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Research Article

Off-label Prescription, Adverse Drug Events and Dosage of Psychotropic Drugs in Children and Adolescents with Obesity - A Retrospective Cohort Study

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Abstract

Background: Children with obesity are more prone to suffer from psychiatric disorders. However, drug dosing in complex, as most psychotropic agents even in low dosage associated with drug-induced weight gain.

Objectives: To describe the extent of off-label use, polypharmacy and potential adverse drug event (ADE) related to psychotropic drugs in children and adolescence with obesity.

Methods: A retrospective cohort study including 1.593 patient records of children admitted to a Children´s Obesity Clinic, receiving at least one psychotropic drug during an eight-year study period. Off label status and potential ADEs were registered by assessing patient records and medical charts.

Results: One hundred-fifty-eight children received at least one psychotropic drug during the study period and 52% received more than one psychotropic drug concurrently. Both antidepressants and antipsychotics were prescribed significantly more to girls > 12 years than boys ($p = 0.02$). In total, 61% of the children had at least 1 ADE registered, with significantly increased ADEs when treated with more than one psychotropic drug ($p < 0.001$). Abnormal weight gain was the most frequently ADE in antipsychotics, affecting 35% of the treated patients. Ninety-one percent had at least one off-label prescription, e.g. non-approved indication (31.5%), age (1.9%), dose (23.8%), and duration of treatment (0.6%).

Conclusion: Off-label use and polypharmacy is frequent among children with obesity treated for psychiatric disorders. It is problematic, since most antipsychotic and antidepressant drugs have metabolic adverse effects. These findings highlight the importance of including this patient population in clinical trials to determine appropriate efficacy-safety relationships.

Keywords: Off-label; Adverse Drug Events; Polypharmacy; Obesity; Children and Adolescents

Introduction

Childhood obesity is one of the most serious public health challenges globally [1]. The prevalence of psychiatric disorders, such as depression, anxiety, and low self-esteem are higher in children with obesity than normal-weight-peers [2,3]. Antidepressants are increasingly being prescribed in subjects with depression [4]. In non-responders, the next steps are to increase the dose, switch to another antidepressant, combine antidepressants or use of a second-generation antipsychotic (SGA) drug as an adjunctive treatment [5].

Treatment of psychiatric disorders in children with obesity is challenging both concerning the appropriate drug of choice and the dosage regiment [6,7]. Weight gain is widely known as an adverse effect associated with the use of most psychotropic drugs even at low dosages, and metabolic disturbances and hypercholesterolemia often worsen [8-14]. A recent systematic review by Alonso-Pedrero., *et al*. found an increased weight of 5% or more of baseline body weight after therapy with antipsychotics and antidepressants in children and adolescent 2 - 18 years of age in general [4]. In addition, one of the largest, prospective, open-label, non-randomized study focusing on changes in weight and metabolic parameters in normal weight pediatric patients aged 4 - 19, naive to antipsychotic medications, showed a weight gain equal or above 7% in 64.4% of patients with risperidone, in 84.4% receiving olanzapine, in 58.4% with aripiprazole [13].

Antipsychotic-induced weight gain is likely to be polygenic, but the pathophysiology of weight gain remains poorly understood and few consistent clinical predictive parameters have been identified [15]. Amongst these are: Body mass index (BMI) prior to onset of the psychiatric disorder, female sex, and younger age [16]. Moreover, there is an obvious imbalance between the available treatment regimens in adults psychopharmacology compared to authorized psychotropic agents for children and adolescences [17].

The lack of approved psychotropic drugs has resulted in off-label prescribing in pediatric patients with psychiatric disorders, which may further increase the risk of adverse drug events (ADEs) [18]. In addition, the concomitant use of multiple psychotropic drugs in outpatient children and adolescents increases the risk of potential pharmacodynamic drug interactions including weight gain [19]. While ADEs and off-label use of psychotropic drugs, have been thoroughly described in pediatric patients with a psychiatric disorder [20,21], little attention has been drawn to children who are obese prior to onset of the psychiatric disorder despite the higher disease burden.

Currently, fluoxetine is the only antidepressant approved for the treatment of major depression in children in Europe [18], and only one second-generation antipsychotic drug (SGA), risperidone, has been investigated in the pediatric population through the Pediatric European Risperidone Studies program (PERS) [22].

