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Correlates and predictors of antipsychotic drug polypharmacy in real-life settings: Results from a nationwide cohort study

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ABSTRACT

Reasons for using antipsychotic polypharmacy (APP) in routine clinical practice, despite a potentially unfavorable risk-benefit ratio, are poorly understood. This research aimed to determine (1) if severe courses of schizophrenia were associated with APP and (2) if a schizophrenia-related acute event would predict a switch to APP in the short term. Observational prospective data (at baseline and 6 months) were drawn from a French nationwide cohort ("*Cohorte Générale Schizophrénie*"), which included 1859 inpatients and outpatients with schizophrenia. APP was defined as the prescription of ≥2 antipsychotic drugs (there being different active substances). Early-onset schizophrenia, legal guardianship, higher lifetime maximal severity of illness and comorbid antisocial personality were used as proxies for severe courses of schizophrenia. Schizophrenia-related acute events included hospitalization and recent suicide attempts. Logistic regression models were used to determine (1) whether the use of APP at baseline (vs. monotherapy) was associated with a severe course of schizophrenia or not, independent of acute events, and (2) if a switch to APP at 6 months (vs. remaining on monotherapy) was associated with acute events, independent of severe courses of schizophrenia. Increased odds of APP use at baseline were independently associated with legal guardianship (OR = 1.6; 95%CI = 1.3, 2.0) and higher lifetime maximum severity of illness (OR = 1.3; 95%CI = 1.2, 1.5). A switch to APP at 6 months was predicted by a hospitalization occurring since baseline (OR = 6.1; 95%CI = 3.9, 9.4). In routine clinical practice, APP is more likely prescribed to patients with severe courses of illness, possibly indicating the difficulty to manage these patients.

1. Introduction

Schizophrenia presents most often as a chronic illness where acute relapses alternate with remission phases, and in which antipsychotic drugs play a central role. Antipsychotic polypharmacy (APP), defined as the simultaneous use of two antipsychotic drugs or more, is common practice in schizophrenia treatment with an estimated prevalence rate ranging from 10% to 70% of patients (Fisher et al., 2014; Gallego et al., 2012; Gaviria et al., 2015; Hou et al., 2016), depending on the clinical setting, the population and the method used. Reported figures point to an increase in APP use over recent decades (Gallego et al., 2012). Nonetheless, international guidelines advocate the use of monotherapy for both short and long-term management of schizophrenia (Hasan et al., 2012, 2013), owing to the risk of incurring interaction with other medications and the increased risk of serious adverse events associated to higher total doses of antipsychotics (Fleischhacker and Uchida, 2014; Hou et al., 2016). The prevalence of APP worldwide calls for a better understanding of the reasons for using APP in routine clinical practice despite a potentially unfavorable risk-benefit ratio. Numerous studies have investigated the efficacy, effectiveness and correlates of APP (Correll and Gallego, 2012). In a meta-analysis of 19 randomized-controlled trials, APP was found to be more efficacious than monotherapy in terms of symptoms improvement (Correll et al., 2009). Observational studies suggest that APP is superior to monotherapy in regard to mortality or hospitalization rates (Katona et al., 2014) but there is no time saving in terms of antipsychotic drug discontinuation (Fisher et al., 2014). Switching patients in a stable clinical condition, from APP to monotherapy was found to increase the severity of symptoms in the long term

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(Constantine et al., 2015), but a recent systematic review suggests that reducing APP is feasible and safe in most patients with schizophrenia (Tani et al., 2013). In terms of patients' characteristics, APP was found to be associated with younger age (Kadra et al., 2016), male gender (Suokas et al., 2013), living alone (Sneider et al., 2015), inpatient status, use of first-generation antipsychotics (FGA) (Gallego et al., 2012), or prescriptions of other psychotropic drugs (Gaviria et al., 2015; Sneider et al., 2015). Some of these characteristics may act as proxies for a more severe form of schizophrenia (e.g., living alone) whereas others may reflect acute relapses (e.g., inpatient status). In other words, it is unclear if APP is related to more severe courses of illness or acute phases, or both.

The present study set out to gain insight into correlates of APP while aiming to find out why – and/or when – APP was initiated. The objectives were to explore whether a more severe course of illness is associated with APP or not, and if acute events might predict a switch to APP in the short term.

2. Material and methods

2.1. Study design and data source and study sample

The study used data from the prospective observational "*Cohorte Générale Schizophrénie*" (CGS) cohort. Briefly, the CGS study measured the effectiveness of antipsychotic drugs in patients with schizophrenia from across France, with a focus on risperidone long-acting injectable (RLAI) (Grimaldi-Bensouda et al., 2012). Between December 2005 and July 2007, 1859 patients fulfilling DSM-IV criteria for schizophrenia, aged between 15 and 65 years, hospitalized for ≤3 months or followed as outpatients were recruited by psychiatrists working in 177 public or private psychiatric hospitals across continental France. Patients were not included if at high risk of fatality in the short term, not covered by Social Security, unable to understand French or were already participating in another study. All data were collected by psychiatrists at baseline and then every 6 months for 24 months. The present study used data collected at baseline and at the first follow-up visit (6 months) for the analyses, in order to minimize any impact of cohort attrition on the statistical power.

