Movement Disorders After Exposure to Antipsychotic Drugs in Patients With Depressive Disorders

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Objectives: The aims of the study were to explore the frequency of movement disorders (MDs) in depressive patients exposed to antipsychotic drugs (APDs) and to compare it with nonexposed depressive patients and APDs-treated schizophrenic patients.

Methods: Four hundred fifty-two depressive patients not exposed to APDs (group A), 156 depressives exposed to APDs (group B), and 75 patients with schizophrenia on APDs (group C) were recruited. Presence of MDs was explored by the Simpson-Angus and UKU scales (Registration: NCT02409823).

Results: Movement disorders were observed in 5%, 9%, and 13% of patients in groups A to C, respectively ($P < 0.001$, χ^2 for linear trend). A logistic multivariate analysis revealed that male sex (odds ratio = 2.26, 95% confidence interval = 1.13–4.49, $P < 0.01$), exposure to first-generation (vs second-generation) APDs (odds ratio = 5.71, 95% confidence interval = 2.08–15.66, $P < 0.01$), and exposure to lithium (odds ratio = 3.99, 95% confidence interval = 1.74–9.14, $P < 0.01$) were independently and significantly associated with MDs.

Conclusions: Male sex, use first-generation APDs, and exposure to lithium were associated with MDs in depression. Therefore, caution is advised with the use of these drugs in depressive patients. Prospective studies are needed to confirm these results.

Key Words: drug-induced movement disorders, antipsychotic drugs, major depressive disorder, bipolar depressive disorder, schizoprhenia, pharmacovigilance

(*Clin Neuropharm* 2018;41: 177–180)

Antipsychotic drugs (APDs) have been used for the treatment of schizophrenia since the 60s.[1] Notwithstanding, their efficacy is jeopardized by the appearance of movement disorders (MDs) as adverse effects, including parkinsonism, dystonia, akathisia, tremor, tics, tardive dyskinesia, and among others.[1] These adverse effects were noticed immediately after the introduction of the first-generation "typical" APDs, which motivated pharmaceutical companies to develop second-generation "atypical" APDs offering less risk of MDs.[2,3]

During the last decade, APDs have been increasingly used for the treatment of major depressive disorder and bipolar disorder unresponsive to classical antidepressants.[4] Several randomized double-blind placebo-controlled have indeed shown good antidepressant efficacy and adequate safety for these indications, with no or mild risk of MDs.[4,5] Notwithstanding, their risk/benefit ratio have been recently questioned,[6] because almost all safety data come from clinical trials, which are not the best tools for assessing drug safety.[7] In this observational study, we explored the frequency of MDs in depressive patients under treatment with APDs and compared it with depressive patients not exposed to APDs and with a group of schizophrenic patients under APDs. The frequency of MDs in patients under first- or second-generation APDs and the factors related to MDs in depressive patients were also explored.

METHODS

Sample

Consecutive male or female subjects of at least 18 years of age and fulfilling *Diagnostic and Statistical Manual of Mental Disorders IV* criteria for major depressive disorder or bipolar depressive disorder, exposed or not to APDs, were recruited. A group of schizophrenic patients on APDs was also recruited for use as a reference. Subjects gave informed consent before entering the study, which was previously approved by the institutional review board.

Study Procedures

Patients were assessed only once. Demographic information and characteristics of the disease were recorded. Disease severity was assessed by means of the Clinical Global Impression Scale.[8] Presence of MDs, including parkinsonism, dystonia, tremor, dyskinesia, tics, and akathisia, was explored by means of the Simpson-Angus and UKU Scales.[9] The Simpson-Angus consists of 10 questions referring to parkinsonian symptoms, including tremor. The UKU assesses the presence of dystonia, dyskinesia, akathisia, and tics.

Type and dose of antipsychotic treatments were also registered and coded by the *Anatomical Therapeutic Chemical* system (WHO).[10] Phenothiazines with aliphatic side chain (Anatomical Therapeutic Chemical code N05AA), phenothiazines with piperazine structure (N05AB), phenothiazines with piperidine structure (N05 AC), butyrophenone derivatives (N05 AD), and diphenylbutylpiperidine derivatives (N05AG) were considered as first-generation (ie, "typical") drugs. Indole derivatives (N05AE), diazepines, oxazepines, thiazepines, and oxepines (N05AH), and benzamides (N05AL) were considered as second-generation (ie, "atypical") drugs. Doses were converted to *defined daily dose*,

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This study was supported by a nonrestrictive educational grant from Drugtech, Recalcine Pharmaceutical Corporation (San José de Costa Rica, Costa Rica). The supporter supplied materials and participated in formulating the outline of the study but had no role in patient selection or interpretation of the evidence. The decision to submit the manuscript was made exclusively by the authors.

