Original article

New users of antipsychotic medication: A population-based cohort study of occupational outcome measures in relation to antipsychotic on-label and off-label prescribing practices

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A B S T R A C T

Background: Treatment with antipsychotic medication is thoroughly investigated in schizophrenia and bipolar disorder but is also widely applied for a diversity of off-label conditions, despite an uncertain risk-benefit ratio. This study examined the relationship between antipsychotic prescribing patterns and labor market affiliation, considering both authority approved and off-label prescriptions and the relation to polypharmacy.
Methods: Register-based cohort study using a dataset of 71,254 new antipsychotic users with a psychiatric diagnosis. Labor market affiliation and duration of welfare payments were analyzed using linear regression models and duration analysis. The analyses were adjusted for the following confounding variables: age, gender, diagnosis, marital status, length of education, and utilization of mental health care services.
Results: The majority of new antipsychotic users received welfare payments for prolonged periods of time during the observation period, even more so for individuals treated with antipsychotic polypharmacy or other antipsychotic combination regimens. The risk of permanently leaving the labor market was also associated with antipsychotic combination regimen.
Conclusions: Antipsychotic treatment, especially in combination with other antipsychotics or other psychotropic drugs, could serve as a marker of subjects with increased need for support to maintain the labor market affiliation. However, causality cannot be inferred from an observational study because of residual confounding that could not be adjusted for in this study.

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1. Introduction

Antipsychotic prescribing is increasing, in Denmark as well as in other European countries, partly as a consequence of new indications, and partly as a consequence of an increasing frequency of off-label use [1,2,4]. Treatment with antipsychotic medications has been thoroughly investigated in schizophrenia and bipolar disorder [3,6,7], which are the two main indications. However, off-label use has only been scarcely evaluated, and there is a lack of evidence to support treatment with antipsychotics for non-approved conditions [8]. A recent cohort study from UK primary care found that for most antipsychotics it was less than half of the people prescribed these medications that had a diagnosis of psychosis or bipolar disorder [9]. Particularly antipsychotic combination treatment is understudied for off-label conditions. Due to the severity of the side effect profile, this lack of a definite therapeutic effect might lead to an unfavorable risk-benefit ratio, possibly hampering the social and vocational abilities of affected subjects. Possible associations of antipsychotic medication use patterns with variables reflecting different aspects of labor market affiliation have not previously been investigated, but the expanding occurrence of antipsychotic medication use calls for further investigations.

The aim of this study was to describe and analyze authority approved (mainly for schizophrenia and bipolar disorder) and off-label antipsychotic prescribing patterns, including polypharmacy, in relation to pragmatic occupational outcome measures.

2. Methods

2.1. Design and materials

Population-based cohort study of antipsychotic prescribing patterns in relation to societal outcome measures in adult new antipsychotic medication users in Denmark. We used population-based national registers that include longitudinal data on the entire vital population with the exception of emigrants. We linked data from the Central Psychiatric Research Register (CPRR), the Register of Medicinal Product Statistics, and Statistics Denmark at the individual subject level, using the unique civil registration number for linkage. The civil registration number is assigned to all Danish residents at birth or upon immigration.

2.2. National registers used

The CPRR contains information on all individual contacts within the secondary mental health care system (psychiatric hospitals and outpatient clinics) in Denmark [10]. From the CPRR, we extracted the *International Classification of Diseases 10th Revision* [12] diagnosis codes (as explained below) and information on the number of psychiatric hospitalizations, the total duration of hospitalizations, the total number of visits in outpatient clinics, and the total number of visits to mental health care emergency rooms. At any contact with the psychiatric hospital system (inpatient, outpatient or emergency room), the patient is given at least one diagnosis in the CPRR. This main diagnosis was extracted for this study. Consequently, the analyses were restricted to patients with one or more hospital contacts in the study period. In Denmark, most patients with moderate or severe symptoms of a mental disorder are treated or at least evaluated in the psychiatric hospital system. Individuals without a diagnosis recorded in the CPRR might have a diagnosis in general practice, or with a practicing psychiatrist. All mental health care services are public and tax-financed, except for pharmaceuticals and a few other services. The degree of co-payment for pharmaceuticals varies along the quantity consumed.