The study was conducted in accordance with the ethical principles regarding human experimentation as set out in the Declaration of Helsinki and was approved by both relevant French Ethics Committees (privacy and data protection authority and the advisory committee on medical research) and the French national board of physicians. Informed consent was obtained from patients or from the patient's guardian.

2.2. Data collection and measurement tools

Baseline data included socio-demographics (age, gender, educational level, employment status, living situation, and legal guardianship if any), psychiatric and medical comorbidities, lifetime history of illness (age at first psychotic symptoms, lifetime maximum severity of symptoms, as estimated by the psychiatrist and rated using the Clinical Global Impression-Severity scale – CGI-S – (Guy, 1976)) and recent history of illness (suicide attempt in the past month (yes/no), number of hospitalizations for schizophrenia and clozapine prescription over the past 12 months). Data collected at baseline and every 6 months included: current symptom severity, global functioning, psychotropic medication (antipsychotic, mode of administration and dosage, other psychotropic drugs), and hospitalization status. The fact that the CGS study objectives required oversampling patients on risperidone at baseline, explains why this antipsychotic drug accounted for about 50% of prescriptions. Antipsychotic drugs were categorized by type (first- or second-generation antipsychotics, FGA/SGA hereafter) and active substance; the type of action was further specified as short- or long-acting antipsychotics.

The Mini-International Neuropsychiatric Interview (MINI) (Lecrubier et al., 2006) was used to screen psychiatric comorbidities at baseline. Symptom severity at the time of collection of data was quantified using the 7-point CGI-S, and the 18-item Brief Psychiatric Rating Score scale (BPRS-18) (Overall and Gorham, 1962); higher scores indicate more severe symptoms for both scales.

2.3. Outcome measures

The primary outcome was "being on APP at baseline" (compared to monotherapy), defined as having a prescription of ≥2 antipsychotics identified by generic name and regardless of the mode of administration (e.g., oral haloperidol and injectable haloperidol counted as one single antipsychotic drug). The secondary outcome was a switch to APP at 6 months (compared to remaining on monotherapy), defined as APP at 6 months in patients using monotherapy at baseline.

2.4. Explanatory variables

Variables potentially reflecting a more severe course of schizophrenia were defined a priori based on clinical assumptions and predictors of treatment-resistant schizophrenia, reported in the literature: (1) early-onset schizophrenia defined as age at onset (first psychotic symptoms) <15 years (Clemmensen et al., 2012; Wimberley et al., 2016); (2) legal guardianship; (3) highest lifetime severity of illness (rated using the CGI-S); and (4) antisocial personality disorder (Wimberley et al., 2016). Schizophrenia relapse was defined as a hospitalization with a concomitant CGI-S score ≥ 6 (Olivares et al., 2013). Other significant acute events included a suicide attempt within the last month (when measured at baseline) or within the last 6 months (when measured at any 6-month interval).

2.5. Statistical analyses

Statistical analyses were performed using the Statistical Analysis System software v9.4 (The SAS Institute Inc., 2008). All tests were two-sided and used a type-1 error $\alpha = 0.05$.

2.5.1. Correlates of APP

Patients not taking antipsychotic drugs at baseline were excluded from the analysis datasets. To explore the correlates of APP prescription (vs. monotherapy) at baseline, we performed cross-sectional analyses using univariate and multivariable logistic regression models. We hypothesized that more severe courses of schizophrenia would be associated with increased odds of APP prescription, independent of acute events. First, four univariate regression models were built with APP (vs. monotherapy) as the dependent variable and the four potential indicators of a more severe course of schizophrenia – 1) early-onset schizophrenia; 2) legal guardianship; 3) highest lifetime severity of illness; and 4) antisocial personality disorder – were tested as independent variables. Those indicators found to be associated with the outcome in univariate analyses ($p < 0.05$) were entered in a multivariable model, in order to explore their independent effect. The model was also adjusted on potential confounding variables identified a priori, based on clinical assumptions and/or data from the literature: age (Kadra et al., 2016), gender (Suokas et al., 2013), schizophrenia relapse, recent suicide attempt, using at least one SGA (Gallego et al., 2012), using at least one long-acting antipsychotic drug, and a prescription of other psychotropic drugs (antidepressants, mood stabilizers and anxiolytics) (Gaviria et al., 2015; Sneider et al., 2015). Collinearity between factors (severe course of schizophrenia) was tested.

2.5.2. Predictors of switch to APP at 6 months

To explore if a hospitalization or suicide attempt could predict a switch to APP at 6 months (vs. remaining on monotherapy), we performed follow-up analyses in patients initially on monotherapy, by

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