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- Identify risk factors for extrapyramidal side effects in your patients taking antipsychotic agents

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Prevalence of and Risk Factors for Extrapyramidal Side Effects of Antipsychotics: Results From the National FACE-SZ Cohort

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ABSTRACT

Background: Extrapyramidal side effects (EPS) have been identified as a complication of antipsychotic treatment. Previous meta-analyses have investigated EPS prevalence and risk factors in randomized clinical trials with highly selected patients, but studies in real-world schizophrenia are missing.

Objective: To examine the prevalence and clinical correlates associated with EPS in a nonselected national multicenter sample of stabilized patients with schizophrenia.

Methods: Between 2010 and 2016, patients suffering from schizophrenia (*DSM-IV-TR* criteria) were recruited through the FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) network and data were collected during a comprehensive 1-day-long standardized evaluation. The Simpson-Angus Scale and the Abnormal Involuntary Movement Scale were used to assess drug-induced parkinsonism (DIP) and tardive dyskinesia, respectively.

Results: The overall prevalence of DIP and tardive dyskinesia was 13.2% and 8.3%, respectively, in this community-dwelling sample of 674 patients. DIP was associated with negative symptoms (Positive and Negative Syndrome Scale [PANSS] subscore) (adjusted odds ratio [aOR] = 1.102, $P < .001$), first-generation antipsychotic prescription (aOR = 2.038, $P = .047$), and anticholinergic drug administration (aOR = 2.103, $P = .017$) independently of sex, age, disorganization (PANSS disorganized factor), and antipsychotic polytherapy. Tardive dyskinesia was associated with PANSS disorganized factor (aOR = 1.103, $P = .049$) independently of sex, age, negative symptoms, excitation, first-generation antipsychotic prescription, and benzodiazepine and anticholinergic drug administration.

Conclusions: Our results indicate the high prevalence of EPS in a nonselected community-dwelling clinically stable sample of outpatients with schizophrenia. In the monitoring of antipsychotic treatment, EPS should be systematically evaluated, especially when negative symptoms and disorganization or cognitive alteration are present. Monotherapy with a second-generation antipsychotic should be preferentially initiated for patients with these side effects.

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Clinical Points

- The prevalence of drug-induced parkinsonism and tardive dyskinesia (TD) was, respectively, 13.2% and 8.3% in a large multicenter cohort of patients with schizophrenia (674 patients).
- Drug-induced parkinsonism was associated with higher negative symptoms level, first-generation antipsychotics, and anticholinergic drugs, and TD was associated with higher disorganization/cognitive symptoms level.
- The choice of monotherapy with second-generation antipsychotics should be recommended as soon as possible to prevent onset of extrapyramidal side effects in patients with schizophrenia.

Extrapyramidal side effects including drug-induced parkinsonism (DIP) and tardive dyskinesia (TD) have been identified as frequent side effects of antipsychotics and have been associated with impaired quality of life[1] and depression[2] in patients with schizophrenia.

More specifically, parkinsonism (bradykinesia, rigidity, and tremor) occurs after a relatively short period of antipsychotic treatment[3] and has been mainly related to the intrinsic antidopaminergic potency of the antipsychotic treatment.[4–7] DIP symptoms usually remit within a few months after medication withdrawal,[8] while they may unmask neurodegenerative dopamine denervation in some patients.[9,10] Clinical studies have underlined that parkinsonism was positively correlated with the intensity of negative symptoms.[11,12]

TD is a drug-induced movement disorder, mainly related to antipsychotic treatment and defined by involuntary, repetitive orofacial movements, often accompanied by choreiform movements of the upper extremities. The term *tardive* means delayed after months of antipsychotic treatment.[13,14] TD can be difficult to treat and may be permanent in some people. Age, duration of treatment with antipsychotics, first-generation antipsychotic (FGA) treatment, treatment with anticholinergics, substance abuse, and negative symptoms have been suggested to be associated with TD.[15]

EPS has been recently investigated in 2 comprehensive meta-analyses including clinical trials to compare second-generation antipsychotics (SGAs) with FGAs.[16,17] Overall, SGAs including clozapine, olanzapine, and risperidone have been found to be associated with fewer EPS than haloperidol (FGA). However, clinical trials are not representative of "real world" schizophrenia, as many patients are administered antipsychotic polytherapy combined with other psychotropic drugs (antidepressant, anxiolytic, anticholinergic), with various degrees of adherence and substance use disorder comorbidities, especially daily tobacco smoking, that may impact blood antipsychotic levels.[11,18–20]

The objective of the present study was to determine the prevalence and clinical correlates associated with antipsychotic extrapyramidal side effects in a nonselected national sample of stabilized community-dwelling outpatients with schizophrenia.