Childhood obesity is an especially important aspect to consider in regard to dosing strategies and the risk ADEs. The assumption of a linear relationship between weight and dose, which is implicit in a weight-based dosing approach, does not account for the non-linear relationship between body weight and physiological factors, such as clearance or volume of distribution [23]. The consequence in children with obesity treated with psychotropic drugs, may be overexposure of e.g. methylphenidate. A fixed dosing regimen, on the other hand, introduces the potential of underexposure in children with obesity, especially if a loading dose is part of the treatment regimen to ensure fast onset of treatment [24].

This study aims to comprehensively describe prescription patterns of psychotropic drugs in children and adolescents with obesity in a clinical treatment facility, given the limited knowledge in this area. The study investigates off-label use, dosage, use of concomitant multiple psychotropic drugs (polypharmacy), and potential safety issues. With this study, we want to highlight the importance of including pediatric patients with obesity in future psychiatric clinical studies, in order to improve safety and to assess risk-benefit balance in a prospective randomized controlled manor.

Material and Methods

Study design

The study is a single-center, retrospective cohort study of outpatients at the Children´s Obesity Clinic, Department of Pediatrics, Holbaek University Hospital in Region Zeeland, in the period January 1st, 2008 to September 1st, 2016. Data from patient records were included for the whole study period. The study was approved by the Data Protection Agency (BBH-2014-045, I-suite 03045).

Patients

All patients less than 18 years of age with a standardized Body Mass Index (BMI SDS) > 1.28 at the first visit to the Children´s Obesity Clinic (corresponding to the 90th percentile according to

the Danish age and sex-adjusted references) [25], and which were receiving at least one psychotropic drug during the study period, were included. The day of first visit was predefined as the baseline. Patient data were collected from the patient record, and prescriptions of psychotropic drugs were collected from medical charts. Only prescriptions with origin from Department of pediatrics or Division of Child and Adolescents Psychiatry were included. Data collection was concluded if the patients turned 18 years of age during the study period.

Data extraction variables

The following demographic data for each participant were registered:

- Date of birth
- Gender
- Date of the first visit
- Baseline weight and height
- Psychiatric diagnoses (F06-F99), according to the International Classification of Diseases version 10 (ICD-10) [26].

Outcome and measures

The drug-specific data included:

- Generic drug.
- Anatomical Therapeutic Chemical (ATC) code: N05, N06 and C02AC02 (guanfacine). N03AX09 (lamotrigine), R06AD02 (promethazine) and R06AE03 (cyclizine) were included, when prescribed for a psychiatric indication [27].
- Date of prescription and date of discontinuation.
- Indication for treatment according to the International Classification of Diseases version 10 (ICD-10) [26], confirmed in the medical record.
- Daily drug dose (milligram).
- Dosage interval.
- Route of administration.
- Off-label use (yes/no).
- Extemporaneous preparation use (yes/no).
- Pro re nata (PRN) use (yes/no).
- ADEs, registered by doctors in the medical record.

For each psychotropic drug prescription following demographic data on entering day (baseline) and during follow-up were extracted:

- Age of the child (years).
- Weight (kg) of the child at the time of prescription, +/- 6 months.

For evaluating off-label use, the Summary of Product Characteristics (SPC) was used as the reference document.

ADEs, documented in the patient record, were evaluated by two medical doctors independently. We coded ADE's in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) and were summarized by System Organ Class (SOC) and Preferred Terms (PT) [28].

Data analysis

The cohort was stratified into 4 subgroups: girls 2 - 11 yrs., boys 2 - 11 yrs., girls 12 - 17 yrs., and boys 12 - 17-yrs. The stratification is according to the International Conference on Harmonization's, ICH-11 criteria, which reflects the age following developmental considerations [29].

Continuous data were summarized as means with standard deviation or medians and range. Off-label prescriptions were categorized hierarchically as described in figure 1. If a prescription fulfilled more than one off-label category, it was only included once at the highest ranking. Prescriptions of melatonin were in all cases categorized as extemporaneous preparations. The categorization was performed by two medical doctors independently. The renewal of a prescription was recorded in the duration of treatment and only counted as one prescription.

