

Original Article

Off-Label Prescribing of Antipsychotics in a Danish Child and Adolescent Mental Health Center: A Register-Based Study

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ABSTRACT

Objective: We analyzed prescribing patterns of antipsychotics for children and adolescent affiliated with a Danish Child and Adolescent Mental Health Center) with respect to age, sex, medicine, diagnoses, off-label status, and time. **Methods:** We included all patients below 19 years of age prescribed antipsychotics during 2007–2008 and as of November 1, 2014. Prescription data included all antipsychotic prescriptions and prescriptions of concomitant psychotropic medications. We defined an antipsychotic user as a patient receiving at least one prescription during the study period, irrespective of any previous history of antipsychotic use. We defined off-label prescribing as prescriptions outside the licensed age group and approved indication. **Findings:** We analyzed 404 antipsychotic prescriptions that were located for 150 patients. The patients were between 7 and 18 years of age. Two-thirds of the prescriptions were for girls and two-thirds of prescriptions for olanzapine and quetiapine. Totally, 92% of all prescribed antipsychotics were used off-label. For typical antipsychotics, this share was 96% and for atypical antipsychotics 90%. As of November 1, 2014, the total share of off-label antipsychotic prescriptions was 96%, and 63% of these were for medications prescribed outside the approved age group, and 26% for nonlicensed indication(s). **Conclusion:** This study demonstrated a high level of off-label prescribing over time with respect to age and indication. The prescribing patterns underpin the need for further economic incentives for pharmaceutical companies to register pediatric indications, particular for off-patent products.

KEYWORDS: *Adolescents, antipsychotics, children, Denmark, off-label, psychiatry*

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INTRODUCTION

According to the European medical directive (2001/83/EC), all pharmaceuticals marketed in the European Union (EU) must contain a mandatory labeling and package leaflet providing a set of comprehensible information enabling the use of the medicinal product safely and appropriately, including information about all approved indications for use, licensed age groups, and routes of administration.^[1] Therefore, mandatory pharmaceutical product information (PI) provided by the regulatory authorities serves as a source of information on safe and effective use of medicines. As PIs represents the official knowledge about the medicines' efficacy and safety profile, the marketing authorization holder must assure that the documents

are up-to-date, so that prescribers can rely on this information when prescribing. Incorrect information can potentially lead to inappropriate prescribing, or physicians avoid prescribing due to lack of sufficient information.^[2,3] Hence, many medicines are prescribed without license (unlicensed) or in disagreement with the PI (off-label). Off-label prescription includes prescribing outside the recommended dosage, indication, route of administration, or age of the patient.^[4]

Empirical studies have shown that prescribing of antipsychotics for children and adolescents has rapidly increased over the past decade in many western

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countries.^[5,6] A systematic literature review showed that antipsychotics are prescribed for numerous indications, but only few of these indications are licensed.^[7] Pediatric off-label use is a well-known and clinically accepted practice in clinical practice, including psychiatric care, despite those potential adverse events are more serious and occur more frequently when medicines are used off-label.^[8] The main reason for off-label medicine use is lack of pediatric clinical trials.^[8] Studying the extent and patterns of off-label use is difficult, as it requires access to individualized prescription data and patients' health records. In the Capital Region of Denmark, the presence of specialized drug monitoring software allows detailed studying of prescription data for patients treated in all hospital clinics, thereby enabling off-label studies. Albeit off-label antipsychotic prescribing has been of concern to health authorities, patients, parents, and prescribers, only limited knowledge of prescribing practice in children and adolescents exists.^[9-22]

Therefore, we aimed to study prescribing patterns of antipsychotics in a Danish child and adolescent Mental Health Center over time with respect to age, sex, diagnoses, medicine, and off-label status.

