OPEN

Characteristics of Patients Experiencing Extrapyramidal Symptoms or Other Movement Disorders Related to Dopamine Receptor Blocking Agent Therapy

Shaina Musco, PharmD,†‡ Laura Ruekert, PharmD, BCPP, BCGP,†‡ Jaclyn Myers, PharmD,§|| Dennis Anderson, MD,¶ Michael Welling, MD,¶ and Elizabeth Ann Cunningham, DO¶*

Abstract:

Purpose/Background: Dopamine receptor blocking agents (DRBAs), also known as antipsychotics, are medications widely used to treat a growing number of mental health diagnoses. However, their utility is limited by the potential to cause serious adverse movement reactions. Akathisia, dystonia, parkinsonism, and tardive dyskinesia (collectively known as extrapyramidal symptoms or EPSs) are associated with reduced social and occupational functioning, negative patient attitudes toward treatment, and nonadherence to pharmacotherapy. Neuroleptic malignant syndrome is a life-threatening reaction that can result from DRBA use and cause musculoskeletal dysfunction. The aim of this study is to profile patients who have developed DRBA-related movement adverse effects and identify risk factors significantly associated with each subtype of EPSs or other movement disorders (OMDs) such as neuroleptic malignant syndrome.

Methods/Procedures: A report of all potential DRBA-related EPSs or OMDs occurrences within a large community hospital network was generated using *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *10th Revision* (*ICD-10*) billing codes. Each patient encounter was manually reviewed to confirm that a documented case of DRBA-related EPSs or OMDs had indeed occurred and subsequently determine the likely causative agent(s).

Findings/Results: The resultant cohort of 148 patients experiencing unique DRBA-related EPS or OMD events was analyzed. The average patient was female, middle-aged, and overweight. The most common DRBAs precipitating EPSs or OMDs were haloperidol and quetiapine. In the population studied, age was significantly associated with the subtype of EPSs experienced such that those patients with akathisia and dystonia tended to be younger, whereas those with tardive dyskinesia tended to be older. Body mass index (BMI) category was also negatively correlated with the incidence of dystonia. In addition, it was observed that exposure to specific DRBAs, classes, and routes of administration significantly affected the risk of developing different subtypes of EPSs or OMDs in the study population.

Implications/Conclusions: To our knowledge, this is the first study to describe an association between age and BMI with the risk of akathisia and dystonia, respectively, in patients taking DRBAs. Other trends observed with age and BMI in patients developing DRBA-related EPSs support previously reported findings. Expanding the knowledge base of individual characteristics associated with the risk of developing different subtypes of EPSs or OMDs can help providers and patients anticipate and attempt to mitigate these reactions, and may ultimately improve adherence to DRBA therapy.

Key Words: dopamine receptor blocking agent, antipsychotic, extrapyramidal symptom, age, body mass index

(*J Clin Psychopharmacol* 2019;39: 336–343)

Dopamine receptor blocking agents (DRBAs) are a dynamic class of medications initially developed to reduce psychotic symptoms in patients suffering from schizophrenia. Since that time, their use has greatly expanded, and DRBAs are now used to treat a variety of psychiatric conditions including major depressive disorder, bipolar disorder, and irritability associated with autistic disorder. The importance of DRBA treatment in patients with first-break psychosis[1] and major depressive disorder not responding to first-line antidepressant monotherapy[2] has recently been demonstrated in terms of reduced hospital admissions and health care costs. Early initiation of long-acting injectable DRBA formulations has also garnered significant value by decreasing hospitalizations and overall costs within contemporary international practice models.[3,4]

The efficacy and versatility of DRBAs have led them to become widely used. However, the rate of nonadherence is high in patients to whom these medications are prescribed.[5,6] A landmark prospective randomized cohort study of patients with chronic schizophrenia found that 74% had stopped taking their DRBA within 18 months of the original prescription date.[7] Outcomes can be extremely poor for these patients, and medication nonadherence in the psychiatric population has been found to correlate with increased hospital admissions, suicide, and mortality.[8,9]

A significant contributing factor to DRBA nonadherence is lack of tolerability.[10–12] This class of medications carries the risk of causing a unique constellation of adverse effects called extrapyramidal symptoms (EPSs), which are exhibited by abnormal movements and/or muscle tone. The physical manifestations of EPSs can range from pacing to paralysis and can have a substantial adverse impact on patients' overall health and well-being.[13–15] Cases of EPSs have even resulted in medical malpractice[16] owing to the severity of symptoms experienced.

Extrapyramidal symptoms have been linked to increased likelihood of DRBA treatment discontinuation.[17–20] Physical manifestations such as tremor, bradykinesia, and rigidity can impair social and occupational functioning.[18] Psychological symptoms of EPSs such as dysphoria, apathy, and cognitive impairment are major contributors to negative patient and caregiver attitudes toward DRBA therapy.[18] Extrapyramidal symptoms have direct adverse effects

From the *Department of Clinical Sciences, High Point University Fred Wilson School of Pharmacy, High Point, NC; †Department of Pharmacy Practice, Butler University College of Pharmacy and Health Sciences; ‡Department of Pharmacy, Community Health Network, Indianapolis; §Department of Pharmacy Practice, Purdue University College of Pharmacy, West Lafayette; ||Office of Research Administration, Community Health Network; and ¶Department of Psychiatry, Community Health Network, Indianapolis, IN.

Received July 27, 2018; accepted after revision April 28, 2019.

Reprints: Shaina Musco, PharmD, Department of Clinical Sciences, High Point University Fred Wilson School of Pharmacy, One University Parkway, High Point, NC 27268 (e-mail: smusco@highpoint.edu).

