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EDITORIAL

First do no harm: use off-label antipsychotic medication in children and adolescents with great caution

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In children and adolescents, antipsychotic medication is regularly prescribed on an off-label base, mostly for disruptive behavior or irritability. Especially in children, these medications have a range of side effects, of which weight gain is perhaps the most worrisome. In this issue of *European Child & Adolescent Psychiatry,* Pozzi and colleagues describe the results of a series of meta-analyses regarding increases in body weight, body mass index (BMI), and waist size associated with medium and long term use of different types of antipsychotics, based on data from observational studies [1]. The advantage of observational studies is that these more closely reflect the use in clinical practice than randomized controlled trials. The findings are really alarming. Six months use of olanzapine appeared to be associated with a BMI increase of 3.47 kg/m^2 (corresponding with a weight gain of almost 11 kg). Also, the more frequently used risperidone led to a substantial increase in BMI of 2 kg/m^2 (4.47 kg) after six months of treatment. While aripiprazole has a reputation of leading to less weight gain, still more than a year of treatment with aripiprazole was associated with an increase in BMI that was as high as 2.1 kg/m^2. Figures for increases in waist size are similarly alarming; e.g., six months of risperidone use was associated with an increase of 8.8 cm. Unfortunately, the observational data did not include Z values of the body measures. As there was no control group, receiving no treatment, Z values would have been of advantage, as they incorporate sex, age, and ethnicity factors and thus would have accounted for increases due to mere ageing. However, BMI-Z values (that are adjusted for age and sex) were available and indicated clear medication-associated increases of up to almost 1 standard deviation. The authors also conducted a meta-regression that indicated that lower pre-treatment BMI was a risk factor for increases in BMI.

Another article in this issue addresses metabolic adverse events associated with the use of antipsychotics, by conducting a so-called sequence symmetry analysis, based on a medication prescription database covering a total of about 40 million young people aged 6–30 years from seven countries across Asia (Hong Kong, Japan, Korea, Taiwan and Thailand), Oceania (Australia), and Europe (Denmark) [2]. The study found that medicines that are used to treat dyslipidemia, hypertension, and hyperglycemia were 22% (95% CI 0–50%) more often prescribed after initiation of antipsychotics than before the start of such medication. This points to an association of antipsychotic medication use and metabolic adverse events. Of note, there was no difference between children and adolescents versus adults and also not between Asian and non-Asian ethnicity. Medications prescribed for dyslipidemia even increased by 51% (95% CI 18–93%). A strength of the study was the focus on apparently required prescribed medication for metabolic adverse events, highlighting the clinical significance of these metabolic events. The authors rightfully point to the importance of metabolic monitoring in all children and young adults who are treated with antipsychotics.

Occurrence of movement disorders is another well-known adverse event associated with the use of antipsychotics [3]. Perhaps less well known is that the risk of movement disorders is higher when risperidone is combined with methylphenidate [3], a combination that is widely used in clinical practice. The association between various antipsychotics and the development of seizures is also not widely known. The risk ratio of seizures is above 4, according to data from a nationwide database from South Korea from 2008 to 2018 [4]. Seizure risk was enhanced further with an increase in the number of antipsychotic drugs used. According to the authors, pediatric patients receiving antipsychotics, especially new or multiple antipsychotic users, should be carefully monitored for seizure development.

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Despite the major health hazards associated with off-label antipsychotics use, we found that guideline recommendations regarding antipsychotic use in children and adolescents are often insufficiently met in clinical practice. This was our conclusion from an analysis of 436 medical records from 155 clinicians of 26 clinics within three Dutch child and adolescent psychiatry organizations [5]. The recommendation that antipsychotics should continuously be prescribed with concomitant psychosocial treatment was especially disregarded; in over half of the patients this was not the case. Also disappointing were our findings regarding consideration of contra-indications, with limited screening of medical risk factors in the patient and family history. Furthermore, there was insufficient education of the patient and the parents about antipsychotics, their effects, and lifestyle changes that may be needed.

It is unfortunate that the off-label use of antipsychotics in children and adolescents is rising in some parts of the world. For example, prescription data from a large Australian primary care database indicated a 62.8% increase of antipsychotics prescriptions from 2011 to 2018. The largest annual increase occurred in 10- to 14-year-olds, with the most frequently prescribed antipsychotics being risperidone (in youth < 15 years) and quetiapine (in 15- to 18-year-olds). In France, second-generation antipsychotic dispensing rates increased from 2.7 to 3.4 per 1,000 children and adolescents from 2006 to 2013. In contrast, according to US Medicaid prescription data, pediatric antipsychotic orders decreased from 54.9 prescriptions per 10,000 person months in the first quarter of 2013 to 34.1 per 10,000 person months in the last quarter of 2017 [6]. Also, antipsychotic prescriptions in Germany in children younger than 6 years decreased from 2.42 per 1000 subjects in 2004 to 0.48 in 2011 [7]. In the Netherlands, since a peak of 9.8 users per 1000 youths in 2009, prevalence rates stabilized, with declining dosages in milligram per kilogram from 2005 to 2015 [8].

Although risperidone is only licensed for the treatment of persistent aggression in conduct disorder in children and adolescents with subaverage intellectual functioning for a period of up to 6 weeks, the typical treatment duration in clinical practice is much longer. Finnish Prescription Registry data of all subjects aged 1–17 years who had started a second-generation antipsychotic drug (risperidone, quetiapine, aripiprazole, or olanzapine) between January 2008 and December 2016 revealed a mean and median treatment duration of 509 and 317 days, respectively [9]. The duration was shorter in girls than in boys ($p < 0.001$). Of all second-generation antipsychotic users, 16.0% used these longer than 600 days. In the Netherlands, the median duration of use was 6 months, with one in eight youths using antipsychotic drugs for 4 years or longer [8].

The notable side effects of antipsychotics are particularly concerning in light of their disappointing effects for treating disruptive behaviors, especially on the long run. For example, the Treatment of Severe Childhood Aggression trial failed to identify long term (i.e., after 52 weeks) benefits of adding risperidone to parent training and stimulant medication for children with co-occurring attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorder, and serious physical aggression [10].

Recent findings suggest that alternative treatment strategies other than prescribing antipsychotics should be prioritized in clinical practice. That is, optimizing the dosing and adherence of stimulant medication and/or applying behavioral treatment may drastically reduce the need for antipsychotic medication for children with aggressive behaviors. This was suggested by a clinical trial directed at the effectiveness of risperidone or divalproex sodium as treatment for children with co-occurring ADHD, disruptive disorder, and significant aggressive behavior after insufficient response to systematically optimized stimulant treatment [11]. The trial failed to reach the target sample size due to the unexpected effectiveness of optimizing stimulant dosing and concurrent family-based behavioral treatment.

As an example of the potential of behavioral treatment, we recently showed substantial effects of home-based behavioral parent training for children with disruptive behavior problems who had not responded sufficiently to prior routine treatment (medication and/or clinic-based parent training) [12]. Compared to a waiting list, children allocated to home-based parent training improved significantly more regarding severity of disruptive behaviors, ADHD and oppositional defiant disorder symptoms, and internalizing problems.

In light of the available effectiveness and safety data, appropriate caution is required with regard to the off-label use of antipsychotics in children and adolescents. These should only be considered for short treatment durations, as a last resort in exceptional cases after behavioral treatments and stimulants have been optimized.

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