METHODS

We analyzed prescription data for antipsychotics extracted from computerized medical records of consecutive patients receiving antipsychotic prescriptions from the CAMHC, Department Bispebjerg, Capital Region of Denmark, Copenhagen, Denmark. CAMHC offers both in- and outpatient services and receives patients from the city of Copenhagen and Frederiksberg and the regional municipality of Bornholm.^[23] We included all patients below 18 years prescribed at least one antipsychotic medicine and admitted to CAMHC, Department Bispebjerg, from January 1, 2007 to January 1, 2008. Data were collected for the patients' entire hospital stay and/or contact with the outpatient contact with the center. For patients diagnosed with more than one disorder, prescriptions were included for each diagnosis. The study was registered with the Danish Data Protection Agency (J. No. 2009-41-3511). According to Danish law, ethical approval of registry-based studies is not required. We extracted information about prescription data that were registered before November 1, 2014, from the study by Braüner *et al.* 2016.^[12]

The patient information was extracted from two databases: diagnoses from the Green System/OPUS and prescription data from the electronic patient medication system. Data included the patients' sex, age, and psychiatric diagnoses according to the 10th edition of International Classification of Diseases,^[24] and medicines coded according to the Anatomical Chemical

Classification system (ATC).^[25] In the ATC system, antipsychotic medicines refers to code N05A. An antipsychotic user was defined as a patient, who had received at least one prescription during the study period irrespective of any previous history of antipsychotic use. Prescription data included all antipsychotic prescriptions and prescriptions of concomitant psychotropic medication. Two types of off-label prescriptions were defined according to the official Danish PI for each of the reported medicines: (i) off-label prescription with respect to age and (ii) off-label prescription with respect to indication. The website of the Danish Medicines Agency provided access to the actual PI information.^[26] During 2007 and 2008, clozapine was licensed for the treatment of resistant schizophrenia (F20) (>16-year-olds) and risperidone for the treatment of irritability (F7X, F.84.4, R41.8) (>5-year-olds) in Denmark. By November 1, 2014, in addition, aripiprazole was approved for the treatment of mania (F30.X, F31.0–2, F.31.6) (>13-year-olds) and schizophrenia (F20) (>15-year-olds), ziprasidone for the treatment of mania (F30X, F31.0–2, F.31.6) (>10-year-olds), and paliperidone for the treatment of schizophrenia (F20) (>15-year-olds).^[27]

RESULTS

During 2007–2008, totally, 150 patients were prescribed at least one antipsychotic medicine corresponding to 404 antipsychotic prescriptions. All patients were between 7- and 18-year-old, and more than one-half of patients were female (66%). The 150 patients received 176 diagnoses and the most frequent diagnoses were schizophrenia (F20–29), eating disorders (F50–59), and autism spectrum disorders (F90–98) [Table 1]. The majority of prescriptions (67%) were for 15–18-year-olds. The median number of antipsychotic prescriptions per patient was three (range 1–8). Atypical antipsychotics were prescribed to 60% of all patients, particularly products containing the substances olanzapine and quetiapine. For typical antipsychotics, chlorprothixene was the most frequently prescribed medicine. During 2007–2008, totally, 92% of all prescriptions were off-label with respect to age and indication [Table 2]. For typical antipsychotics, this proportion was 96% and for atypical antipsychotics 90%. For typical antipsychotics, the proportion of off-label prescriptions with respect to age was 93% and with respect to indication 46%. For atypical antipsychotics, the proportion of off-label prescriptions with respect to age was 88% and with respect to indication 37%. As of November 1, 2014, the overall off-label prescribing rate was 96%. For typical antipsychotics, the proportion of off-label prescriptions with respect to age was 100% and 0% with respect to indication. For atypical antipsychotics, this proportion was 58% with respect to age and 26% with respect to indication.

Table 1: Demographic and clinical data for included children and adolescents, 2007-2008

Age (years)	7-10		11-14		15-18		Total
	Male	Female	Male	Female	Male	Female	
Sex (male/female)							
Patients (n)	7	3	15	38	29	58	150 (51/99)
Diagnoses (n)							
F10-19	-	-	-	2	5	9	16
F20-29	2	-	8	10	21	41	82
F30-39	-	1	1	3	6	6	17
F40-48	-	1	1	4	-	10	16
F50-59	-	-	2	10	2	13	27
F60-69	-	-	1	-	-	1	2
F80-89	3	1	5	3	1	7	20
F90-98	2	1	2	11	4	4	24
Other*	-	-	-	1	1	4	6
Patients with 2 or more diagnosis	-	1	4	4	3	10	22
Antipsychotic medicines (number of prescriptions) [#]							
Typical	2	1	14	28	40	79	164
Atypical	8	4	29	46	56	97	240
Total	10	5	43	74	96	176	404