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001061

on cognitive function as well.[20] Dopamine receptor blocking agents with high anticholinergic burden or requiring the use of adjunctive anticholinergic agents to treat EPSs can impair cognitive processes such as learning and memory.[18]

Extrapyramidal symptoms negatively impact overall outcomes related to efficacy, functioning, caregiver burden, and quality of life.[18] This is especially critical in a patient population that may already be at high risk for poor outcomes owing to issues with motivation and beliefs about treatment. Patients prescribed DRBAs tend to harbor unfavorable attitudes toward treatment and perceive EPSs to be more severe than other adverse effects such as weight gain.[21]

Akathisia is a particularly distressing form of EPS and has been implicated in many negative outcomes, including worsening psychotic symptoms, increased suicidality, nonadherence to DRBA therapy, and subsequent relapse.[18,22] Akathisia can manifest as anxiety and often go undiagnosed or mistaken for agitation.[16,22] Tardive dyskinesia (TD), a type of DRBA-related movement disorder that can lead to serious physical impairment, is associated with stigma, decline in social functioning, and increased mortality.[18] Orofacial movements associated with TD have been linked to workplace discrimination[23] and increased mortality owing to respiratory infections.[24] These secondary consequences attributable to EPSs or OMDs can be severe enough to offset any benefit from reduction in positive symptoms garnered by the use of a DRBA.[18]

Neuroleptic malignant syndrome (NMS) is an adverse reaction to DRBAs not classified as a type of EPSs, but similarly characterized by abnormal movements and the potential for serious sequelae. Hereafter, NMS will be referred to as an *other movement disorder* or *OMD*. Patients with NMS can present with muscle rigidity, tremor, abnormal reflexes, and seizures.[25] Considerable morbidity is associated with NMS, including medical complications such as rhabdomyolysis, acute respiratory failure, acute kidney injury, and sepsis.[26] Furthermore, NMS continues to carry risk for mortality despite advances in treatment,[26] making recognition and avoidance of this adverse reaction critical.

Based on what is known about the severity of EPSs or OMDs and the overall burden of these adverse effects to patients taking DRBA medications, it is vital to understand risk factors associated with their development. Existing literature provides some clues as to which patient may be at greater risk for experiencing these outcomes and potential strategies to mitigate that risk. For example, patients with first episode psychosis are more sensitive to developing EPSs from DRBAs,[27] and new users of DRBAs have a significantly greater risk of EPSs than chronic users, independent of agent, diagnosis, or treatment setting.[28] As a result, it is especially important to start at low doses of DRBAs and taper up slowly in treatment naive individuals to avoid development of EPSs. Certain other patient populations taking DRBAs may be at an increased risk for such effects based on predisposing baseline characteristics.

There is a paucity of data to guide the use of DRBAs to reduce the risk of adverse movement reactions such as EPSs or OMDs. Nonadherence due to poor tolerability can result in negative patient outcomes, including excess mortality. Patients taking DRBAs may be at an increased risk for certain subtypes of EPSs or OMDs based on predisposing individual characteristics. If known, steps may be taken to identify and mitigate these risks early in an effort to improve the likelihood of treatment success. The primary objective of the present study is to determine if a statistically significant relationship exists between subtype of EPSs or OMDs experienced by patients taking DRBAs and each of the following patient characteristics: age, sex, body mass index (BMI) category, DRBA name, DRBA classification, DRBA route of administration, number of DRBAs prescribed, daily chlorpromazine equivalents, and the presence of DRBA overdose.

MATERIALS AND METHODS

A report of all potential DRBA-related EPSs or OMDs occurrences over a 5-year period was generated using *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *10th Revision* (*ICD-10*), billing codes (see Supplementary Appendix 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A579, for complete list). The study was conducted at a large community hospital network that serves a primarily suburban population in the Midwestern United States and includes a 120-bed inpatient psychiatric facility. This study was approved by the local institutional review board on September 19, 2017, after qualifying for expedited review.

Patients of any age or sex with an encounter between September 17, 2012, and November 1, 2017, at a site within the health system using Epic Hyperspace 2015 electronic medical records were included. Vulnerable populations (pregnant, incarcerated, or fetuses) were excluded. Each resultant patient encounter was manually reviewed and vetted for accuracy by author S.M. and acknowledged research assistants to ensure that the documented reaction was indeed EPS or OMD and that the patient had taken a DRBA immediately before or during the encounter. For single encounters in which a patient exhibited symptoms of multiple subtypes of EPSs or OMDs, each was counted as an individual occurrence for that subtype of EPSs or OMDs (n = 12). In addition, the same patient could be counted multiple times for the same subtype of EPSs or OMDs if it occurred in unique encounters (n = 12).

