Tampere University

KIRSI KAKKO

Second-generation Antipsychotic Medications in Child Psychiatric Patients

Prescribing and Monitoring Practices

Tampere University Dissertations 521

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the Jarmo Visakorpi auditorium
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 17 December 2021, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Finland

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-2210-6 (print)
ISBN 978-952-03-2211-3 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2211-3

PunaMusta Oy – Yliopistopaino
Joensuu 2021

To my family

To all the families who made this book possible

ABSTRACT

Second-generation antipsychotic medications (SGAs) are used in children and adolescents for multiple indications, and their use has emerged worldwide during the last decade. Since especially SGA-induced metabolic disturbances are common in children, prescribing and monitoring practices need to be systematic.

This study focused on the safety and monitoring practices of SGAs in child psychiatric patients under 13 years of age, and it was performed in two phases at Tampere University Hospital child psychiatric unit during the years 2013-2019. The first phase (Studies I and II) was a retrospective patient report-based study and the second a prospective study (Study III), where a systematic SGA-monitoring protocol was implemented. Sociodemographic and medical background factors and SGA-induced benefits, possible adverse effects and monitoring practices were recorded. The patients' standardised body mass index adjusted for age and sex (zBMI) was calculated, and blood pressure, fasting plasma triglyceride (TG), high-density lipoprotein (HDL) and glucose (FPG) values were collected. Further, in the prospective study, fasting insulin values were recorded and homeostatic model assessments for insulin resistance (HOMA-IR) and TG/HDL ratio were calculated to assess the possible development of insulin resistance and increased cardiometabolic risk. Similar metabolic parameter cut points were used in both study samples, but in the prospective study also a lower FPG cut point ($\geq$ 5.6 mmol/), indicating impaired fasting glucose, was used in addition to the > 6.1 mmol/l used in the retrospective study. The study was extended with a case report of a severe neurological adverse effect after long-term SGA treatment (Study IV).

Altogether 188 children participated in this study. In the retrospective study (n = 133), the mean age of the study patients was 9.3 years and 81% of the patients were boys. In the prospective study (n= 55), the respective numbers were 9.9 years and 76%. The median duration of follow-up was 20.4 months and 9 months, respectively. The most commonly prescribed SGAs were risperidone, aripiprazole, and quetiapine. Psychotropic polypharmacy was common. The most common diagnoses were ADHD or conduct or mixed conduct and emotional disorders. Diagnosis of psychotic illness was rare (2-5%). SGAs were often initiated for

aggression and disturbances in behavioural and emotional regulation. All SGA prescriptions in the study patients were off-label.

Weight gain was reported as an adverse effect in 33% and 38%, and neurological adverse effects in 10% and 7%, in the retrospective and prospective study, respectively. The zBMI increased in 75% of the retrospective study patients, and in 64% of the prospective study patients with sufficient information for comparisons. A significant zBMI increase was detected in both study samples, and the proportion of overweight patients increased during the follow-up. Further, a significant disadvantageous shift was seen in TG and HDL values in both study samples and in the FPG and insulin values of the prospective study patients. This disadvantageous metabolic shift emerged early during the treatment, but only a small proportion of the patients exceeded the chosen metabolic cut points. However, in the prospective study, the proportion of patients exceeding the lower FPG cut point was 21-29% and also, HOMA-IR and TG/HDL ratios increased during the follow-up. The increase in HOMA-IR appeared earlier and was more marked compared to the TG/HDL ratio. The HOMA-IR increase was not solely explainable with increasing age. The zBMI, blood pressure and all metabolic parameters were assessed at baseline more often in the prospective study. Further, the frequency of patients with sufficient information for examining metabolic trends was higher in the prospective study.

The findings of this study indicate that SGA-induced adverse effects are common in children. The implementation of the systematic monitoring protocol improved the monitoring and the detection of the disadvantageous effects during the study period. However, adversities may still remain undetected, or unreported, in clinical work, and more emphasis should be put on detecting early adverse tendencies. Careful weight monitoring with growth charts, or zBMI, using the cut point of ≥ 5.6 mmol/l in FPG, and the calculation of HOMA-IR could benefit the early detection of metabolic changes. Further, attention should be paid to the neurological adverse effects of SGAs. Open dialogue about the target symptoms, possible adverse effects and lifestyle habits between the patient, the caregiver and the physician is beneficial. Liaisons between paediatrics and child psychiatry should be encouraged.

The implementation of a systematic SGA monitoring protocol in child psychiatric units may increase SGA medication safety. Monitoring should be promoted and enabled at the organisational level and made as easy as possible to perform in clinical work.

TIIVISTELMÄ

Toisen polven psykoosilääkkeitä käytetään lapsilla ja nuorilla useiden erilaisten psykiatristen häiriöiden ja oireiden hoidossa ja niiden käyttö on lisääntynyt viime vuosikymmenen aikana. Koska erityisesti psykoosilääkkeiden metaboliset haitat ovat lapsilla yleisiä, lääkehoidon aloitus- ja seurantakäytäntöjen yhtenäisyys on tärkeää.

Tässä tutkimuksessa selvitettiin psykoosilääkehoidon turvallisuutta ja seurantakäytäntöjä alle 13-vuotiailla potilailla. Tutkimus toteutettiin Tampereen yliopistollisen sairaalan (Tays) lastenpsykiatrian vastuualueella kaksivaiheisena vuosien 2013–2019 aikana. Tutkimuksen ensimmäinen vaihe (osatyöt I ja II) oli retrospektiivinen potilasasiakirjoihin perustuva selvitys. Toinen vaihe (osatyö III) oli prospektiivinen tutkimus, jonka aikana Tays:ssa otettiin käyttöön lasten psykoosilääkehoidon seurantaohjelma. Tutkimuksen molemmissa vaiheissa kerättiin tietoa psykoosilääkkeitä käyttävien lasten sosiaalisista ja lääketieteellisistä taustatekijöistä, lääkehoidon hyödyistä, haitoista ja seurannan käytännöistä. Lisäksi tutkimuspotilailta määritettiin iän ja sukupuolen mukainen painoindeksi (zBMI) ja kerättiin tiedot verenpaineesta, plasman triglyseridi- (TG) ja HDL-kolesteroliarvoista sekä paastoverensokeriarvoista. Tutkimuksen toisessa vaiheessa kerättiin lisäksi tieto potilaiden paastoinsuliiniarvoista ja laskettiin insuliiniresistenssin homeostaasimalli (HOMA-IR) sekä TG/HDL-suhde insuliiniresistenssin ja sydän- ja verisuonisairauksien riskin arvioimiseksi. Tutkimuksen molemmissa vaiheissa käytettiin samoja laboratorioviitearvoja, mutta jälkimmäisessä vaiheessa käytettiin koholla olevan paastoverensokerin raja-arvona viitearvon > 6,1 mmol/l lisäksi myös matalampaa viitearvoa ≥ 5,6 mmol/l. Tutkimuksen kolmantena osana (osatyö IV) kuvattiin tapausselostuksena lapsuusiän pitkäkestoiseen psykoosilääkehoitoon liittynyt vakava neurologinen haittavaikutus.

Tutkimukseen osallistui yhteensä 188 lasta, joiden keski-ikä oli tutkimuksen ensimmäisessä vaiheessa (n = 133, poikia 81%) 9,3 vuotta ja toisessa vaiheessa (n = 55, poikia 76%) 9,9 vuotta. Lääkehoidon seuranta-ajan mediaanikesto aineistoissa oli vastaavasti 20,4 kuukautta ja 9 kuukautta. Yleisimmin käytetyt psykoosilääkkeet olivat risperidoni, aripipratsoli ja ketiapiini, joiden lisäksi potilailla oli usein käytössä myös muita psykiatrisia lääkehoitoja. Yleisimmät diagnoosit olivat tarkkaavaisuus- ja ylivilkkaushäiriö (ADHD) ja käytöshäiriö tai samanaikainen käytös- ja tunnehäiriö.

Potilaista vain 2–5%:lla oli psykoosidiagnoosi. Tavallisimmat syyt psykoosilääkehoidon aloittamiselle olivat aggressiivisuus tai käyttäytymisen ja tunne-elämän säätelyn häiriöt. Kaikkien tutkimuksessa mukana olleiden potilaiden psykoosilääkehoito oli virallisten käyttöaiheiden ulkopuolista (off-label).

Lääkärit raportoivat psykoosilääkehoidon haittoina painonnousua 33%/38%:lla ja neurologisia haittoja 10%/7%:lla potilaista tutkimuksen ensimmäisessä/toisessa vaiheessa. Iän ja sukupuolen mukainen painoindeksi nousi 75%/64%:lla niistä potilaita, joilla oli riittävästi tietoa zBMI-arvojen vertailua varten. Ylipainoisten potilaiden määrä lisääntyi seurannan aikana. zBMI- ja TG- arvoissa havaittiin tilastollisesti merkitsevä nousu ja HDL-kolesteroliarvoissa vastaavasti lasku. Tutkimuksen toisessa vaiheessa havaittiin myös tilastollisesti merkitsevä nousu paastoverensokeri- ja insuliiniarvoissa. Metaboliaa kuvaavien laboratorioarvojen epäedullinen kehitys tuli usein esiin jo hoidon alkuvaiheessa, mutta vain pienellä osalla potilaista viitearvot ylittyivät seurannan aikana. Tutkimuksen toisen vaiheen seurannan aikana 21–29% potilaista kuitenkin ylitti matalamman paastoverensokerin raja-arvon. Myös HOMA-IR- ja TG/HDL-suhteen arvot nousivat seurannan aikana. HOMA-IR:ssä havaittu nousu oli selvempi ja ilmaantui aiemmin TG/HDL-suhteen nousuun verrattuna. HOMA-IR arvojen nousu ei ollut selitettävissä ainoastaan potilaiden iällä. Psykoosilääkehoidon seurantaohjelman käyttöönotto lisäsi metabolisten mittausten määrää sekä psykoosilääkehoidon aloitusvaiheessa että lääkehoidon seurannan aikana. Prospektiivisen tutkimuksen aikana myös toistettujen mittausten määrä lisääntyi ja näin ollen potilaiden metabolia-arvojen kehityksen seuranta mahdollistui paremmin.

Tutkimuksessa havaittiin, että psykoosilääkkeiden aiheuttamat metaboliset haitat ovat lapsilla yleisiä. Seurantaohjelman käyttöönotto tehosti psykoosilääkehoidon seurantaa ja auttoi haitallisten muutosten havaitsemisessa tutkimuksen aikana. Kliinisessä työssä psykoosilääkehoidon haitat saattavat kuitenkin edelleen jäädä havaitsematta ja varhaiseen tunnistamiseen tulisikin kiinnittää huomiota. Huolellinen kasvukäyriin tai zBMI-arvoihin perustuva painon seuranta, paastosokerin viitearvon $\geq$ 5,6 mmol/l käyttäminen ja HOMA-IR:n laskeminen voisivat edistää psykoosilääkehoidon mahdollisten metabolisten haittojen varhaista havaitsemista. Myös neurologisten haittojen tunnistamiseen tulisi kiinnittää huomiota kliinisessä työssä.

Lääkehoidon kohdeoireiden ja mahdollisten haittojen määrittäminen yhteistyössä lääkärin, lapsen ja huoltajan kanssa sekä elämäntapoihin liittyvä keskustelu tukevat turvallista lääkehoitoa. Lastenpsykiatrian ja lastentautien välinen yhteistyö on suositeltavaa. Psykoosilääkehoidon systemaattisen seurantaohjelman käyttöönotto

voi lisätä lasten lääkehoidon turvallisuutta. Lääkehoidon seurannan toteuttaminen tulisi tehdä kliinisessä työssä mahdollisimman helpoksi ja seurantaa tulisi edistää organisaatiotasolla.

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ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
AGRP	Agoutine-related peptide
ASD	Autism spectrum disorder
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area under the receiver-operating characteristic (ROC) curve
BL	Baseline
BMI	Body mass index
BP	Blood pressure
CNS	Central nervous system
ECG	Electrocardiogram
EMA	European Medicines Agency
EPS	Extrapyramidal movement symptoms
FDA	United States Food and Drug Administration
FFA	Free fatty acids
FGA	First-generation antipsychotic
FPG	Fasting plasma glucose
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment for insulin resistance
HoNOSCA	Health of the Nation Outcome Scales for Children and Adolescents
ID	Intellectual disability
IR	Insulin resistance
Md	Median
NPY	Neuropeptide Y
POMC	Pro-opiomelanocortin
Q_1, Q_3	First and third quartile
QTc	Rate-corrected QT interval
ROC	Receiver-operating characteristic
SD	Standard deviation
SGA	Second-generation antipsychotic

SHP	School Health Promotion study
SSRI	Serotonin selective reuptake inhibitor
TAUH	Tampere University Hospital
TD	Tardive dyskinesia
TG	Triglycerides
zBMI	Standardised body mass index adjusted for age and sex

ORIGINAL PUBLICATIONS

This dissertation is based on original publications, which have been referred to in the text by their Roman numerals (I-IV):

Publication I Kakko, K., Pihlakoski, L., Salmelin, R., Puura, K., Tamminen, T. (2017). Clinical use of second-generation antipsychotics in children. Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, 5(2),77-88.

Publication II Kakko K., Pihlakoski L., Keskinen P., Salmelin R., Puura K. (2020). Current follow-up practices often fail to detect metabolic and neurological adverse reactions in children treated with second-generation antipsychotics. Acta Paediatrica, 109(2), 342–348.

Publication III Kakko K., Pihlakoski L., Keskinen P., Salmelin R., Puura K. (2021). In search of measures to improve the detection of increased cardiometabolic risk in children using second-generation antipsychotic medications. Nordic Journal of Psychiatry, 1-7, Advance online publication.

Publication IV Kakko, K., Bjelogrlic-Laakso, N., Pihlakoski, L., Lehtimäki, K., & Järventausta, K. (2019). Tardive dyskinesia should not be overlooked. (Case-report, Letter to the editor) Journal of Child and Adolescent Psychopharmacology, 29(1), 72-74.

AUTHOR'S CONTRIBUTION

Study I and Study II:
The author was responsible for planning the study together with the supervisors and the research group. The author also read all the medical records and went through the laboratory test results of the study patients and collected the data for study purposes. The author also actively participated in the planning of the statistical analyses, followed their execution, and evaluated and interpreted the results together with the research group. The author took the main responsibility both for writing the manuscripts and revising the text as the first author.

Study III:
The author was responsible for planning the study together with the supervisors and the research group. The author translated the "Physician Handbook for Metabolic Monitoring for Youth with Mental Illness treated with Second-Generation Antipsychotics" and the monitoring form from the Canadian original publications (with the permission of the original authors). Together with the research group, the author modified them to fit Finnish clinical practices and study purposes and introduced them to the physicians of TAUH child psychiatric unit. The author also coordinated the data gathering. The author also read the monitoring forms and went through the laboratory test results of the study patients and collected the data for study purposes. The author also actively participated in the planning of the statistical analyses, followed their execution, and evaluated and interpreted the results together with the research group. The author took the main responsibility for both writing the manuscript and revising the text as the first author.

Study IV:
The author was responsible for reading the medical records and writing the manuscript and revising the text together with the research group as the first author.

1 INTRODUCTION

Antipsychotic medications are a heterogenous group of medications affecting multiple receptors in the central nervous system (CNS). They can be divided into two groups based on their mechanisms of action: typical first-generation antipsychotics (FGA) and atypical second-generation antipsychotics (SGA). The main therapeutic effect of antipsychotics is mediated by blockage of the dopamine receptors (Ferrin et al., 2016; Ritter et al., 2018a; Yang and Tsai, 2017). FGAs bind to dopamine receptors more tightly than SGAs, which contributes to their effectiveness, but also to their well-known potency to cause extrapyramidal movement symptoms (EPS) (Stahl, 2013a). SGAs also act on multiple other receptors, and these actions contribute to their benefits and adverse effects (Ferrin et al., 2016; Olten and Bloch, 2018). SGAs are as efficient as FGAs in reducing psychotic symptoms, but in addition, they may alleviate negative symptoms and have anti-depressive effects (Ferrin et al., 2016; Lee et al., 2018; Liemburg et al., 2012; Stahl, 2013a). Due to their multiform receptor profile, SGAs have less neurological adverse effects, but metabolic adverse effects, such as weight gain, dyslipidaemia, insulin resistance and type 2 diabetes, may be more common (Ballon et al., 2014; Lee et al., 2018; Roerig et al., 2011; Siafis et al., 2018).

Children seem to be especially vulnerable to SGA-induced metabolic adverse effects, but neurological adverse effects are not absent, either. These adverse effects may emerge early during the SGA treatment, and a longer treatment duration elevates the risk of both (Correll, 2008; Galling et al., 2016; Garcia-Amador et al., 2015; Libovitz and Nurmi, 2021; Martínez-Ortega et al., 2013; Nicol et al., 2018; Rasimas and Liebelt, 2012; Sjo et al., 2017). Furthermore, very little is known about the long-term effects of SGAs on cardiovascular health and the developing human CNS (Correll and Blader, 2015).

SGA use has increased notably in children and adolescents during the last decade (Hálfdánarson et al., 2017; Højlund et al., 2019; Kalverdijk et al., 2017; Kronström et al., 2018; Piovani et al., 2019; Varimo et al., 2020). SGA initiation in children is most often associated with severe mental disorders that require long-term symptomatic treatment, such as psychosis, bipolar disease, Tourette's syndrome and

aggression related to developmental and conduct disorders (Kendall et al., 2013; Lee et al., 2018; Loy et al., 2017; Schneider et al., 2014). SGAs have shown efficacy in treating these disorders, but at present most efficacy and safety studies in children cover only short-term treatment. Official indications in children under the age of 13 years are few (Duodecim lääketietokanta; Lee et al., 2018). In child psychiatry, SGAs are often prescribed outside the official indications (off-label), most commonly as a symptomatic treatment for aggression, behavioural disturbances and affect dysregulation (Kloosterboer et al., 2018; Piovani et al., 2019; Oerbeck et al., 2021).

While the efficacy in off-label use is not guaranteed and concerns about safety exist, individual risk assessment and the systematic monitoring of outcome and adverse effects are essential (Brauner et al., 2016; Kokki, 2017; Lehtonen, 2019; Putignano et al., 2019; Santosh et al., 2017; Sharma et al., 2016). Several guidelines for the monitoring of SGA treatment in children highlight the need for careful diagnostics, the screening of individual risk factors and the estimation of sufficient psychosocial treatments (Dinnissen et al., 2020; Kealey et al., 2014). Further, to prevent and detect possible adverse effects, life-style education and the regular monitoring of growth, metabolic parameters, neurological status and outcome are recommended (Dinnissen et al., 2020; Kealey et al., 2014; Melamed et al., 2021; Pringsheim et al., 2011b). However, at present, the majority of children using SGAs do not receive adequate monitoring (Chen et al., 2018; Coughlin et al., 2018; Dinnissen et al., 2020; Hayden et al., 2019; Javaheri et al., 2019; Jazi et al., 2020; Kealey et al., 2014; Okumura et al., 2018). Studies have described interventions that aim to improve SGA monitoring in children and adolescents, but the results have been modest and monitoring rates have varied (Melamed et al., 2021).

In child psychiatry, psychosocial interventions have traditionally been the first-line treatment, but in recent decades, psychotropic medications have established their place alongside them. When psychiatric symptoms are severe and affect daily functioning, medication may offer relief and enhance the possibility to benefit from psychosocial treatments. However, medication alone is not enough, and the availability of evidence-based psychosocial interventions prior to and concomitant with SGAs is important (Kealey et al., 2014). Furthermore, safe and efficacious SGA treatment includes regular monitoring. If adverse effects are noticed, the re-evaluation of medication, monitoring and lifestyle is needed, and liaisons with paediatrics should be considered (Correll et al., 2020; Melamed et al., 2021; Sjo et al., 2017).

When this study was initiated, there was very little information available on SGA use in Finnish children. Further, there has been no clear consensus on how

antipsychotic medications should be monitored in children. The main aim of the present study was to explore whether implementation of a systematic monitoring protocol could improve SGA medication safety in child psychiatric patients. This study also aimed to describe the clinical use of SGAs and the patients' medical and socio-demographic background factors at a university hospital child psychiatric unit in Finland. Furthermore, the study aimed to describe SGA prescribing and monitoring practices and the detected benefits and adverse effects before and after the monitoring protocol implementation, and to assess how the implemented monitoring protocol was followed in a clinical setting.