Conflicts of Interest and Source of Funding: B.R. has lectured for Pfizer, Asofarma, Lundbeck, and Roche. M.R. has lectured for Bial, Astrazeneca, Asofarma, and Pfizer. F.E.R.E. has lectured for Asofarma and Abbott. A.A. was employed by Drugtech. M.V.R. is CEO of Etymos Consulting Group. L.M., B.P., J.C., and S.P.L. has nothing to disclose.

DOI: 10.1097/WNF.0000000000000300

thus allowing comparisons between drugs. Exposure to drugs known to cause MDs, including penicillin derivates and amphotericin, antiepileptics, antidepressants, antiemetics, flunarazine and cinnarazine, antiarrhythmics, opiods, and CNS stimulants,[11] was recorded.

Statistical Analysis

Comparisons between depressive patients exposed or not to APDs and schizophrenic patients were performed by 1-way analysis of variance or χ^2 test. Similarly, χ^2 test was employed to compare the frequency of MDs between subjects exposed to first- or second-generation APDs. Finally, logistic regression was used to identify variables independently and significantly related to MDs in depressive patients. Statistical analysis was performed by SPSS v22 (IBM, NY).

RESULTS

In total, 683 patients were recruited for this study (452 depressive patients not exposed to APDs, 156 depressive patients exposed to APDs, and 75 patients with schizophrenia). Sample characteristics are shown in Table 1. There were no differences in age, but a significantly larger proportion of schizophrenic patients were males compared with those affected by depression. Use of APDs is described in Table 2. There were no major differences between depressive and schizophrenic patients, except for flupherazine, which was more frequently administered to the latter, and quetiapine dose, which was higher in patients with schizophrenia. There was a significant difference in the frequency of MDs, which were reported by 5% of depressive patients not exposed to APDs, 9% of depressives on APDs, and 13% of schizophrenic patients (Table 1).

The frequency of MDs in depressive or schizophrenic patients exposed to first- or second-generation APDs is shown in Table 3. As can be observed, MDs were significantly more frequent with first-generation drugs, both in depressive or schizophrenic patients.

Differences between depressive patients with or without MDs are shown in Table 4. The multivariate logistic regression analysis revealed that in addition to exposure to first-generation APDs, exposure to lithium and male sex were also significantly and independently related to MDs.

DISCUSSION

Although APDs have been extensively used in schizophrenic patients, the experience with their use in depression is more restricted. Given the limitations of clinical trials for the assessment of drug safety,[7] more studies on the safety profile of APDs in

TABLE 1. Characteristics of Schizophrenic or Depressive Patients Treated or Not With APDs

	Depression No APDs (n = 452)	Depression APDs (n = 156)	Schizophrenia (n = 75)	*P*
Age, y	43.4 ± 16.1	41.0 ± 14.7	40.8 ± 13.9	0.13
Males	131 (29%)	56 (36%)	48 (64%)	0.001
BMI, kg/m^2	26.5 ± 5.6	26.2 ± 5.5	26.2 ± 5.6	0.84
Overweight	260 (58%)	81 (52%)	40 (53%)	0.8
Bipolar depression	244 (54%)	106 (68%)	—	0.001
Disease duration, y	7.0 ± 8.6	7.1 ± 8.0	10.8 ± 10.3	0.003
Disease severity (CGI)	5.4 ± 1.0	5.0 ± 0.9	5.6 ± 1.0	0.001
EQ-5D VAS score	51.9 ± 19.8	57.4 ± 17.2	51.4 ± 17.3	0.007
Epworth score	3.0 ± 4.2	3.9 ± 4.7	3.7 ± 5.2	0.048
Orthostatic symptoms	4 (1%)	0	1 (1%)	0.43
MDs	24 (5%)	14 (9%)	10 (13%)	0.006*
≥2	4 (1%)	4 (3%)	5 (7%)	0.001*
Parkinsonism	3 (1%)	0	3 (4%)	0.007
Dystonia	5 (1%)	2 (1%)	0	0.63
Dyskinesia	0	3 (2%)	0	0.16
Tremor	16 (4%)	6 (4%)	7 (9%)	0.05
Tics	2 (<1%)	4 (3%)	3 (4%)	0.003*
Akathisia	3 (1%)	6 (4%)	3 (4%)	0.005
Antipsychotics				
Dose (DDDs)	—	0.7 ± 0.7	0.7 ± 0.5	0.7
Treatment duration, y	—	1.4 ± 2.5	2.2 ± 3.4	0.06
First-generation drugs	—	24 (15%)	24 (32%)	0.001
Drugs related to MDs	205 (45%)	113 (72%)	36 (48%)	0.001
Lithium	36 (8%)	17 (11%)	2 (3%)	0.44
Antiarrhythmics	1 (<1%)	0	0	0.7
Opioids	0	0	0	—
Antidepressants	132 (29%)	60 (38%)	6 (8%)	0.001
Antiepileptics	118 (26%)	77 (49%)	30 (40%)	0.001
Psychostimulants	1 (<1%)	2 (1%)	1 (1%)	0.1