*Other: F700, F062, X6010, X6110, Z032, #37 patients entered into two or more age groups. F10–19=Mental and behavioral disorders due to psychoactive substance use, F20–29=Schizophrenia, schizotypal and delusional disorders, F30–39=Mood (affective) disorders, F40–48=Neurotic, stress-related and somatoform disorders, F50–59=Behavioral syndromes associated with physiological disturbances and physical factors, F60–69=Disorders of adult personality and behavior, F80–89=Disorders of psychological development, F90–98=Behavioral and emotional disorders with onset usually occurring in childhood and adolescence

Table 2: Prescribing of antipsychotics in children and adolescents, Mental Health Center for Child and Adolescent Psychiatry, Copenhagen, Denmark

Period	Off-label categories								
	2007–2008				November 1 st 2014*				
	Prescriptions, n	Patients, n	Off-label, n (%)	Age, n (%)	Indication, n (%)	Prescriptions, n	Off-label, n (%)	Age, n (%)	Indication, n (%)
Total (n)	404	150	372 (92)	363	165	546	522 (96)	332 (63)	136 (26)
Typical antipsychotics (n)	164	NA	157 (96)	152 (93)	76 (46)	74	74 (100)	74 (100)	0
Chlorprothixene	119	91	117 (98)	115 (97)	66 (55)	63	63 (100)	63	0
Haloperidol	6	5	4 (67)	4 (67)	2 (33)	5	5 (100)	5	0
Levomepromazine	18	15	16 (89)	15 (83)	3 (17)	3	3 (100)	3	0
Melperone	2	2	2 (100)	2 (100)	0	0	0	0	0
Perphenazine	10	6	9 (90)	8 (80)	1 (10)	0	0	0	0
Amisulpirid	0	0	0	0	0	3	3 (100)	3	0
Zuclophenthixol	9	5	9 (100)	8 (89)	4 (44)	0	0	0	0
Atypical antipsychotics (n)	240	NA	215 (90)	211 (88)	89 (37)	472	448 (95)	258 (58)	136 (26)
Aripiprazole	31	27	31 (100)	30 (97)	13 (42)	121	101 (84)	26 (10)	75 (55)
Clozapine	3	3	1 (33)	1 (33)	1 (33)	5	5 (100)	5 (8)	0
Olanzapine	90	70	87 (97)	85 (94)	41 (46)	68	68 (100)	68 (26)	0
Paliperidone	0	0	0	0	0	5	2 (40)	2 (<1)	0
Quetiapine	73	55	69 (95)	68 (93)	21 (29)	156	156 (100)	156 (60)	0
Risperidone	31	23	17 (55)	17 (55)	10 (32)	113	112 (99)	1 (<1)	57 (42)
Sertindole	9	7	7 (78)	7 (78)	2 (22)	0	0	0	0
Ziprasidone	3	3	3 (100)	3 (100)	1 (33)	4	4 (100)	0	4 (3)

Data extracted from: Braüner J, Johansen LM, Roesbjerg T, Pagsberg AK. Off-label prescription of psychopharmacological drugs in child and adolescent psychiatry. *J Clin Psychopharmacol* 2016; 36:500-7. NA=Not available

DISCUSSION

In this study, we aimed to study patterns in off-label prescribing of antipsychotics among children and adolescents in a psychiatric mental health center.