2 REVIEW OF THE LITERATURE

2.1 Antipsychotic medications in child psychiatry

Mental disorders often have their onset during childhood or adolescence (Kessler et al., 2007). Early interventions aiming to promote healthy development, minimise disability and reduce the distress of patients and families are important. Treatment methods in child psychiatry have traditionally been based on psychosocial interventions. However, in recent decades, evidence concerning psychotropic medications has emerged. When used concurrently with psychosocial treatments, psychotropic medications may be helpful or even necessary, especially in the treatment of severe mental disorders during childhood (Solmi et al., 2020).

2.1.1 History

The discovery of chlorpromazine and its antipsychotic effects in 1952 launched a new era in psychiatry (Howland, 2016; Shen, 1999). Chlorpromazine and the development of other first-generation antipsychotic agents (FGA) between 1954 and 1975 led to the decrease of severe symptoms and hospitalisation rates in patients with schizophrenia or other psychoses (Aringhieri et al., 2018; Shen, 1999). Clozapine, the first of the atypical or second-generation antipsychotics (SGA), was discovered in 1959 and released to the European market in the early 1970s. Due to a severe adverse effect (agranulocytosis), which led to the death of several patients in Finland in 1975, it was temporarily withdrawn, but reintroduced in 1990 with directions for careful blood count monitoring (Crilly, 2007; Idänpää-Heikkilä et al., 1975; Shen, 1999). The re-entry of clozapine led to the development of other SGAs. Risperidone was released in 1994, olanzapine in 1996 and quetiapine in 1997 (Shen, 1999). Notably, SGAs showed efficacy not only against the positive symptoms of schizophrenia, but they also decreased cognitive deterioration and therefore

increased the patients' integration into society (Aringhieri et al., 2018). The clinical status of SGAs was further strengthened due to the reduced appearance of extrapyramidal movement symptoms (EPS) (Lee et al., 2018).

At the beginning, SGAs were mostly used on adult patients. The United States Food and Drug Administration (FDA) approved risperidone in 2006 and aripiprazole in 2009 for limited paediatric use (irritability in autistic disorder) (Pathak et al., 2010; Seida et al., 2012). In 2008, risperidone was approved in Europe for the short-term treatment of aggression in children from the age of 5 years with subaverage intellectual functioning or mental retardation. At present, there are 20 FGAs and 13 SGAs available on the Finnish market (Duodecim lääketietokanta). However, only risperidone and ziprasidone are approved for children under the age of 13 years. Despite the official approval, ziprasidone is not often used for children in Finland (Saastamoinen et al., 2017).

2.1.2 SGA prescriptions in children

Prior to 1980-90, child psychiatric assessment was mostly dominated by the psychoanalytical framework, and diagnosis was not considered as a necessary goal (Cantwell, 1996; Hirshbein, 2019). However, with the introduction of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) III in 1980 and especially the DSM IV in 1994, followed by the 10th revision of the International Classification of Diseases (ICD-10) in 1996, diagnostics and the conceptualisation of childhood psychiatric disorders began to change towards a more symptom-based model, favouring the acceptance of psychotropic medications (Cantwell, 1996; Hirshbein, 2019). This change in conceptualisation, possibly together with the broadening of indications of antidepressant drugs, contributed to the emergence of psychotropic treatment in children (Hirshbein, 2019; Najjar et al., 2004; Safer et al., 1997).

Stimulant prescriptions in the child and adolescent population began to emerge in the USA already in the early 1970s (Safer et al., 1996; Safer et al., 1997; Zito et al., 2003). A marked overall increase in psychotropic prescriptions occurred in the USA between 1991 and 1996, and stimulants and antidepressants were the most prescribed psychotropic medications for children and adolescents (Safer et al., 1996; Safer et al., 1997; Zito et al., 2003). During the same period, the overall rate of antipsychotic prescriptions remained constant, but SGAs began to replace FGAs. Since the introduction of SGAs, the prescribing of antipsychotics for children and

adolescents has increased in many western countries (Najjar et al., 2004; Verdoux et al., 2010). Concurrently, the non-psychotic indications of SGAs have increased (Verdoux et al., 2010). Even though SGA prescription rates differ between countries, the rates have continued to increase during the past decades (Hálfdánarson et al., 2017; Højlund et al., 2019; Kalverdijk et al., 2017; Kronström et al., 2018; Piovani et al., 2019). However, in some countries with high prescription rates (e.g. the USA and the Netherlands), a levelling or even decreasing trend has been seen in recent years (Hálfdánarson et al., 2017; Kalverdijk et al., 2017; Piovani et al., 2019). The rates of antipsychotic prescriptions are generally higher in the USA compared to European countries (Hálfdánarson et al., 2017). In Finland, the incidence of antipsychotic use did not significantly change in preschoolers, but increased 1.4-fold in primary schoolers (7-12 years) and 2.2-fold in adolescents (13-17 years) between 2008 and 2017, with an especially marked increase between 2015 and 2017 (Varimo et al., 2020).

2.1.3 Factors associated with SGA prescriptions in children

The most prescribed SGAs in children and adolescents are risperidone, aripiprazole, quetiapine and olanzapine (Højlund et al., 2019; Nesvåg et al., 2016; Saastamoinen et al., 2017; Varimo et al., 2020). In children and adolescents in Scandinavia, quetiapine has overtaken risperidone in recent years, and the incidence of SGA prescriptions in girls has exceeded that of boys (Højlund et al., 2019; Varimo et al., 2020). Further, overall doses have reduced, possibly reflecting the increase of off-label prescribing (Højlund et al., 2019).

During childhood, boys are prescribed SGAs more often and for longer periods. However, in adolescence the gender difference diminishes and the incidence of prescriptions in girls exceeds that of boys (Kloosterboer et al., 2018; Piovani et al., 2019; Saastamoinen et al., 2017). Common diagnoses among children and adolescents using SGAs are hyperkinetic disorders, anxiety and autism spectrum disorders (ASD) (Nesvåg et al., 2016; Saastamoinen et al., 2017; Varimo et al., 2020). Diagnoses of psychosis and bipolar disorder are less frequent, accounting for approximately 10-15% of all diagnoses (Nesvåg et al., 2016; Saastamoinen et al., 2017). Risperidone is commonly prescribed to primary school-aged boys for symptoms related to attention deficit hyperactivity disorder (ADHD), intellectual disability (ID), and ASD (Nesvåg et al., 2016; Saastamoinen et al., 2017). Quetiapine,

on the other hand, is commonly prescribed to adolescent girls for anxiety, affective disorders and psychotic symptoms (Nesvåg et al., 2016; Saastamoinen et al., 2017).

In a recent study, the mean duration of SGA treatment in Finnish children and adolescents was approximately 17 months (Varimo et al., 2021). The respective figure in a Dutch study was 19 months (Kloosterboer et al., 2018). Male gender, earlier treatment initiation and risperidone as the first SGA were associated with a longer treatment duration, whereas quetiapine was associated with a shorter treatment duration (Kloosterboer et al., 2018; Varimo et al., 2021).

2.1.4 Special populations with high rates of SGA prescriptions

Children with ID and ASD are more likely to be prescribed antipsychotics than their peers, mainly for aggression (Brophy et al., 2018; Henderson et al., 2021; Park et al., 2016). Children with ID are younger at the time of SGA medication initiation, and the duration of the treatment is longer than in their peers (Brophy et al., 2018). Furthermore, male gender, diagnosis of epilepsy or ADHD, and difficulties in school increase the likelihood of SGA initiation in this patient group (Brophy et al., 2018). Children in residential or foster care are also prescribed SGAs more often than their peers, and in this patient group off-label indications and psychotropic polypharmacy are common (Crystal et al., 2016; McLaren et al., 2018; Oerbeck et al., 2021).

2.2 Indications and efficacy of SGAs in children

SGA initiation in children is most often associated with severe and long-lasting disorders, such as psychosis, bipolar disease, Tourette's syndrome and aggression related to ASD, ID, ADHD and conduct disorders (Kendall et al., 2013; Lee et al., 2018; Loy et al., 2017; Schneider et al., 2014). At present, most studies assessing the efficacy and safety of SGAs in children cover only short-term treatment and highlight the need for the careful individual assessment of benefits and risks.

2.2.1 Official indications

In Europe and the USA, medicines need to be authorised by the European Medicines Agency (EMA) and the FDA, respectively. The authorisation decisions of the EMA and FDA are usually well aligned, but sometimes their estimations of

efficacy may differ (Kashoki et al., 2019). The EMA- and FDA-approved SGAs in children are presented in Table 1. Clozapine, iloperidone and cariprazine are not approved for children (EMA; Lee et al., 2018).

Table 1. Official indications for children under the age of 13 years in Finland (according to the EMA) and the United States (according to the FDA) ([1] Duodecim lääketietokanta; [2] Lee et al., 2018).

SGA	Indication for children under the age of 13 years in Finland[1]	Indication for children under the age of 13 years according to the FDA[2]
Risperidone	Aggression and/or conduct disorder in patients ≥ 5 years of age with diagnosis of intellectual disability (max 6 weeks)	Bipolar mania (≥10 years) Irritability associated with autism (≥5 years)
Quetiapine		Bipolar mania (≥10 years)
Aripiprazole		Bipolar mania (≥10 years) Irritability associated with autism (≥6 years) Tourette's disorder (≥6 years)
Olanzapine		Bipolar depression (≥10 years)
Asenapine		Bipolar mania (≥10 years)
Lurasidone		Bipolar depression (≥10 years)
Paliperidone		Schizophrenia (≥12 years)
Ziprasidone	Manic or mixed episodes of bipolar disorder (≥ 10 years)	

2.2.2 Off-label use

Off-label refers to prescriptions outside the official indications with respect to age, dosage, indication or route (EMA; Putignano et al., 2019). Off-label prescribing may be advantageous, but it should be based on a careful clinical evaluation and evidence of safety, efficacy, and clinical experience. Further, informed consent is required (Kokki, 2017; Lehtonen, 2019; Putignano et al., 2019; Sharma et al., 2016). Due to the limited paediatric pharmacological trials, approximately half of all paediatric prescriptions are off-label (Kokki, 2017; Putignano et al., 2019). Excluding ADHD medications, psychotropics and especially SGAs are mainly prescribed off-label in children, usually because of the indication or the duration of the treatments (Brauner et al., 2016; Schneider et al., 2014; Varimo et al., 2021).

2.2.3 Efficacy

Most studies concerning the efficacy of SGAs in children cover "short-term" treatments (Lee et al., 2018; Loy et al., 2017; Pagsberg et al., 2017). "Short-term" commonly refers to a treatment of days to weeks, whereas "long-term" refers to at least six months (Loy et al., 2017; Vitiello et al., 2009).

Different SGAs, excluding ziprasidone and asenapine, have showed equal efficacy in the short-term treatment of early onset schizophrenia and psychotic

symptoms in children and adolescents (Coustals et al., 2020; McClellan et al., 2018; Pagsberg et al., 2017; Xia et al., 2018). Furthermore, in manic or mixed bipolar episodes, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone and asenapine may be effective (Bipolar disorder: Current Care Guideline, 2021; Coustals et al., 2020; Lee et al., 2018; Masi et al., 2015). In bipolar depressive episodes, only olanzapine combined with a serotonin selective re-uptake inhibitor (SSRI) fluoxetine and lurasidone monotherapy may have efficacy (Bipolar disorder: Current Care Guideline, 2021; Findling et al., 2018; Lee et al., 2018).

Risperidone and aripiprazole are effective at least in the short term in Tourette's syndrome and in the treatment of irritability and aggression related to ASD and ID (Coustals et al., 2020; Lee et al., 2018; McQuire et al., 2015; Shafig and Pringsheim, 2018; Sharma et al., 2018). Furthermore, olanzapine may have efficacy in irritability and aggression related to ASD, but its unfavorable metabolic effects have limited its use (Sharma et al., 2018). More studies on quetiapine and ziprasidone are needed (Sharma et al., 2018). There is also some evidence that risperidone can reduce aggression and irritability across diagnoses in the short-term in paediatric use, especially in children with conduct disorders and ADHD (Conduct disorder: Current Care Guideline, 2018; Coustals et al., 2020; Lee et al., 2018; Loy et al., 2017; Pringsheim et al., 2015; Schalkwyk et al., 2017; Shafig and Pringsheim, 2018). Again, more studies are needed.

Due to the limited data especially on the long-term effects in children, SGA medication should be reserved for the treatment of severe mental disorders after proper diagnostics. Short-term treatment and the lowest possible effective doses are recommended (Shafig and Pringsheim, 2018). Further, there are evidence-based psychosocial treatments available, e.g. for conduct disorder, and SGA treatments should always be preceded or accompanied with individually tailored psychosocial treatments (Conduct disorder: Current Care Guideline, 2018; Shafig and Pringsheim, 2018).

2.3 Mechanisms of action of antipsychotic medications

The therapeutic and adverse effects of psychotropic medications are mediated by the receptors they involve (Marin and Escóbar, 2013). The main neurotransmitter systems in the central nervous system (CNS) are serotonin, dopamine, norepinephrine, acetylcholine, histamine, glutamate and gamma-aminobutyric acid (GABA) (Stahl, 2013b). Psychotropic medications can either activate or inhibit

neurotransmitter receptors or affect the amount of the neurotransmitters in the synaptic cleft (Marin and Escóbar, 2013). Antipsychotic agents affect mainly dopamine neurotransmission, but they also have diverse effects on other neurotransmitters, especially on the serotonergic and histaminergic systems.

2.3.1 The brain dopaminergic system

The brain dopaminergic system consists of five pathways (Stahl, 2013b). The mesolimbic and mesocortical pathways originate from the ventral tegmental area (VTA) in the brainstem. The mesolimbic pathway projects to the limbic system, and it participates in the regulation of emotions, motivation, pleasure and reward. The mesocortical pathway projects to the prefrontal cortex and has a role in cognition and executive functions and the regulation of emotions. The nigrostriatal dopaminergic pathway is a part of the extrapyramidal nervous system and participates in movement control. The tuberoinfundibular pathway connects the hypothalamus to the anterior pituitary and takes part in lactation through influencing prolactin synthesis and release. The recently discovered thalamic dopaminergic pathway may regulate sleep and arousal.

It is hypothesised that psychotic, aggressive and manic symptoms are mediated by mesolimbic hyperactivity, whereas negative symptoms of psychosis, such as a lack of sense of pleasure (anhedonia), lack of motivation and social withdrawal are mediated by mesocortical hypoactivity (Stahl, 2013b; Stahl, 2018; Yang and Tsai, 2017). Consistently, drugs that increase dopamine activity in the CNS, such as dopamine agonists and amphetamine, can trigger psychotic symptoms (Ritter et al., 2018a). However, diffuse neurotransmitter systems such as dopamine, serotonin, GABA and glutamate are highly interconnected and modulate one another (Yang and Tsai, 2017). It is hypothesised that neurodevelopmental dysfunction between glutamate receptors and GABAergic interneurons in the prefrontal cortex can lead to the reduction of inhibition to excitatory glutaminergic neurons, and further on, contribute to dopaminergic hyperactivity in the mesolimbic area, thus leading to positive psychotic symptoms. However, in the prefrontal cortex, this dysfunction reduces the activity of dopamine neurons, and in the mesocortical pathway it promotes the inhibitory effects of GABA to dopamine release, thus resulting in negative symptoms (Ritter et al., 2018a; Stahl, 2013b). Consistently drugs acting as glutamate-antagonists, such as ketamine and phencyclidine, may induce both positive and negative symptoms (Stahl, 2013b). Furthermore, serotonergic

hyperactivation in the prefrontal cortex may result in the downstream release of glutamate and thus to positive and negative symptoms (Stahl, 2018). This can also be demonstrated with psychedelics, such as LSD, which is a $5HT_{2A}$ agonist (Stahl, 2018).

2.3.2 Dopamine receptors in the brain

Dopamine receptors are G-protein coupled receptors that are classified into two functional classes with five different types of receptors: 1) D_1-type (including D_1 and D_5 receptors) and 2) D_2-type (including D_2, D_3 and D_4 receptors), based on their structural and functional properties (Aringhieri et al., 2018; Nash, 2017; Ritter et al., 2018b). D_1 and D_2 receptors are expressed in different but partly overlapping areas in the frontal cortex, striatum, limbic system, thalamus and hypothalamus (Ritter et al., 2018b). D_2 receptors are also found in the pituitary gland. In addition to dopaminergic neurons, D_2 receptors are found in glutamatergic, GABAergic and cholinergic nerve terminals. However, dopamine receptors are also found outside the CNS, including in the pancreas, kidneys and vascular system (Nash, 2017).

2.3.3 Effects of FGAs and SGAs

All antipsychotic agents affect dopamine transmission, but there are important pharmacodynamic differences between FGAs and SGAs.

The main mediator of antipsychotic effects is the blockage of dopamine D_2 receptors in the mesolimbic pathway (Ferrin et al., 2016; Ritter et al., 2018a; Yang and Tsai, 2017). D_2 antagonism may cause anhedonia and a lack of motivation, as the mesolimbic area participates in the experience of pleasure and reward (Stahl, 2013a). Mesocortical D_2 antagonism contributes to the worsening of negative symptoms. In the nigrostriatal and tuberoinfundibular pathways, D_2 antagonism leads to EPS and hyperprolactinemia, respectively.

FGAs have a higher affinity to D_2 receptors compared to SGAs (Ferrin et al., 2016; Girgis et al., 2008; Stahl, 2013a). Some SGAs are partial agonists, i.e. they bind and activate D_2 receptors but to a lesser extent than dopamine itself (Ferrin et al., 2016; Girkis et al., 2008; Stahl, 2013a). SGAs also act on multiple other receptors, most importantly serotonin (5HT), but also histaminergic (H_1), muscarinic ($M_{1\text{-}4}$) (cholinergic) and adrenergic (α_1) receptors (Correll, 2008, Stahl, 2013a, Ferrin et al.,

2016). The multiform receptor profile is a benefit but also contributes also to SGAs' adverse effects (Table 2) (Ferrin et al., 2016; Olten and Bloch, 2018).

The prefrontal cortex, which is rich in dopaminergic receptors, participates in cognitive processing, attention, executive functioning, memory and affect regulation (Liemburg et al., 2012). The weaker D_2 affinity and concomitant 5HT-antagonism of SGAs seems to increase or preserve prefrontal activation compared to FGAs. In different brain areas, 5HT receptor activity may also promote anti-depressive effects (Ferrin et al., 2016; Stahl, 2013a). These effects may further contribute to the alleviation of negative symptoms in psychotic illnesses (Liemburg et al., 2012). In the striatal area, SGA-induced 5HT receptor activity may contribute to dopamine increase and the mitigation of EPS, whereas in the tuberoinfundibular pathway, 5HT antagonism reduces D_2 antagonism-induced hyperprolactinemia (Ferrin et al., 2016; Stahl, 2013a). Through the antagonism of M_1 and H_1-receptors, SGAs influence sleep and arousal, and induce, e.g. sedation and cognitive problems. Furthermore, α_1-antagonism may cause postural hypotension, and $5HT_{2C}$-, H_1- and M_3-antagonism contributes to increased appetite and weight gain (Correll 2008; Heal et al., 2021; Stahl, 2013a) (Table 2).

Table 2. Effects and adverse effects of receptor blockage, relative binding affinities and adverse effect profiles of commonly used SGAs (modified from the tables of Correll 2008, Ferrin et al., 2016, Fereira et al., 2020, Heal et al., 2012, Siafis et al., 2018, Stahl 2013).