METHODS

Study Participants

The FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) cohort is based on a French national network of 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, and Versailles) set up by a scientific cooperation foundation in France, the FondaMental Foundation (www.fondation-fondamental.org), and formed by the French Ministry of Research to create a platform that links thorough and systematic assessment to research. Clinically stable patients aged above 16 years are referred by their general practitioner or psychiatrist, who subsequently receives a detailed evaluation report with suggestions for personalized interventions. Patients diagnosed with schizophrenia or schizoaffective disorders according to *DSM-IV-TR* criteria were enrolled in the FACE-SZ cohort. This study includes patients recruited between March 2010 and January 2016.[21]

The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18, 2010)

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and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects gave informed consent prior to their inclusion in the study.

Data Collection

Sociodemographic and clinical variables. Clinical and sociodemographic factors were collected during an extensive evaluation. Standardized assessments were used to assess psychotic and negative symptoms and general psychopathology with the Positive and Negative Syndrome Scale (PANSS) subscores.[22] For the purposes of this study and to explore specifically depressive and cognitive symptoms, we used the validated 5-factor model of the PANSS[23] described as follows: "positive symptoms," "negative symptoms," "disorganized/concrete" (ie, the factor found to account for the largest share of the PANSS association with cognition [IQ]), "excitement," and "depression." Depressive symptoms were also assessed with the French-validated Calgary Depression Rating Scale for Schizophrenia (CDRS).[24] A cutoff of 6 was considered as a current major depressive episode. Treatment adherence was evaluated using the Brief Adherence Rating Scale[25] and the Medication Adherence Rating Scale.[26] Daily tobacco smoking and alcohol and cannabis use disorders were defined according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders. Type and number of ongoing psychotropic treatments were recorded (antipsychotics, antidepressants, benzodiazepines, and anticholinergics). Chlorpromazine equivalent doses (CPZ100eq) were calculated according to the minimum effective dose method.[27] All patients were on stable medication for more than 4 weeks.

Drug-induced parkinsonism. The Simpson-Angus Scale (SAS) is a 10-item scale used in clinical and research practices to assess DIP. One item measures gait, 6 items measure stiffness, and 3 items measure tremor, salivation, and palpebral reflex. This scale is validated and is among those most used in individuals with schizophrenia in naturalistic conditions.[28] We used a cutoff of 0.65 to define presence of DIP. This threshold was previously used and validated.[29]

Tardive dyskinesia. The Abnormal Involuntary Movement Scale (AIMS), a 10-item scale designed to record the occurrence of dyskinetic movements, was used to assess the incidence of TD.[30] Items evaluate dyskinetic movements in 3 body regions (facial and oral, extremity, trunk) on a 5-point scale (with 0 indicating no dyskinetic movements and 4 indicating severe dyskinetic movements) for a total score ranging from 0 to 40. Each item on the AIMS ranges from 0 to 4, and the total AIMS score was calculated by adding items 1–7. In accordance with a recent meta-analysis,[20] we used the widely recognized Schooler-Kane criteria to define patients with TD. Thus, dyskinesia was classified as present when an AIMS score of 2 was noted in at least 2 items or when a score of > 2 was noted in at least 1 item.[20]

Statistical Analysis

The sociodemographic and clinical characteristics, presence of substance use disorder, medications, and the scores for each scale were compared between the 2 groups for each side effect studied ("DIP" vs "No DIP" and "TD" vs "No TD") using the Student *t* test for continuous variables and χ^2 test for categorical variables. A logistic regression analysis was used to estimate the odds ratio (OR) for risk factors associated with DIP and TD, after adjusting for confounding factors. Variables relevant to the model were selected based on their clinical interest and/or a threshold *P* value ≤ 0.20 in univariate analyses (exclusion of collinear variables). The final model incorporated the adjusted odds ratios (aORs) with 95% confidence interval. An aOR > 1 was considered as an increased risk factor for the presence of studied side effects, and an aOR < 1, as a protective risk factor for studied side effects. The statistical significance level was set at *P* = .05 in a 2-sided test. Data were analyzed using SPSS 20.0 software.

Table 1. Characteristics of the Whole Sample (N = 674)

	Values
Sociodemographic characteristics	
Sex, male, n (%)	494 (73.29)
Age, mean (SD), y	32.62 (9.89)
Clinical variables	
Schizoaffective disorder, n (%)	154 (22.85)
Illness duration, mean (SD), y	10.97 (8.24)
PANSS positive factor, mean (SD)	9.33 (4.39)
PANSS negative factor, mean (SD)	17.51 (6.62)
PANSS disorganized factor, mean (SD)	8.33 (3.49)
PANSS excited factor, mean (SD)	5.77 (2.44)
PANSS depressed factor, mean (SD)	7.27 (3.19)
PANSS total score, mean (SD)	71.31 (19.15)
CDRS score, mean (SD)	4.03 (4.27)
Substance disorders and addictions, n (%)	
Current daily tobacco smoking	356 (52.82)
Current daily cannabis abuse or dependence	92 (13.65)
Current alcohol abuse or dependence	61 (9.05)
Adherence to treatment, mean (SD)	
BARS score	86.19 (24.06)
MARS score	6.19 (2.26)
Current treatment[a]	
SGA, n (%)	513 (90.80)
FGA, n (%)	154 (27.26)
Antipsychotic polytherapy, n (%)	214 (37.88)
FGA + FGA	86 (15.22)
SGA + SGA	15 (2.65)
FGA + SGA	113 (20.00)
Antidepressant drug, n (%)	189 (33.45)
Benzodiazepines, n (%)	161 (28.50)
Anticholinergic drug, n (%)	114 (20.18)
Antipsychotic dose (CPZ100eq), mean (SD)[b]	6.15 (6.21)

