Extrapyramidal side effects of antipsychotics: prevalence and risk factors. Results from the national FACE-SZ cohort Cover title Extrapyramidal side effects and antipsychotics

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Title page

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Cover title

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Words count

Total word count for the manuscript: 2651 words

Total word count for abstract: 246 words

Keywords

Schizophrenia; Antipsychotic; Side-effects; Extrapyramidal symptoms; Tardive dyskinesia

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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.

Objectives: To examine the prevalence and clinical correlates associated with EPS in a non-selected national multicentric sample of stabilized patients with schizophrenia.

Method: Between 2010 and 2016,patients suffering from schizophrenia (DSM-IV-TR) 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 and Angus Scale and the Abnormal Involuntary Movement Scale were used to assess respectively Drug-Induced Parkinsonism (DIP) and Tardive Dyskinesia (TD).

Results: The overall prevalence of DIP and TD was respectively 13.2% and 8.3% in our community-dwelling sample of 674 patients. DIP was associated with negative symptoms (PANSS sub-score) (aOR = 1.102, p<.001), First Generation Antipsychotic (FGA) (aOR = 2.038, p=.047) and anticholinergic drug administration (aOR = 2.103, p=.017) independently of sex, age, disorganization, and antipsychotic polytherapy. TD was associated with PANSS disorganized factor (aOR = 1.103, p=.049) independently of sex, age, negative symptoms, excitation, first-generation antipsychotic, benzodiazepine and anticholinergic drug administration.

Conclusion: Our results indicate the high prevalence of EPS in a non-selected community-dwelling clinically stable sample of outpatients with schizophrenia. EPS should be systematically evaluated, especially in case of negative symptoms and disorganization or cognitive alteration in the monitoring of antipsychotic treatment. Monotherapy with an SGA should be preferentially initiated for patients with these sides-effects.

Introduction

Extrapyramidal side effects including Drug Induced Parkinsonism (DIP) and Tardive Dyskinesia (TD) were 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 recover within a few months after medication withdrawal [8], while it 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 two comprehensive meta-analyses including clinical trials to compare second-generation antipsychotics (SGA) with FGA [16,17]. Overall, SGA 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 drug comorbidities, especially daily tobacco smoking that may impact antipsychotic blood 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 non-selected national sample of stabilized community-dwelling outpatients with schizophrenia.

Method

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 created by the French Ministry of Research in order 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. The 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 18th, 2010). All subjects gave their informed consent prior to their inclusion in the study.

Data collection

Socio demographic and clinical variables

Clinical and socio-demographic 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 purpose of this study and to explore specifically depressive and cognitive symptoms, we used the validated five-factor model of the PANSS [23] described as follows: ‘‘positive symptoms”; ‘‘negative symptoms”; disorganized/concrete factor accounted for the largest share with cognition (IQ); ‘‘excitement” and ‘‘depression”. Depressive symptoms were also assessed with the French-validated Calgary Depression Rating Scale for Schizophrenia (CDRS) [24]. A cut-off of 6 was considered as a current major depressive episode. Treatment adherence was evaluated using the Brief Adherence Rating Scale (BARS) [25] and the Medication Adherence Rating Scale [26]. Daily tobacco smoking,

alcohol and cannabis use disorder was defined according to SCID 1.0. Ongoing type and number of psychotropic treatment was recorded (antipsychotics, antidepressant, benzodiazepines and anticholinergic). 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 (DIP)

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

Tardive Dyskinesia (TD)

The Abnormal Involuntary Movement Scale (AIMS) is a 10-item scale designed to record the occurrence of dyskinetic movements, which was used to assess the incidence of TD [30]. Items evaluate dyskinetic movements in three 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. Dyskinesia was classified as present in a particular subject with an AIMS score of at least three (moderate degree) in any body part or with at least two (mild degree) in two or more body parts (Schooler-Kane criteria) [20]. Each item on the AIMS ranges from 0 to 4, and the total AIMS score was calculated by adding items 1–7.