Daily chlorpromazine equivalents were calculated using published conversion rates.[29] The dose ranges used for analysis correspond to low or acute dosing (<200 mg), average maintenance therapy dosing for schizophrenia (200–1000 mg), and supratherapeutic dosing

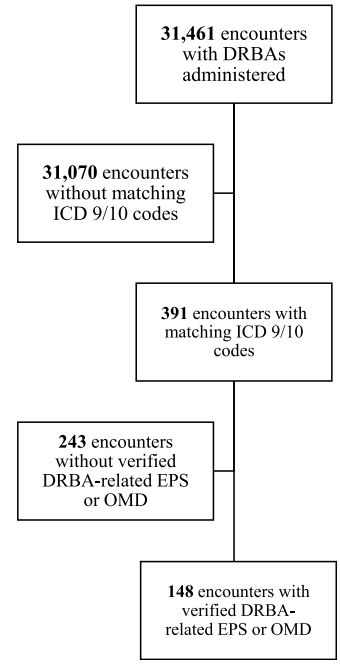

FIGURE 1. Patient selection process. There were over 30,000 eligible unique patient encounters in which DRBA was administered during the 5-year study period. A total of 391 were billed for using *ICD* codes indicative of DRBA-related EPSs or OMDs. After manual chart review was completed, 148 encounters were verified as having DRBA-related EPSs or OMDs. Of the 243 encounters not verified, 77 had no clear adverse drug reaction, 98 had a non-DRBA–related adverse drug reaction, and 65 had a DRBA-related adverse drug reaction that was not EPS or OMD.

(>1000 mg) and are based on values reported in the literature.[30,31] The Anticholinergic Cognitive Burden (ACB) scale was used to quantify the anticholinergic properties of each DRBA examined, where 0 denoted *no known properties*, 1 denoted *possible anticholinergic*, and 2 or 3 denoted *definite anticholinergic*.[32]

Descriptive statistics were used to analyze patient characteristics including age, sex, BMI category, DRBA name, DRBA classification, DRBA route of administration, number of DRBAs prescribed, daily chlorpromazine equivalents, and the presence of DRBA overdose. Dopamine receptor blocking agent overdose in this study was defined as the intentional or unintentional exposure to a dose of a given agent that exceeded the prescribed dose. Dopamine receptor blocking agent overdose was identified qualitatively and confirmed using notes in the electronic medical record by S.M. and assistants.

A Shapiro-Wilk test was performed to determine if data distribution was normal for associations between patient characteristics and each subtype of EPSs or OMDs. When calculating correlation coefficients, Pearson correlation tests were used for parametric data and Spearman ρ tests were used for nonparametric data. Bivariate correlation was performed between baseline characteristics and the subtype of EPSs or OMDs. χ^2 Tests and Fisher exact tests were used to compare between DRBA and the subtype of EPSs or OMDs. A P value of <0.05 was considered to be statistically significant in all tests. All analyses were done using SPSS v28.

RESULTS

A total of 391 billed encounters were obtained using *ICD* codes corresponding to DRBA-related EPSs or OMDs diagnoses (Fig. 1). After manual chart review, 148 patient encounters with unique DRBA-related EPS or OMD events were included for further analysis. The average patient in the study population was female, middle-aged, and overweight (Table 1). All subtypes of EPSs or OMDs investigated in this study were well-represented in the group. Tardive dyskinesia and parkinsonism were the most commonly experienced subtypes, whereas dystonia and NMS were the least common.

TABLE 1. Baseline Demographic Characteristics of Patients Experiencing a Validated DRBA-Related EPSs or OMDs Event

Characteristic	Description (N = 148)	
Age, y	Mean, 53.8 (range, 14–96; SD, 18.8)	
	<18	3 (2.0%)
	18–29	18 (12.2%)
	30–49	29 (19.6%)
	50–70	66 (44.6%)
	>70	32 (21.6%)
Sex	Male	50 (33.8%)
	Female	98 (66.2%)
BMI category, kg/m^2	Mean, 28.9 (range, 16.0–48.8; SD, 6.6)	
	Underweight (<18.5)	3 (2.0%)
	Normal (18.5–25)	39 (26.4%)
	Overweight (25–30)	50 (33.8%)
	Obese (>30)	56 (37.8%)
Subtype of EPSs or OMDs*	Akathisia	29 (19.6%)
	Dystonia	22 (14.9%)
	Parkinsonism	37 (25.0%)
	TD	37 (25.0%)
	NMS	22 (14.9%)
	Other	6 (4.1%)

*Total > 100%, as some patients experienced multiple subtypes of EPSs or OMDs.

TABLE 2. Dopamine Receptor Blocking Agent Pharmacotherapy Regimen Characteristics of Patients Experiencing a Validated DRBA-Related EPS or OMD Event

Characteristic	Description (N = 148)	
Agent*†	Aripiprazole	13 (8.8%)
	Asenapine	3 (2.0%)
	Clozapine	9 (6.1%)
	Haloperidol	37 (25.0%)
	Iloperidone	10 (6.8%)
	Lurasidone	9 (6.1%)
	Olanzapine	21 (14.2%)
	Paliperidone	10 (6.8%)
	Perphenazine	4 (2.7%)
	Quetiapine	38 (25.7%)
	Risperidone	24 (16.2%)
	Thiothixene	1 (0.7%)
	Ziprasidone	11 (7.4%)
Classification*†	First generation	43 (29.1%)
	Second generation	125 (84.5%)
	Both	22 (14.9%)
Total no. agents	1	110 (74.3%)
	2	34 (23.0%)
	3	2 (1.4%)
	4	2 (1.4%)
Route of administration*†	IM	17 (11.5%)
	IV	4 (2.7%)
	LAI	14 (9.5%)
	PO	126 (85.1%)
Total daily chlorpromazine equivalents, mg†	Median, 266.3 (range, 26.7–1500.0)	
	<200	47 (31.8%)
	200–1000	83 (56.1%)
	>1000	10 (6.8%)
Total daily anticholinergic Cognitive burden score†	0	12 (8.1%)
	1	56 (37.8%)
	2	11 (7.4%)
	3	48 (32.4%)
	4	13 (8.8%)
	5	0
	6	4 (2.7%)
	7	1 (0.7%)
	8	1 (0.7%)
DRBA overdose	Yes	7 (4.7%)
	No	141 (95.3%)

*Total ≠ 100%, as some patients were taking multiple DRBAs.