The Register of Medicinal Product Statistics contains information on the use of all prescription medicines collected outside hospitals. When a person purchases his or her prescription medication, the transaction is recorded in the Register of Medicinal Product Statistics. If a person does not collect the medication, the prescription is not recorded in the register. For each transaction, the following information is recorded: the civil registration number of the patient (allowing for linkage with other registers), the Anatomic Therapeutic Classification (ATC) code [13], the dosage per sold package, and the date of the purchase. Consequently, the medication exposure in this study comprised the collected (i.e. purchased) medication at all pharmacies in Denmark, which is an exhaustive measure of out-of-hospital use of prescription medications. For schizophrenia patients, however, all antipsychotic medications are fully reimbursed for the first two years after the diagnosis and therefore not recorded in the database during this period. Consequently, the index prescription for patients with a schizophrenia diagnosis does not indicate a new antipsychotic prescription but marks an interval of two years from the initial diagnosis.

The registers in Statistics Denmark comprise information on a variety of socioeconomic and demographic data. We extracted the following data from these population-based registers: length of education, marital status, employment status, including welfare payments, living independently, and gross income. We compared these variables in the year of the index prescription in order to obtain the best possible comparability between subjects.

2.3. Study population, diagnostic classification and exposure definition

The study population comprised all Danish adult residents who collected a minimum of one antipsychotic prescription during the years 2007–2012. Subjects who had collected at least one prescription for an antipsychotic compound up to three years before the observation period were excluded in an attempt to use approximate incidence-based measures. For each included subject, the diagnosis was defined as the psychiatric diagnosis (coupled with a psychiatric inpatient/outpatient/emergency room contact) given in closest proximity to the date of the index antipsychotic prescription.

Individuals without any contact to the psychiatric hospital system (and hence without a diagnosis in the CPRR) were not analyzed further. We traced antipsychotic prescriptions across the observation period divided into intervals of 60 days. The interval duration of 60 days was based on an a priori assumption of antipsychotic prescription duration, which was verified in a subsample of the population.

Within each 60-days interval, we defined antipsychotic medication treatment as continued monotherapy (collecting a prescription of the same antipsychotic as in the preceding interval), switched (collecting a prescription of another antipsychotic than in the preceding interval), discontinued (not collecting any prescriptions of antipsychotics within two successive 60-days intervals), or combined with another antipsychotic, antidepressant or benzodiazepine. Antipsychotic polypharmacy (APP) was defined as collection of two (or more) different antipsychotic compounds within two successive intervals of 60 days. Add-on treatment was defined as concomitant collection of two (or more) prescriptions of antidepressants (AP/AD), benzodiazepines (AP/BZ), or both (AP/AD/BZ) within an interval of 60 days. Each subject could be in none, one, or two of these combined medication groups, and therefore the numbers do not add up to a 100%. During the first two months after the index prescription, almost 40% continued the same pharmaceutical as in the first prescription, 52% had no antipsychotic prescription in the second period and about 8% switched antipsychotic medication. Among the continuers and the switchers, 46% also collected a prescription of antidepressants, 20% collected benzodiazepines, and 4% had prescriptions for more than one antipsychotic in the first period. The latter three proportions may be mutually overlapping.

2.4. Study medication

Pharmaceutical compounds with the following ATC codes were included in the study:

- Antipsychotics N05A (except the following: acepromazine N05AA04, prochlorperazine N05AB04, periciazine N05AC01, tetrabenazine N05AK01 and lithium N05AN01).
- Tricyclic antidepressants N06AA, selective serotonin reuptake inhibitors N06AB and other antidepressants N06AX.
- Benzodiazepines as anxiolytics N05BA, benzodiazepines as hypnotics N05CD, benzodiazepine-related drugs N05CF and clonazepam N03AE01 (traditionally used as an anxiolytic agent in Denmark despite not being approved for this indication).

Conventional mood stabilizers (lithium and anticonvulsants) were not considered in this study because ambulatory prescriptions of these medications were anticipated to be of less relevance in a sample of new antipsychotic users. Furthermore, off-label prescriptions of these medications were expected to be much less frequent than for the psychotropic drugs included in the study.