[a]N = 549; 125 missing values for current treatment.
[b]According to the minimum effective dose method (Leucht et al[27]).The mean antipsychotic dose in the sample was equivalent to 615 mg/d chlorpromazine.
Abbreviations: BARS = Brief Adherence Rating Scale, CDRS = Calgary Depression Scale for Schizophrenia, CPZ100eq = dose equivalent to 100 mg/d of chlorpromazine, FGA = first-generation antipsychotic, MARS = Medication Adherence Rating Scale, PANSS = Positive and Negative Syndrome Scale, SGA = second-generation antipsychotic.

RESULTS

Sample Characteristics

Altogether, 674 outpatients suffering from schizophrenia were included in this study. Clinical and demographic

Table 2. Factors Associated With Drug-Induced Parkinsonism (DIP) According to the Simpson-Angus Scale in a Sample of 674 Patients With Schizophrenia[a]

	Univariate Analysis						Multivariate Model			
	No DIP (n = 585)	DIP[b] (n = 89)	t/χ^2	95% CI		*P*	aOR	95% CI		*P*
Sociodemographic characteristics										
Sex, male, n (%)	430 (73.50)	64 (71.91)	0.100	0.659	1.782	.751	0.607	0.316	1.166	.134
Age, mean (SD), y	32.31 (9.50)	34.71 (12.04)	−1.796	−5.047	0.250	.075	1.025	0.999	1.053	.063
Clinical variables, mean (SD)										
Illness duration, y	10.78 (7.98)	12.25 (9.82)	−1.519	−3.371	0.431	.129				
PANSS positive factor	9.27 (4.25)	9.74 (5.25)	−0.588	−1.634	0.706	.433				
PANSS negative factor	**16.98 (6.39)**	**21.00 (7.09)**	**−5.089**	**−5.482**	**−2.553**	**<.001**	**1.102**	**1.055**	**1.151**	**<.001**
PANSS disorganized factor	**8.15 (3.35)**	**9.49 (4.14)**	**−3.804**	**−2.267**	**−0.422**	**.005**	0.997	0.920	1.080	.940
PANSS excited factor	5.73 (2.33)	6.01 (3.07)	−0.988	−0.829	0.274	.324				
PANSS depressed factor	7.17 (3.09)	7.92 (3.73)	−1.863	−1.582	0.083	.077				
PANSS total score	**69.93 (17.93)**	**80.40 (23.97)**	**−3.913**	**−15.784**	**−5.164**	**<.001**				
CDRS score	3.96 (4.21)	4.45 (4.67)	−0.989	−1.458	0.481	.323				
Substance disorders and addictions, n (%)										
Current daily tobacco smoking	311 (53.16)	45 (50.56)	0.210	0.577	1.408	.647				
Current daily cannabis abuse or dependence[c]	80 (13.68)	12 (13.48)	0.002	0.512	1.889	.558				
Current alcohol abuse or dependence[c]	54 (9.23)	7 (7.87)	0.175	0.369	1.908	.843[d]				
Adherence to treatment, mean (SD)										
BARS score	85.80 (24.60)	88.75 (19.99)	−1.229	−7.717	1.804	.221				
MARS score	6.16 (2.24)	6.34 (2.40)	−0.654	−0.695	0.336	.515				
Current treatment										
Second-generation antipsychotic, n (%)	449 (76.75)	64 (71.91)	0.042	0.396	2.119	.838				
First-generation antipsychotic, n (%)	**123 (21.03)**	**31 (34.83)**	**11.023**	**1.402**	**3.898**	**.001**	**2.038**	**1.010**	**4.111**	**.047**
Antipsychotic polytherapy	180 (30.77)	34 (38.20)	3.459	0.972	2.644	.063	0.864	0.441	1.692	.669
Antidepressant drug, n (%)	164 (28.03)	25 (28.09)	0.084	0.642	1.817	.772				
Benzodiazepines, n (%)	136 (23.25)	25 (28.09)	1.566	0.827	2.349	.211				
Anticholinergic drug, n (%)	**88 (15.04)**	**26 (29.21)**	**13.705**	**1.565**	**4.563**	**<.001**	**2.103**	**1.143**	**3.869**	**.017**
Antipsychotic dose (CPZ100eq), mean (SD)	6.07 (6.26)	6.61 (5.90)	−0.677	−2.127	1.037	.499				