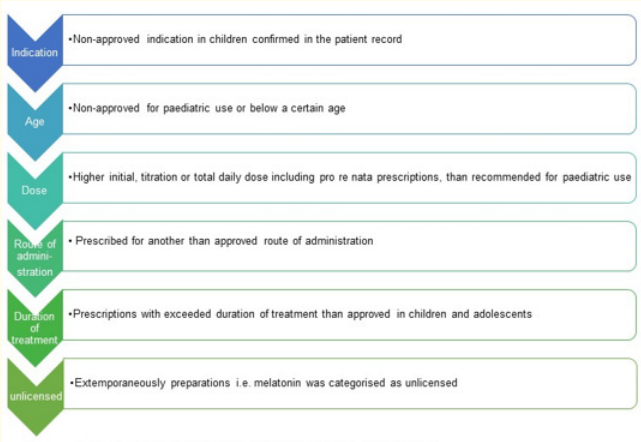

Figure 1: Off-label prescriptions were categorised hierarchically.

If there were concurrent prescriptions of the same active ingredients of a psychotropic drug, a total daily dose was calculated. For PRN prescriptions, we counted the maximal daily dose. If the total daily dose of concurrent prescriptions of the same active ingredient (IMP) exceeded maximal recommended dose, we classified these prescriptions as off-label according to dose.

An ADE was only registered once in relation to psychotropic drug treatment, independently of the total number of drug prescriptions, and if the same ADE was registered in the patient record more than once.

Statistical analysis of psychotropic polypharmacy was determined using Python 3.6 [30]. A chi-square test (χ^2-tests) was performed to determine any statistical significant difference between boys and girls in the use of psychotropic drugs. P-values below 5% was considered statistically significant.

Results

Demographics

Demographic and clinical characteristics are summarized in table 1a. In total, 1593 patient records and medical charts were screened for eligibility, comprising all children and adolescents referred to the Children´s Obesity Clinic within the study period. Almost 10% (N = 158; 47% boys and 53% girls) of these patients received at least one psychotropic drug during the study period. The study patients contributed to 656 observation-years (mean 4.15 years). Hyperkinetic disorder, pervasive developmental disorders (primarily autism spectrum disorders), and depressive episodes were among the most prevalent disorders registered independently of gender (Table 1B).

Characteristics of drug prescriptions

A total number of 1037 of prescriptions were administered during the study period. Average doses and dose ranges of single and contemporary prescriptions are shown in table 2. The distribution according to age and gender is illustrated in figure 2. If a psychotropic treatment was ongoing, when entering the study, we included the age of the child at this time point. An overview of approval status for pediatric use of psychotropic drugs in general is provided in table 3.

A			
Number of study participants, N (%)	2-11 yrs.	12-17 yrs.	Total
Boys	34	41	75 (47)
Girls	40	43	83 (53)
BMI SDS, median (range)	2-11 yrs.	12-17 yrs.	Total
Boys	3.35 (1.54-5.28)	3.24 (1.44-4.35)	3.24 (1.44-5.28)
Girls	2.63 (1.46-3.78)	2.78 (1.86-3.89)	2.76 (1.46-3.89)
B			
Number of registered psychiatric diagnoses, N[a]	Baseline	Follow-up	Total
F10-19 Mental and behavioural disorders due to psychoactive substance use			
F12 Mental and behavioral disorders due to use of cannabinoids	-	3	3
F19 Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	-	1	1
F20-29 Schizophrenia, schizotypal and delusional disorders			
F20 Schizophrenia	1	1	2
F21 Schizotypal disorder	-	1	1
F22 Persistent delusional disorders	-	1	1
F23 Acute and transient psychotic disorders	-	3	3
F25 Schizoaffective disorders	-	1	1
F28 Other nonorganic psychotic disorders	-	3	3
F29 Unspecified nonorganic psychosis	-	1	1

F30-39 Mood [affective] disorders			
F31 Bipolar affective disorder	1	-	1
F32 Depressive episode	9	12	21
F33 Recurrent depressive disorder	1	-	1
F40-F48 Neurotic, stress-related and somatoform disorders			
F40 Phobic anxiety disorders,	3	8	11
F41 Other anxiety disorders,	4	6	10
F42 Obsessive-compulsive disorder,	5	6	11
F43 Reaction to severe stress, and adjustment disorders	-	5	5
F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors			
F50 Eating disorders	-	8	8
F60-F69 Disorders of adult personality and behaviour			
F60 Specific personality disorders	1	21	22
F70-F79 Mental retardation			
F70 Mild mental retardation	1	7	8
F71 Moderate mental retardation	-	1	1
F79 Unspecified mental retardation	2	2	4
F80-F89 Disorders of psychological development			
F80 Specific developmental disorders of speech and language	-	2	2
F81 Specific developmental disorders of scholastic skills	-	2	2
F83 Mixed specific developmental disorder	2	2	4
F84 Pervasive developmental disorders	23	19	42
F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence			
F90 Hyperkinetic disorder	45	39	84
F92 Mixed disorders of conduct and emotions	1	-	1
F93 Emotional disorders with onset specific to childhood,	-	6	6
F94 Disorders of social functioning with onset specific to childhood and adolescence	1	6	7
F95 Tic disorders			
F98 Other behavioral and emotional disorders with onset usually occurring in childhood and adolescence	7	7	14
	13	11	24
[a] Some children had more than one psychiatric diagnosis registered.			