†Total ≠ 100%, as complete medication administration history (DRBA name, dose, and route) was not available for some patients.

IM indicates intramuscular; IV, intravenous; LAI, long-acting injectable; PO, oral.

Most patients were prescribed monotherapy with an oral second-generation DRBA, such as quetiapine (Table 2). The majority of doses prescribed were within the normal therapeutic range for maintenance treatment of a psychotic disorder, with a median daily exposure of 226.3 mg of chlorpromazine equivalents (CPZEs) and anticholinergic burden of 2. Dopamine receptor blocking agent overdose was rare and only associated with EPSs or OMDs in

TABLE 3. Concurrent Use of Interacting Medications in Patients Experiencing a Validated DRBA-Related EPSs or OMDs Event

Interaction	Agent	Frequency (N = 148)
Agents independently associated with EPSs or OMDs	Bupropion	5 (3.4%)
	Meclizine	1 (0.7%)
	Metoclopramide	1 (0.7%)
	Perphenazine	3 (2.0%)
	Prochlorperazine	1 (0.7%)
	Promethazine	8 (5.4%)
Agents that could interact with DRBAs via CYP450	Bupropion	5 (3.4%)
	Ciprofloxacin	2 (1.4%)
	Clarithromycin	1 (0.7%)
	Duloxetine	8 (5.4%)
	Estradiol	1 (0.7%)
	Fluoxetine	6 (4.1%)
	Fluvoxamine	1 (0.7%)
	Paroxetine	4 (2.7%)
	Phenytoin	4 (2.7%)
	Sertraline	13 (8.8%)
	Verapamil	1 (0.7%)
Agents that could ameliorate/mask EPSs or OMDs symptoms	Alprazolam	6 (4.1%)
	Amantadine	1 (0.7%)
	Benztropine	28 (18.9%)
	Clonazepam	15 (10.1%)
	Diazepam	5 (3.4%)
	Diphenhydramine	13 (8.8%)
	Lorazepam	31 (20.9%)
	Propranolol	13 (8.8%)
	Trihexyphenidyl	8 (5.4%)

4.7% of patients. Most patients (73.6%) were prescribed a concurrent non-DRBA medication that either caused EPSs or OMDs independently (12.8%), had the potential to interact with a DRBA (31.1%), or could ameliorate/mask symptoms of EPSs or OMDs (81.1%) (Table 3; see Supplementary Appendix 2, Supplemental Digital Content 2, http://links.lww.com/JCP/A580, for complete list).

A statistically significant correlation was observed between subtypes of EPSs or OMDs and the patient characteristics of age, BMI category, and total ACB score (Table 4). Negative correlation coefficients were observed between age and akathisia ($r = -0.365$, $P < 0.05$) and dystonia ($r = -0.269$, $P < 0.05$), meaning that the likelihood of these subtypes of EPSs increased as age decreased. There was a noted positive correlation between TD and age ($r = 0.274$, $P < 0.05$). Body mass index category (underweight, normal, overweight, or obese) was negatively correlated with dystonia ($r = -0.203$, $P < 0.05$), indicating that the likelihood of dystonia was greater in underweight and normal weight patients as compared with overweight or obese patients in this population. Daily anticholinergic burden was also negatively correlated with dystonia ($r = -0.170$, $P < 0.05$), such that as anticholinergic burden increased, the incidence of dystonia decreased.

Fisher exact test was used to compare subtypes of EPSs or OMDs and dichotomous variables (female sex, DRBA overdose, etc) (Table 5). Odds ratios (ORs) greater than 1 indicate an increased likelihood of a certain subtype of EPSs or OMDs occurring in the presence of a given characteristic or exposure, whereas an OR of less than 1 indicates a decreased likelihood. Female sex, DRBA polytherapy, daily CPZE, and DRBA overdose were not found to be significantly associated with any subtype of EPSs or OMDs.

Statistically significant associations were, however, seen with individual DRBAs and the development of different subtypes of EPSs or OMDs. Clozapine (n = 9) exposure was highly predictive of NMS in this population (OR, 8.824; $P = 0.004$), whereas iloperidone (n = 10) and lurasidone (n = 9) were associated with an over 4-fold increase in the likelihood of NMS (OR, 4.370; $P = 0.044$) and parkinsonism (OR, 4.102; $P = 0.046$), respectively. First-generation DRBAs as a class were associated with a nearly 3-fold greater likelihood of akathisia (OR, 2.897; $P = 0.021$), likely driven by haloperidol exposure (OR, 2.790; $P = 0.028$). Akathisia was also more commonly observed in patients who were taking long-acting injectable (LAI) formulations of a DRBA (OR, 3.580; $P = 0.034$).