[a]Significant associations are in bold.
[b]Drug-induced parkinsonism was defined by a score ≥ 0.65 on the Simpson-Angus Scale.
[c]As defined in the Structured Clinical Interview for *DSM-IV* Disorders.
[d]Fisher exact test.
Abbreviations: aOR = adjusted odds ratio, BARS = Brief Adherence Rating Scale, CDRS = Calgary Depression Scale for Schizophrenia, CPZ100eq = dose equivalent to 100 mg/d of chlorpromazine, MARS = Medication Adherence Rating Scale, PANSS = Positive and Negative Symptoms Scale for Schizophrenia.

characteristics are presented in Table 1. Patients were mostly men (73.3%), the mean age at inclusion was 32.6 years (SD = 9.9), and the mean illness duration was 11.0 years (SD = 8.2). Criteria for current tobacco smoking were met by 52.8% of the patients, and current alcohol and cannabis use disorders were present in, respectively, 9.1% and 13.7%. SGAs were prescribed in 90.8% of patients, 114 (20.2%) patients were administered an anticholinergic drug, and 214 patients (37.9%) were treated with antipsychotic combination therapy.

Drug-Induced Parkinsonism

The global prevalence of DIP in our sample was 13.2% (89/674). In the multivariate analysis, after adjustment for sex, age, disorganization, and antipsychotic polytherapy, DIP remained significantly associated with higher negative symptoms (PANSS subscore, aOR = 1.102 [95% CI, 1.055–1.151], *P* < .001), prescription of FGAs (aOR = 2.038 [1.010–4.111], *P* = .047), and coprescription of an anticholinergic drug (aOR = 2.103 [1.143–3.869], *P* = .017) (Table 2). Concerning the PANSS negative factor, scores on all items, which include N1 (Blunted affect), N2 (Emotional withdrawal), N3 (Poor rapport), N4 (Passive/apathetic social withdrawal), N6 (Lack of spontaneity and flow of conversation), and G7 (Motor retardation), were significantly higher in patients with DIP.

The details of the administered antipsychotics and the related proportions of patients with DIP are presented in Table 3. In the analysis of all drugs, patients with DIP had lower prescription rates of quetiapine than those without DIP (2.2% vs 8.6%, *P* = .047).

Tardive Dyskinesia

The overall prevalence of tardive dyskinesia was 8.3% (56/674). Thirteen patients (1.9%) had both of these 2 extrapyramidal side effects (DIP and TD).

In the multivariate analysis, after adjustment for confounding factors (sex, age, negative symptoms, excitation, FGA prescription, and benzodiazepine and anticholinergic drug administration), TD remained significantly associated with higher disorganization level (PANSS subscore, aOR = 1.103, [1.000–1.217], *P* = .049) (Table 4). The PANSS disorganized factor is composed of P2 (Conceptual disorganization), N5 (Difficulty in abstract thinking), and G11 (Poor attention) items, which were significantly higher in patients with TD.

The TD frequency according to antipsychotic classes is presented in Table 5. In the analysis of all drugs, patients

Table 3. Prevalence of Drug-Induced Parkinsonism (DIP) According to the Administered Drugs in Monotherapy or Polytherapy[a]

	All SGA				Amisulpride				Aripiprazole				Clozapine				Olanzapine				Quetiapine				Risperidone				All FGA			
	Total		DIP		Total		DIP		Total		DIP		Total		DIP		Total		DIP		Total		DIP		Total		DIP		Total		DIP	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Monotherapy	296	53.8	29	9.8	25	59.5	2	8.0	66	51.2	4	6.1	37	44.6	7	**18.9**	50	56.8	5	10.0	29	51.8	1	3.4	89	58.6	10	11.2	26	11.3	5	**19.2**
Polytherapy (overall)	254	46.2	36	**14.2**	17	40.5	3	**17.6**	63	48.8	8	12.7	46	55.4	8	**17.4**	38	43.2	4	10.5	27	48.2	1	3.7	63	41.4	12	**19.0**	204	88.7	32	**15.7**
Polytherapy with SGA (overall)	136	24.7	12	8.8	14	33.3	3	**21.4**	40	31.0	1	2.5	29	34.9	4	**13.8**	16	18.2	1	6.3	11	19.6	0	0	26	17.1	3	11.5	118	51.3	24	**20.3**
Amisulpride	14	2.5	3	**21.4**	…	…	…	…	5	3.9	0	0	5	6.0	2	**40.0**	0	0	0	0	0	0	0	0	4	2.6	1	**25.0**	3	1.3	0	0
Aripiprazole	40	7.3	1	2.5	5	11.9	0	0	…	…	…	…	17	20.5	1	5.9	8	9.1	0	0	4	7.1	0	0	6	3.9	0	0	23	10.0	7	**30.4**
Clozapine	29	5.3	4	**13.8**	5	11.9	2	**40.0**	17	13.2	1	5.9	…	…	…	…	1	1.1	0	0	1	1.8	0	0	5	3.3	1	**20.0**	17	7.4	4	**23.5**
Olanzapine	16	2.9	1	6.3	0	0	0	0	8	6.2	0	0	1	1.2	0	0	…	…	…	…	1	1.8	0	0	6	3.9	1	**16.7**	22	9.6	3	**13.6**
Quetiapine	11	2.0	0	0	0	0	0	0	4	3.1	0	0	1	1.2	0	0	1	1.1	0	0	…	…	…	…	5	3.3	0	0	16	7.0	1	4.5
Risperidone	26	4.7	3	11.5	4	9.5	1	**25.0**	6	4.7	0	0	5	6.0	1	**20.0**	6	6.8	1	**16.7**	5	8.9	0	0	…	…	…	…	37	16.1	9	**24.3**
Polytherapy with FGA (overall)	118	21.5	24	**20.3**	3	7.1	0	0	23	17.8	7	**30.4**	17	20.5	4	**23.5**	22	25.0	3	**13.6**	16	28.6	1	6.3	37	24.3	9	**24.3**	86	37.4	8	9.3
Overall	550	100	65	11.8	42	100	5	11.9	129	100	12	9.3	83	100	15	**18.1**	88	100	9	10.2	56	100	2	3.6	152	100	22	**14.5**	230	100	37	**16.1**