Receptor	Effect	Relation to adverse effects	ZIPD[1]	APZ[2]	QUET[3]	RIS[4]	OLZ[5]	CLZ[6]
D2	Antipsychotic Antimanic	EPS Prolactin increase Increased food intake	+++	+++[7]	+	+++	++	+
$5HT_{1A}$[7]	Antidepressant Anxiolytic	Decreased food intake Anti-EPS Prolactin decrease	++	+++	+	+	+/-	+
$5HT_{2A}$	Antidepressant Anxiolytic	Increased food intake Weight gain Anti-EPS	++++	++	++	++++	+++	++
$5HT_{2C}$		Increased food intake	++	++	+	++	++	++
α_1		Increased food intake Postural hypotension Sedation	++	++	+++	+++	++	+++
α_2	Antidepressant	Decreased food intake Increased blood pressure	+/++	+/++	+	++	++	++
H_1	Anxiolytic	Increased food intake Sedation Anti-EPS	++	++	+++	++	+++	+++
M_1		Anti-EPS Memory Cognition Dry mouth	+/-	+/-	++	+/-	++	+++
Adverse effect profile								
Sedation			+	+/-	++	+	+/++	+++
Cognitive impairment			-	-	+/++	-	++	+++
EPS			+	-	-	++	-	-
Tardive dyskinesia			+/-	+/-	+/-	+/-	+/-	-
Weight gain			-	+	++	+++	++++	+++++
Glucose abnormality			+/-	+/-	+/++	+/++	+++	+++
Hyperlipidaemia			+/-	+/-	++	+	+++	++
Hyperprolactinaemia			+	-	-	+++	+	+

[1]ziprasidone, [2]aripiprazole, [3]quetiapine, [4]risperidone, [5]olanzapine, [6]clozapine, [7]partial agonist

2.4 Neurological adverse effects of SGAs

An antipsychotic effect is induced with a mesolimbic D_2 receptor occupancy of 65–75%, but when the level of occupancy increases to > 80%, the risk of EPS is evident (Ferrin et al., 2016; Rasimas and Liebelt, 2012) (Table 2 and Table 3).

Long-term nigrostriatal D_2 blockage may result in tardive dyskinesia (TD), which is a complex and potentially irreversible EPS, usually manifesting after months or years of antipsychotic exposure (Table 3) (Lerner et al., 2017; Stahl, 2013a). The exact pathophysiology is unknown, but suggested reasons are long-term D_2 blockage-induced receptor up-regulation and dopamine hypersensitivity, disturbed balance between dopamine and other neurotransmitters, and neurotoxicity (Lerner et al.,

2015; Solmi et al., 2020). Genetic factors, old age, female sex, ID, brain damage and prior EPS increase the risk of TD (Solmi et al., 2018). Sometimes if antipsychotic medication is discontinued early enough, symptoms may gradually cease, but severe TD is often permanent. Treatment options include pharmacological interventions (Lerner et al., 2015). Tardive dystonia is a subtype of TD, and younger individuals may be more prone to this form of TD (Pringsheim et al., 2011a).

Neuroleptic malignant syndrome is a rare but potentially fatal syndrome associated with D_2 blockage in the nigrostriatal pathway (Table 3) (Ghaziuddin et al., 2017; Rasimas and Liebelt, 2012; Stahl, 2013a).

Table 3. Description of antipsychotic-induced neurological adverse effects (Pringsheim et al., 2011a; Rasimas and Liebelt, 2012; Stahl, 2013a).

Symptom	Description
Acute dystonia/dyskinesia (in days after SGA initiation)	Repetitive movements and muscle contractions (cranial, neck and trunk muscles)
Akathisia	Restlessness, compulsive need to move Feeling of tension Shaking, rocking movements Feeling of discomfort and anxiety Agitation
Parkinsonism	Resting tremor Slowness of movements Rigidity
Tardive dyskinesia (TD)	Stereotypic repetitive movements Chewing Affects often mouth, lips, trunk
Tardive dystonia (subtype of TD)	Involuntary, choreo-athetotic movements of limbs, trunk, neck and face
Withdrawal dyskinesia (Following abrupt discontinuation of SGA)	Dyskinesias/muscle contractions affecting limbs, trunk, neck after discontinuation of antipsychotic medication
Neuroleptic malignant syndrome	Muscular rigidity Hyperthermia Altered mental status Autonomic dysfunction (e.g. tachycardia, hypertension) Coma

2.5 Metabolic adverse effects in SGAs

Multiple psychiatric disorders – such as schizophrenia, depression, anxiety and ADHD – increase the risk of metabolic disorders, cardiovascular disease, and premature mortality (Penninx et al., 2018). The mechanisms are various, but lifestyle factors, a reduced likelihood of seeking medical care and psychotropic medications contribute to the risk (Pennnix et al., 2018).

Even though SGAs are associated with a lower risk of EPS than FGAs, they associate with an increased risk of metabolic effects, such as weight gain, dyslipidaemia, insulin resistance (IR) and type 2 diabetes (Roerig et al., 2011). The metabolic risk differs between SGAs and between individuals (Table 2) (Roerig et

al., 2011). Several predisposing genetic factors have been proposed, but in clinical settings it is not yet possible to identify this genetic vulnerability (Bretler et al., 2019; Libowitz and Nurmi, 2021).

Regulation of body energy intake and metabolism happens on the central and peripheral levels and these systems connect through complex neural and endocrine systems, both of which are targeted by SGAs (Ballon et al., 2014; Roerig et al., 2011; Siafis et al., 2018). Increased appetite and weight gain are important but not the only factors behind SGA-induced metabolic effects (Ballon et al., 2014; Stahl, 2013a). SGAs induce a complex imbalance in body energy homeostasis, which affects both the intake and expenditure of energy (Table 2) (Endomba et al., 2020; Roerig et al., 2011; Singh et al., 2019). Neurotransmitters, hormones, low-grade inflammation, and the gut microbiome contribute to these effects (Endomba et al., 2020; Singh et al., 2019). The detailed molecular and neurochemical mechanisms and their interplay are not fully understood (Ballon et al., 2014; Heal et al., 2021; Nash 2017; Singh et al., 2019; Stahl, 2013a).

2.5.1 Central regulation of energy intake and SGAs

Central regulation of energy intake is located in the satiety and hunger centres in the hypothalamus and brainstem, and in the reward and pleasure systems in the corticolimbic area (Galen et al., 2021; Siafis et al., 2018). Furthermore, cognition contributes to food intake (Singh et al., 2019). In the hypothalamic area, appetite-stimulating (orexigenic) and -inhibiting (anorexigenic) neurons receive and integrate information from other parts of the CNS and peripheral organs, thus regulating energy intake. Neuronal activity is influenced by multiple neurotransmitters and hormones (Libowitz and Nurmi, 2021; Roerig et al., 2011; Singh et al., 2019; Sohn, 2015). Orexigenic peptides – e.g. orexin, neuropeptide Y (NPY) and agouti-related peptide (AgRP) – and anorexigenic peptides – e.g. pro-opiomelanocortin (POMC) – mediate the responses in these neuronal circuits (Roerig et al., 2011; Singh et al., 2019). SGAs increase the expression of AgRP and NPY and reduce the expression of POMC, mainly through effects on different neurotransmitters (Carli et al., 2021).

Dopamine's effects on food intake associate with the reward-pleasure system in the corticolimbic area (Nash et al., 2017). SGA-induced D_2 antagonism increases appetite and the seeking of calorie-rich food and reduces the motivation for physical activity (Nash, 2017; Singh et al., 2019).

5HT associates with both the reward-pleasure and hunger-satiety systems (Galen et al., 2021). Stimulation of 5HT receptors results in satiety, but SGA-induced $5HT_{2A}$ and $5HT_{2C}$ antagonism results in an increased appetite (Roerig et al., 2011).

H_1 receptors mediate anorexigenic effects in the hypothalamus (Roerig et al., 2011; Singh et al., 2019; Sohn, 2015). H_1 antagonism results in increased food intake and is one of the key mechanisms responsible for SGA-induced weight gain (Deng et al., 2010; Kaar et al., 2020; Roerig et al., 2011; Singh et al., 2019).

The role of $M_{1\text{-}4}$- and α_1-receptors in SGA-induced weight gain is not clear (Reynolds et al., 2017).

2.5.2 Peripheral regulation of energy intake and SGAs

Peripheral energy intake regulation involves the gastrointestinal system, liver, pancreas, muscles and adipose tissue (Ballon et al., 2014; Siafis et al., 2018). Ghrelin, leptin and adiponectin are peripheral peptide hormones that participate in the regulation of energy intake.

Ghrelin is an orexigenic peptide produced in the stomach, and it signals to the brain to stimulate food intake. Ghrelin levels rise before meals and go down after (Heisler and Lam, 2017; Roerig et al., 2011). In the hypothalamic area, ghrelin stimulates orexigenic neurons and inhibits anorexic neurons, thus leading to increased food intake (Singh, 2019). Obese individuals have high ghrelin levels (Weis and Lustig, 2014).

Leptin is an anorexigenic peptide hormone produced in the adipose cells. It participates in the long-term regulation of appetite and metabolic activity and mediates information from adipose tissue energy reserves to the hypothalamus (Luo and Liu, 2016; Roerig et al., 2011; Weis and Lustig, 2014). It stimulates hypothalamic POMC neurons and inhibits NPY/AgRP neurons, resulting in a decreased appetite (Libowitz and Nurmi, 2021; Luo and Liu, 2016; Roerig et al., 2011). Usually, low levels of leptin increase the appetite. However, obese individuals may have elevated leptin levels due to a possible resistance to leptin's appetite-inhibiting effects (Luo and Liu, 2016). Leptin functions also as a cytokine, and increased leptin levels contribute to inflammation (Singh et al., 2019). Adipose tissue also produces other pro-inflammatory cytokines, and obesity increases their formation (Tagi et al., 2019).

Adiponectin is an adipose tissue-originating orexigenic peptide with anti-inflammatory properties (Reynolds et al., 2017). It has the ability to block local

inflammatory cytokine production. Adiponectin also increases insulin sensitivity in multiple tissues, primarily in the liver (Luo and Liu, 2016; Reynolds et al., 2017).

Insulin is a peptide hormone produced in the pancreatic β-cells. It has a wide distribution of receptors, and it participates in metabolic regulation through both central (regulation of food intake) and peripheral (liver, adipose tissue, muscle) mechanisms (Ighbariya et al., 2017; Nash et al., 2017; Tagi et al., 2019; Weis and Lustig, 2014). Insulin secretion is regulated by the nutritional state, hormones, and autonomic nervous system (Sperling et al., 2014). Glucose ingestion stimulates and fasting inhibits insulin release (Sperling et al., 2014). In the hypothalamus, insulin activates anorexigenic neurons and inhibits feeding (Weis and Lustig, 2014). Both insulin and leptin also participate in the modulation of reward and pleasure stimuli in the corticolimbic area (Libowitz and Nurmi, 2021; Weis and Lustig, 2014).

In the liver, insulin reduces the production of glucose (gluconeogenesis) and promotes the formation of free fatty acids (FFA) and triglycerides (TG) (lipogenesis) (Weis and Lustig, 2014). In the adipose tissue, insulin stimulates the uptake of glucose to adipose cells and lipogenesis (Luo and Liu, 2016; Tagi et al., 2019). Insulin also promotes the differentiation of adipocytes (Luo and Liu, 2016; Tagi et al., 2019). In the muscles, insulin promotes the storage of glucose (Ighbariya et al., 2017; Tagi et al., 2019). Furthermore, insulin contributes to the ovarial production of androgens and the retention of sodium in the kidneys (Tagi et al., 2019). Notably, insulin is also associated with learning and memory (Nash et al., 2017).

SGAs have been associated with increased ghrelin and leptin levels and decreased adiponectin levels (Liebowitz and Nurmi, 2021; Roerig et al., 2011; Singh et al., 2019). These changes contribute to orexigenic stimulation and anorexigenic inhibition in the hypothalamus, but it is not clear whether these are the direct effects of SGAs or result from weight gain (Roerig et al., 2011; Singh et al., 2019). Furthermore, a disturbed balance between leptin and adiponectin contributes to the expression of inflammatory cytokines (Ferreira et al., 2020; Liebowitz and Nurmi, 2021; Roerig et al., 2011; Singh et al., 2019).

SGAs' direct effects on adipose tissue fatty acid synthesis and adipocyte differentiation contribute to lipid accumulation (Carli et al., 2021; Ferreira et al., 2020; Singh et al., 2019). SGAs, excluding quetiapine, increase fasting plasma TGs and may negatively influence plasma HDL (Heal et al., 2012). Increased plasma FFA further reduces muscle insulin sensitivity and contributes to the development of IR (Carli et al., 2021).

2.5.3 Insulin resistance and SGAs

Insulin resistance (IR) refers to decreased tissue response to insulin, and it is closely related to obesity. However, in puberty physiological IR promotes growth and pubertal development (Tagi et al., 2019). During the insulin resistant state, hyperinsulinemia is needed to maintain glucose uptake to the liver and muscles. In the liver, hyperinsulinemia hyperactivates lipogenesis, resulting in increased plasma TG and low plasma high-density lipoprotein (HDL) levels (Ighbariya et al., 2017; Tagi and Chiarelli, 2020). Accumulation of TGs in the liver contributes to the formation of fatty liver disease (Tagi and Chiarelli, 2020). In the adipose tissue, IR accelerates lipolysis and the increased release of FFA (Weis and Lustig, 2014). In the kidneys, hyperinsulinemia stimulates sodium reabsorption and promotes hypertension, and in the ovaries it promotes androgen production and contributes to polycystic ovaries (Ighbariya et al., 2017; Tagi and Chiarelli, 2020).

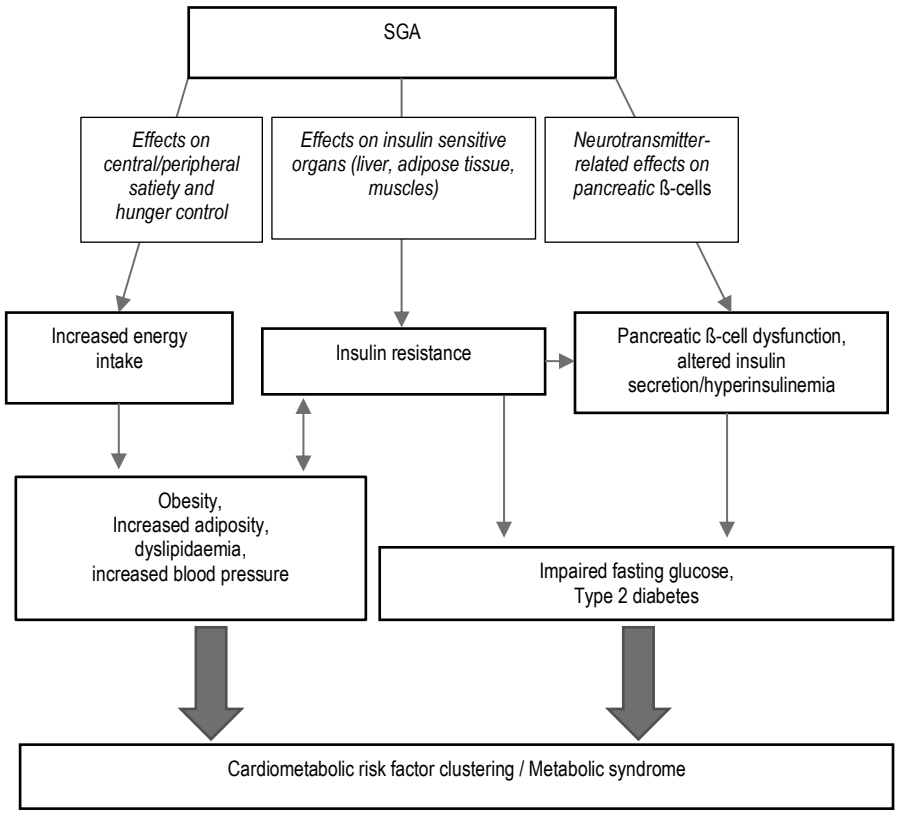
The exact mechanisms of IR are unclear. Obesity and excess adipose tissue are common, but not the only causes. Contributing factors may be obesity-induced FFA, the acceleration of insulin secretion from pancreatic β-cells, and systemic inflammation (Nash, 2017).

SGAs are associated with hyperinsulinemia and IR (Heal et al., 2012; Ighbariya et al., 2017; Libowitz and Nurmi, 2021). This risk is partly mediated by previously mentioned mechanisms, but SGAs also have direct effects on pancreatic β-cells (Carli et al., 2021; Heal et al., 2012; Nash 2017; Roerig et al., 2011). In adults, an SGA-induced decrease in insulin sensitivity appeared during the first two weeks, whereas weight gain became evident after it, suggesting an independent mechanism (Burghard et al., 2018).

Peripheral dopamine and 5HT usually inhibit β-cell insulin secretion, and D_2 antagonism contributes to hyperinsulinemia (Carli et al., 2021). Further, 5HT antagonism can reduce glucose uptake and induce IR in liver and muscle tissues, but direct effects on pancreatic β-cells are not yet clear (Ballon et al., 2014; Carli et al., 2021; Roerig et al., 2011).

H_1 antagonism can reduce glucose uptake in the muscles (Carli et al., 2021). Antimuscarinic properties and α-antagonism of SGAs may have an impact on β-cell insulin secretion, resulting in hyperinsulinemia (Carli et al., 2021; Reynolds et al., 2017, Roerig et al., 2011; Singh et al., 2019) (Figure 1).

Figure 1. Mechanisms of SGA-induced metabolic adverse effects (Modified from Ballon et al., 2014).



2.6 Cardiovascular adverse effects of SGAs

SGAs may prolong the QT interval in an electrocardiogram (ECG) (Haddad and Andersson, 2002; Jensen et al., 2015). Prolongation of rate-corrected QT (QTc) is a signal of the increased risk of ventricular arrythmia and further ventricular fibrillation and sudden death (Haddad and Andersson, 2002; Roessner et al., 2017). The risk for QTc prolongation differs between SGAs and the dosage (Haddad and Andersson, 2002). However, with individual susceptibility, QTc prolongation can appear regardless of the dose (Haddad and Andersson, 2002). Further, polypharmacy and

concomitant medications, such as ADHD medications may increase the risk (Palanca-Maresca et al., 2016).

Studies have observed a risk of sudden cardiac death in adults using antipsychotics (Haddad and Andersson, 2002; Ray et al., 2009; Zhu et al., 2019). The risk seems to be dose-dependent and varies between different antipsychotics (Ray et al., 2009; Salvo et al., 2016; Zhu et al., 2019). However, in patients with schizophrenia, long-term antipsychotic use seems conversely to decrease all-cause mortality (Taipale et al., 2020).

2.7 Adverse effects of SGAs in children

The body composition and metabolism of children differs from that of adults (Schneider et al., 2014; Vinks et al., 2011). While SGAs are primarily metabolised in the liver, the relatively larger liver mass of children accelerates their metabolism (Lorberg et al., 2019; Rasimas and Liebelt, 2012). Drug distribution and accumulation in children are affected by the larger amount of body water, lower proportion of adipose tissue and smaller amount of plasma albumin for drugs to bind to (Lorberg et al., 2019; Vinks et al., 2011). Thus, children may need relatively larger doses or more frequent dosing compared to adults (Correll, 2011; Lorberg et al., 2019). Furthermore, individual and drug-specific differences, dosages, and durations of treatment contribute to the response and adverse effects (Correll, 2011; Fraguas et al., 2011; Lee et al., 2018; Rasimas and Liebelt, 2012).

SGA treatment causes particularly metabolic but also neurological adverse effects that may emerge early during the treatment. Longer exposure increases the risks (Correll, 2008; Galling et al., 2016; Garcia-Amador et al., 2015; Libovitz and Nurmi, 2021; Nicol et al., 2018; Sjo et al., 2017). Most studies of SGAs in children cover only short-term treatment, and the knowledge of long-term and cumulative effects is insufficient (Correll, 2011; Geller, 2018; Libowitz and Nurmi, 2021).

Increased appetite, weight gain and other negative metabolic effects may affect even 60% of children and adolescents using SGAs, thus contributing to an increased risk for cardiovascular morbidity (Libowitz and Nurmi, 2021; Menard et al., 2019). Further, weight gain negatively affects psychosocial well-being and medication adherence and may thus worsen the overall response (Martínez-Ortega et al., 2013).

2.7.1 Neurological adverse effects in children

SGAs can induce similar neurological adverse effects in children and adults (Carbon et al., 2015; Garcia-Amador et al., 2015). EPS rates in children and adolescents vary across studies depending on the study population, diagnoses and measures (Table 4.). In short-term treatments, EPS have been mild and transient, but longer treatment duration, higher doses, polypharmacy, younger age, lower functional capacity and diagnoses of ID, schizophrenia or bipolar disorder may increase the overall risk and the risk for more severe manifestations (Garcia-Amador et al., 2015; Tural Hesapcioglu et al., 2020; Pringsheim et al., 2017; Rasimas and Liebelt, 2012). Risperidone and olanzapine, probably due to the higher affinity to D_2 receptors, have been associated with a higher risk of EPS compared to quetiapine (Biscontri et al., 2017; Garcia-Amador et al., 2015). Even though the risk is smaller with quetiapine, it is not absent (Biscontri et al., 2017). Further on, a common combination of risperidone and methylphenidate in patients with ADHD may increase the risk for EPS (Stämpfli et al., 2020).