Table 1: A. Characteristics of the study population at the day of first visit to the children's obesity clinic (baseline). B. Distribution of psychiatric diagnoses at baseline and during follow-up.

Psychotropic drug	Number of prescriptions	Off-label category, N				Average dose per prescription, mg (range)	Average dose on contemporary prescriptions, mg (range)
		Indication	Age	Dose	Duration		
Total	1037	327	20	247	6		
Citalopram	27	27	-	-	-	19.7 (2.5-40)	19.7 (2.5-40)
Escitalopram	1	1	-	-	-	20 (-)	20 (-)
Fluoxetine	31	18	-	11	-	27.1 (10-60)	27.1 (10-60)
Mirtazapine	3	3	-	-	-	25 (15-30)	25 (15-30)
Sertraline	78	56	-	5	-	86.5 (25-200)	92.8 (25-200)
Venlafaxine	2	2	-	-	-	75 (-)	75 (-)
Lamotrigine	4	4	-	-	-	206.3 (25-500)	206.3 (25-500)
Aripiprazole	40	37	2	-	-	6.6 (1.25-20)	7.1 (1.25-20)
Chlorprothixene	64	64	-	-	-	50.7 (7.5-200)	62.3 (15-200)
Olanzapine	7	7	-	-	-	14.3 (5-20)	24.3 (5-40)
Quetiapine	62	62	-	-	-	178.4 (12.5-900)	312.9 (12.5-1000)
Risperidone	22	8	-	5	6	1.1 (0.25-4)	1.1 (0.25-4)
Sulpiride	1	1	-	-	-	200 (-)	200 (-)
Ziprasidone	5	5	-	-	-	44 (20-80)	44 (20-80)
Oxazepam	1	1	-	-	-	45 (-)	45 (-)
Triazolam	2	2	-	-	-	0.2 (0.125-0.25)	0,2 (0.125-0.25)
Zolpidem	4	4	-	-	-	6.3 (5-7.5)	6.3 (5-7.5)
Atomoxetine	83	-	-	4	-	45.6 (10-100)	49.7 (10-100)
Dexamphetamine	6	-	-	2	-	7.5 (5-10)	10.0 (5-15)
Guanfacine	2	-	-	-	-	1.5 (1-2)	1.5 (1-2)
Lisdexamphetamine	39	-	-	7	-	44.7 (15-70)	47.3 (15-100)
Methylphenidate	454	-	18	213	-	33.7 (5-216)	51.2 (5-260)
Circadin	15	15	-	-	-	2.3 (2-4)	2.3 (2-4)
Melatonin[a]	73	-	-	-	-	4.1 (3-9)	4.1 (3-9)
Promethazine	10	10	-	-	-	25 (5-50)	25 (5-50)

[a] Melatonin was characterized as extemporaneously preparation.

Table 2: Distribution off-label prescriptions and average doses, according to single prescriptions and contemporary prescriptions.

	Psychotropic drug	Approved indication	Approved in children, age (years)	Initial maximal dosage/ Maximal titration dosage per week	Recommended dosage per day. Maximal duration
Antidepressants + Lamotrigine	Citalopram	Off-label[a]	-	-	-
	Escitalopram	Off-label[a]	-	-	-
	Fluoxetine	Moderate and severe depression	+8	10 mg/10 mg	20 mg
	Fluvoxamine	OCD	+8	25 mg/25 mg	Max 200 mg
	Lamotrigine	Off-label[a]	-	-	-
	Mirtazapine	Off-label[a]	-	-	-
	Sertraline	OCD	+6	6-12 year: 25 mg/25 mg 13-17 year: 50 mg/50 mg	200 mg
	Venlafaxine	Off-label[a]	-	-	-