Data was analyzed by t-test or Chi-square test.

*χ^2 for linear trend.

CGI indicates clinical global impression; EQ-5D VAS, EQ-5D Visual Analogue Scale; DDD, daily defined dose.

TABLE 2. Antipsychotic Drugs Use by Group

	Depression No APDs (n = 452)	Depression APDs (n = 156)	Schizophrenia (n = 75)	*P*
First-generation drugs				
Chlorpromazine	—	2 (1%)	4 (5%)	0.07
Dose (DDD)	—	1.0 ± 0.1	0.8 ± 0.8	0.80
Levomepromazine	—	1 (<1%)	0	0.80
Dose (DDD)	—	—	—	—
Fluphenazine	—	6 (4%)	10 (13%)	<0.01
Dose (DDD)	—	3.9 ± 3.8	2.3 ± 1.4	0.69
Thioridazine	—	3 (2%)	1 (1%)	0.74
Dose (DDD)	—	0.4 ± 0.2	—	—
Haloperidol	—	15 (10%)	10 (13%)	0.39
Dose (DDD)	—	1.4 ± 0.6	2.0 ± 1.4	0.26
Second-generation drugs				
Ziprasidone	—	1 (<1%)	1 (1%)	0.59
Dose (DDD)	—	0.5 ± 0.1	1.0 ± 0.1	0.90
Loxapine	—	1 (<1%)	—	0.48
Dose (DDD)	—	—	—	—
Clozapine	—	3 (2%)	2 (3%)	0.71
Dose (DDD)	—	0.3 ± 0.1	0.8 ± 0.2	0.33
Olanzapine	—	37 (24%)	16 (21%)	0.68
Dose (DDD)	—	1.3 ± 1.4	1.1 ± 0.6	0.93
Quetiapine	—	88 (56%)	28 (37%)	0.07
Dose (DDD)	—	0.5 ± 0.4	0.7 ± 0.4	0.05
Sulpiride	—	0	1 (1%)	0.90
Dose (DDD)	—	—	2.5 ± 0.1	—
Risperidone	—	41 (26%)	25 (33%)	0.26
Dose (DDD)	—	1.1 ± 1.7	0.7 ± 0.4	0.21
Aripiprazole	—	2 (1%)	1 (1%)	0.97
Dose (DDD)	—	1.3 ± 1.1	0.3 ± 0.1	0.67
Paliperidone	—	0	2 (3%)	0.75
Dose (DDD)	—	—	1.0 ± 0.1	—

Means ± SDs are shown. Data were compared by χ^2 or Mann-Whitney tests. Missing data are signaled with a dash.

DDD indicates daily defined dose.

depressive patients are needed. In this observational, real-setting study, we observed that the frequency of MDs in depressive subjects exposed to APDs was greater than that in nonexposed ones. Interestingly, the risk of MDs with second-generation agents was lower compared with first-generation drugs, both in depressive or schizophrenic patients. Other risk factors included male sex and use of lithium.

The main limitation of this study is that we included prevalent cases, thus increasing the bias of misclassifying the degree of exposure to APDs. Indeed, some patients who discontinued APDs because of any other causes would not have been included in this study. Therefore, the risk of MDs with APDs might have been underestimated in this study. In addition, we cannot exclude that differences in the frequency of MDs might have been related to factors specific to patient's psychiatric condition and not the drug itself. Finally, even if more than 600 depressive patients were included in this study, power might not be high enough to study with individual MDs.