Neuroleptic malignant syndrome is rare, but not absent in children. However, the research literature concerning children is mainly limited to case reports (Ghaziuddin et al., 2017).

Table 4. Rates of neurological adverse effects of second-generation antipsychotics in children and adolescents.

AE	Medicine; Duration	Incidence of AE (%)	n; Mean age (SD) and/or range (years)	Comments	Study
Acute dystonia/dyskinesia	Aripiprazole; exposure varied	4.8	785; 0-18	Meta-analysis In most included studies duration of < 12 weeks, length of the overall exposure not defined	Bernagie et al., 2016
	Aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone; 12 weeks	8.3	342; 13.6 (3.5), 4-19	Naturalistic prospective study, no control group	Carbon et al., 2015
	SGAs (94%), FGAs (6%), combinations (risperidone 52%, aripiprazole 12%, olanzapine 10%); Mean 99.5 (SD 223) days	2.4 (single SGA)	441; 13.3 (3.5), 4-19	Retrospective study	Tural Hesapcioglu et al., 2020
Akathisia	Aripiprazole; exposure varied	8.8	1660; 0-18	Meta-analysis, in most included studies duration of < 12 weeks, length of the overall exposure not defined	Bernagie et al., 2016
	Risperidone and psychotropic polypharmacy; Mean 3.1 (SD 2.0) years	24	114; 11.0 (2.6), 5-17	Randomised, placebo-controlled study risperidone treatment at least one year	Calarge et al., 2016
	Aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone; 12 weeks	4.8	342; 13.6 (3.5), 4-19	Naturalistic prospective study, no control group	Carbon et al., 2015
	Quetiapine; 26 weeks	3.7	380; 14.4 (2.2), 10-17	Open-label continuation study	Findling et al., 2013
	Risperidone, aripiprazole; Mean 10 months (1-30)	11	57; 11.3 (2.63), 6-17	Prospective study, no control group	Pringsheim et al., 2017
Parkinsonism	Risperidone and psychotropic polypharmacy; Mean 3.1 (SD 2.0) years	7	114; 11.0 (2.6), 5-17	Randomised, placebo-controlled study risperidone treatment at least one year	Calarge et al., 2016
	Aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone;12 weeks	15.2	342; 13.6 (3.5), 4-19	Naturalistic prospective study, no control group	Carbon et al., 2015

	Aripiprazole; exposure varied	20.8	755; 0-18	Meta-analysis, in most included studies duration of < 12 weeks, length of the overall exposure not defined	Bernagie et al., 2016
Tardive dyskinesia	Aripiprazole; exposure varied	1.7	1261; 0-18	Meta-analysis, in most included studies duration of < 12 weeks, length of the overall exposure not defined	Bernagie et al., 2016
	Risperidone and psychotropic polypharmacy; Mean 3.1 (SD 2.0) years	2	114; 11.0 (2.6), 5-17	Randomised, placebo-controlled study risperidone treatment at least one year	Calarge et al., 2016
	Any SGA; Weighted mean 330 days	Annual rate 0.3-0.4	783; 9.74, 4-18	Systematic review	Correl and Kane, 2006
	Risperidone, olanzapine, quetiapine; 1 year	5.8	265; 14.4 (2.9), 4-17	Naturalistic prospective study, no control group	Garcia-Amador et al., 2015
Any EPS	Aripiprazole; exposure varied	17.1	1446; 0-18	Meta-analysis, in most included studies duration of < 12 weeks, length of the overall exposure not defined	Bernagie et al., 2016
	Quetiapine; 26 weeks	10	380; 14.4 (2.2), 10-17	Open-label continuation study	Findling et al., 2013
	Risperidone, aripiprazole; Mean 10 months (1-30)	35	57; 11.3 (2.63), 6-17	Prospective study, no control group	Pringsheim et al., 2017
	Risperidone (lo/high dose), placebo; 26 weeks	8	79; 9 (3.1), 5-17	Randomised double-blind (6 weeks) placebo controlled, open-label extension	Kent et al., 2013
	Aripiprazole, placebo; 8 weeks	6.8 (ap- naïve), placebo 0	326 (Aripiprazole 212); mean 9.4-10, 6-17	Randomised double-blind placebo controlled	Mankoski, 2013
	Risperidone, aripiprazole (monotherapy or psycho-tropic polypharmacy); Mean 8.4 (SD 4.5) months	15.4	200; 12 (3), 6-18	Prospective study, no control group	Menard et al., 2019
	Any SGA; Weighted mean 330 days	15.7	198; 9.74	Systematic review	Correl and Kane, 2006
	Risperidone, placebo; 53 days (2-62)	27.5 (placebo 12.8)	79 (risperidone 40); 7.6 (2.3) (risperidone), 5-12	Randomised, double-blind, placebo controlled	Shea et al., 2004

2.7.2 Metabolic adverse effects in children

All SGAs may cause weight gain, but the magnitude of risk differs between SGAs. Clozapine and olanzapine have the highest metabolic risk and aripiprazole and ziprasidone the lowest (Table 2) (Martínez-Ortega et al., 2013; Stahl, 2013a). Children seem to have a greater risk compared to adults, and the younger the child, the higher is the risk (Almandil et al., 2013; Galling and Correll, 2018; Libowitz and Nurmi, 2021; Martínez-Ortega et al., 2013). Marked weight gain seems to appear early during the treatment and may be followed by a slower increase and a possible plateau (Van der Esch et al., 2020). Even though the weight gain seems to slow down or even cease with long-term use, the weight generally does not fall back to the baseline level (Van der Esch et al., 2020). Interestingly, in a recent meta-analysis by Pozzi et al. (2020), the pace of the weight gain differed, e.g. between risperidone (fast) and aripiprazole (slow), but the gain was similar after one year of treatment (Pozzi et al., 2020; Schoemakers et al., 2019). Children with a lower baseline weight may gain weight faster, but children who are heavier at baseline are most likely to be heavier also during the treatment (Martínez-Ortega et al., 2013; Van der Esch et al., 2020). Concomitant psychotropic medication can influence weight gain, e.g. stimulants may lower the risk (Van der Esch et al., 2020).

Adverse development in fasting TG, HDL, glucose (FPG) and insulin levels have been reported in children during SGA treatment. Changes in body adiposity and insulin sensitivity may emerge already during the first 12 weeks of treatment (Galling and Correll, 2018; Ilies et al., 2018; Nicol et al., 2018; Sjo et al., 2017). The risk for IR and type 2 diabetes increases during the first year, and longer, cumulative exposure further elevates it (Bobo et al., 2013; Galling et al., 2016; Galling and Correll, 2015). The risk for type 2 diabetes is two- to three-fold in SGA-treated children and adolescents compared to psychiatric and healthy controls, and it may stay elevated for up to a year after discontinuation (Bobo et al., 2013; Galling et al., 2016). The risk for type 1 diabetes is not elevated (Bobo et al., 2013).

In adults, SGA treatment is associated with metabolic syndrome, which can be defined as the clustering of elevated blood pressure, low HDL levels, high TG levels, high FPG levels and abdominal obesity (Cook et al., 2004; Correll et al., 2009). In children the concept of metabolic syndrome is controversial, but SGAs increase the risk for cardiometabolic risk factor clustering also in children (Devlin et al., 2012; Libowitz and Nurmi, 2021; Panagiotopoulos et al., 2012).

The effects of SGAs on bone health and sexual development are not known (Pringsheim et al., 2011b). Prolactin increase may affect bone development through the reduction of estrogen and testosterone production (Rice et al., 2018). However, there is a lack of information especially concerning the effects of chronic non-symptomatic prolactin elevation in children (Okumura et al., 2018).

2.7.3 Cardiovascular adverse effects and unexpected death in children

Most SGAs, especially ziprasidone and risperidone, may prolong the QT interval in children (Hiippala and Happonen, 2021; Jensen et al., 2015). However, in otherwise healthy children and adolescents, the risk for SGA-induced pathological QT prolongation is suggested to be small (Alda et al., 2016; Aman et al., 2015; Jensen et al., 2015; Palanca-Maresca et al., 2016; Roessner et al., 2017; Vo et al., 2016). Nevertheless, it should be noted that most studies cover only short-term SGA treatment and patients with clinically relevant risk factors (e.g. elevated baseline QTc, overweight, concomitant psychotropic use) are excluded (Jensen et al., 2015; Vo et al., 2016). In children and adolescents, SGAs may also associate with orthostatic hypotension and tachycardia (Cheng-Shannon et al., 2004).

In healthy children and adolescents, unexpected deaths are rare. However, in a large study by Ray et al. (2019), children and youths receiving high-dose antipsychotic treatment (>50 mg chlorpromazine equivalents) had a 3.5-fold increased risk of unexpected death compared to the control group. In the lower-dose group, the risk was not elevated. The risk for suicide or lethal injuries was not increased.

2.8 Monitoring practices of antipsychotic medications in children

Overall, the monitoring practices of SGAs are cursory. Finnish Current Care guidelines for schizophrenia and bipolar disorder recommend the regular follow-up of the medication and metabolic measures, but the intervals are not clearly defined. There are various international guidelines for children, but there is no clear consensus on monitoring measures and intervals. Since official indications are few for children, and recommendations are only for short-term use, defining the methods and intervals for long-term use are contradictory.

2.8.1 Existing monitoring recommendations for children

There are several guidelines available for monitoring SGA treatment in children (Dinnissen et al., 2020; Kealey et al., 2014). Most of these highlight the general quality of care, thorough diagnostics, the definition of a target symptom, screening of contraindications and individual risk factors, and information on off-label prescribing before SGA initiation (Dinnissen et al., 2020; Kealey et al., 2014). They also point out the assessment of psychosocial treatments prior and concomitant to prescription, information concerning the medication (benefits and adverse effects) and lifestyle education, and, furthermore, regular evaluation of the need for the medication (Dinnissen et al., 2020; Kealey et al., 2014).

Guidelines recommend regular monitoring of growth (weight, height, BMI), waist circumference, blood pressure and metabolic parameters (FPG and lipids) (Kealey et al., 2014; Melamed et al., 2021). Monitoring of ECG and neurological adverse effects is recommended (Blair et al., 2004; Koskentausta and Tolmunen, 2016; Pringsheim et al., 2011b). Recommendations concerning regular prolactin monitoring vary (Okumura et al., 2018). However, all international guidelines have different perspectives to the frequency and methods of monitoring, leaving room for interpretation (Minjon et al., 2018). In Finland, there are no national guidelines available for monitoring the SGA treatment of paediatric patients. The Finnish Textbook of Child and Adolescent Psychiatry recommends the active evaluation of response and adverse effects, and the general principles are in line with the international recommendations (Koskentausta and Tolmunen, 2016). Further, recognition and prevention of weight gain and metabolic disturbances is especially noted (Koskentausta and Tolmunen, 2016) (Table 5).

Table 5. Recommendation for the monitoring of antipsychotic medication in children and adolescents (Koskentausta and Tolmunen, 2016).

Measurement	Baseline	Follow-up[1]				
		At the beginning of the treatment weekly	One month after baseline	3 months after baseline	Every three months	Annually
Growth, BMI	X	X[2]			X	
Blood pressure, pulse	X					
ECG	X		X			
Blood count	X			X		X
Fasting glucose	X			X		X
Fasting lipids	X			X		X
S-sodium	X			X		X
S-potassium	X			X		X
S-Alat	X		X	X		X
S-Prolactin	X					

[1] More frequent monitoring should be considered during a switch or dose increase

[2] If there is no significant change during the first months, monitoring can be done every three months

2.8.2 Monitoring of neurological adverse effects in child psychiatry

Monitoring the neurological adverse effects of SGAs in children is less noticed compared to metabolic monitoring (Pringsheim et al., 2017). In the Finnish monitoring recommendation, EPS are not mentioned (Koskentausta and Tolmunen, 2016). However, the risk of EPS or even TD is not absent in children, and screening is important (Pringsheim et al., 2011a, b). There are several rating scales for EPS, which could be beneficial in monitoring and improve the recognition of EPS in clinical settings. However, these scales are not validated for children and not routinely used in child psychiatric clinical work (Pringsheim et al., 2011a; Carbon et al., 2015). Nevertheless, a neurological examination as part of monitoring is indicated in children using SGAs (Pringsheim et al., 2011a).

2.8.3 Monitoring of cardiac safety in child psychiatry

When planning the medication, a risk evaluation for SGA-induced cardiac adverse effects is needed. It consists of a careful history of individual and family-related risk factors (e.g. diagnosed cardiac abnormalities, long QT syndrome and/or other cardiac diseases, syncope, arrhythmia or family history of sudden deaths, sudden infant deaths and sudden drowning), the evaluation of concomitant medications and

a physical examination, including cardiac auscultation and measurement of blood pressure (Blair et al., 2004; Hiippala and Happonen, 2021). Additional monitoring with physical examination and ECG is recommended with cardiac symptoms, SGA dose increase or initiation of concomitant medication (Blair et al., 2004; Hiippala and Happonen, 2021).

2.8.4 Metabolic monitoring practices in child psychiatry

Even though metabolic adverse effects are common, the majority of children using SGAs do not receive adequate monitoring (Chen et al., 2018; Coughlin et al., 2018, Hayden et al., 2019; Javaheri et al., 2019; Jazi et al., 2020; Okumura et al., 2018). Weight, height, and FPG seem to be the most common follow-up measures, but even their monitoring rates have been modest, varying at around 50% or even lower (Chen et al., 2018; Coughlin et al., 2018; Hayden et al., 2019; Jazi et al., 2021; Okumura et al., 2018). Most child psychiatrists are aware of the available monitoring guidelines, but there is great variability in practices and a minority of prescribers have adopted all recommendations in their clinical work (McLaren et al., 2017; Minjon et al., 2019). There are no previous studies concerning SGA monitoring in children available from Finland.

2.8.5 Barriers of monitoring

Several studies have addressed possible barriers influencing SGA monitoring in child and adolescent psychiatry. These may relate to physicians, patients, parents, clinical settings and health care systems (Coughlin et al., 2018; Jazi et al., 2020; McLaren et al., 2017; Rodday et al., 2015; Ronsley et al., 2011).

Physicians' knowledge, skills, attitudes, and confidence towards monitoring, physical examination and metabolic parameters affect monitoring practices in child and adolescent psychiatry (Rodday et al., 2015; Ronsley et al., 2011). Physicians who consider guidelines easy to follow and important for patient care are more likely to monitor (McLaren et al., 2017). Further, clinical experience may influence monitoring; shorter clinical experience seems to relate to more frequent monitoring (Jazi et al., 2020; McLaren et al., 2017; Rodday et al., 2015). Physicians who have completed their training recently and work in academic settings may be better aware of the latest guidelines and have more confidence in ordering and interpreting laboratory tests (Jazi et al., 2020; McLaren et al., 2017). System-related factors, such

as excessively busy schedules and limited access to appropriate equipment, may also be obstacles for monitoring (Rodday et al., 2015; Ronsley et al., 2011).

Challenging behaviour, the difficulty of obtaining blood tests, and child or parental resistance can be reasons for unsuccessful monitoring (Jazi et al., 2020; Kara and Penner 2021; McLaren et al., 2017). In studies, patient-related factors that seem to increase the likelihood of monitoring include an older age (adolescence), diagnosis of psychotic or affective disorder, fewer comorbid diagnoses, frequent emergency department visits and a higher SGA dose (Coughlin et al., 2018; Jazi et al., 2020). Concomitant ADHD medication seems to decrease the likelihood of monitoring (Jazi et al., 2020). Lack of understanding the importance of monitoring may reduce the motivation of children and caregivers (McLaren et al., 2017). This highlights the importance of shared decision making and psychoeducation.

2.8.6 Efficient ways to improve prescribing and monitoring in clinical work

Despite interventions to improve monitoring, monitoring rates have continued to vary (Melamed et al., 2021). Melamed et al. (2019) reviewed six studies that described interventions aiming to improve SGA monitoring in children and adolescents. Only modest improvements in monitoring rates were detected, and the improvement was seen more often in growth monitoring compared to laboratory tests. It was concluded that the monitoring of the SGA medication's effects may be improved if the protocol is tailored to local resources and if the organisation is committed to monitoring. Mackie et al. (2021) studied 17 Medicaid (a medical insurance system for low-income families in USA) system-wide interventions aiming to improve antipsychotic prescribing and monitoring practices in children and adolescents. Programs including "prior authorisation" (secondary assessment by a specialist or other colleague) resulted in reductions of SGA prescriptions (Mackie et al., 2021). Prescribing support for clinicians (training and initiatives to improve quality of care) seemed effective in improving metabolic monitoring, at least in the short term (Mackie et al., 2021). Implementation of such a protocol, including staff training workshops, a handbook and monitoring recommendations, was associated with better monitoring, and further, a decline in SGA prescriptions in community settings (Ronsley et al., 2012). However, the monitoring still varied, and the improvement seemed to wane as time passed (Melamed et al., 2021; Ronsley et al., 2012).

Making physicians more aware of the guidelines is probably not the only key to improving monitoring (Kara and Penner, 2021; McLaren et al., 2017). To succeed,

monitoring protocols should address physician-, system-, and patient-related barriers (Melamed et al., 2021). Further, they should be informative, simple, tailored to local clinical practices and balanced between the benefits and burdens for the monitored children (Melamed et al., 2021; Minjon et al., 2018). In addition, psychoeducation of a healthy lifestyle and liaisons with paediatrics concerning the treatment of metabolic disorders are essential (Melamed et al., 2021; Sjo et al., 2017). The involvement of nurses and multidisciplinary teamwork can be beneficial (Jazi et al., 2020). Also, proper facilities, sufficient equipment for physical examination and, e.g. a predetermined lists of laboratory tests can improve monitoring (Ronsley et al., 2011). However, more studies on the matter are needed.

3 AIMS OF THE STUDY

This dissertation aimed to study whether the implementation of a systematic monitoring protocol improves SGA medication safety in child psychiatric patients. The study was performed in two phases. The specific aims were:

1. To describe the clinical use of SGAs and medical and socio-demographic background factors of child psychiatric patients using SGAs prior to (Study I) and after the implementation of a systematic monitoring protocol (Study III);
2. To describe SGA prescribing and monitoring practices prior to (Studies I and II) and after (Study III) the implementation of a systematic monitoring protocol;
3. To describe the detected benefits and adverse effects of SGAs prior to (Studies I, II and IV) and after (Study III) the implementation of a systematic monitoring protocol;
4. To assess how the implemented systematic monitoring protocol was followed in a clinical setting (Study III).

4 MATERIALS AND METHODS

This study was conducted at the Tampere University hospital (TAUH) child psychiatric unit, which offers specialist-level in-patient and out-patient psychiatric services for children aged 0 to 12 years. TAUH is one of the five university hospitals in Finland, and its catchment area is approximately 900,000 people.

The first phase of this study was a retrospective patient report-based study. The second phase was a prospective intervention study, which examined the implementation of a systematic SGA monitoring protocol at TAUH child psychiatric unit. The protocol mainly focused on metabolic and outcome monitoring. The study was extended with a case report of a severe neurological adverse effect after long-term SGA treatment.

4.1 Retrospective study (Studies I and II)

All child psychiatric patients at TAUH taking ongoing antipsychotic medication between 1 October 2013 and 1 October 2014 were identified from the medical database based on the Anatomical Therapeutic Chemical Classification codes (ATC). The study inclusion criteria were: 1) antipsychotic initiation at TAUH, 2) ongoing SGA treatment during the study period, and 3) age < 13 years at the time of antipsychotic initiation. These criteria were met by 133 patients. The study endpoints were: 1) antipsychotic discontinuation, 2) a referral of the patient elsewhere, or 3) 31 May 2015, whichever came first. Data for study purposes were collected from medical and laboratory records, and the patients and their families were not contacted. The study was approved by the Pirkanmaa hospital district Ethics Committee.