Antipsychotics	Aripiprazole	Schizophrenia Bipolar disorders	+15 +13	2 mg/3 mg after 2 days and 5 mg after 2 additional days	30 mg 10 mg, Max 12 weeks
	Chlorprothixene	Off-label[a]	-	-	-
	Olanzapine	Off-label[a]	-	-	-
	Paliperidone	Schizophrenia	+15	3 mg/3 mg	≤51kg max 6 mg >51kg max 12 mg
	Quetiapine	Off-label[a]	-	-	--
	Risperidone	Persistent aggression in conduct disorder in children with sub average intellectual functioning or mental retardation.	+5	< 50 kg: 0.25 mg/0.25 mg per 2 days ≥ 50 kg: 0.5 mg/0.5 mg per 2 days	<50kg: 0.75 mg ≥50kg: 1.5 mg, Max 6 weeks
	Sulpiride	Off-label[a]	-	-	-
	Ziprasidone	Bipolar disorder	+10	20 mg/-	<45kg 80 mg >45kg 160 mg
Benzodiazepines	Oxazepam	Off-label[a]	-	-	-
	Triazolam	Off-label[a]	-	-	-
	Zolpidem	Off-label[a]	-	-	-
Central stimulant drugs	Atomoxetine	ADHD	+6	40 mg/-	≤70kg: 1.8 mg/kg >70kg: 100 mg
	Dexamphetamine	ADHD	+6	10 mg/5 mg	40 mg
	Guanfacine	ADHD	+6	1 mg/1 mg	0.12 mg/kg
	Lisdexamphetamine	ADHD	+6	30 mg/20 mg	70 mg
	Methylphenidate	ADHD	+6	18 mg[b]/18 mg[c] and 10 mg[b]/10 mg[c]	2.1 mg/kg [b,c] or 54 mg[b]/60 mg[c]
Sedatives	Circadin	Off-label[a]	-	-	-
	Cyclizine	Off-label[a]	-	-	-
	Promethazine	Off-label[a]	-	-	-
	Melatonin	Extemporaneous preparation [d]	-	-	-

[a] Off-label for use in children and adolescents..[b] Long-acting formulation. [c] Modified extended release.

[d] Extemporaneous preparation for use in children and adolescents. Reference: respective Summery of Product Characteristics.

Table 3: Summary of approval status of prescribed psychotropic drugs in children and adolescents.

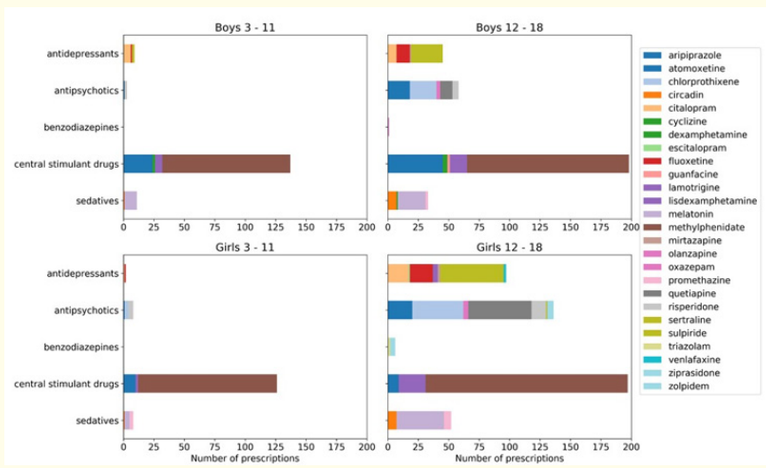

Figure 2: Number of prescriptions according to age and gender.

760 (73.3%) of all psychotropic drug prescriptions were approved for use in children and adolescents, according to the respective SPC's (Table 3). Nonetheless, 91% of the patients had at least one off-label prescription during the study period. The causes for off-label status for all prescriptions according to hierarchical categorization, were non-approved indication (31.5%), age (1.9%), dose (23.8%) and duration of treatment (0.6%). In addition, 7.0% of all prescriptions were administered as extemporaneous preparations (Table 2).

The total number of children redeemed medication for hyperkinetic disorder was 98 and accounted for the largest proportion of all registered prescriptions (56.3%) (Table 2). The most frequently prescribed drug was methylphenidate with 77.7% followed by atomoxetine (14.2%). Boys of 12 years of age or older, tended to have initiated treatment (or treatment were ongoing at baseline) with more frequently compared with girls in the same age group, but the difference was statistically insignificant (N = 36 vs. N = 23; p = 0.091).

