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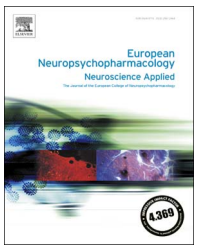

Mental disorder diagnoses among children and adolescents who use antipsychotic drugs

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Abstract
Antipsychotic drugs are used increasingly by children and adolescents and there is concern about off-label use. We aimed to study which substances, and for which mental disorder diagnoses, antipsychotic drugs were prescribed to 0–18-year-old boys and girls in Norway. Linked data from the national health registry for prescription drugs in 2010 and mental disorder diagnoses in 2008–2012 were used to study the prevalence of antipsychotic drug use, the type of antipsychotic drug substances used, mental disorder diagnoses in users and distribution of drugs per diagnostic category across gender. In total, 0.18% of Norwegian children and adolescents were prescribed antipsychotic drugs during 2010, of which there were more boys (0.23%) than girls (0.13%). Risperidone was the most frequently used substance among boys (57.4%) and girls (32.3%), followed by aripiprazole (19.4%) in boys and quetiapine (27.4%) in girls. The most common mental disorder diagnoses among male users were hyperkinetic (49.9%) and autism spectrum disorder (27.1%), while anxiety disorders (41.5%) and depressive illness (33.6%) were most common among female users. A schizophrenia-like psychosis diagnosis was given to 11.1% of the male and 18.2% of the female users. A hyperkinetic disorder was diagnosed among 56.9% and 52.4% of the male risperidone and aripiprazole users, respectively. Among female quetiapine users, 57.1% were diagnosed with anxiety disorders and 52.4% with depressive illness. These results demonstrate that children and adolescents who use antipsychotic drugs are predominantly diagnosed with non-psychotic mental disorders such as hyperkinetic disorder among boys and anxiety disorder or depressive illness among girls.

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1. Introduction

In adults, antipsychotic drugs are used to treat psychotic symptoms in psychotic disorders such as paranoid psychosis, schizophrenia or bipolar disorder. However, some of the newer atypical antipsychotic drugs are used to treat symptoms of depression and mania too. Older types of antipsychotics (i.e. first generation antipsychotics, FGAs), such as levomepromazine and chlorprotixene, are mostly used as sedatives in a range of psychiatric disorders in Norway. FGA use has been minimal in paediatric populations but the advent of second generation antipsychotics (SGAs), with less severe adverse effects, has led to an increase in use of antipsychotic drugs among children and adolescents (Bachmann et al., 2014; Patten et al., 2012). At present, five types of SGAs are approved for use in children and adolescents in the USA. Risperidone, aripiprazole and quetiapine may all be prescribed to patients with schizophrenia from 13 years of age and to patients with acute mania from 10 years of age. Olanzapine is approved for treatment of schizophrenia or bipolar mania from 13 years of age, and paliperidone is approved for schizophrenia treatment from 12 years of age. Risperidone and aripiprazole are also approved for treating symptoms of irritability in patients with autism spectrum disorders (ASD) from 5 and 6 years of age, respectively. In Norway, only three types of SGAs are approved for paediatric use. Risperidone is approved for treatment of behavioural problems as part of conduct disorder from 5 years of age, aripiprazole is approved for use in patients from 15 years of age with schizophrenia and patients from 13 years of age with bipolar mania, and ziprasidone is approved for treating bipolar disorder from 10 years of age.