4.1.1 Collected data

The following data were collected from the medical records:

1) Background information: birthdate, gender,

2) Diagnoses,
3) Information on the psychiatric and relevant medical history of the patient and family,
4) Other sociodemographic factors (family status, parental employment, reported adverse life-experiences),
5) Other psychotropic medications,
6) Information concerning SGA medication
- Generic name,
- Indications or main symptoms (either recorded or deduced from the patient reports),
- Date of initiation and possible discontinuation,
- Reasons for discontinuing or changing medication (categorised as: adverse effect, no benefits, adverse effects more significant than possible benefits, symptoms diminished so that the medication was no longer needed, and no information),
7) Reported benefits (categorised as: considerable benefit, some benefit, uncertain, no benefit, and no information),
8) Reported adverse effects,
9) Information concerning the follow-up protocol
- Dates of the follow-up visits,
- Weight (kilograms) and height (centimetres),
- Blood pressure (BP, mmHg),
- Consultations (e.g. cardiology, paediatrics).

The following values were collected from the laboratory records (date and value):
1) Fasting plasma lipids (TG, HDL),
2) FPG (categorised as: test made, value > 6.1 mmol/l or not).

4.1.2 Patients and study groups

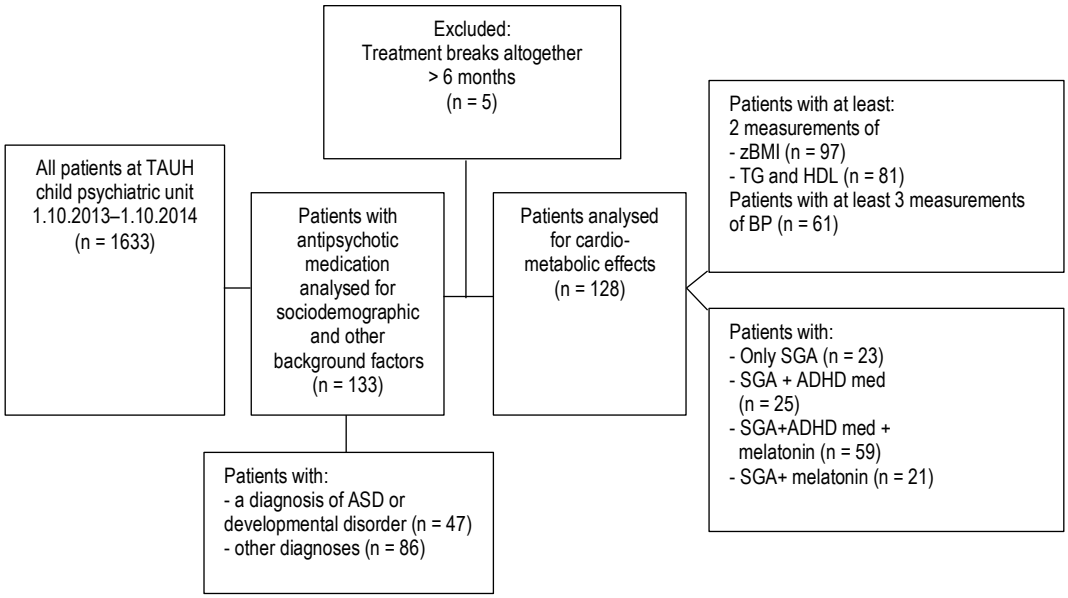
All patients (n = 133) were included in the analysis concerning the background information and sociodemographic factors. For further analyses, the study group was divided into two groups according to diagnosis (Figure 2) (Study I):
1. Patients with a diagnosis of ASD or developmental disorder,
2. Patients with other diagnoses.

For metabolic analyses, five patients were excluded due to treatment breaks longer than 6 months. The remaining 128 patients were analysed in separate groups (Figure 2) (Study II):

1. Based on available growth information and fasting plasma lipid values (at least two measurements during the study period) and BP values (at least three measurements during the study period),
2. Based on psychotropic medication use

- SGA monotherapy,
- SGA and ADHD medication (stimulant or atomoxetine),
- SGA, ADHD medication and melatonin,
- SGA and melatonin.

Figure 2. Patients and study groups in the retrospective study.



4.2 Prospective study (Study III)

The study was conducted at TAUH child psychiatric unit between 15 January 2015 and 31 January 2019, and it was approved by the Pirkanmaa hospital district Ethics Committee.

4.2.1 Clinical development project as a part the prospective study

As a clinical development project, a monitoring protocol for children treated with SGAs was introduced at TAUH child psychiatric unit prior to the study period. With the permission of the original authors, a handbook and a monitoring form were translated from the Canadian original publication "A Physician Handbook for Metabolic Monitoring for Youth with Mental Illness treated with Second-Generation Antipsychotics", developed by Drs Panagiotopoulos, Davidson and Raghuram (2010). The documents were modified to fit Finnish clinical practices. The handbook (Appendix 1) contains basic information about SGAs and their monitoring. The physicians were encouraged to use the monitoring protocol for all patients medicated with SGAs.

For the prospective study's purposes, separate monitoring forms for the baseline and follow-up visits were developed (Appendix 2 and 3). The intended timing of the follow-up visits and laboratory tests were: 1) baseline (BL), 2) at one month, 3) at 4 months, 4) at 10 months and 5) at 16 months after the BL and every six months thereafter. At BL and during the follow-up, assessment of symptom severity and functional capacity was recommended to be performed by using a HoNOSCA (Health of the Nation Outcome Scales for Children and Adolescents) form (Gowers et al., 1999 a, b).

4.2.2 Prospective study entry process and study patients

During the study period, physicians were asked to inform patients and their guardians about the possibility of entering the study when SGA medication was either initiated or changed. Recruiting patients and the use of the monitoring protocol was optional for the physicians.

The study participants received treatment as usual; only SGA monitoring was performed according to the study protocol. The inclusion criteria for the study were a maximum age of 13.0 years when entering the study and at least one documented follow-up visit after the baseline visit. Data for study purposes were recorded from the monitoring forms and laboratory reports.

Informed consent was asked from all the study patients who were over 7 years of age and from their legal guardians at the baseline. If a child was in foster care, informed consent was required from the biological parent or guardian, not from the foster parents or social worker. Due to the study entry process, the prospective study

sample does not represent all patients who were prescribed SGAs during the study period.

4.2.3 Study sample

Fifty-five patients were included in the study. The study sample size was originally calculated by using the change in the HoNOSCA score. HoNOSCA is a physician-rated measure comprising 13 questions that was developed to assess psychiatric symptom severity, functional capacity and individual response to psychiatric treatment in child mental health services (Gowers et al., 1999; Garralda et al., 2000). HoNOSCA was used as part of the implemented monitoring protocol to assess patients' psychiatric symptoms and functional capacity. The clinically relevant change in the HoNOSCA total score was estimated by using two different estimates: the mean 3.6 (SD 4.7) points (Garralda et al., 2000) and 7.7 (SD 5.4) points (Gowers et al., 1999). Regarding a single question, a change of one point was considered clinically relevant. By using the power of 0.9 and type I error of 0.05, the sample size was estimated to be 38. It was presumed that some patients would be lost in the follow-up, so the actual sample size was decided to be 59, of whom 55 patients fulfilled the inclusion criteria. This sample size was estimated to reveal the most common adverse effects. As the importance of metabolic factors became apparent, power calculations were conducted for metabolic variables. With the selected sample size and type I error 0.05, the power for FPG, HDL, TG, and fasting plasma insulin was 1.0, for HOMA-IR 0.97, for zBMI 0.69 and for TG/HDL ratio 0.31.

4.2.4 Monitoring protocol

The monitoring forms included a wide range of information (Appendix 2 and 3). The following information was used in this thesis:

At baseline (Appendix 2)

1) Background information: birthdate, gender,
2) Diagnoses,
3) Family status,
4) Cardiometabolic (diabetes, cardiovascular disease, hyperlipidemia) and psychiatric disorders of the patient and family,
5) Exercise and sport hobbies.

At baseline and follow-up visits (Appendix 2 and 3)

1) Date of the assessment,
2) SGA medication
   - Generic name,
   - Dose,
   - Indications,
3) Other medications,
4) Physical examination
   - Weight (kilograms),
   - Height (centimetres),
   - BP (mmHg),
   - HoNOSCA.

At follow-up visits (Appendix 3):

1) Clinically relevant adverse effects of SGA (yes/no):
   - Weight gain,
   - Neurological symptoms,
   - Mammary symptoms,
   - Menstrual disturbances,
   - Other.

4.2.5 Laboratory tests

Laboratory tests and an electrocardiogram (ECG) were performed close to the BL and each follow-up visit. An easy-to-order set of laboratory tests was generated in co-operation with Fimlab laboratory services. The selection of tests (Appendix 2 and 3) was based on the Canadian non-specific antipsychotic monitoring form (Pringsheim et al., 2011b), which was modified to fit local clinical practices in co-operation with a paediatric endocrinologist. Blood samples were drawn after approximately 12 h fasting, and concentrations were assessed using standard enzymatic methods. The following laboratory values were analysed in this thesis:

1) FPG,
2) Fasting plasma insulin,
3) Fasting plasma TG,
4) Fasting plasma HDL.

4.3 Metabolic reference values

The following metabolic reference values were used both in the retrospective and prospective studies (Studies I-III).

4.3.1 Body mass index

If the patient's weight and height were both measured at the same time point, the raw body mass index (BMI) was calculated with the usual formula weight (kg)/height $(m)^2$. It cannot be directly used to estimate potential deviance, however, as children's BMI and its normal range changes during their growth. Instead, growth curves must be applied. Therefore, the standardised body mass index adjusted for age and sex (BMI z-score, zBMI), defining the BMI percentile of the child at the time of the measurement, was calculated. The formula applied was $((\text{rawBMI}/\text{muBMI})^{\text{nuBMI}} - 1) / (\text{nuBMI} \times \text{sigmaBMI})$, where muBMI, nuBMI and sigmaBMI were retrieved from the Finnish national growth reference tables (Saari et al., 2011). In addition, based on the recommendations of the International Obesity Task Force expert panel, these BMI percentiles were compared to the curves passing through the BMIs of 25 kg/m^2 and 30 kg/m^2 at the age of 18 years, defining the limits for overweight and obesity, respectively (Saari et al., 2011). These were the 87.8^{th} and 98.2^{th} percentiles for girls and the 78.2^{th} and 95.6^{th} percentiles for boys.

In the retrospective study, to detect possible changes in the zBMI, the minimum and maximum zBMI were identified when at least two zBMIs were available during the follow-up period. These were either one at BL and at least one follow-up value or at least two follow-up values. The maximum score occurring after the minimum score was considered weight gain and vice-versa for weight loss. In the prospective study, the zBMI at BL was considered the reference point for detecting possible changes. In the calculation of the zBMI change, the zBMIs were rounded to one decimal place to avoid detecting minimal changes.

4.3.2 Fasting plasma lipids, glucose and insulin

Cut points for fasting plasma lipid and FPG values were defined according to the recommendations of the United States National Cholesterol Education Program for metabolic syndrome in children and adolescents, namely HDL $\leq$ 1.03 mmol/l, TG $\geq$ 1.24 mmol/l, FPG > 6.1 mmol/l (Cook et al., 2004; Owens et al., 2014). In the

prospective study, also a lower cut point of FPG ≥ 5.6 mmol/l, was used to define impaired fasting glucose (Styne et al., 2016; American Diabetes Association, 2014; Obesity: Current Care Guideline, 2020). For fasting insulin, a cut point of > 25 mU/l was used. This cut point is used by Fimlab laboratory services and it represents fasting insulin levels of the 99th percentile or above in boys (21.4-22.6mU/l) and girls (24.4-25.9 mU/l) in all weight groups at the age of 10 to 11 years (Peplies et al., 2016).

4.3.3 Assessment of insulin resistance and increased cardiometabolic risk (Study III)

The homeostatic model assessment for IR (HOMA-IR) is an indirect marker based on the relationship of FPG and insulin levels, with higher values representing more severe IR and increased cardiometabolic risk (Shashaj et al., 2016). HOMA-IR correlates well with the euglycemic-hyperinsulinemic clamp, which is considered the gold standard for measuring IR (Wallace et al., 2004; Tagi et al., 2019). HOMA-IR is also usable in repeated measurements and in the assessment of individual changes in glucose tolerance (Wallace et al., 2004; Tagi et al., 2019). HOMA-IR was calculated by using the formula: fasting insulin (mU/l) × FPG (mmol/l)/22.5 (Wallace et al., 2004). Further, HOMA-IR percentile tables specific for age, sex and dichotomised BMI percentile (normal or overweight/obese) were used to define the percentile of each measurement. The patient was considered to have IR or increased cardiometabolic risk if the HOMA-IR percentile was ≥ 75th percentile (Shashaj et al., 2015). The cut point used to define overweight/obesity in these percentile calculations was the age- and sex-specific 85th BMI percentile, acquired from the Finnish national growth reference tables (Shashaj et al., 2015; Saari et al., 2011).

The TG/HDL ratio is another marker for the assessment of impaired glucose tolerance and increased cardiometabolic risk in children (Tagi et al., 2019; Nur Zati Iwani et al., 2019; Manco et al., 2016; Di Bonito et al., 2015). The absolute value of the TG/HDL ratio was calculated as the straightforward ratio of the values.

4.3.4 Blood pressure

Blood pressure was measured with automatic blood pressure monitors using a cuff size appropriate to the patient's arm circumference. To make the raw systolic and diastolic blood pressure values of all patients comparable, they were replaced by

percentiles using the age-, sex- and height-specific reference tables of the American Academy of Pediatrics' Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents (Flynn et al., 2017). The percentile of each BP measurement was set according to the guideline if a height measurement was available within two months of that measurement. At each measurement point, the lower of the systolic and diastolic BP percentile was selected. BP was considered elevated if it was $\geq$ 90th percentile on three separate occasions with at least a week between the readings, and hypertensive if it was $\geq$ 95th percentile using the same criteria.

4.4 Case report (Study IV)

The patient received the usual treatment, and data for study purposes was collected from the medical records. Due to the patient's intellectual disability and communicative deficits, informed consent was asked from the legal guardian of the patient.

4.5 Statistical methods

The categorised variables were reported as frequencies (numbers of cases or percentages, as appropriate). For normally distributed continuous variables, means and standard deviations (SD) were given, whereas medians (Md) and quartiles (Q_1, Q_3) were reported for non-normally distributed continuous variables. To test the statistical significance of the differences between groups, Pearson's chi-square test, Fisher's exact test, the Mann–Whitney U-test or the Kruskal–Wallis test was used, as appropriate. The Wilcoxon sign rank test was applied to examine whether the changes in zBMI, FPG, fasting insulin, HDL, TG, HOMA-IR and TG/HDL ratio differed statistically significantly from zero.

In the prospective study, receiver-operating characteristic (ROC) analysis was used to find the optimal cut point of HOMA-IR and the TG/HDL absolute value for screening cardiometabolic risk. The analysis was first repeated separately for BL and the first four follow-up visits (T1-T4), in which the number of patients was sufficient. Caseness at each visit was defined by the HOMA-IR percentile being $\geq$ 75th percentile. To estimate an overall cut point, caseness was defined by the HOMA-IR percentile being $\geq$ 75th percentile at least once between BL and the fourth follow-up visit, and both the mean and maximum of HOMA-IR and TG/HDL across the

same visits were used. The sensitivity and specificity of the resulting cut points were then calculated. A p value of less than 0.05 was considered significant, a value between 0.05 and 0.10 was indicative and values up to 0.10 were reported. SPSS Statistics, versions 23, 25 and 27 (IBM Corporation, New York, USA) were used for all the statistical analyses.

5 SUMMARY OF RESULTS

5.1 Patient and family characteristics (Studies I and III)

The following results concern all 133 children who fulfilled the retrospective study inclusion criteria and the 55 patients who fulfilled the prospective study inclusion criteria.

5.1.1 Patient characteristics

The mean age of the study patients was 9.3 years (SD 2.1, min 4.7, max 13.0) in the retrospective study and 9.9 years (SD 1.8, min 5.9, max 13.0) in the prospective study ($p = 0.056$). Eighty-one per cent of the retrospective study patients and 76% of the prospective study patients were boys.

Ninety-one per cent of the retrospective study patients and 80% of the prospective study patients were under the age of 12 years at SGA initiation ($p = 0.050$). The proportions of girls among the under 12-year-olds were 17% (retrospective) and 21% (prospective), the difference being statistically significant in the retrospective ($p = 0.049$) but not in the prospective study sample. Of those patients who were 12 years of age or older, 42% (retrospective) and 36% (prospective) were girls.

All except one patient in the prospective study had at least one psychiatric diagnosis (ICD-10 Mental and behavioral disorders) at the time of SGA initiation (Table 6). The frequency of patients having at least two diagnoses was 75% in the retrospective study and 60% in the prospective study. The most common diagnoses in both study phases were ADHD and conduct or mixed conduct and emotional disorders. ICD-10 Z-diagnosis (factors influencing health status and contact with health services), implying environmental factors influencing mental health, were more common in the retrospective than in the prospective study patients (39% vs 13%).

In the retrospective study, 35% of the patients had a diagnosis of ASD or a developmental disorder (Table 6). These patients were younger at the time of SGA

initiation compared to children with other diagnoses in the retrospective study (mean 8.6 years, SD 2.0 vs mean 9.7 years, SD 2.0, $p = 0.002$).

Seventy-nine per cent of the retrospective study patients had been in psychiatric in-patient care at least once (day wards included). In the prospective study, this figure was not reported.

In the prospective study, information concerning hobbies was available for 82%, of whom 27% had sport as a hobby.

5.1.2 Family characteristics

The frequency of patients who had both biological parents as caregivers at the time of SGA initiation was less than 40% in both study groups. Eighteen per cent of the retrospective study patients and 13% of the prospective study patients lived in foster or residential care. There were no statistically significant differences in family characteristics between the retrospective and prospective study patients (Table 6).

In the retrospective study, where sociodemographic factors were recorded in more detail, adverse life experiences related to violence (e.g. exposure to violence between other family members, physical punishment, war experiences) were reported in 41% of the patients. The retrospective study patients with a diagnosis of ASD or developmental disorders had both biological parents as caregivers more often (57% vs 26%, $p < 0.001$) and were less frequently placed out-of-home (6% vs 24%) compared to the patients with other diagnoses in the retrospective study ($p < 0.001$). Further, the employment of mothers was statistically significantly more common (68% vs 53%, $p= 0.018$) and exposure to experiences related to violence indicatively less common (30% vs 48%, $p = 0.065$) in these patients.

Table 6. Background factors of the study patients in the retrospective and prospective studies.

		Retrospective (n = 133) %	Prospective (n = 55) %	*p*
Caregiver/family				ns
Both biological parents		37	36	
Parental separation		40	51	
Foster care		18	13	
Other (e.g. adoption)		5	-	
Diagnosis	ICD-10 class			
Psychosis	F20-29	5	2	ns
Bipolar affective disorder	F31	5	4	ns
Depressive episode	F32	6	4	ns
Obsessive compulsive disorder	F42	3	4	ns
Reaction to severe stress/adjustment disorder	F43	10	4	ns
Developmental disorders	F83-84	35	18	0.023
Hyperkinetic disorders	F90	50	49	ns
Conduct/Mixed conduct and emotional disorders	F91-92	40	46	ns
Emotional disorder with onset specific to childhood	F93	7	9	ns
Disorders of social functioning with onset specific to childhood and adolescence	F94	13	4	0.066
Tic disorders	F95	8	7	ns
Indication for SGA initiation				
Information clearly stated		60	100	< 0.001
Aggression		75	60	0.052
Conduct problems and/or defiance		76	33	< 0.001
Aggression, and conduct problems and/or defiance		72	26	< 0.001
Mood swings		20	42	0.003
Psychosis or hallucinations/delusions		19	22	ns
Anxiety/ fears		24	15	ns
Self-destructive behaviour		13	13	ns
		(n = 128)	(n = 55)	
Other psychotropic medication				
ADHD medication		66	40	0.002
SSRI		14	13	ns
Benzodiazepines		14	2	0.015
Melatonin		63	47	0.072
The availability of family history of				
Psychiatric disorders		84	86	ns
Cardiometabolic diseases		53	91	< 0.001

5.1.3 SGAs and concomitant psychotropic medications

Risperidone was the most commonly initiated SGA in both studies (93% vs 58%). However, in the prospective study SGA treatment was initiated statistically significantly more often with aripiprazole and quetiapine compared to the retrospective study (29% vs 2% and 13% vs 6%, respectively, $p < 0.001$). At the prospective study BL, 84% of the patients were antipsychotic naive, the rest (n = 8) were switching from one SGA to another.