Antidepressants were prescribed to 48 children and adolescents. 87% of antidepressants were prescribed off-label, due to non-approved indication and - dose. Sertraline were most frequently prescribed in all ages (54.9%), followed by fluoxetine (21.8%) and citalopram (19.0%). Significantly more girls of 12 years of age or above were treated with antidepressants compared to boys in the same age group (N = 29 vs. N = 14; p = 0.022) (Table 2).

In total. 52 children and adolescents received antipsychotics. 98% of the antipsychotics were prescribed off-label, primary because of non-approved indication. Chlorprothixene was the most frequently prescribed antipsychotic drug independent of ages (31.8%), followed by quetiapine (30.8%) and aripiprazole (19.9%) (Table 2). Similarly, to antidepressants significantly more girls of 12 years of age or above, were treated with antipsychotics compared to boys in the same age group (N = 31 vs. N = 15; p = 0.018).

All benzodiazepines and sedatives were prescribed off-label due to non-approved indication, and all melatonin prescriptions were categorized as extemporaneous preparation. In addition, 42% of redeemed medication for hyperkinetic disorder were off-label prescriptions, primarily due to non-approved initial dose-, titration dose- or concomitant prescriptions (Table 2). The majority included methylphenidate. A few patients had prescriptions of antipsychotic drugs corresponding to the maximal recommended dose for adults, e.g. quetiapine, olanzapine, and chlorprothixene (Table 2).

Combinations of psychotropic drugs

52% of the patients had more than one psychotropic drug prescribed concomitantly during the study period. Antipsychotics were often prescribed concomitant to medication for hyperkinetic disorder, primarily aripiprazole (n = 17), whereas chlorprothixene was most commonly added to an antidepressant. Two different antipsychotic drugs were prescribed concomitantly to 11 patients, and in four patients, three different antipsychotics were administrated concomitantly, predominately combinations with chlorprothixene. Moreover, 14 patients had two different medication for hyperkinetic disorder prescribed concomitantly, primarily methylphenidate and atomoxetine.

Adverse drug events

Overall, 302 ADEs were registered, with 61% of the patients having at least one ADE registered. Patients treated with more than one psychotropic drug, during the study period were more prone to have registered at least one ADE (74%), compared to patients treated with exclusively monotherapy (47%), p < 0.001. 20% of the patients experienced ADEs from more than one psychotropic drug. Frequencies of the most common ADEs for each specific psychotropic drug are shown in table 4.

Psychotropic drug [a]	Number of treated patients	Number of ADEs	1st most frequent ADE, N (%)	2nd most frequent ADE, N (%)	3rd most frequent ADE, N (%)
Antidepressants					
Citalopram	9	4	Affective disorder, anger, irritability, nausea, 1 (11%)	-	-
Fluoxetine	15	17	Nausea, 4 (27%)	Anxiety, 2 (13%)	Abdominal pain, abnormal weight gain, diarrhoea, dizziness, dry mouth, fatigue, flatulence, headache, paraesthesia, rash, restlessness, 1 (7%)
Sertraline	28	31	Fatigue, 6 (21%)	Abnormal weight gain, 5 (18%)	Dizziness, increased appetite, nausea, 3 (11%)

Antipsychotics					
Aripiprazole	19	48	Abnormal weight gain, 9 (47%)	Extrapyramidal disorder, 6 (31%)	Fatigue, 5 (26%)
Chlorprothixene	26	12	Sedation, 5 (19%)	Increased appetite, 2 (8%)	Abnormal weight gain, blunted affect, circadian dysrhythmia, dizziness, headache, 1 (4%)
Olanzapine	4	2	Abnormal weight gain, tremor, 1 (25%)	-	-
Quetiapine	16	22	Abnormal weight gain, 6 (38%)	Sedation, 3 (19%)	Fatigue, restlessness, 2 (13%)
Risperidone	12	17	Abnormal weight gain, 4 (33%)	Increased appetite, 3 (25%)	Nausea, 2 (17%)
Central stimulant drugs					
Atomoxetine	24	23	Decreased appetite, fatigue, 3 (13%)	Abdominal pain, headache, insomnia, irritability, restlessness, 2 (8%)	Aggression, anger, confusion, dry mouth, increased appetite, rash, vomiting, 1 (4%)
Dexamphetamine	2	3	Anger, decreased appetite, depressed mood, 1 (50%)	-	-
Lisdexamphetamine	16	7	Decreased appetite, 2 (13%)	Anger, insomnia, palpitations, tremor, weight decreased, 1 (6%)	-
Methylphenidate	89	112	Decreased appetite, 21 (24%)	Insomnia, 16 (18%)	Abdominal pain, 11 (12%)

[a] Only psychotropic drugs with registered ADEs is mentioned. Some children had more than one ADE from a psychotropic drug.