[a]Polytherapies with a DIP rate higher than the global DIP prevalence of our cohort (13.2%) are in bold. Antipsychotic treatment with amisulpride, clozapine, risperidone, or 2 FGAs was associated with higher prevalence of DIP.

Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

with TD had higher prescription rates of chlorpromazine (3.6% vs 0.3%, $P = .032$) and haloperidol (16.1% vs 7%, $P = .013$) than those without TD.

DISCUSSION

Our major findings may be summarized as follows: the overall prevalence of DIP and TD was, respectively, 13.2% and 8.3% in a national stabilized community-dwelling sample of 674 outpatients with schizophrenia. After adjustment for confounding factors, DIP remained significantly associated with higher negative symptoms level, FGA treatment, and anticholinergic administration, while TD remained significantly associated only with higher disorganization symptoms level.

The DIP rate of 13.2% found in this study is the lowest rate of all published studies to date (with DIP ranging from 14% to 40%[6,31–34]). The different scales and thresholds, different treatments, and different population characteristics may explain this discrepancy. In the current study, the threshold of 0.65 was used to increase the scale's specificity (62%).[29] This choice may contribute to an underestimation of DIP prevalence in this sample of community-dwelling stabilized outpatients. DIP has been previously associated with antipsychotic daily dose.[34] However, antipsychotic daily dose was not associated with higher DIP rates in our results, which suggests that other factors may be involved, including other psychotropic drugs, addictive behavior (such as tobacco smoking), lifestyle habits, and diet. The young mean age and the high proportion of men in our cohort may explain our low prevalence, which could be a limitation. No association of tobacco smoking with DIP was found in the present study, which is not consistent with previous studies suggesting that an inducer effect of daily tobacco smoking may lower the blood antipsychotic level.[35,36]

The present results confirm that the risk for DIP was associated with current FGA administration in real-world schizophrenia. This finding is consistent with the results of a large meta-analysis including only randomized controlled trials with highly selected patients (ie, with good compliance and without comorbidities and suicide risk).[16] Our descriptive analyses show that patients with DIP are most often (56.4%) treated with antipsychotic combination therapy (18.2% with an FGA/FGA combination, 27.3% with an SGA/SGA combination, and 54.5% with an FGA/SGA combination), and 43.6% are treated with a single antipsychotic (14.7% with an FGA monotherapy and 85.3% with an SGA monotherapy). While these results are only cross-sectional, it may be reasonably suggested that antipsychotic combination should be avoided as soon as possible in patients with DIP, especially when associated with negative symptoms. Polytherapy has never, to date, been associated with higher effectiveness,[37] which suggests that the benefit/risk ratio is in favor of monotherapy, especially in cases of DIP and negative symptoms. Future interventional studies should determine if switching from polytherapy to antipsychotic monotherapy might alleviate both DIP and negative symptoms.