In the retrospective study, nine patients were simultaneously using another antipsychotic medication during the study period, most commonly (n = 5)

levomepromazine. Psychotropic polypharmacy, most commonly the combination of SGA and ADHD medication, or SGA and melatonin, was significantly more common (except for SSRIs) in the retrospective study patients (Table 6).

The SGA was changed at least once in 23% of the retrospective study patients and in 35% of the prospective study patients during the study period. Due to these changes, altogether 94% of the retrospective study and 64% of the prospective study patients used risperidone, 18% (retrospective) and 55% (prospective) aripiprazole, and 17% (retrospective) and 16% (prospective) quetiapine at some point during the study period.

The reasons for changing or discontinuation of SGA medications were documented only in the retrospective study, where the most common reasons for change were adverse effects (52%) or an unfavourable relation of benefits and adverse effects (48%). Retrospective study patients who had a diagnosis of ASD or developmental disorder had fewer changes in their medication than those with other diagnoses (17% vs 34%, $p = 0.034$). In the retrospective study, the SGA was discontinued in 15% of the patients, most commonly due to a relief of symptoms (52%) or an unfavourable relation of benefits and adverse effects (30%).

5.1.4 SGA indications

The indication for SGA initiation was clearly stated in 61% of the retrospective study patients and in all of the prospective study patients ($p < 0.001$) (Table 6). The indications and reported main symptoms were diverse in both studies, but in the retrospective study, significantly more patients had at least two indications (92% vs 80%, $p = 0.043$). Aggression was the most common indication in both studies. Behavioural disturbances were more common in the retrospective study, whereas mood swings were more common in the prospective study patients ($p < 0.001$). SGA use was off-label in all study patients. Psychotic-type symptoms were reported as an indication in one fifth of the patients in both studies (Table 6).

5.1.5 Duration of SGA use

In the retrospective study, the median duration of the SGA treatment was 20.5 months (Q_1 9.4, Q_3 34.8). In the patients with a diagnosis of ASD or developmental disorder, the treatment duration was longer compared to other retrospective study patients (Md 32.8 vs 18.4 months, $p < 0.001$). Five patients had treatment breaks

that lasted altogether longer than 6 months. When these breaks were taken into account, the median duration of the SGA treatment was 20.4 months (Q_1 9.1, Q_3 34.6).

In the prospective study, the median duration of the follow-up was 9 months (Q_1 3.6, Q_3 18.2).

5.2 Monitoring and metabolic parameters (Studies II and III)

The following results concern the 128 children in the retrospective study who did not have treatment breaks longer than 6 months during the study period and the 55 patients who fulfilled the prospective study inclusion criteria.

5.2.1 Assessment of medication response and reported adverse effects

In the retrospective study, physicians reported SGA medication benefits in 81% of the patients. In 16% the benefits were uncertain or not reported. One adverse effect was reported in 32% and two or more in 40% of the retrospective study patients, while in 28% no adverse effects were reported. The most frequent adverse effects were increased appetite (36%), weight gain (35%) and fatigue/somnolence (33%). Neurological adverse effects (akathisia, tics, stiffness or sluggishness) were reported in 10%. Thirty-six per cent of the retrospective study patients were referred to paediatric cardiological consultation during the study period, mostly because of suspected ECG deviance, but no absolute obstacles for SGA continuation were found in any of the patients. Further, 31% of the retrospective study patients were referred to other paediatric consultations, 26% of these patients to a paediatric endocrinologist due to a metabolic disturbance and 29% to a paediatric neurologist, but for reasons other than adverse effects.

In the prospective study, the physician's assessment of psychiatric symptoms (HoNOSCA) was available for 98% at BL and for 89%, 98%, 90% and 100% of the patients at T1-T4, respectively. The physician's report of adverse effects was available for 96%, 98%, 97% and 95% at T1-T4. At least one adverse effect was reported at T1-T4 in 47%, 55%, 50% and 50%, respectively. During the entire prospective study period, adverse effects were reported in 69% of the patients. Weight gain was reported at least once in 38%, deviations in laboratory values in 16%, fatigue in 15% and neurological symptoms in 7% of the patients.

5.2.2 Monitoring and metabolic parameters at baseline

At the BL of the retrospective study, the calculation of zBMI was possible in 34% of the patients, and 27% of them were overweight. Laboratory testing was more frequent compared to the measurement of weight, height and BP (Table 7). FPG was the most commonly tested metabolic parameter (Table 7).

The assessment of all BL metabolic parameters was significantly more common in the prospective study compared to the retrospective study ($p < 0.001$) (Table 7). At the BL of the prospective study, the calculation of zBMI was possible in 91% of the patients, and one third of them were overweight or obese. ECG was registered in 91% of the prospective study patients at BL (Table 8).

The majority of the metabolic laboratory parameters and BP measurements in both study phases were within the normal limits at BL (Table 7).

Table 7. Frequencies of somatic measurements and their abnormal values at the baseline and during the follow-up period of the retrospective (n = 128) and prospective (n = 55) studies.

Measurement[1]	Abnormal value cut point	Measured			Value abnormal[2]		
		Retro-spective %	Pro-spective %	*p*	Retro-spective %	Pro-spective %	*p*
At baseline							
BMI	≥25[3]	34	91	< 0.001	27	30	ns
FPG	> 6.1 mmol/l	49	87	< 0.001	0	0	-
HDL	≤ 1.03 mmol/l	40	87	< 0.001	0	2	ns
TG	≥ 1.24 mmol/l	39	87	< 0.001	4	4	ns
BP[4]	elevated or hypertensive[4]	27	75	< 0.001	7	7	ns
		At least one measurement			At least one abnormal value[2]		
During the study period		Retro-spective %	Pro-spective %	p	Retro-spective %	Pro-spective %	p
BMI	≥25[3]	92	98	ns	42	41	ns
FPG	> 6.1 mmol/l	95	100	ns	7	4	ns
HDL	≤ 1.03 mmol/l	86	100	0.002	6	4	ns
TG	≥ 1.24 mmol/l	86	100	0.002	15	24	ns
BP[4]	elevated or hypertensive[4]	81	98	0.002	26	19	ns

[1] Body mass index (BMI), fasting plasma glucose (FPG), high-density lipoprotein (HDL), triglycerides (TG), blood pressure (BP)

[2] Of those measured

[3] Percentile defined by the Finnish growth curve tables' age- and sex-adjusted BMI z-score being above the percentile corresponding to BMI 25 kg/m^2 at the age of 18 years

[4] Percentile set by the age-, sex- and height-specific reference tables of the American Academy of Pediatrics' Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents, being above the ≥ 90th percentile

Table 8. Age of the patients, frequency of performed metabolic tests, proportion of abnormal values and absolute values of derived metabolic parameters in the prospective study patients at baseline (BL) and at follow-up visits (T1-T4).

	BL (n = 55)			T1 (n = 55)			T2 (n = 43)			T3 (n = 31)			T4 (n = 21)		
	Md[1]	Q_1[1]	Q_3[1]	Md	Q_1	Q_3	Md	Q_1	Q_3	Md	Q_1	Q_3	Md	Q_1	Q_3
Age (years)	10.1	8.8	11.5	10.3	8.9	11.8	10.5	9.0	11.6	10.7	9.5	12.2	10.6	9.3	12.8
Follow-up time (months)	-	-	-	1.4	1.1	2.0	4.4	3.9	5.7	10.3	7.8	13.2	16.4	11.6	18.4
Proportion of performed metabolic tests (of all patients in the visit)	%			%			%			%			%		
zBMI	91			87			98			87			86		
BP	75			84			86			77			86		
FPG	87			95			86			77			100		
Insulin	82			91			84			77			100		
TG	87			95			86			77			100		
HDL	87			95			86			77			100		
HOMA-IR															
Absolute value	82			91			84			77			100		
Percentile[2]	73			78			79			74			86		
TG/HDL	87			95			86			77			100		
Proportion of abnormal metabolic parameters (of those measured)															
BMI $\geq$ 25[3]	30			25			43			52			44		
Blood pressure elevated or hypertensive[4]	7			4			11			8			6		
Fasting															
Glucose > 6.1 mmol/l	0			4			3			0			0		
Glucose $\geq$ 5.6 mmol/l	6			21			27			21			29		
Insulin > 25 mU/l	0			0			3			4			10		
Triglycerides ≥ 1.24 mmol/l	4			8			8			17			10		
HDL ≤ 1.03 mmol/l	2			2			3			4			5		
HOMA-IR															
Percentile[2] $\geq$ 75th	40			60			68			57			72		
Absolute values of zBMI and derived metabolic parameters	Md	Q_1	Q_3	Md	Q_1	Q_3	Md	Q_1	Q_3	Md	Q_1	Q_3	Md	Q_1	Q_3
zBMI	0.05	-0.66	0.97	0.26	-0.57	0.90	0.58	-0.32	1.28	0.80	-0.35	1.68	0.54	-0.21	1.68
HOMA-IR	1.49	0.92	2.38	1.92	1.33	2.61	2.12	1.68	3.32	2.46	1.29	3.30	2.58	1.62	3.84
TG/HDL ratio	0.94	0.61	1.37	0.91	0.73	1.29	0.93	0.65	1.30	0.92	0.61	1.28	1.11	0.80	1.65

[1] Median, lower and upper quartile

[2] Age-, sex- and BMI-specific

[3] Percentile defined by the Finnish growth curve tables' age- and sex -adjusted BMI z-score being above the percentile corresponding to BMI 25 kg/m^2 at the age of 18 years

[4] Percentile set by the age-, sex- and height-specific reference tables of the American Academy of Pediatrics' Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents, being above the ≥ 90th percentile

5.2.3 Monitoring and metabolic parameters during the study period

During the retrospective study period, information for the calculation of minimum and maximum zBMI (at least two simultaneous measurements of weight and height) was available in 76% (n = 97). The zBMI increased in 75% and decreased in 21% of these patients. The median zBMI change was 0.46 (Q_1 0, Q_3 0.92), differing

statistically significantly from zero ($p < 0.001$). In 55%, the weight increased within the normal weight category. However, during the study period the frequency of overweight and obesity increased. The minimum BMI indicated normal weight in 76%, overweight in 17% and obesity in 7%, whereas the respective figures for maximum BMI were 54%, 26% and 21%. In 8%, it was not possible to calculate any zBMI.

During the prospective study, the calculation of the trend in zBMI was possible significantly more often compared to the retrospective study ($p = 0.012$) (Table 9). In 64% of prospective study patients with at least two measurements (93%, n = 51) zBMI increased and in 33% it decreased. The median zBMI change was 0.37 (Q_1 -0.20, Q_3 0.71, $p = 0.007$). In 42% of those who gained weight, the weight remained in the normal category. However, between BL and T2 (the first 4 months), the frequency of overweight or obesity increased from 30% to 43% and further to 52% at T3 (10.3 months). After T3, the weight gain seemed to plateau (Table 8 and Figure 3).

In the retrospective study, BP measurements allowing the evaluation of BP elevation (at least three different measurements) were available in 48% (n = 61), and three patients met the criteria for elevated BP or hypertension. The calculation of minimum and maximum HDL and TG values (at least two measurements) was possible in 63% (n = 81) of the retrospective study patients. In 54% of them, HDL decreased, and TG increased. The median change in HDL was -0.25 mmol/l (Q_1 -0.43, Q_3 -0.15) and in TG 0.28 mmol/l (Q_1 0.11, Q_3 0.46), both differing statistically significantly from zero ($p < 0.001$ for both). The worsening in HDL and TG appeared within the normal range in 89% and 82%, respectively.

During the prospective study period, at least one measurement of BP, TG and HDL was available significantly more often compared to the retrospective study (Table 7). Further, the frequency of patients who had sufficient information available to examine the trends of metabolic parameters was statistically significantly more common ($p < 0.001$ for all) (Table 9). During the prospective study period, none of the patients who had at least three BP measurements (66%, n = 36) fulfilled the criteria of elevated or hypertensive BP. Even the individual measurements were rarely above normal limits (Table 9). In 52% of patients with at least two measurements of TG and HDL (98%, n = 54), the values worsened (TG Md 0.40 mmol/ l, Q_1 0.21, Q_3 0.62, $p < 0.001$ and HDL Md -0.28 mmol/l, Q_1 -0.41, Q_3 -0.20, $p < 0.001$). However, TG and HDL values were seldom above the selected cut points (Table 8 and Figure 3).

During the retrospective study, 7% of the patients had at least one FPG value >6.1 mmol/l. However, the absolute FPG values and trends were not examined in the retrospective study. During the prospective study period, FPG increased in 56% of patients with at least two measurements (98%, n = 54). The median change was 0.40 mmol/l (Q_1 0.20, Q_3 0.70, $p < 0.001$). FPG was rarely above 6.1 mmol/l, but the proportion of patients with FPG ≥ 5.6 mmol/l increased during the study period (Table 8).

In 75% of the prospective study patients with at least two measurements of fasting insulin (93%, n = 51) the values increased, the median change being 6.0 mU/l (Q_1 3.0, Q_3 10.0, $p < 0.001$). However, values were seldom above the selected cut points (Table 8 and Figure 3).

Retrospective study patients using SGA and ADHD medication (with or without melatonin) had their baseline BP measured more often than others (35% vs 14%, $p = 0.013$). Furthermore, hypertensive systolic BP was indicatively more common in these patients compared to other retrospective study patients (47% vs 27% $p = 0.086$). These patients also gained weight less often compared to SGA monotherapy patients (64% vs 93%, $p = 0.012$). In patients with SGA and melatonin, weight gain appeared more often within the limits of normal weight compared to other patients ($p = 0.024$).

Table 9. The proportion of patients with sufficient measurements to examine the trend in the retrospective study (n = 128) and in the prospective study (n = 55).

Measurement	Retro-spective %	Pro-spective %	*p*
BMI[1]	76	93	0.012
FPG[1]	77	98	< 0.001
HDL[1]	63	98	< 0.001
TG[1]	63	98	< 0.001
BP[2]	46	66	0.016

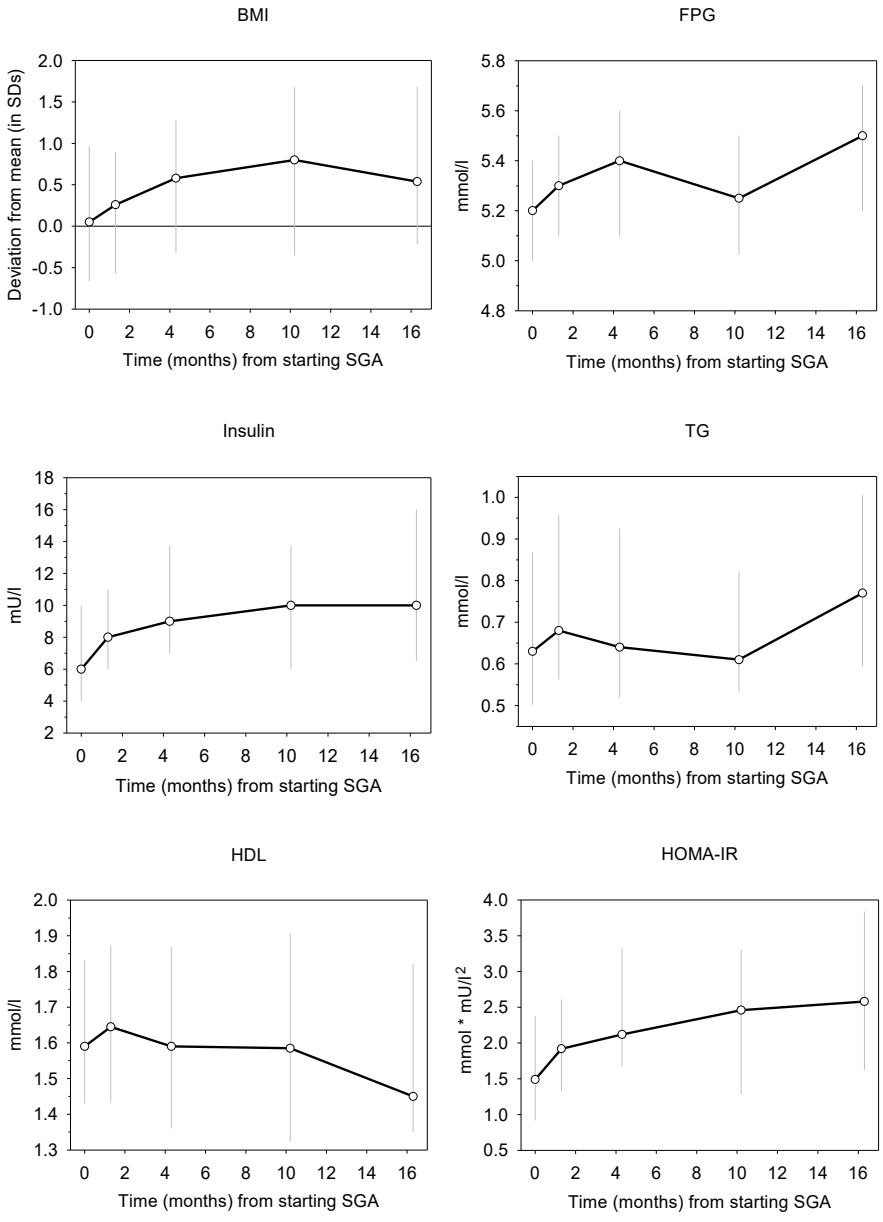
[1] Body mass index (BMI), fasting plasma glucose (FPG), high-density lipoprotein (HDL), triglycerides (TG): at least two measurements
[2] Blood pressure (BP): at least three measurements

5.2.4 HOMA-IR and TG/HDL ratio

At the prospective study BL, 40% of the patients with sufficient information for the calculation of age-, sex- and BMI-specific HOMA-IR percentiles had values ≥ 75th

percentile (Table 8). During the study period, the median increase in HOMA-IR was 1.47 (Q_1 0.25, Q_3 2.47), which differed statistically significantly from zero ($p < 0.001$) (Figure 3). The median increase in the TG/HDL ratio was 0.25 (Q_1 -0.40, Q_3 0.79, $p = 0.072$). The overall cut point values for HOMA-IR suggested by the ROC analysis were 1.47 (AUC 0.90) when the BL-T4 mean was used and 1.98 (AUC 0.95) when the respective maximum value was used. In both cases, the sensitivity and specificity were 83%. The respective cut points for TG/HDL were 1.01 (AUC 0.52) and 1.28 (AUC 0.55), resulting in sensitivities of 51% and 53%, respectively, and a specificity of 50% for both.

Figure 3. Development of metabolic parameters during the prospective study period. Medians and quartiles at each visit are shown, the visit time point being the median length of time from SGA initiation.



5.3 Changes in monitoring during the prospective study

The implementation of the metabolic monitoring protocol during the prospective study period significantly improved the BL monitoring and the possibility to evaluate metabolic trends (Table 7, Table 9). The monitoring protocol and its timing was followed well by the clinicians during the study (Table 8). The indication of an SGA was reported significantly more often at BL (61% vs 100%, $p < 0.001$). Further, the history of cardiometabolic risk factors in the family was inquired significantly more often during the prospective study (53% v 92%, $p < 0.001$) (Table 6). The reported frequencies of abnormal values in those who had at least one measurement were very similar in retrospective and prospective studies (Table 7). Based on these proportions and the detected frequency of measurements in the prospective and retrospective studies, the results indicate a statistically significant benefit in the detection of possible abnormal values of all metabolic parameters except for the BL HDL measurements and follow-up BP measurements during the prospective study period when systematic monitoring protocol was used (Table 7).