Statistical Analysis

The socio-demographic and clinical characteristics, presence of substance use disorder, medications, and the scores for each scale were compared between the two groups for each side-effect studied (“DIP” vs “No DIP” and “TD” vs “No TD”) using the Student’s t-test for continuous variables and Chi-squared test for categorical variables. A logistic regression analysis was used to estimate the odd ratios (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 odd ratios (aOR) with 95% confidence interval. An aOR > 1 was considered as an increased risk factor for the presence of studied side effect, and an aOR < 1 as a protective risk factor for studied side-effects. The statistical significance level was set at $p = 0.05$ in a two-sided test. Data were analyzed using SPSS 20.0 software.

Results

Sample characteristics

Altogether, 674 outpatients suffering from schizophrenia were included in this study. Clinical and demographic characteristics are presented in Table 1. Patients were mostly men (73.3%), the average age at inclusion was 32.6 years (SD = 9.9) and the mean illness duration was 11.0 years (SD = 8.2). 52.8% were current tobacco smokers, and current alcohol and cannabis use disorders accounted respectively for 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, [1.055–1.151], p < .001), prescription of FGA (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 2a). Concerning PANSS negative factor, 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) items) scored significantly higher in patients with DIP.

The detail of the administered antipsychotics and the related proportion of patients with DIP are presented in Table 2b. By analyzing all drugs, only quetiapine was associated with a lower rate of 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 these two extrapyramidal side effects (DIP and TD).

In the multivariate analysis, after adjustment for confounding factors (sex, age, negative symptoms, excitation, FGA, benzodiazepine and anticholinergic drug administration), TD remained

significantly associated with higher disorganization level (PANSS sub score, aOR = 1.103, [1.000–1.217], p = .049) (Table 3a). The PANSS disorganized factor is composed of P2 (Conceptual disorganization), N5 (Difficulty in abstract thinking) and G11 (Poor attention) items, which were are significantly higher in patients with TD.

The TD frequency according to antipsychotic classes is presented in Table 3b. By analyzing all drugs, patients with TD had a higher prescription rate 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 and anticholinergic administration while TD remained only significantly associated with higher disorganization symptoms level.

The DIP rate was 13.2 % in the present study. This is the lower 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 populations' 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.

The present results confirm that the risk for DIP was associated with current FGA administration in real-world schizophrenia. This is consistent with the results of a large meta-analysis including only randomized controlled trials with highly-selected patients (i.e. with good compliance and without comorbidities and suicide risk) [16]. Descriptive analyses show that patients with DIP are mostly (56.4%) treated with antipsychotic combination therapy (18.2% with a FGA/FGA combination, 27.3% with a SGA/SGA combination and 54.5% with a FGA/SGA combination), and 43.6% with a single antipsychotic (14.7% with a FGA monotherapy and 85.3% with a 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 been associated with higher effectiveness to date [35], 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 be prescribed anticholinergic by their psychiatrists. However, these results suggest that anticholinergics are not sufficient to correct DIP

in real-world SZ subjects, due to a potential under-dosage 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 DIP than the FGA-anticholinergic association. Moreover, anticholinergic drugs have been associated with cognitive impairment in SZ subjects [36]. Altogether, these results suggest that in case of persistent DIP under 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 [11,37]. This co-occurrence has been suggested to be due to a common neurobiological basis [38,39]. 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 [40] with a possible direct neurotoxic effect of antipsychotics on dopamine neurons [41]. 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), 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, dopaminergic neurons degeneration has been identified in 45% SZ subjects with a two years SPECT follow-up, which suggested the potential benefit of levodopa therapy in this subgroup [9].