Patients with anticholinergic treatment had significantly more DIP. This result is plausibly due to the prescription bias: patients with higher DIP are more prone to being prescribed anticholinergic medication by their psychiatrists. However, these results suggest that anticholinergics are not sufficient to correct DIP in real-world patients with schizophrenia, due to potential underdosage or insufficient effectiveness. This result is consistent with the results from a recent meta-analysis,[16] which found that clozapine and olanzapine induced significantly fewer EPS than the FGA-anticholinergic association. Moreover, anticholinergic drugs have been associated with cognitive impairment in patients with schizophrenia.[38]

Table 4. Factors Associated With Tardive Dyskinesia (TD) According to the Abnormal Involuntary Movement Scale in a Sample of 674 Patients With Schizophrenia[a]

	Univariate Analysis						Multivariate Model			
	No TD (n = 618)	TD[b] (n = 56)	t/χ^2	95% CI		*P*	aOR	95% CI		*P*
Sociodemographic characteristics										
Sex, male, n (%)	455 (73.62)	39 (69.64)	0.416	0.670	2.211	.519	0.882	0.421	1.848	.740
Age, mean (SD), y	32.51 (9.76)	33.86 (11.23)	−0.972	−4.053	1.368	.331	1.008	0.976	1.041	.633
Clinical variables, mean (SD)										
Illness duration, y	10.87 (8.13)	12.15 (9.41)	−1.088	−3.605	1.035	.277				
PANSS positive factor	9.32 (4.37)	9.43 (4.67)	−0.369	−1.328	1.124	.870				
PANSS negative factor	**17.24 (6.56)**	**20.54 (6.57)**	**−3.045**	**−5.125**	**−1.465**	**<.001**	1.037	0.988	1.090	.144
PANSS disorganized factor	**8.16 (3.41)**	**10.15 (3.90)**	**−4.708**	**−2.946**	**−1.021**	**<.001**	**1.103**	**1.000**	**1.217**	**.049**
PANSS excited factor	5.71 (2.40)	6.48 (2.81)	−1.960	−1.564	0.016	.055	0.978	0.860	1.112	.736
PANSS depressed factor	7.29 (3.17)	7.07 (3.38)	−0.308	−0.678	1.101	.641				
PANSS total score	**70.61 (18.87)**	**79.18 (20.66)**	**−3.174**	**−13.881**	**−3.271**	**.002**				
CDRS score	4.03 (4.24)	3.96 (4.63)	0.118	−1.130	1.274	.906				
Substance disorders and addictions, n (%)										
Current daily tobacco smoking	328 (53.07)	28 (50.00)	0.195	0.512	1.528	.659				
Current daily cannabis abuse or dependence[c]	86 (13.92)	6 (10.71)	0.447	0.309	1.784	.684[d]				
Current alcohol abuse or dependence[c]	56 (9.06)	5 (8.93)	0.001	0.377	2.566	1.000[d]				
Adherence to treatment, mean (SD)										
BARS score	86.39 (23.76)	83.87 (27.21)	0.732	−4.248	9.301	.464				
MARS score	6.17 (2.27)	6.33 (2.16)	−0.498	−0.814	0.484	.619				
Current treatment										
Second-generation antipsychotic, n (%)	474 (76.70)	39 (69.64)	0.266	0.291	2.057	.606				
First-generation antipsychotic, n (%)	137 (22.17)	17 (30.36)	3.116	0.933	3.338	.078	1.263	0.603	2.642	.536
Antipsychotic polytherapy, n (%)	196 (31.72)	18 (32.14)	0.187	0.613	2.148	.666				
Antidepressant drug, n (%)	175 (28.32)	14 (25.00)	0.042	0.482	1.805	1.000				
Benzodiazepines, n (%)	**142 (22.98)**	**19 (33.93)**	**4.822**	**1.066**	**3.700**	**.028**	1.568	0.793	3.099	.196
Anticholinergic drug, n (%)	**100 (16.18)**	**14 (25.00)**	**4.044**	**1.007**	**3.852**	**.044**	1.349	0.635	2.867	.437
Antipsychotic dose (CPZ100eq), mean (SD)	5.99 (5.72)	7.85 (10.28)	−1.125	−5.182	1.475	.267				

[a]Significant associations are in bold.
[b]Tardive dyskinesia was defined by a score of at least 3 (moderate degree) in any body part or with at least 2 (mild degree) in 2 or more body parts on the Abnormal Involuntary Movement Scale (Schooler-Kane criteria).
[c]As defined in the Structured Clinical Interview for *DSM-IV* Disorders.
[d]Fisher exact test.
Abbreviations: aOR = adjusted odds ratio, BARS = Brief Adherence Rating Scale, CDRS = Calgary Depression Scale for Schizophrenia, CPZ100eq = dose equivalent to 100 mg/d of chlorpromazine, MARS = Medication Adherence Rating Scale, PANSS = Positive And Negative Syndrome Scale for Schizophrenia.

Altogether, these results suggest that if persistent DIP occurs during FGA and anticholinergic drug prescription, the treatment should be switched to SGA if possible.