5.4 Case report (Study IV)

From the perspective of neurological adverse effects, this study was extended with a case report concerning a young man with diagnoses of ASD and ID who developed a severe TD after long-term exposure to risperidone. Risperidone 0.25 mg was first prescribed for aggression and tantrums when the patient was 8 years old. The daily dose was increased during the first two years to 0.4 mg. Already during childhood, higher doses of risperidone caused sedation and tics, but the treatment response was favourable. However, during adolescence the behavioural symptoms worsened, and the risperidone dose was gradually increased to 3 mg daily. The patient also used valproate for epilepsy and melatonin and chlorprothixene for transient sleep problems. The increased risperidone dose showed no response to behavioural symptoms, but the patient became restless and aggressive. Simultaneously, movement disorders appeared in the upper limbs. Due to aggression, the risperidone dose was further increased to 4.5 mg daily. This triggered compulsive involuntary movements, shivering and sweating. At that point, chlorprothixene and risperidone were discontinued, and the movement symptoms ameliorated. However, due to behavioural symptoms, quetiapine (150-200 mg daily) was initiated. This led to the re-emergence of movement symptoms. Haloperidol and benzodiazepines were

prescribed, but the behavioural and movement symptoms worsened. The movement symptoms gradually became constant, and the patient's communicative abilities deteriorated. Eventually, approximately five months after the emergence of the movement symptoms, all antipsychotics were discontinued. Despite the discontinuation, the patient suffered from severe tardive dystonia, including choreo-athetoid movements of the trunk, limbs, neck, and facial area, and dyskinetic extensions of the back and neck area. The symptoms led to severe physical and psychological distress, weight loss, self-mutilation, and further to severe infections. After multiple conservative treatment approaches to TD, deep brain stimulation led to the amelioration of the severe movement symptoms.

6 DISCUSSION

SGA prescriptions for children and adolescents have increased globally. There is very little clinical data available on the clinical use and monitoring of SGAs in Finnish children. The main aim of this dissertation was to study whether the implementation of a systematic monitoring protocol could improve SGA medication safety in child psychiatric patients. The specific aims were to describe the clinical use of SGAs as well as the medical and socio-demographic background factors of child psychiatric patients using SGAs. Furthermore, an aim was to describe prescribing and monitoring practices and the detected benefits and adverse effects of SGAs before and after the implementation of a systematic monitoring protocol, and to assess how the monitoring protocol was followed in a clinical setting.

6.1 Patients and indications – aggression and affect dysregulation

Altogether 188 children who were prescribed SGAs during their childhood years participated in this study in two separate phases. The median age of the study children was approximately 9 years at SGA initiation, the retrospective study patients being indicatively younger than those of the prospective study. In both the retrospective and prospective studies, the median duration of treatment exceeded the short term (median duration 20 months and 9 months, respectively), and the prescriptions were off-label. These findings are in line with a recent Finnish nationwide register study in which the mean SGA treatment duration in children and adolescents was approximately 1.5 years and the majority of prescriptions were off-label (Varimo et al., 2021). Studies of SGA use in children cover mainly short-term treatment (weeks to 6 months) (Lee et al., 2018; Loy et al., 2017), but in clinical reality SGA prescriptions are associated with severe and long-lasting disorders in need of long-term symptomatic treatment, which was also noted in the present study. Off-label prescriptions are common in children, especially concerning psychotropic medications. If safety and the evidence base are considered, an off-label prescription

may benefit the patient (Brauner et al., 2016; Kokki, 2017; Lehtonen, 2019; Putignano et al., 2019; Sharma et al., 2016; Schneider et al., 2014).

Concomitant psychotropic medications, especially ADHD medications, are common in children using SGAs (Olfsson et al., 2015). In both the retrospective and the prospective phases of this study, ADHD medications (66% and 40%, respectively) and melatonin (63% and 47%, respectively) were common. However, polypharmacy, requisite benzodiazepine medications, and melatonin were significantly more common in the retrospective study patients. Further, most of the retrospective study patients had received in-patient care at some point of their childhood.

The official indication for risperidone in Finland is aggression and conduct disorder in patients over five years of age with a diagnosis of ID for a maximum duration of 6 weeks. However, risperidone is often used as a symptomatic treatment of behavioural disturbances and affect dysregulation also outside of ID (Kloosterboer et al., 2018; Piovani et al., 2019; Oerbeck et al., 2021). In both the retrospective and prospective study patients, aggression was, indeed, the most common SGA target symptom independent of diagnosis. In the retrospective study, aggression was often accompanied by other behavioural problems. In the prospective study, affect dysregulation was more common. Psychotic symptoms were reported as an indication in one fifth of the patients in both study groups.

A recent study reported that most children go through a diagnostic evaluation and receive psychosocial treatment before their first antipsychotic prescription (Dinnisen et al., 2020). In this study, all except one child had an ICD-10 F-category psychiatric diagnosis. Comorbidities were common in both study phases, but even more so in the retrospective study. As in previous studies, ADHD, conduct disorder, or mixed conduct and emotional disorder were the most typical diagnoses (Nesvåg et al., 2016; Saastamoinen et al., 2017). However, ASD or developmental disorder were more common in the retrospective study patients and associated with earlier SGA initiation and longer treatment duration. The frequency of psychotic diagnoses was low. In patients with ADHD and ASD, the common SGA target symptoms, namely aggression and disturbances in behavioural and emotional regulation, are common (Christiansen et al., 2019; Faraone et al., 2019; Hyman et al., 2020; Magalotti et al., 2019). These symptoms can be related to numerous factors, such as stress, regulation of arousal and attention, impulsivity or lack of inhibition, medical conditions, communicational deficits or underlying psychiatric comorbidity (Christiansen et al., 2019; Faraone et al., 2019; Hyman et al., 2020; Magalotti et al., 2019).

Parental separation was common in both study populations, and 18% of the children in the retrospective study and 13% in the prospective study were placed in foster or residential care. In the retrospective study, patients with ASD or developmental disorder lived more often with both their biological parents and were less frequently placed in foster care compared to the other patients. There were more ICD-10 Z-category diagnoses, implying environmental factors influencing the psychiatric symptoms in the retrospective study patients. Further, approximately 40% of the retrospective study patients had been exposed to violence-related life experiences during childhood.

Foster care and adverse life events were more common in the study patients compared to the normal population. During 2013-2018, around 1.4% of Finnish children and adolescents were annually living in foster or residential care (THL statistics). According to the School Health Promotion study (SHP, 2019), which regularly monitors the well-being, health and schoolwork of Finnish children and adolescents, approximately 10% of 10- to 11-year-olds reported exposure to some form of physical violence among their family members during the previous year and approximately 5% reported caregiver violence at least once during their lifetime (THL, 2019). However, it is possible that these self-reported figures are underestimates. Among foster care children, experiences of childhood adversity are more common than in the general child population. Neglect, maltreatment and serious behavioural problems are common reasons for placements (Oerbeck et al., 2021), and the placement itself may be severely stressful. According to a Norwegian study, 80% of children in foster care had experienced at least one traumatic life event during their childhood, 16% had been exposed to violence among family members and 19% had been subjected to caregiver violence (Lehmann et al., 2020). Approximately half of the children in the child welfare system meet diagnostic criteria for a mental disorder, most commonly an externalising disorder (Bronsard et al., 2016). These children are also prescribed SGAs more often than their peers, and they often do not receive adequate psychosocial treatments (Crystal et al., 2016; McLaren et al., 2018; Oerbeck et al., 2021). Children with adverse life events often have difficulties in behavioural and emotional regulation (Compas et al., 2017; McLauglin et al., 2019). Experiences of threat and violence change the processing of and reactions to social and emotional stimuli, and may further increase negative reactivity and a tendency to misinterpret situations as threatening (McLaughlin et al., 2019). Children with adverse life experiences are also more likely to receive an ADHD diagnosis (Hunt et al., 2017).

The participants of this study were mostly boys who were prescribed risperidone as a symptomatic treatment for behavioural disturbances and affect dysregulation, which is in accordance with previous studies in prepubertal patients using SGAs (Kloosterboer et al., 2018; Piovani et al., 2019; Oerbeck et al., 2021). Generally, boys are referred to psychiatric services at a younger age compared to girls, and often due to externalising symptoms (Friberg et al., 2019; Hansen et al., 2021; Kronström et al., 2016; Lempinen et al., 2019). Externalising symptoms are easily noticed by caregivers and teachers compared to internalising symptoms, which may affect girls more often and may remain unrecognised (Joelsson et al., 2016; Lempinen et al., 2019). Boys are also more often prescribed psychotropics, such as ADHD medications and SGAs during their childhood years (Joelsson et al., 2016; Kloosterboer et al., 2018; Kronström et al., 2016; Olfsson et al., 2015; Piovani et al., 2019; Vuori et al., 2020). SGA prescriptions emerge in girls during adolescence, often targeting anxiety and depression, which generally have a later onset compared to ADHD (Kloosterboer et al., 2018; Olfsson et al., 2015; Saastamoinen et al., 2017). Also in this study, among older patients (over 12 years old), the male preponderance diminished.

The findings of this study highlight that common SGA target symptoms, such as aggression, irritability and difficulties in emotional regulation, are transdiagnostic phenomena that have multiple individual and environment-related aetiological background factors (Faraone et al., 2019; Hyman et al., 2020; Magalotti et al., 2019; McLaren et al., 2018). They are rather symptoms than disorders and their successful treatment requires a thorough diagnostic process to identify the underlying disorder (Faraone et al., 2019, Magalotti et al., 2019). Further, evidence-based psychosocial treatments and individually targeted supportive interventions for the home and school environment are essential (Faraone et al., 2019; Hyman et al., 2020; Magalotti et al., 2018).

6.2 SGA treatment response and its assessment

To measure treatment response, target symptoms need to be defined. The indication of SGA was defined in 61% of the retrospective study patients, and in 16% the benefits were uncertain or not reported. Despite this, the duration of SGA medication was often long. This hardly indicates that there was no response, but the response evaluation process was not visible in the medical records. In the

prospective study, the treatment response of most patients was assessed as part of the monitoring protocol at each visit.

Due to the wide range of target symptoms, a definition of clinically relevant improvement may be difficult. Many individual and environmental factors may contribute to symptoms and, further, to treatment response. In a randomised study by Farmer et al. (2015), children with ADHD who had high rates of anger, irritability and ADHD symptoms and less manic symptoms showed a faster response compared to other patients when a stimulant and parental training were augmented with risperidone. However, the efficacy was similar at the study endpoint (9 weeks). Interestingly, also parental education affected the response. Children with more highly educated mothers benefitted more from stimulant treatment combined with parent training, whereas children with mothers having both high and low levels of education benefitted equally well when risperidone was added to the treatment.

To avoid medicating the child instead of intervening in the environmental factors, aetiological factors contributing to the emergence and continuity of the target symptoms should be considered when the SGA response is evaluated (Geller, 2018). Medication alone is not sufficient in the treatment of severe mental disorders in children, but it may enhance the possibility of benefitting from psychosocial treatments. Research data on the SGAs' effects on the general functioning, school performance and family life of children and adolescents is limited (Loy et al., 2017; Santosh et al., 2017; van der Schans et al., 2016). During SGA monitoring, changes in target symptoms and daily functioning should be noted, as should the family's overall situation (Santosh et al., 2017; van der Scahns et al., 2016).

6.3 Adverse effects

SGAs' various effects on the CNS and energy metabolism may appear at a different pace depending on their mechanisms and individual susceptibility. Neurotransmitter-related effects, such as EPS, orexigenic effect and sedation may appear relatively quickly, whereas adipose tissue-related effects and inflammation may take a longer time to develop (Burghard et al., 2018; Correll, 2008; Garcia-Amador et al., 2015; Libovitz and Nurmi, 2021; Pringsheim et al., 2011a; van der Esch et al., 2020). Very little is known about the cumulative and long-term effects of SGAs on cardiovascular health and the developing human brain (Correll and Blader, 2015).

6.3.1 Weight gain – detection and prevention

Risperidone was the most common SGA in the study patients. It has repeatedly been associated with weight gain, which seems to emerge early during treatment (Almandil et al., 2013; Martínez-Ortega et al., 2013; Pozzi et al., 2019 and 2020; Sjo et al., 2017; van der Esch et al., 2020; Vanderberghe et al., 2018). As in previous studies, a significant zBMI increase was detected in both the retrospective and prospective study patients, and the frequency of overweight patients increased during the follow-up. Even though the rates of overweight and obesity have increased globally in all age groups (Ng et al., 2014), the frequency was higher in the study population compared to their peers. According to the Finnish Current Care guideline (Obesity: Children, Adolescents and Adults 2018), approximately 27% of boys and 18% of girls were overweight or obese in 2018. In the prospective study patients, the frequency of overweight varied between 30% and 50% during the follow-up.

In the retrospective study, concomitant psychotropic medication showed some effects on weight gain. Children using SGA monotherapy or an SGA-melatonin combination gained weight most often. However, concomitant melatonin had a weak association with weight gain within normal limits. Some studies have reported a possible mitigating effect of melatonin on SGA-induced weight gain, but melatonin has also been associated with increased glucose concentrations in adults (Agahi et al., 2018; Mostafavi et al., 2018; Tuomi et al., 2016). Children who used an SGA-ADHD medication combination gained weight less often compared to other children. The moderating effect of stimulants on SGA-induced weight gain have been described earlier (van der Esch et al., 2020).

Weight gain was reported as an adverse effect fairly seldom (33% retrospectively and 38% prospectively) compared to the frequency of actual weight gain (75% and 64%, respectively). This finding indicates that weight gain may remain undetected or unreported in clinical work. It may also associate with weight gain appearing within the normal BMI limits. However, even a smaller weight gain contributes to cardiometabolic risk and psychosocial wellbeing, and without interventions it may continue.

Studies show that SGA-induced weight gain is most pronounced in the first weeks and months of the treatment depending on the SGA (Nicol et al., 2018, van der Esch et al., 2020; Pozzi et al., 2020), and a similar tendency was observed also in the prospective study patients. Early weight gain seems to predict continuing weight gain (Van der Esch et al., 2020; Vanderberghe et al., 2018). In a study by Vanderberghe et al. (2018), a weight gain larger than 4% after one month of SGA

treatment predicted a weight gain of over 15% after 3 months in adolescents. However, weight gain may show a levelling off during long-term treatments (Pozzi et al., 2020; van der Esch et al., 2020), which was also seen in the prospective study. It seems that during a long-term SGA treatment, a new metabolically disadvantageous equilibrium is achieved, and the weight may stabilise at an unhealthy level and further contribute to future cardiovascular ill health (Calarge et al., 2014; Pozzi et al., 2020; van der Esch et al., 2020). With aripiprazole, which is considered metabolically more neutral, weight gain may appear slowly but ultimately reach similar levels compared to, e.g. risperidone (Pozzi et al., 2019 and 2020; van der Esch et al., 2020). Switching a metabolically potent SGA (e.g. olanzapine) to aripiprazole may be helpful, but weight gain can still continue (Pozzi et al., 2020), However, discontinuation of an SGA, even after years of treatment, may lead to the normalisation of zBMI and other metabolic parameters (Calarge et al., 2014).

Absolute weight change in kilograms is not informative in growing children (Pozzi et al., 2020); instead, zBMI and percentage of weight gain are more feasible indicators. In this study, the overall median zBMI change was 0.46 in the retrospective and 0.37 in the prospective study patients. However, there was individual variation. In the clinical work, an SGA-induced zBMI increase of 0.5 or weight gain of 4-7% should be considered clinically relevant and worrisome changes leading to the re-evaluation of medication, monitoring and life-style guidance (Correll, 2008b and 2011; De Hert et al., 2011; Pozzi et al., 2020; Vanderberghe et al., 2018). Weekly weight monitoring at the beginning of treatment, e.g. by a school nurse, and a follow-up visit at one month are advisable clinical practices that may benefit the early detection and prevention of weight gain (Koskentausta and Tolmunen, 2016; Van der Esch et al., 2020). Special attention should be paid to the monitoring of already overweight patients, as a higher baseline zBMI may predict a higher future zBMI (Pozzi et al., 2020; van der Esch et al., 2020).

At SGA initiation, preventive lifestyle education should be given to all patients and their caregivers (Melamed et al., 2021; Sjo et al., 2017). Further, children and caregivers should be informed of possible SGA-related increased appetite and weight gain. Instead of general lifestyle counselling, practical individual advice, such as caregiver guidance in planning healthy grocery shopping and snacks together with the child, may be more beneficial (Nicol et al., 2016; Nyboe et al., 2019). Special attention should be paid to socially disadvantaged children and their caregivers, as well as to already overweight patients, who may have more lifestyle-related risk factors for metabolic disorders (Melamed et al., 2021; Nicol et al., 2016; Pozzi et al., 2020; van der Esch et al., 2020).

In the prospective study, and likewise in clinical reality with SGA-treated children, only a few children were physically active or had sport hobbies. Aerobic exercise interventions could benefit children with SGAs (Nicol et al., 2016; Nyboe et al., 2019). However, lack of motivation to exercise together with the SGA-induced need to seek calorie rich food is a complex challenge to solve (Nicol et al., 2016; Nyboe et al., 2019). Further, disturbances in behavioural regulation and already existing overweight complicate the child's participation in group games and activities that might otherwise be helpful. Therefore, it is important to motivate and encourage caregivers to facilitate healthy behaviour at home, e.g. motivate the child to move by setting a good example and using games and mobile applications (Nicol et al., 2016). Physical activity benefits mental health and the treatment of psychiatric disorders, and it associates with pro-social behaviour in children and adolescents (ADHD: Current Care Guideline 2019; Laukkala et al., 2019; Super et al., 2019). Sport hobbies with a low entry threshold and sufficient adult support should be available on the community level to support physical activity and the formation of social relationships. Further, mobile applications could benefit the monitoring and increase the child's motivation to move (Nicol et al., 2016).

When SGA-induced weight gain has already emerged, the treatment is more complex. Lifestyle education may not be sufficient alone to prevent further weight gain, rather re-evaluation of the SGA and liaison with paediatrics concerning the treatment of metabolic disorders should be considered (Correll et al., 2020; Melamed et al., 2021; Sjo et al., 2017).

6.3.2 Blood pressure and ECG monitoring

BP measurements fulfilling the official criteria on elevated hypertensive BP were rare. Three patients in the retrospective study and none of the patients in the prospective study fulfilled the criteria. Studies have shown diverse findings of BP elevation in SGA-treated children. In a study by Sjo et al. (2017), no significant change in BP was seen during 12 months of SGA treatment. However, in other studies elevated BP was more common in SGA-treated children compared to peers (Panagiotopoulos et al., 2012; Devlin et al., 2012). It is possible that for the detection of SGA-induced hypertension (if any), the present study had too short a follow-up period (Sjo et al., 2017). In the retrospective study, patients with an SGA-ADHD medication combination had individual hypertensive systolic BP measurements indicatively more often compared to other patients. This finding is in line with the

fact that blood pressure elevation is a relatively common adverse effect of stimulant medications (ADHD: Current Care Guideline 2019). Interestingly, in patients with an SGA-melatonin combination, individual systolic BP measurements were indicatively less often hypertensive compared to others. A similar tendency has previously been described in adult patients using an SGA-melatonin combination, but more studies on the matter are needed (Agahi et al., 2018).

In the prospective study, an ECG was measured in most patients at BL and at least once during the follow-up. In the retrospective study, the frequency of ECG monitoring was not reported, but in 36% of the patients a paediatric cardiologist was consulted, most often due to a suspected ECG deviance. Studies indicate that the risk of SGA-induced QT prolongation is small – but not absent – in children and adolescents (Alda et al., 2016; Aman et al., 2015; Jensen et al., 2015; Palanca-Maresca et al., 2016; Roessner et al., 2017; Vo et al., 2016). According to paediatric cardiologist responses in retrospective study patients, no absolute obstacles for SGA continuation were detected in the retrospective study patients. However, in the clinical work, the child's individual susceptibility, different SGAs' potencies to induce QT prolongation, SGA dosage, and other concomitant medications may contribute to the risk (Haddad and Andersson, 2002; Palanca-Maresca et al., 2016). At present, there is no clear consensus concerning the frequency of ECG follow-up in SGA-treated children. Individual assessment of patient- and family-related risk factors and a physical examination at BL and during the follow-up are essential (Hiippala and Happonen, 2021). An ECG should be considered with a low threshold, especially in cases where there is even a slight suspicion of risk or the information concerning the risk factors is lacking. Further, concomitant medications should be noted. Paediatric cardiological consultation may be relevant (Hiippala and Happonen, 2021).