DISCUSSION

This study represents a pilot investigation describing the characteristics of patients seen within a community hospital system that experienced DRBA-related EPSs or OMDs. Descriptive analysis of the population as a whole revealed that these patients tended to be middle-aged, overweight females. Most were taking a single oral second-generation DRBA at a typical maintenance dose at the time of diagnosis, and overdose on these agents was not commonly associated with the patient's presentation. These findings are interesting to consider in the context of published literature describing a dose-dependent relationship for DRBA-related EPSs[16,20–22,28,33] and linking risk of EPSs to factors such as dopamine D_2 receptor binding affinity[22] and association rate.[34] Nevertheless, we know this interdependence to be complex and variable based on characteristics of the patient population and treatment. For example, aripiprazole demonstrates a dose-dependent risk of EPSs and other treatment-emergent adverse effects in children, but no noted dose-dependency for these effects in adults.[35] Regarding treatment differences, the rates of EPSs for certain second-generation DRBAs such as risperidone and olanzapine positively correlate with dose,[15] whereas others such as clozapine and quetiapine do not exhibit dose-dependency effects.[22]

The concept of dopamine blocking potency is important to consider when accounting for the differences in risk of EPSs or OMDs observed with each DRBA. First-generation agents such

TABLE 4. Correlations Coefficients for Associations Between Patient Characteristic and Subtype of EPSs or OMDs

	Akathisia	Dystonia	Parkinsonism	TD	NMS
Age*	−0.365‡	−0.269‡	0.154	0.274‡	−0.040
BMI category†	−0.113	−0.203‡	0.065	0.107	0.089
Total daily ACB score†	−0.054	−0.170‡	0.064	0.074	0.084

*Pearson correlation test was used to calculate correlation coefficient (parametric data).

†Spearman ρ test was used to calculate correlation coefficient (nonparametric data).

‡Correlation is statistically significant ($P < 0.05$).

TABLE 5. Odds Ratios for Associations Between Patient Characteristics and Subtype of DRBA-Related EPSs or OMDs

	Akathisia	Dystonia	Parkinsonism	TD	NMS
Female sex	0.555	1.110	0.580	2.207	0.558
Agent					
Aripiprazole	2.989	1.027	0.509	0.874	1.027
Asenapine	9.000	—	1.486	—	—
Clozapine	0.509	—	0.833	0.833	8.824*
Haloperidol	2.790*	2.374	0.376	0.376	0.846
Iloperidone	0.449	0.608	0.309	0.309	4.370*
Lurasidone	1.220	—	4.102*	0.833	0.690
Olanzapine	0.181	0.248	0.908	1.583	0.930
Paliperidone	3.111	1.928	0.309	0.721	0.608
Perphenazine	1.420	—	3.057	9.529	—
Quetiapine	0.733	0.811	1.820	0.887	1.400
Risperidone	0.817	0.209	1.263	1.603	0.464
Thiothixene	—	—	—	—	—
Ziprasidone	0.400	3.714	1.114	0.635	1.278
Classification					
First Generation	2.897*	1.873	0.486	0.728	0.681
Second Generation	0.722	0.504	2.242	0.824	1.810
Polytherapy	1.711	0.601	1.098	0.602	1.430
Route of administration					
IM route	1.282	2.077	0.567	0.339	2.077
IV route	4.269	2.070	—	0.935	—
LAI route	3.580*	2.775	0.746	0.746	—
PO route	0.990	0.188	2.500	1.478	1.083
Total daily chlorpromazine equivalents, mg					
<200	0.987	0.619	1.099	1.291	1.077
200–1000	0.999	1.327	1.010	1.177	0.644
>1000	1.050	1.556	0.679	—	2.849
Overdose	3.317	—	4.364	—	0.952

—, Insufficient number of patients to calculate OR.

*Association is statistically significant ($P < 0.05$).

IM indicates intramuscular; IV, intravenous.

as haloperidol are believed to have a propensity to cause EPSs owing to their stronger dopamine blocking effects and lack of serotonin signaling.[13,15,20,36] Analysis of the study population did indeed demonstrate that first-generation agents were associated with significantly greater odds of developing akathisia, which is supported by previously published findings.[37] First-generation DRBAs are also associated with an increased risk of NMS because of their high dopamine binding affinity.[38] However, under the current treatment paradigm, these medications are not used as commonly as second-generation DRBAs for chronic therapy, as reflected in the study population. Although the second-generation class purportedly possesses lower risk of EPSs overall, significant variability exists between agents.[15,16,21,36] Clozapine and quetiapine have low dopamine receptor occupancy, whereas that of olanzapine is intermediate, and the binding of risperidone and ziprasidone is considered high.[15,22] This corresponds to the risk of developing EPSs with exposure to each agent,[20,39,40] with the exception of akathisia, which is thought to be equal across all second-generation agents.[22] Besides this idiosyncrasy with akathisia, it has not been established if different presentations of EPSs or OMDs vary in their frequency with exposure to the individual DRBAs.

Analysis of the study population did in fact reveal significant associations between certain DRBAs and the subtype of EPSs or OMDs experienced by a patient. Haloperidol was discovered to confer excess risk for the development of akathisia and lurasidone for parkinsonism, both results which are supported by clinical trial data.[41,42] The odds of a patient in the study population experiencing NMS were higher if they were exposed to iloperidone, a finding which supports the notion that greater dopamine blocking affinity is a precipitating factor for the development of NMS, as iloperidone is considered to have high dopamine D_2 receptor binding affinity.[43,44] Conversely, the association of clozapine with NMS does not follow this pattern, as clozapine is a low potency DRBA.[45] This observation may instead reflect the fact that a large percentage of patients (40%) who experienced NMS while taking clozapine were prescribed multiple DRBA agents, which is a known risk factor for the development of NMS.[25]

It is important to consider these findings in the context of the single patient population in which they occurred. The reported ORs representing the risk of experiencing different subtypes of EPSs or OMDs with exposure to various DRBAs, for instance, are intended to be descriptive and not predictive. A larger or more statistically meaningful relationship for one DRBA than another does not imply that one agent confers a comparatively higher risk for a given outcome, only that in specific population studied, exposure to that agent resulted in a greater risk compared with no

exposure. Haloperidol, for example, was found to have a significant positive association with akathisia, whereas lurasidone did not. Nevertheless, in our clinical experience, akathisia tends to be a relatively more problematic adverse movement reaction with lurasidone treatment than with haloperidol.