DIP has been associated with higher negative symptoms in the present sample, which is consistent with the results of previous studies. This co-occurrence has been suggested to be due to a common neurobiological basis.[39,40] The strong associations between negative and motor features in antipsychotic-treated subjects may be explained by drug-induced negative symptoms and motor signs as a consequence of drug-related dopamine blockade[41] with a possible direct neurotoxic effect of antipsychotics on dopamine neurons.[42] Motor symptoms may be related to the dysfunction of the nigrostriatal dopaminergic system, while negative symptoms may be the consequence of blocking receptors of the meso-cortico-limbic dopaminergic system. Beyond motor symptoms, patients with Parkinson's disease also show bradyphrenia (G7), as well as many of the negative symptoms (N1 [Blunted affect], N2 [Emotional withdrawal], N4 [Passive/apathetic social withdrawal], N5 [Difficulty in abstract thinking], and N6 [Lack of spontaneity and flow of conversation]), at least in part because of impaired function of meso-cortico-limbic neurons. Similarly to Parkinson's disease, degeneration of dopaminergic neurons has been identified in 45% of patients with schizophrenia with a 2-year single-photon emission computerized tomography follow-up, which suggested the potential benefit of levodopa therapy in this subgroup.[9]

The TD rate was 8.3% in the present study, and 27.2% of this sample was currently prescribed at least 1 FGA. The prevalence of TD was lower than expected, which may be due to sociodemographic characteristics, especially the relatively young age of the sample (mean age of 32.6 years). Younger age may also explain the absence of significant association between TD and age in the present sample, which is inconsistent with previous results.[15,20,43] In a recent meta-analysis including 41 studies (11,493 patients, mean age = 42.8 years) using the same scale and cutoff (AIMS with Schooler-Kane criteria), the global mean TD prevalence was 25.3% (95% CI = 22.7%–28.1%) vs 7.2% in the 4 studies including only FGA-naive patients.[20] The present study did not report the lifetime prescription of antipsychotic, which is a limitation. Future studies should include the lifetime number of antipsychotic treatments and the mean dose/mean duration of exposure for each antipsychotic treatment. Altogether, these studies combined with the present study

Table 5. Prevalence of Tardive Dyskinesia According to the Administered Drugs in Monotherapy or Polytherapy[a]

	All SGA				Amisulpride				Aripiprazole				Clozapine				Olanzapine				Quetiapine				Risperidone				All FGA			
	Total		TD		Total		TD		Total		TD		Total		TD		Total		TD		Total		TD		Total		TD		Total		TD	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Monotherapy	296	53.8	21	7.1	25	59.5	4	**16.0**	66	51.2	3	4.5	37	44.6	3	8.1	50	56.8	1	2.0	29	51.8	3	**10.3**	89	58.6	7	7.9	26	11.3	3	**11.5**
Polytherapy (overall)	254	46.2	17	6.7	17	40.5	0	0	63	48.8	3	4.8	46	55.4	2	4.3	38	43.2	3	7.9	27	48.2	4	**14.8**	63	41.4	5	7.9	204	88.7	17	**8.3**
Polytherapy with SGA (overall)	136	24.7	4	2.9	14	33.3	0	0	40	31.0	2	5.0	29	34.9	1	3.4	16	18.2	0	0	11	19.6	0	0	26	17.1	1	3.8	118	51.3	13	**11.0**
Amisulpride	14	2.5	0	0	…	…	…	…	5	3.9	0	0	5	6.0	0	0	0	0	0	0	0	0	0	0	4	2.6	0	0	3	1.3	0	0
Aripiprazole	40	7.3	2	5.0	5	11.9	0	0	…	…	…	…	17	20.5	1	5.9	8	9.1	0	0	4	7.1	0	0	6	3.9	1	**16.7**	23	10.0	1	4.3
Clozapine	29	5.3	1	3.4	5	11.9	0	0	17	13.2	1	5.9	…	…	…	…	1	1.1	0	0	1	1.8	0	0	5	3.3	0	0	17	7.4	1	5.9
Olanzapine	16	2.9	0	0	0	0	0	0	8	6.2	0	0	1	1.2	0	0	…	…	…	…	1	1.8	0	0	6	3.9	0	0	22	9.6	3	**13.6**
Quetiapine	11	2.0	0	0	0	0	0	0	4	3.1	0	0	1	1.2	0	0	1	1.1	0	0	…	…	…	…	5	3.3	0	0	16	7.0	4	**25.0**
Risperidone	26	4.7	1	3.8	4	9.5	0	0	6	4.7	1	**16.7**	5	6.0	0	0	6	6.8	0	0	5	8.9	0	0	…	…	…	…	37	16.1	4	**10.8**
Polytherapy with FGA (overall)	118	21.5	13	**11.0**	3	7.1	0	0	23	17.8	1	4.3	17	20.5	1	5.9	22	25.0	3	**13.6**	16	28.6	4	**25.0**	37	24.3	4	**10.8**	86	37.4	4	4.7
Overall	550	100	38	6.9	42	100	4	**9.5**	129	100	6	4.7	83	100	5	6.0	88	100	4	4.5	56	100	7	**12.5**	152	100	12	7.9	230	100	20	**8.7**