Table 4: Most common adverse drug events (ADEs) for psychotropic drugs prescribed according to MedDRA classification.

In total, 52 ADEs were registered among 48 children treated with antidepressants, with nausea and fatigue registered in 15% of the patients treated. Abnormal weight gain was the third most frequent ADE registered in 12.5% of patients treated with antidepressants up to 8 kg, most frequent registered in relation to sertraline treatment (18%) (Table 4).

For antipsychotics, abnormal weight gain of up to 24 kg was the most frequent ADE accounting for 21% of the registrations, affecting 35% of the treated patients. Abnormal weight gain was the most frequently registered ADE for aripiprazole (47%), while weight gain was only registered in 4% of the patients treated with chlorprothixene (Table 4).

Among medication for hyperkinetic disorder, the most frequent ADEs were decreased appetite, registered in 28% and insomnia, registered in 19% of treated patients. There was a significant difference between the number of ADEs registered for all causes of off-label methylphenidate treatment (66%) compared to on-label treatment (41%), p = 0.045.

Discussion

This study highlights some of the challenges and implications when prescribing psychotropic drugs to obese children and adolescents. There are multiple studies reporting weight gain in normal weight patients naive to anti-psychotic treatment equal to or above 7%, similar to our findings [5,31,32]. With the extreme weight gain of up to 24 kg in some patients in the current study taken aripiprazole, quetiapine and risperidone. Other metabolic effects, such as increased glucose level and insulin resistance that are know to be precursors to diabetes are associated with initiating an anti-psychotic drug and the relationship is more profound among children and adolescents, than among adults [9,33]. These findings are of particular concern, as we have previously found significant differences in mean value of low density lipoprotein (LDL), total triglyceride, and diabetic biomarkers (insulin and C-peptide) in obese children compared to non-obese peers in a treatment naive cohort [34].

While in high-fat diet-induced type 2 diabetes, the compensatory ability of β-cells is gradually damaged, the use of anti-psychotic

drugs more likely to cause a direct β-cell damage [33]. Thus, multiple mechanism may accelerate insulin resistance and increase rapid onset of diabetes in children with obesity after initiation of anti-psychotic treatment. Prevention of these changes could be critical for improving clinical outcomes [33].

In line with this, we found that abnormal weight gain was the most frequently registered ADE for antipsychotics. Fraguas., *et al*. made a comprehensive head-to-head comparison between SGAs in children and adolescents with psychiatric and bipolar disorders and demonstrated that these drugs behave inconsistently as a drug class in terms of both safety and efficacy in this patient group [35]. The findings were mainly attributed to differences in the rate and severity of ADEs, especially weight gain. Aripiprazole was found to be the SGA that caused the least weight gain [35]. These findings were supported by a study by Correll., *et al*. [13], who found aripiprazole associated with the lowest, and olanzapine with the highest weight gain in children and adolescents.

Furthermore, Sikich., *et al*. compared molindone, a first-generation antipsychotic drug (FGA), with two SGAs (olanzapine and risperidone) in adolescents with schizophrenia and found that olanzapine was the SGA associated with the highest risk of weight gain [14]. Studies comparing SGAs that cause less weight gain, e.g. aripiprazole, with FGAs have not been performed to date [35]. Moreover, recent studies have made the picture less clear, demonstrating that weight gain is also frequently reported with the use of aripiprazole [36], similar to our findings. In the present study, only four children had olanzapine prescribed. Furthermore, chlorprothixene and olanzapine were primarily prescribed PRN and predominantly in combination with other antipsychotics. This could partly explain the low prevalence of ADEs reported, including abnormal weight gain since it might be more challenging to distinguish which drug had predominately contributed to the weight gain observed.