Analysis showed that prescribing patterns during 2007–2008 varied with respect to age and sex, and we documented off-label prescribing rates above 90%. Two-thirds of prescriptions were for girls; the most

frequently prescribed antipsychotics were olanzapine and quetiapine. As of November 1, 2014, the total rate of off-label antipsychotic prescriptions was 96%. Almost 63% of antipsychotic off-label prescriptions were due to age and 26% due to lack of licensed indication(s). More than one-half of off-label prescriptions were for boys (53.4%).^[12] The most frequently used antipsychotics were quetiapine, aripiprazole, and risperidone. These prescribing patterns were also observed in other empirical studies analyzing prescribing patterns of psychotropic medicine in children and adolescents.^[9-22] Despite that, more antipsychotics were approved for pediatric use in younger children in 2014 than during 2007–2008; the overall off-label prescribing rate remained almost unchanged. Therefore, the observed decrease in off-label prescriptions for atypical antipsychotics with respect to age (88% vs. 58%) as of November 1, 2014, was expected. A recent Danish study also found an off-label prescription rate for children receiving psychotropic medicines other than Attention Deficit/Hyperactivity Disorder medications of more than 95%.^[11] The study was a cross-sectional study assessing records on patients treated with psychotropic medicine at two child and adolescent psychiatric wards, on 1 day in 2014. In Danish national treatment guidelines, atypical antipsychotics are recommended as first-line therapy in the pediatric population for pharmacological treatment of psychiatric disorders.^[27] Our study confirmed that physician adheres to national guidelines, as atypical antipsychotics were prescribed to more than two-thirds of included patients.^[27] In the database, several prescriptions on chlorprothixene were found, as the medicine, due to its marked sedative effect, is often prescribed as acute rescue medication.^[12]

This study was based on prescription data from a large Child and Adolescent Mental health Center in Denmark covering around one-half of the Danish pediatric population.^[23] Direct electronic access to prescription data allowed us to examine a large number of prescriptions and clinical data in a detailed way, resulting in a more accurate and complete registration of off-label medicine, than if the analysis was based on data collected through questionnaires, or nonindividualized prescribing information present in national registers.^[28] Comorbid diagnoses were not extracted, as they were not considered relevant compared to the study objective. However, some study limitations must be observed in relation to the patient cohort. Since CAMCH has specialized functions for children with eating disorders, more teenage girls than boys were admitted to the center comparing to other Danish Mental Health Centers. This could potentially have resulted in higher rates of off-label prescriptions, as no antipsychotics are licensed for eating disorders, but this issue was not studied further. The study was designed

as a pilot study using a specialized software tool to extract data from patient records to study the prevalence of off-label prescribing in a selected patient cohort. Due to the low number of included patients, the few reviewed prescriptions, and that patients received more than one prescription, we did not conduct statistical analysis, as they would not be able to detect any significant differences in off-label prescribing at all. Further studies of the off-label prevalence of antipsychotics in the entire Danish pediatric population would require electronic access to individualized prescription data, information about diagnosis and contacts to physicians linked to individual information extracted from patient records.

Off-label prescribing is legal and necessary when no licensed treatments exist. Hence, the prescribing will be entirely on the physicians' liability.^[29] This study demonstrated that off-label use of antipsychotics in children and adolescents is high, and only a little decrease was observed over time despite the physicians' efforts to prescribe on-label when possible. The challenges with off-label prescribing are uncertainties about beneficial and potential harms. Effects, as well as side effects, may vary, and extrapolation from adult doses to weight-adjusted dosages is difficult, as factors such as age, the development of central nervous system and other organs, concomitant diseases, comedication, and genetic variations can contribute to varying drug metabolism.^[30] The low evidence has severe implications for patients' consent to medical treatment with antipsychotics, and therefore, further economic incentives for pharmaceutical companies to register pediatric indications must be implemented at EU level.^[31] Consequently, pharmaceutical companies must conduct placebo-controlled clinical studies evaluating the efficacy and safety and dosage regime of antipsychotics used in children and adolescents.

This study demonstrated a high level of off-label prescribing over time with respect to age and indication. The prescribing patterns underpin the need for further economic incentives for pharmaceutical companies to register pediatric indications, particular for off-patent products.

AUTHORS' CONTRIBUTION

Kristine Tøfting Kornø and Lise Aagaard designed the study, analyzed data, and wrote the first version of the manuscript. Kristine Tøfting Kornø carried out the data sampling and handling. All authors saw and approved the final version of the manuscript. No sources of funding were used to assist in the preparation of this study.

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Conflicts of interest

There are no conflicts of interest.

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