In a recent meta-analysis including 41 studies (11,493 patients, mean age = 42.8 years) using the same scale and cut-off (AIMS with Schooler-Kane criteria) [20], the global mean TD prevalence was 25.3% (95% CI = 22.7%–28.1%) vs. 7.2% in the four studies including only FGA-naive patients. In the present sample, 27.2% of the sample was currently prescribed at least one FGA, however the TD prevalence was only 8.3%. The prevalence of TD was therefore lower than expected in the present sample, which may be due to sociodemographic characteristics, especially the relatively young age of the present sample (32.6 years). This may also explain the absence of significant association between

TD and age in the present sample, which is inconsistent with previous results [15,20,42]. The present study did not report the lifetime prescription of antipsychotic, which is a limit. Future studies should include the total number of antipsychotic treatment and the mean dose / mean duration of exposure for each antipsychotic treatment. Altogether, these studies combined with the present study underlie the difficulty to define and assess TD [43]. These inconsistent results are due to the differences of the following factors including population age (higher age), sex, region (high geographical variation), medication type and dosing (higher rates during FGA than during SGA treatment), duration of treatment, the duration of illness [20].

TD has been associated with higher disorganized/cognitive score in the current study [23]. This factor was highly correlated with cognitive functions evaluated with the WAIS 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 [44–47]. It has been suggested that this association was mediated by decreased Brain-Derived Neurotrophic Factor (BDNF), which may play a critical role in cognitive function and may reflect a compensatory response to severe cerebral damages [48,49]. 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 SZ subjects with TD. It has been hypothesized that TD may result primarily from antipsychotics' induced dopamine supersensitivity in the nigrostriatal pathway (D2 dopamine receptor) [50]. 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 [51]. Cognitive evaluations should be carefully evaluated when evaluating the benefit/risk ratio of switching or adjusting antipsychotic treatment in case 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 have not been 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 adapted for prospective studies. As above-mentioned, lifetime exposure to antipsychotics was not reported due to memory bias, as some patients had more than 10 years of illness duration.

Conclusion

The present findings suggest a high prevalence of DIP and TD in a relatively young sample of SZ subjects with a mean illness duration of almost 11 years, as well as a complex relationship with respectively negative (for DIP) and disorganized/cognitive (for TD) symptomatology. More than one quarter of the subjects were administered FGA, and were found to have higher DIP levels despite of the prescription of anticholinergic drugs. SGA monotherapy appears to be the best strategy to date to improve DIP in SZ subjects. The benefit-risk ratio of switching the treatment for SGA monotherapy should be carefully evaluated in case of DIP and/or TD in patients with FGA and/or anticholinergic drug prescription.

Clinical Points:

Statements

Acknowledgments and funding source

This work was funded by the hospital Charles-Perrens, by the AP-HP (Assistance Publique des Hôpitaux de Paris), AP-HM (Assistance Publique des Hôpitaux de Marseille), Fondation FondaMental (RTRS Santé Mentale), by the Investissements d'Avenir program managed by the ANR under reference ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01, and by INSERM (Institut National de la Santé et de la Recherche Médicale). We express all our thanks to the nurses, and to the patients who were included in the present study. We thank Hakim Laouamri M.Sc (FondaMental Foundation), and his team (Stéphane Beaufort, M.Sc; Seif Ben Salem, M.Sc; Karmène Souyris, M.Sc; Victor Barteau, M.Sc; and Mohamed Laaidi, M.Sc) for the development of the FACE-SZ computer interface, data management, quality control and regulatory aspects. Thanks for critical reading and the neurological point of view to Prof. François Tison (MD, PhD) and Prof. Dominique Guehl (MD, PhD) of Bordeaux University Hospital. All these peoples reports no conflicts of interest with this study.

Role of the funding agency

Fondation Fondamental (RTRS Santé Mentale) provided data management support. Hospital Charles-Perrens, AP-HP (Assistance Publique des Hôpitaux de Paris), AP-HM (Assistance Publique des Hôpitaux de Marseille) and Investissements d'Avenir program had no role in the conduct or publication of the study.

Conflicts of interest

None

Contributors

AT and AD performed the statistical analysis. AT, AD and DM wrote the first complete manuscript. PML, GF and WGM edited earlier versions of the manuscript for important intellectual content. All authors were involved in the patients' recruitment, the clinical evaluation, acquisition of the clinical data and approved the final manuscript.

Patient consent

All subjects gave their informed consent prior to their inclusion in the study.

Ethics approval

The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18th, 2010). This study has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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