzapine	1 (9.0)	2 (8.0)	1.00
Median dose	20 mg	5 mg	
Quetiapine	4 (36.4)	8 (32.0)	1.00
Median dose	100 mg	75 mg	
Risperidone	2 (18.3)	11 (44.0)	.26
Median dose	0.5 mg	0.5 mg	
FAST stage (%)			
Stage 1-4	1 (9.0)	8 (32.0)	.22
Stage 5-6c	4 (36.4)	8 (32.0)	1.00
Stage 6d-7e	3 (27.3)	6 (24.0)	1.00
Unknown	3 (27.3)	3 (12.0)	.34

FAST = functional assessment of staging for Alzheimer disease; SSRI = selective serotonin reuptake inhibitors.

is possible SSRI therapy was still effective in these patients, but the prescriber chose not to change the medication regimens due to stability of symptoms. A potential future study is to observe the effects of SSRIs in a population in which antipsychotic reduction attempts are mandated, such as a long-term care setting.

The study's inclusion and exclusion criteria were developed to decrease confounding factors that could have influenced the outcomes. Only patients with Alzheimer dementia were included in the study. Patients with other dementias, psychotic disorders, or bipolar disorder were excluded. Furthermore, included patients had to be prescribed the SSRI and antipsychotic for dementia-related symptoms and not for psychiatric symptoms that were diagnosed before the dementia onset. Patients were also excluded if they were prescribed other psychiatric medications that could have influenced the outcomes, such as non-SSRI antidepressants and mood stabilizers.

Despite the authors' efforts to develop a good trial design, there were still several weaknesses to the study. After screening patients for study criteria, the authors were left with a smaller patient population than anticipated. By identifying study patients based on pharmacy data (those prescribed a cholinesterase inhibitor and/or memantine), all patients with an Alzheimer dementia diagnosis were not captured. The authors attempted to reduce this bias by searching for additional patients enrolled in the geriatric psychiatry clinic, but even with this additional step, potential study patients were likely missed. Further, eligible patients may have been missed because they had a misdiagnosed or nonspecific dementia listed in the chart instead of Alzheimer dementia.

TABLE 2: Selective serotonin reuptake inhibitors (SSRI) use

	Responders to SSRI (N = 11)	Nonresponders to SSRI (N = 25)	*P* Value
SSRI (%)			
Citalopram	8 (72.7)	8 (32)	.034
Fluoxetine	0	1 (4.0)	
Paroxetine	0	1 (4.0)	
Sertraline	3 (27.3)	15 (60)	.146
Maximum median dose/d			
Citalopram	20 mg	20 mg	NS
Fluoxetine	...	30 mg	...
Paroxetine	...	30 mg	...
Sertraline	50 mg	50 mg	NS
SSRI discontinued (%)	0	3 (12.0)	.538

NS = not significant; ... = data not applicable.

Because the trial was retrospective, prescription data were used to determine whether antipsychotic therapy was discontinued or reduced, which could have led to overestimation or underestimation of the results. For example, it could not be determined exactly why a patient's antipsychotic dose was decreased or not refilled. In some cases, the reduced use could have been due to adverse effects from the antipsychotic and not necessarily

TABLE 3: Antipsychotic use 6 months after selective serotonin reuptake inhibitors initiation

Antipsychotic Use at 6 Months	No. of Patients (%)
Responders	
No longer taking antipsychotic	10/36 (27.8)
Antipsychotic dose decreased	1/36 (2.78)
Total	11 (30.6)
Nonresponders	
Antipsychotic dose increased	7/36 (19.4)
Antipsychotic use/dose remained the same	16/36 (44.4)
Switched antipsychotics	2/36 (5.56)
Total	25 (69.4)

because the patient had improvement in symptoms. In addition, if patients were prescribed any behavioral medications outside the Veterans Affairs system, this could not be captured. Last, the authors could not be certain of the amount of benzodiazepine medications specific patients used during the study period. Patients prescribed scheduled doses of benzodiazepines were excluded from the study, but those with an "as needed" prescription were still included. It was possible these "as needed" prescriptions were used on a consistent basis for some patients.

Conclusion

Approximately 30% of patients with Alzheimer dementia who were prescribed antipsychotics for BPSD were able to discontinue the medication or had a dose reduction after starting SSRI therapy. In this study, more responders were prescribed citalopram compared to other SSRIs.

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