Like antipsychotics, antidepressants are associated with weight gain. SSRI data are controversial in that short-term anorectic action of fluoxetine has been recognized, but long-term follow-up reveals that its weight-reducing effects are transient, even leading to weight gain over time [37,38]. Also, sertraline, venlafaxine, and citalopram are associated with weight gain [37,39]. Sertraline was the most frequently prescribed antidepressant, which may reflect that sertraline has been tested in trials and approved for use in pediatric patients. Of note, sertraline is only approved for the treatment of Obsessive-Compulsive Disorder (OCD) in pediatric patients. The second most frequently prescribed drug was fluoxetine. Fluoxetine is approved for children from 8 years of age for the treatment of major depression. Citalopram, mirtazapine, and venlafaxine are not approved for any indication in children. None of the antidepressants have been investigated in obese children and adolescents. In the current study, of the drugs not approved for pediatric use, only citalopram was used to a larger extent.

Moreover, 52% of patients received multiple psychotropic drugs at least once during the study period, increasing the risk of ADEs and pharmacodynamic drug-drug interactions [40,41]. Our findings are similar to recent results in a retrospective study conducted by Tucker., *et al*. which showed that among obese pediatric patients treated with psychiatric medication, 60.9% received at least two psychotropic drugs concomitantly [6]. In the present study, we found that antipsychotics were often prescribed in combination with antidepressants. The evidence for use of this combination in children and adolescents has not thoroughly been investigated. In adults, augmentation with an SGA has shown a significant effect on depression compared to monotherapy with an anti-depressant [42]. However, the significant occurrence of ADEs like weight gain, sedation, extrapyramidal symptoms and a potential increase in prolactin makes this treatment strategy less attractive in pediatric patients, especially in patients with obesity [42].

The prevalence of off-label prescriptions in the present study was almost twice as high as previously reported in two independent Danish pediatric studies of psychotropic drugs, with 65% compared to 27.6% and 32.3%, respectively [20,21]. The lower prevalence of off-label prescriptions reported in the previous studies could partly be explained by the relatively high proportion of patients receiving medication within approved age and dose-range, as part of treatment for hyperkinetic disorder [20,21]. In this study, almost one-fifth of the prescriptions exceeded the maximum recommended dose mainly treatment of methylphenidate. In children, the methylphenidate maintenance dose is weight-based, with a maximum dose of 60 mg per day [43]. This may suggest that the children in the present study were dosed either by total body weight, i.e. mg/kg or required higher doses to achieve a therapeutic effect. Dosing regimens that are appropriate for children with obesity remain largely unknown [23,24,44-47]. Of note, we categorized concurrent prescriptions of the same psychotropic drug as off-label, if the total maximum daily dose exceeded the recommendation in the SPC.

Limitations

A major strength of the present study is the manual review of patient records that made it possible to define the indication for each drug and dosing strategy for each drug prescription and include a long-term study period for each patient. In general, information about prescriptions in the Danish hospital-based program "OPUS medicine" is valid because doctors are committed to updating the medicine prescriptions at every hospital visit. We counted total daily dose when a patient had contemporary/concurrent prescriptions of the same drug. The bioavailability may vary between formulations, but has not to be accounted for when estimating the total daily exposure. We also counted PRN prescriptions, so there is a risk that we have overestimated dosage. On the other hand, it is not possible to assess to know the exact dosage and compliance, since most patients are outpatients.

We registered all ADEs spontaneously documented in the patient records, thus minimizing recall bias. A possible selection bias might, however, result from including only one hospital; therefore, the investigated prescription habits may not reflect all medical doctors working in this field. Due to the retrospective nature of the study, valid measurements such as the Hamilton Rating Scale for Depression, to rate the effectiveness of each drug treatment, were not available. Also, we did not include blood work such as lipid profile, blood sugar level, prolactin, etc. Finally, we did not include a control group. Therefore, off-label use, polypharmacy, and potential ADEs were not compared to normal-weight peers. ADEs might be underestimated due to missing and varying documentation, and potentially lack of recognition and awareness of ADEs. Furthermore, the study patients were on a diet during part of the study period, which could underestimate the extent of potential weight gain.

Conclusion

Off-label use and polypharmacy of psychotropic drugs were frequent among pediatric patients with obesity, and the latter was associated with an increased risk of an ADE. We further found that abnormal weight gain was the most frequently registered ADR among antipsychotic drugs prescribed. In this subpopulation, it was common that the dose of psychotropic drugs, approved for use in children and adolescents, was above recommendations in the SPC. These findings highlight the importance of pharmacokinetic and - dynamic studies on psychotropic drugs in children with obesity to optimize future treatment strategies in this vulnerable population. In particularly highlighting the importance to prevent diabetes.

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Informed Consent

Informed consent was obtained from all individual patients included in the study.

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