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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