One of the most relevant findings of this study is that the frequency of MDs was lower in depressive or schizophrenic patients exposed to second-generation APDs. Second-generation APDs were developed hoping to offer effective antipsychotic efficacy with less MDs,[1] but some findings have suggested that this might not be the case.[11–14] Notwithstanding, the matter is not settled and some limitations in studies suggesting an equal risk with both generations of APDs can be cited. For example, in the study by Peluso et al,[13] the risk of MDs with second-generation agents was 60% and 30% lower at 12 and 52 weeks of follow-up, but these figures did not achieve statistical significance, probably because of lack of power.[13] Rochon et al,[14] on the other hand, concluded that parkinsonism risk was similar between low doses of first-generation agents and high-doses of second-generation APDs, thus mixing effects from dose and type of APDs. More information is needed on this subject before conclusions can be drawn. Another important finding is that subjects exposed to lithium had an increased risk of MDs, thus confirming previous findings.[15]

In summary, we observed a higher frequency of MDs in depressive patients exposed to APDs compared with those who were not receiving the drug. Risk seemed to be lower for second-generation drugs and higher with lithium. Therefore, physicians should carefully assess MDs in depressive patients treated with APDs, and caution is especially advised when mixing these drugs with lithium.

TABLE 3. Movement Disorders in Schizophrenic or Depressive Patients According the Type of Antipsychotic

		Depression (n = 156)		Schizophrenia (n = 75)	
	Depression No APDs (n = 452)	First-Generation (n = 24)	Second-Generation (n = 132)	First-Generation (n = 24)	Second-Generation (n = 51)
MDs	24 (5%)	7 (29%)	7 (5%)*	6 (25%)	4 (8%)*
≥2	4 (1%)	2 (8%)	2 (2%)†	4 (17%)	1 (2%)*
Parkinsonism	3 (1%)	0	0	2 (8%)	1 (2%)
Dystonia	5 (1%)	2 (8%)	0*	0	0
Dyskinesia	0	2 (8%)	1 (1%)*	0	0
Tremor	16 (4%)	3 (13%)	3 (2%)*	5 (21%)	2 (4%)*
Tics	2 (<1%)	1 (4%)	3 (2%)	2 (8%)	1 (2%)
Akathisia	3 (1%)	3 (13%)	3 (2%)*	2 (8%)	1 (2%)

Frequency of MDs in depressive patients not exposed to APDs is shown for reference but was not included in statistical comparisons.

*$P < 0.05$ and †$P < 0.01$ vs first-generation APDs, all other comparisons showed P - values > 0.05 (χ^2 test).

TABLE 4. Characteristics of Depressive Patients With or Without MDs (MDs)

	MDs (n = 38)	No MDs (n = 570)	*P*	OR (95% CI)
Age, y	44.0 ± 16.6	42.7 ± 15.7	0.52	
Males	19 (50%)	168 (29%)	0.008	2.26 (1.13–4.49)
BMI, kg/m^2	26.8 ± 5.1	26.4 ± 5.6	0.85	
Overweight	24 (63%)	317 (56%)	0.34	
Disease duration, y	7.8 ± 9.5	7.1 ± 8.3	0.60	
Disease severity (CGI)	5.2 ± 1.2	5.3 ± 1.1	0.75	
First-generation APDs	7 (18%)	17 (3%)	0.001	5.71 (2.08–15.66)
Dose (DDDs)	0.5 ± 0.2	1.1 ± 1.2	0.15	
Treatment duration, y	6.7 ± 4.8	3.1 ± 7.8	0.17	
Second-generation APDs	9 (24%)	130 (23%)	0.91	
Dose (DDDs)	0.3 ± 0.2	0.5 ± 0.5	0.23	
Treatment duration, y	0.4 ± 0.6	0.6 ± 1.4	0.75	
Lithium	10 (26%)	43 (8%)	0.001	3.99 (1.74–9.14)
Dose (DDDs)	0.6 ± 0.4	0.9 ± 0.3	0.08	
Treatment duration, y	3.8 ± 4.9	1.7 ± 2.6	0.23	
Any drug related to MDs	22 (58%)	296 (52%)	0.47	

Bivariate comparisons were performed by t-test or chi-sq tests. All variables with *P* - values < 0.05 were entered in the logistic multivariate model (i.e. gender, exposure to first-generation APDs and exposure to lithium).

CI indicates confidence interval; OR, odds ratio; CGI, clinical global impression; DDD, daily defined dose.

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