When examining associations between study population characteristics and subtype of EPSs or OMDs, age emerged as another important patient-related risk factor. Associations of age with dystonia and TD match those found in the literature.[46,47] It appears that this work is the first to describe a statistically significant relationship between age and the development of akathisia with the use of DRBAs. To date, prospective cohort studies of community-dwelling patients with schizophrenia[48] and literature reviews exploring the epidemiology of drug-induced akathisia[49,50] have not been able to draw firm conclusions regarding age as a risk factor for akathisia. It is possible that including a wider age group of patients in the present study population (range, 14–96 years old) allowed for differences in akathisia risk to emerge. This result is intriguing and may provide additional insight into the mechanism and management of a poorly understood subtype of EPSs. Further investigation could assess the interplay of variables such as receptor sensitivity and body composition on the observed relationship of age and akathisia risk.

Another patient-specific factor found to be significantly associated with the risk of developing a specific subtype of EPSs was BMI category. Lower BMI category increased the odds of DRBA-related dystonia in the study population. Age and BMI category were not significantly correlated, so this effect was independent of the increased risk of dystonia seen in younger patients.[51] One potential explanation is duration of therapy. Dystonia can occur immediately after administration of a DRBA, compared with weeks or months of exposure required to develop other subtypes of EPSs.[46] Accordingly, it is less likely that these patients would have suffered significant weight gain from chronic DRBA use at the time of developing dystonia. It is also possible that there exists an interaction between DRBA-induced metabolic syndrome and the risk of EPSs that has not previously been identified. Assuming that dystonia, like other subtypes of EPSs, is related to total incident exposure, perhaps it could be related to BMI by way of alterations in some pharmacokinetic and/or pharmacodynamic factors related to nutrition, such as protein binding capacity, end organ function, CYP450 enzyme activity, epigenetic modifications, blood-brain barrier permeability, or vitamin/mineral status.[52–57]

It was surprising that the patient characteristic of sex was not observed to be significantly associated with a subtype of EPSs or OMDs in the study population, as previous research demonstrated that dystonia and NMS are more common in males, whereas parkinsonism and TD are more common in females.[13,41] This unexpected outcome may have resulted from the relatively low number of males (n = 50, 33.8%) represented in the study group. There was also noted to be a significant correlation between age and sex in this population, such that males tended to be younger and females tended to be older. This intrinsic relationship may have influenced observed associations between age, sex, and subtype of EPSs or OMDs, and can offer an explanation as to why certain known risk factors were not detected in the study population.

The lack of an observed interaction with DRBA dose was also interesting to note. Daily CPZE was not found to be significantly associated with any subtype of EPSs or OMDs in the study population. The pathogenesis of EPSs is complex and likely results from activity at multiple different receptor subtypes besides simply dopamine D_2. Chlorpromazine equivalent may therefore serve as more of a surrogate marker for EPS or OMD-inducing potential of DRBAs,[31] which may explain why a clear association was not detected in the present study. It is important to note that many patients in this study were prescribed concurrent anticholinergic medications (33.1%) or benzodiazepines (38.5%), which can have mitigating effects on musculoskeletal dysfunction and are often used to treat EPSs or OMDs.[15] As would be predicted, increasing anticholinergic burden was found to have a significant negative correlation with the development of dystonia in the study population. Overall, the lack of a dose-dependent effect as measured by number of agents, overdose, and daily CPZE suggests that the DRBA itself and specific characteristics of the patient taking it are more important in determining the subtype of EPSs or OMDs experienced than the dose.

This retrospective, outcome-driven study has several limitations. First, EPSs are known to occur spontaneously in patients with psychiatric disorders, independently of drug treatment[58] and may be similar in terms of severity.[59] There was no way to uniformly differentiate disease-related EPSs from drug-related EPSs in this study. It also failed to account for differences in diagnoses, which is significant because patients with mood disorders are observed to have higher rates of DRBA-related EPSs than patients with schizophrenia.[17,60,61] Furthermore, DRBA route of administration was not controlled for in this study, which is known to influence the risk of EPSs. For example, EPSs incidence is believed to be lower for depot DRBAs than oral.[28] In the study population, akathisia was more commonly observed in patients prescribed LAI formulations of a DRBA (OR, 3.580; $P = 0.034$), although this finding was likely a function of the specific agents available as LAIs. Of the 11 patients taking LAI DRBAs, 7 were prescribed paliperidone and 2 were prescribed aripiprazole. These particular LAI agents, paliperidone (Invega Sustenna [package insert]; Janssen Pharmaceuticals, Inc, Titusville, NJ) and aripiprazole (Aristada [package insert]; Alkermes, Inc, Waltham, MA), are associated with elevated rates of akathisia in patients taking typical maintenance doses. Finally, the number of DRBA-related EPS or OMD events observed in the study population compared with the number of inpatient encounters during the same time period where DRBAs were administered (148/31,461 = 0.5%) was significantly lower than published prevalence rates of EPSs or OMDs,[16,62] which may limit generalizability of this research.

Understanding the nature of patient-treatment interactions can be helpful to predict which individuals might be at risk for developing certain subtypes of EPSs or OMDs related to DRBA therapy. Future directions for this research could include exploring additional patient characteristics such as markers of nutritional status (eg, albumin and vitamin D), as well as searching for risk factors associated with the development of other DRBA-related adverse effects (eg, hyperprolactinemia, hyperglycemia, hyperlipidemia, sedation, hypotension, anticholinergic, and QT interval prolongation). Ultimately, this information can assist clinicians with identifying at-risk patients, setting expectations to anticipate probable adverse effects, and using early intervention strategies aimed to improve adherence and overall outcomes with DRBA therapy.