[a]Polytherapies with a TD rate higher than the global TD prevalence of our cohort (8.3%) are in bold. Antipsychotic treatment with amisulpride, 2 FGAs, FGA/risperidone, and FGA/olanzapine was associated with higher prevalence of TD.
Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic, TD = tardive dyskinesia.

underlie the difficulty of defining and assessing TD.[44] These inconsistent results are due to differences in factors including population age (higher age), sex, region (high geographical variation), medication type and dosing (higher rates during FGA than SGA treatment), and illness and treatment duration.[15,20,43] The prevalence of EPS should be interpreted in relation to the relatively low illness duration in the present sample (11 years). TD has been shown to increase with age and lifetime duration of antipsychotic treatment.[15,20] No gender effect has been found in the present study, which is consistent with previous findings.[20,45]

TD was associated with higher disorganized/cognitive score in the current study.[23] This factor was highly correlated with cognitive functions evaluated with the Wechsler Adult Intelligence Scale IQ and general cognitive ability.[23] This is consistent with previous studies suggesting that TD was associated with cognitive impairment such as orientation, memory, silence, attention, and muteness in schizophrenia.[44,46–48] It has been suggested that this association was mediated by decreased brain-derived neurotrophic factor, which may play a critical role in cognitive function and may reflect a compensatory response to severe cerebral damages.[49,50] Future studies should explore the specific cognitive functions associated with TD in real-world schizophrenia and determine which intervention may be effective in improving both TD and cognitive functioning in patients suffering from schizophrenia with TD. It has been hypothesized that TD may result primarily from antipsychotics' induced dopamine supersensitivity in the nigrostriatal pathway (D_2 dopamine receptor).[51] This would be consistent with observations of Parkinson's disease in which dyskinesia is induced by an "overdose" of dopaminergic treatment, which may also result in positive psychotic symptoms.[52] Cognitive evaluations should be carefully evaluated when evaluating the benefit/risk ratio of switching or adjusting antipsychotic treatment in cases of iatrogenic TD.

Our study has several limitations. The cross-sectional design does not allow us to infer the causal nature of the observed associations. Secondary negative symptoms were not differentiated from primary negative symptoms in the present study. Differentiating primary from secondary negative symptoms remains difficult in populations with long duration of illness due to the memory bias and is adjusted for in prospective studies. No significant associations were found between EPS and depression (CDRS). Previous studies suggested that antipsychotics could increase depressive symptoms due to their D_2 high affinity,[18] and this point should be explored in future studies. As mentioned above, lifetime exposure to antipsychotics was not reported due to memory bias, as some patients had more than 10 years of illness duration.[45] Finally, parkinsonism was defined according to the SAS score based on trained clinician assessment. A DaTscan examination should be considered in future studies for patients with DIP or TD to confirm alterations in dopamine circuits and discriminate DIP from other causes of parkinsonism including Parkinson's disease.

CONCLUSION

The present findings suggest a high prevalence of DIP and TD in a relatively young sample of patients with schizophrenia with a mean illness duration of approximately 11 years and a complex association of negative (for DIP) and disorganized/cognitive (for TD) symptomatology. More than one-fourth of the patients were administered at least 1 FGA, and these patients were found to have higher DIP levels despite the prescription of anticholinergic medications. The present findings indicate that the choice of monotherapy with SGAs should be recommended as soon as possible to prevent EPS onset in patients with schizophrenia.

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POSTTEST

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1. **Extrapyramidal side effects (EPS), including drug-induced parkinsonism (DIP) and tardive dyskinesia (TD), are a frequent complication of antipsychotic treatment. Which statement below is *true*?**
   a. In clinical trials, second-generation antipsychotics (SGAs) have been found to be associated with more EPS than first-generation antipsychotics (FGAs)
   b. TD usually occurs after about one month of treatment
   c. DIP occurs after a relatively short period of antipsychotic treatment and requires a systematic clinical examination for bradykinesia, rigidity, and tremor
   d. DIP is defined by involuntary, repetitive orofacial movements
2. **According to the results of this study, the prevalence of DIP and TD in community-dwelling patients with stable schizophrenia is 13.2% and 8.3%, respectively. Which risk factors are significantly linked with DIP in the current study?**
   a. Substance use disorders and treatment adherence rates
   b. Sex and age
   c. Higher level of depression and longer illness duration
   d. Greater negative symptoms, prescription of FGAs, and coprescription of an anticholinergic medication
3. **A 35-year-old male patient with schizophrenia is treated by a combination of two antipsychotics, and he presents with symptoms of severe rigidity and tremor. After an attentive clinical examination, you retain the diagnosis of DIP. After a first prescription of anticholinergic medication, symptoms of DIP are reduced but still present. Among the following proposals, which one describes the *best* next strategy, according to the present study?**
   a. Maintain the combination of antipsychotics and the anticholinergic drug and explain to the patient how to manage the side effects
   b. Propose a trial of SGA monotherapy with a monthly examination of DIP symptom severity
   c. Stop the antipsychotic medications until needed again for positive symptoms