Recent findings from a large prescription database sample in the US demonstrated that 0.1% of 1–6-year-old children, 0.8% of 7–12-year-old children, and 1.2% of 13–18-year-old adolescents received at least one prescription of an antipsychotic drug during 2010 (Olfson et al., 2015). Diagnostic information was available for a subset of the sample, with the most common diagnosis being Attention-Deficit/Hyperactivity Disorder (ADHD), although over half of the patients had no medical claim indicating a mental disorder diagnosis. A review of epidemiological studies demonstrated that antipsychotic medication is more commonly prescribed to children and adolescents in the USA than in Europe, more often prescribed to boys than girls and is increasingly prescribed for ADHD (Patten et al., 2012). Recent studies from the UK (Rani et al., 2008), Germany (Bachmann et al., 2014), Denmark (Steinhausen and Bisgaard, 2014), Iceland (Zoega et al., 2009) and Norway (Hartz et al., 2016) have demonstrated that antipsychotic drugs are increasingly used by children and adolescents. The trend may partly be explained by increased use of mental health services by children and adolescents (Steinhausen, 2015). There is, however, major concern that SGAs are increasingly prescribed off-label to children and adolescents despite a lack of consistent evidence regarding efficacy, safety and long-term consequences for mental and somatic health in this age group (Harrison et al., 2012; Vitiello et al., 2009). A detailed analysis of prevalence of use, types of antipsychotic drug substance prescribed and underlying mental disorders among younger antipsychotic drug users is needed.

Using linked data from national health registries we aimed to estimate 1) one-year prevalence of use of any antipsychotic drug among 0–18 year old boys and girls. Among the prevalent users we further investigated the distribution of 2) types of antipsychotic drugs prescribed, 3) mental disorder diagnoses and 4) which type of antipsychotic drugs were prescribed for which diagnoses.

2. Experimental procedures

The study population consisted of individuals aged 0–18 years (born in the period 1992–2010) who were dispensed an antipsychotic drug at least once in 2010 according to data from the Norwegian Prescription Database (NorPD). The NorPD covers all prescription drugs dispensed to the entire Norwegian population, except those given in institutions. Since January 2004, all Norwegian pharmacies are obliged to send data electronically to the Norwegian Institute of Public Health for all prescribed drugs (irrespective of reimbursement) dispensed to individuals in ambulatory care. The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. For the present study, information was retrieved for all antipsychotic drugs (ATC-code N05A, except N05AN01 – Lithium). The drugs were classified as FGAs, i.e. perphenazine (N05AB03), haloperidol (N05AD01) and zuklopentixole (N05AF05), SGAs, i.e. ziprasidone (N05AE04), olanzapine (N05AH03), quetiapine (N05AH04), risperidone (N05AX08), aripiprazole (N05AX12), paliperidone (N05AX13) and clozapine (N05AH02), or FGAs usually prescribed as auxiliary treatment for agitation, anxiety or insomnia in Norway (AUX), i.e. levomepromazine (N05AA02) and chlorprotixene (N05AF03).Dispensed antipsychotic drugs recorded in the NorPD will be henceforth referred to as used drugs.

Prescription data were linked with diagnostic information from the Norwegian Patient Register (NPR). The NPR is a national health registry covering all sectors of the governmental-funded specialised health care services in Norway, including somatic, psychiatric and substance abuse treatment facilities. All hospitals and clinics who receive government reimbursement are obliged to report activity and diagnostic data to the NPR. In Norway, there are publicly-funded mental health care facilities for in- and outpatient treatment throughout the country, including clinics for child and adolescent mental health. Mental health care is free of charge for children and adolescents up to age 18. The private sector plays a negligible part in the health care system for children and adolescents with severe mental disorders. Since 2008, the NPR has included unique personal identification number so the registry contains nationwide individual-level specialist health care data from 2008 and onwards, including diagnostic codes according to the International Classification of Diseases, 10th version (ICD-10) for up to two main conditions and up to 19 secondary conditions for each visit or hospital stay. For the present study, data on mental and behavioural disorders (ICD-10 codes F00-F99) were obtained for all individuals in the study population, i.e. those who were dispensed an antipsychotic drug during 2010. To obtain as much diagnostic information as possible, we used NPR data reported by in- and outpatient clinics, and substance abuse treatment facilities for the period 2008–2012. Mental disorder diagnoses were grouped as follows: schizophrenia-like psychosis (F20-F29), bipolar disorder (F30-F31), depressive illness (F32-F34), anxiety disorders (F40-F48), mental retardation (F70-F79), ASD (F84), hyperkinetic disorder (F90, equivalent to ADHD according to the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5)) and conduct disorder (F91). Data from the NorPD and the NPR were linked using

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