ACKNOWLEDGMENTS

The authors would like to acknowledge the collaborative contributions by Sun Lee, PharmD; Jessalynn Henney, PharmD; pharmacy students Megan Harshman, Amber Ooley, and Hayley Robertson; and medical students Gabe Martinez and Rohn Nahmias.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

REFERENCES

1. Munday J, Greene M, Chang E, et al. Early initiation of long-acting injectable antipsychotic treatment is associated with lower hospitalization

rates and healthcare costs in patients with schizophrenia: real-world evidence from US claims data. *Curr Med Res Opin*. 2019;1.

2. Yermilov I, Greene M, Chang E, et al. Earlier versus later augmentation with an antipsychotic medication in patients with major depressive disorder demonstrating inadequate efficacy in response to antidepressants: a retrospective analysis of US claims data. *Adv Ther*. 2018;35:2138–2151.
3. Pilon D, Tandon N, Lafeuille MH, et al. Treatment patterns, health care resource utilization, and spending in Medicaid beneficiaries initiating second-generation long-acting injectable agents versus oral atypical antipsychotics. *Clin Ther*. 2017;39:1972–1985.e2.
4. Brugnoli R, Rapinesi C, Kotzalidis GD, et al. Model of Management (Mo.Ma) for the patient with schizophrenia: crisis control, maintenance, relapse prevention, and recovery with long-acting injectable antipsychotics (LAIs). *Riv Psichiatr*. 2016;51:47–59.
5. Valenstein M, Ganoczy D, McCarthy JF, et al. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry*. 2006;67:1542–1550.
6. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry*. 2002;63:892–909.
7. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353: 1209–1223.
8. Chapman SC, Horne R. Medication nonadherence and psychiatry. *Curr Opin Psychiatry*. 2013;26:446–452.
9. Higashi K, Medic G, Littlewood KJ, et al. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Ther Adv Psychopharmacol*. 2013;3:200–218.
10. Ascher-Svanum H, Zhu B, Faries D, et al. A prospective study of risk factors for nonadherence with antipsychotic medication in the treatment of schizophrenia. *J Clin Psychiatry*. 2006;67:1114–1123.
11. Lambert M, Conus P, Eide P, et al. Impact of present and past antipsychotic side effects on attitude toward typical antipsychotic treatment and adherence. *Eur Psychiatry*. 2004;19:415–422.
12. Perkins DO. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry*. 2002;63:1121–1128.
13. Divac N, Prostran M, Jakovcevski I, et al. Second-generation antipsychotics and extrapyramidal adverse effects. *Biomed Res Int*. 2014; 1–6.
14. Blair DT, Dauner A. Extrapyramidal symptoms are serious side-effects of antipsychotic and other drugs. *Nurse Pract*. 1992;17:56, 62–64, 67.
15. Dayalu P, Chou KL. Antipsychotic-induced extrapyramidal symptoms and their management. *Expert Opin Pharmacother*. 2008;9:1451–1462.
16. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics. *Drug Saf*. 2005;28:191–208.
17. Kulkarni SK, Naidu PS. Pathophysiology and drug therapy of tardive dyskinesia: current concepts and future perspectives. *Drugs Today (Barc)*. 2003;39:19–49.
18. Tandon R, Jibson MD. Extrapyramidal side effects of antipsychotic treatment: scope of problem and impact on outcome. *Ann Clin Psychiatry*. 2002;14:123–129.
19. McEvoy JP, Howe AC, Hogarty GE. Differences in the nature of relapse and subsequent inpatient course between medication-compliant and noncompliant schizophrenic patients. *J Nerv Ment Dis*. 1984;172:412–416.
20. Tandon R. Safety and tolerability: how do newer generation "atypical" antipsychotics compare? *Psychiatr Q*. 2002;73:297–311.
21. Chiang YL, Klainin-Yobas P, Ignacio J, et al. The impact of antipsychotic side effects on attitudes towards medication in people with schizophrenia and related disorders: impact of antipsychotic side effects in people with schizophrenia. *J Clin Nurs*. 2011;20:2172–2182.
22. Shirzadi AA, Ghaemi NS. Side effects of atypical antipsychotics: extrapyramidal symptoms and the metabolic syndrome. *Harv Rev Psychiatry*. 2006;14:152–164.
23. Boumans CE, de Mooij KJ, Koch PA, et al. Is the social acceptability of psychiatric patients decreased by orofacial dyskinesia? *Schizophr Bull*. 1994;20:339–344.
24. Youssef HA, Waddington JL. Morbidity and mortality in tardive dyskinesia: associations in chronic schizophrenia. *Acta Psychiatr Scand*. 1987;75:74–77.
25. Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalists. *Neurohospitalist*. 2011;1:41–47.
26. Modi S, Dharaiya D, Schultz L, et al. Neuroleptic malignant syndrome: complications, outcomes, and mortality. *Neurocrit Care*. 2016;24:97–103.
27. Haddad PM, Das A, Keyhani S, et al. Antipsychotic drugs and extrapyramidal side effects in first episode psychosis: a systematic review of head-head comparisons. *J Psychopharmacol*. 2012;26(suppl 5):15–26.
28. Schillevoort I, Herings RM, Hugenholtz GW, et al. Antipsychotic-induced extrapyramidal syndromes in psychiatric practice: a case-control study. *Pharm World Sci*. 2005;27:285–289.
29. Patel MX, Arista IA, Taylor M, et al. How to compare doses of different antipsychotics: a systematic review of methods. *Schizophr Res*. 2013;149: 141–148.
30. Yorston G, Pinney A. Chlorpromazine equivalents and percentage of British National Formulary maximum recommended dose in patients receiving high-dose antipsychotics. *Psychiatr Bull*. 2000;24:130–132.
31. Danivas V, Venkatasubramanian G. Current perspectives on chlorpromazine equivalents: comparing apples and oranges! *Indian J Psychiatry*. 2013;55:207–208.
32. Boustani M, Campbell N, Munger S, et al. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*. 2008;4: 311–320.
33. Mathews M, Gratz S, Adetunji B, et al. Antipsychotic-induced movement disorders: evaluation and treatment. *Psychiatry (Edgmont)*. 2005;2:36–41.
34. Sykes DA, Moore H, Stott L, et al. Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D2 receptors. *Nat Commun*. 2017;8:763.
35. Pae CU. A review of the safety and tolerability of aripiprazole. *Expert Opin Drug Saf*. 2009;8:373–386.
36. Bruijnzeel D, Suryadevara U, Tandon R. Antipsychotic treatment of schizophrenia: an update. *Asian J Psychiatr*. 2014;11:3–7.
37. Bratti IM, Kane JM, Marder SR. Chronic restlessness with antipsychotics. *Am J Psychiatry*. 2007;164:1648–1654.
38. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. *Am J Psychiatry*. 2007;164:870–876.
39. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. *CNS Drugs*. 2002;16:23–45.
40. Werner FM, Coveñas R. Safety of antipsychotic drugs: focus on therapeutic and adverse effects. *Expert Opin Drug Saf*. 2014;13:1031–1042.
41. Van Putten T, May PR, Marder SR. Akathisia with haloperidol and thiothixene. *Arch Gen Psychiatry*. 1984;41:1036–1039.
42. Zheng W, Cai DB, Yang XH, et al. Short-term efficacy and tolerability of lurasidone in the treatment of acute schizophrenia: a meta-analysis of randomized controlled trials. *J Psychiatr Res*. 2018;103:244–251.
43. Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. *Eur J Pharmacol*. 1996;317: 417–423.
44. Kalkman HO, Subramanian N, Hoyer D. Extended radioligand binding profile of iloperidone: a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist for the management of psychotic disorders. *Neuropsychopharmacology*. 2001;25:904–914.

45. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed. Cambridge, NY: Cambridge University Press; 2013.

46. Wirshing WC. Movement disorders associated with neuroleptic treatment. *J Clin Psychiatry.* 2001;62(suppl 21):15–18.

47. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res*. 1999;(suppl 35):S61–S66.

48. Berna F, Misdrahi D, Boyer L, et al. Akathisia: prevalence and risk factors in a community-dwelling sample of patients with schizophrenia. Results from the FACE-SZ dataset. *Schizophr Res*. 2015;169:255–261.

49. Sachdev P. The epidemiology of drug-induced akathisia: part I. Acute akathisia. *Schizophr Bull.* 1995;21:431–449.

50. Sachdev P. The epidemiology of drug-induced akathisia: part II. Chronic, tardive, and withdrawal akathisias. *Schizophr Bull.* 1995;21:451–461.

51. Van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. *BMJ.* 1999;319:623–626.

52. Trobec K, Kerec Kos M, von Haehling S, et al. Pharmacokinetics of drugs in cachectic patients: a systematic review. *PLoS One*. 2013; 8:e79603.

53. Benabe JE, Martinez-Maldonado M. The impact of malnutrition on kidney function. *Miner Electrolyte Metab*. 1998;24:20–26.

54. Perris C, Dimitrijevic P, Jacobsson L, et al. Tardive dyskinesia in psychiatric patients treated with neuroleptics. *Br J Psychiatry.* 1979;135:509–514.

55. Hasselbalch SG, Knudsen GM, Jakobsen J, et al. Blood-brain barrier permeability of glucose and ketone bodies during short-term starvation in humans. *Am J Physiol*. 1995;268(6 Pt 1):E1161–E1166.

56. Shimojo N. Cytochrome P450 changes in rats with streptozocin-induced diabetes. *Int J Biochem*. 1994;26:1261–1268.

57. Maxwell CS, Antoshechkin I, Kurhanewicz N, et al. Nutritional control of mRNA isoform expression during developmental arrest and recovery in C. elegans. *Genome Res*. 2012;22:1920–1929.

58. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. *Psychol Med*. 2009;39:1065–1076.

59. Peralta V, de Jalón EG, Campos MS, et al. Phenomenological differences between spontaneous and drug-related extrapyramidal syndromes in patients with schizophrenia-spectrum disorders. *J Clin Psychopharmacol*. 2013;33:438–440.

60. McIntyre RS, Konarski JZ. Tolerability profiles of atypical antipsychotics in the treatment of bipolar disorder. *J Clin Psychiatry.* 2005;66(suppl 3): 28–36.

61. Cha DS, McIntyre RS. Treatment-emergent adverse events associated with atypical antipsychotics. *Expert Opin Pharmacother.* 2012;13:1587–1598.

62. Novick D, Haro JM, Bertsch J, et al. Incidence of extrapyramidal symptoms and tardive dyskinesia in schizophrenia: thirty-six-month results from the European schizophrenia outpatient health outcomes study. *J Clin Psychopharmacol*. 2010;30:531–540.