6.3.3 Lipid and glucose metabolism

In this study, a disadvantageous shift was seen in the FPG and insulin values of the prospective study patients, and in the TG and HDL values in both study samples. The elevation of FPG and insulin levels have also been reported in previous studies in children and adolescents using SGAs (Arango et al., 2014; Galling and Correll, 2016). Even though type 2 diabetes is not common in children, SGAs increase the risk two- to three-fold (Bobo et al., 2013; Galling et al., 2016). Further, in a study by Arango et al. (2014), when SGA-treated children and adolescents were compared,

children under the age of 12 years (who represented the majority in the present study population) were reported to have a higher risk for disturbances in glucose metabolism (Arango et al., 2014). SGA treatment has also been associated with elevated TG and low HDL levels (Arango et al., 2014; Correll et al., 2009; Galling and Correll, 2015; Panagiotopoulos et al., 2012; Sjo et al., 2017). However, the assessment of lipid levels may be complicated during puberty, as there seems to be a physiological decrease in HDL levels and increase in TG levels especially in male patients (Eissa et al., 2016; Cho and Kim, 2021).

Very few patients in this study exceeded the chosen metabolic cut points, but the disadvantageous shift started to emerge early during the treatment (Figure 3). A similar tendency has been reported in previous studies in weight gain, adiposity and glucose metabolism (Arango et al., 2014; Bobo et al., 2013; Nicol et al., 2016; Panagiotopoulos et al., 2010; Pillay et al., 2018; Sjo et al., 2017). At first, the shift appears within the reference ranges, but it may progress during long-term exposure and vary with different SGAs and dosages (Arango et al., 2014; Calarge et al, 2014.; Laita et al., 2007; Srisawasdi et al., 2021). Detecting these tendencies may be difficult in clinical work. In the prospective study, the lower FPG cut point (5.6 mmol/l) seemed to be a more feasible risk indicator compared to other metabolic laboratory values. The frequency of patients who exceeded this cut point emerged early and remained between 20-29% during the follow-up. Impaired fasting glucose may indicate an increased risk for diabetes (American Diabetes Association, 2014). Further, it may be a sensitive measure to detect cardiometabolic risk factor clustering in children and adolescents using SGAs (Panagiotopoulos et al., 2012).

SGA treatment in children associates with elevated insulin levels (Arango et al., 2014; Galling and Correll 2016), which was also seen in the prospective study patients. Elevated insulin concentration may indicate hyperinsulinemia, but alone it does not benefit the detection of impaired glucose tolerance. Age-, gender- and weight-related differences and the lack of general cut points hinders the diagnostic value (Styne et al., 2016; Tagi et al., 2019). It is not possible to reliably differentiate between normal and abnormal values of insulin concentrations, thus its use is not recommended in clinical practice (Styne et al., 2016).

In the prospective study, the patients' HOMA-IR and TG/HDL ratios were calculated to assess the development of possible IR and increased cardiometabolic risk. An increase was seen in both values during the follow-up. Similar findings have been reported in studies of SGA-treated children and adolescents (Arango et al., 2014; Correll et al., 2009; Galling and Correll, 2015; Panagiotopoulos et al., 2012; Srisawasdi et al., 2021). HOMA-IR represents the relation of glucose and insulin,

and it offers a possibility to assess insulin sensitivity (Tagi et al., 2019). It also correlates well with the euglycemic-hyperinsulinemic clamp, the gold standard measure, but it is much easier to perform and allows repeated measurements (Wallace et al., 2004; Tagi et al., 2019). The TG/HDL ratio has also been proposed for the assessment of IR and cardiometabolic risk in obese children and, further, in children treated with SGAs (Correll et al., 2009; Manco et al., 2016; Nur Zati Iwani et al., 2019; Tagi et al., 2019; Wallace et al., 2004). However, the clinical use of both these measures is restricted due to the lack of cut points for children (Shashaj et al., 2016). In studies, HOMA-IR cut points from 1.68 to 3.54 have been associated with increased cardiometabolic risk, lower values being suitable for children with normal weight (Arellano-Ruiz et al., 2019; Shashaj et al., 2016). Suggested cut points for the TG/HDL ratio have varied between 1.36 and 2.2 (Behiry et al., 2019; Di Bonito et al., 2015; Manco et al., 2016).

In this study, the increase in HOMA-IR appeared earlier and was more marked compared to the TG/HDL ratio. The HOMA-IR increase was not solely explainable with increasing age, because the proportion of patients who exceeded the age-, gender- and zBMI-specific percentile cut points also increased during the follow-up. Of those patients who were monitored at T4 (median treatment duration 16 months), approximately three quarters exceeded the percentile cut point. In this study, regardless of the patients' zBMI, an HOMA-IR cut point as low as 1.98 seemed to represent good sensitivity and specificity. The cut points for the TG/HDL ratio generated in this study were lower compared to those of previous studies, but the sensitivity and specificity were at most average.

Psychiatric disorders are often accompanied by an unhealthy lifestyle and poor physical health. Even though the concept of metabolic syndrome is controversial in children, SGAs increase cardiometabolic risk factor clustering and may endanger lifelong cardiovascular health (Correll et al., 2020; Devlin et al., 2012; Libowitz and Nurmi, 2021; Panagiotopoulos et al., 2012; Sjo et al., 2017; Tagi et al., 2019). Based on the findings in this study, the focus of SGA monitoring should be on detecting adverse metabolic tendencies before the actual disorder, e.g. type 2 diabetes, emerges. An FPG cut point $\leq$ 5.6 mmol/l could be beneficial in the monitoring of glucose levels. Further, calculation of HOMA-IR could benefit the early detection of adverse metabolic shift when age-, weight- and gender-related variation is taken into account. Children are often afraid of blood tests, and a single counted ratio such as HOMA-IR could easily add value to basic monitoring. When such an adverse tendency is noted, the re-evaluation of medication-, lifestyle- and monitoring-related factors is needed.

6.3.4 Neurological adverse effects

Neurological adverse effects were reported in 7-10% of all study patients, which is slightly less compared to previous studies. Neurological adverse effects are less common than metabolic adverse effects in children, and in short-term treatment they are usually mild (Garcia-Amador et al., 2015; Tural Hesapcioglu et al., 2020; Pringsheim et al., 2017; Rasimas et al., 2012; Roerig et al., 2011).

In the field of paediatric psychopharmacology, SGA-induced neurological adverse effects have received less attention than metabolic adverse effects (Pringsheim et al., 2017). In the present study, the frequency of performed neurological examination was not noted. The monitoring protocol did not include the systematic rating for EPS, and neurological adverse effects were only written in the patient reports when detected. The overall lack of systematic monitoring in SGA-treated children indicates that neurological examination is probably not a common practice (Chen et al., 2018; Coughlin et al., 2018, Hayden et al., 2019; Javaheri et al., 2019; Jazi et al., 2020; Okumura et al., 2018).

It is possible that neurological adverse effects remain unrecognised or underreported. In a study by Pringsheim et al. (2017), where the frequency of EPS in SGA-treated children and adolescents was systematically assessed with a rating scale, the prevalence was found to be up to 35%. This finding indicates that the systematic assessment of EPS in children using SGAs should be common practice. The use of rating scales would be helpful, but there are no validated scales for children (Carbon et al., 2015; Pringsheim et al., 2011a). All SGAs, especially the widely used risperidone, carry a risk for EPS in children (Biscontri et al., 2017; Garcia-Amador et al., 2015; Tural Hesapcioglu et al., 2020; Pringsheim et al., 2017; Rasimas et al., 2012). Further, akathisia (including restlessness and the compulsive need to move) may be misinterpreted as agitation or the worsening of psychiatric symptoms (Rasimas et al., 2012). This kind of misinterpretation probably influenced the development of severe TD in the patient described in the case report. Individual predisposing factors may contribute to the emergence of EPS, and at worst, to TD. In the case report, the patient had several of these risk factors: a prior history of mild EPS, long treatment duration, high SGA dose, and diagnosis of ID (Solmi et al., 2018). In this case, young age and extremely severe symptoms – which did not manifest as classical TD but rather as the dystonic subtype of TD (Pringsheim et al., 2011a) – together with communicational deficits delayed the diagnosis and led to severe complications.

6.3.5 Consultations and co-operation between paediatric specialties

Increased SGA prescriptions have created new educational needs and an increased demand for liaisons between paediatric specialties (Pisano et al., 2016; Rasimas and Liebelt, 2012). In the present study, the frequency and reasons for paediatric consultations were reported only in the retrospective study. Paediatric consultations were relatively common, and the most consulted specialist was a paediatric cardiologist (in 36%), followed by a paediatric neurologist and endocrinologist. The interpretation of the child's ECG requires practice and experience (Hiippala and Happonen, 2021). The same is true for interpreting metabolic parameters, or neurological symptoms, and their relation to SGA medication (Rasimas and Liebelt, 2012). Liaisons with paediatric specialists, low-threshold consultations and joint decision making, especially with difficult-to-treat patients, improves SGA medication safety in children and, further, offers educational benefits for all specialties.

6.4 The implementation of the monitoring protocol

SGA follow-up practices at TAUH child psychiatric unit were found to be diverse and especially BL monitoring was lacking before the implementation of the monitoring protocol. During the prospective study period, the implementation improved the BL and follow-up monitoring as well as the frequency of repeated metabolic measures. However, the measurement of metabolic parameters at BL and the BP follow-up still require attention. The implementation also systematised the assessment of familial cardiometabolic risk factors and the definition of SGA indication and target symptoms during the prospective study period. Further, the assessment of response to SGA treatment improved.

Even though the monitoring improved in the study patients, the wider effects on SGA monitoring at TAUH child psychiatric unit are unknown and need to be studied further locally, but multisite studies are needed as well. The handbook and the monitoring forms were available for all physicians, but their use was not mandatory nor followed outside the study. Further, the continuation of the improved monitoring is not known. Prior studies have shown that the benefits of monitoring protocol implementation may wane as time passes (Melamed et al., 2021; Ronsley et al., 2012).

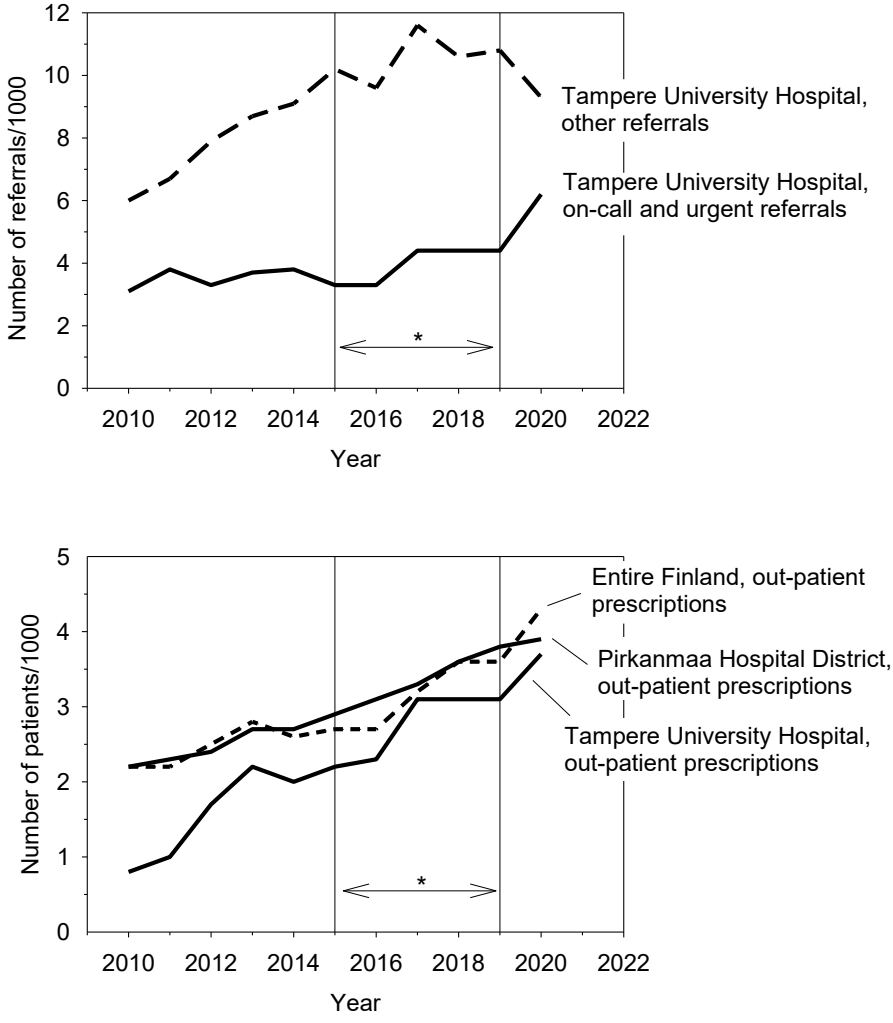
6.5 SGA prescriptions at TAUH

Prescribing SGAs for children has increased in recent years also at TAUH (Figure 4.) In a study by Ronsley et al. (2012), implementing metabolic monitoring in community health clinics decreased SGA prescriptions for children. At TAUH child psychiatric unit, there was a slight levelling seen in the number of SGA prescriptions during the study period between 2017 and 2019 (Figure 4). However, during 2020, SGA prescriptions increased again at TAUH as well as in the whole of Finland. Reasons for the transitory levelling seen at TAUH are not known and are only speculative, but they may be partly related to the present study and implementation of the monitoring protocol, making the issue more notable in clinical work.

TAUH represents specialist-level child psychiatric services treating the most severe mental disorders, which often require psychotropic medication. Simultaneous with the general increase in SGA prescriptions, the demand for child mental health services and acute psychiatric treatment has increased (Carubia et al., 2016; Say et al., 2019; Friberg at al., 2019; Lempinen et al., 2019), which is also the case at TAUH (Figure 4). Common reasons for psychiatric emergency referrals in children are suicidal ideation, aggression and serious behavioural disturbances, which often require psychotropic medications (Carubia et al., 2016; Say et al., 2019, Friberg at al., 2019). Simultaneous with the two-year plateau in SGA prescriptions at TAUH, the rise in urgent referrals temporarily declined but continued to increase again in 2019. In 2020, the COVID-19 pandemic affected the availability and demand of child psychiatric non-urgent treatment, but the need for urgent care continued to rise. The effects of the pandemic on child mental health are most likely far-reaching and need to be studied further. In a recent study by Rauf et al. (2021), lockdowns during the COVID-19 pandemic resulted in the increased use of psychotropic medications in children and adults with ID and ASD (Rauf et al., 2021).

The reasons that contribute to the increase in SGA prescriptions and the increased demand for acute psychiatric treatment in children are most likely numerous and need to be studied further. However, strengthening low threshold psychiatric out-patient services for children and families could be beneficial, and, in the long run, decrease the need for specialist-level psychiatric care in children. This might contribute to the need for SGAs in children as well.

Figure 4. Number of on-call and urgent (0-28 days) referrals, and other (non-urgent) referrals to TAUH child psychiatric unit and, number of antipsychotic prescriptions in children under the age of 13 years in Finland, Pirkanmaa hospital district, and TAUH. (Prescriptions in the Pirkanmaa hospital district include TAUH prescriptions and community-level health care.)



* Prospective study period (during which an SGA monitoring protocol was intoduced at TAUH)

6.6 Strengths and limitations

A major strength of this study is that it describes real-life prescribing and monitoring practices at a Finnish child psychiatry unit. In both study phases, the initiation and choice of medication was based on clinical judgement only. The retrospective study provided a naturalistic perspective to the clinical reality and long-term SGA treatment. It also disclosed targets for monitoring. The major strength of the prospective study was the systematic monitoring protocol, which improved clinical practices and promoted safer SGA prescription and monitoring practices. It also enabled the estimation of change in metabolic parameters.

However, in both study phases major limitations were the lack of control group and the relatively small sample size, which limit the generalisability of the results. Further, there were differences in the study populations regarding the background factors, concomitant medication and SGA indications. These differences, which affect the comparability of the research groups, were most likely due to the study characteristics. The retrospective study probably gives a more naturalistic view of the clinical use, whereas the prospective study may be biased with more out-patients than in-ward patients. This is probably due to the prospective study entry process, which required time and peace for conversation with both the patient and caregivers. Such a conversation is seldom possible upon admission to in-ward care during on-call hours, or with an acutely agitated or aggressive patient. Further, recruiting patients to the study and the use of the monitoring protocol was optional for the physicians at TAUH child psychiatric unit, and not all the patients' prescribed SGAs were systematically included in the study.

In the retrospective study, the lack of BL measurements restricted comparisons of metabolic values, and the minimum and maximum values were compared instead, affecting the generalisability of the results. Furthermore, mechanisms of SGA-induced metabolic changes are complex and partly unknown. The reasons for disadvantageous changes in the glucose and lipid metabolism can result from weight gain, medication, or both. Simultaneous psychotropic medication, overweight, developmental status, gender, ethnicity and haemolysis of blood samples may also have affected the results, so causal relationships remain partly unresolved. More studies with larger samples are needed to improve the detection of underlying risk factors and the definition of, e.g. optimal monitoring intervals.

Moreover, outcome monitoring and the availability and use of evidence-based psychosocial treatments were not studied in these children.

7 CONCLUSIONS

Development from infancy to adulthood is a complex process involving genetic and environmental factors. It is a dynamic and interactive process between the individual and social and cultural context (Sameroff, 2010). One of the most important challenges during childhood is to learn to regulate emotions and aggression (Compas et al., 2017; Sameroff, 2010; Tremblay et al., 2018). These skills are learned through social, emotional and cognitive experiences during the developmental years. Even though the individual ability to identify and control emotions and behaviour evolves with the development of cognitive and executive functions, a "safety net" provided by others – parents, teachers and other safe adults – is needed, especially in situations where the capacity for self-regulation fails (Compas et al., 2017; Sameroff, 2010). Childhood mental disorders have various aetiological factors, many of which are not reachable by medication.

However, SGAs are important in the treatment of severe childhood mental disorders. When the severity of aggression or other disabling symptom diminishes with the medication, the possibility to benefit from psychosocial treatments and to integrate with the peer group may improve. Further, when aggressive behaviour burdens the whole family, medication may promote positive interaction with caregivers and siblings and allow the child to live at home instead of in an institution. However, medication alone is usually not sufficient and psychosocial treatment modalities are essential.

The main aim of this dissertation was to study whether the implementation of a systematic monitoring protocol could improve SGA medication safety in child psychiatric patients. The specific aims were: 1) to describe the medical and socio-demographic background factors of child psychiatric patients using SGAs, 2) to describe SGA prescribing and monitoring practices and the detected benefits and adverse effects before and after the implementation of the systematic monitoring protocol, and 3) to assess how the monitoring protocol was followed in a clinical setting. Based on the reviewed literature and the present study findings, the following conclusions can be made:

1. In the present study, SGAs were commonly prescribed as a symptomatic treatment for behavioural disturbances and affect dysregulation irrespective of the diagnosis. Environmental factors also influenced the psychiatric symptoms. All SGA prescriptions in this study were off-label, and treatment duration exceeded the short term. The findings of this study highlight the fact that the common SGA target symptoms in children are transdiagnostic phenomena that may have multiple individual and environmental aetiological factors. Successful treatment of these symptoms requires a thorough diagnostic process and multidimensional treatment approach that targets both the child and the environment factors to support developmental progression. The choice of medication should be based on evidence. Evidence-based psychosocial treatments and other individually tailored supportive measures for the child and family should be offered prior to and concomitant with the medication.

2. Before the monitoring protocol implementation, the SGA follow-up practices at TAUH child psychiatric unit were found to be diverse, and especially baseline monitoring was lacking. During the study period, the implementation improved the baseline and follow-up monitoring, as well as the frequency of repeated metabolic measures.

   A significant disadvantageous shift in measured metabolic parameters was seen early during the SGA treatment, but the measures seldom exceeded the cut points. Further, weight gain was reported as an adverse effect less frequently compared to actual weight gain. These findings indicate that adverse metabolic tendencies may remain undetected in clinical work. Neurological adverse effects were seldom reported but were not absent.

   In the light of these findings, the following issues need to be considered during the initiation and follow-up of SGA treatment in child psychiatric patients:

   Upon SGA initiation,
   - the overall treatment plan should be evaluated, including the availability and use of psychosocial treatments and supportive measures for the child and the family;
   - the target symptom should be defined in co-operation with the patient and the caregivers;

- individual risk factors and a physical examination, including cardiovascular and neurological status, should be assessed and accompanied with an ECG and basic laboratory tests, including metabolic parameters;
- growth using growth charts should be assessed systematically;
- the possible effects of concomitant medications to SGA and the risk of adverse effects should be estimated;
- information should be given to the patient and the caregiver if the SGA prescription is off-label;
- information should be given to the patient and the caregiver about the possible benefits and adverse effects. Open dialogue between the child, the caregiver and the physician should be encouraged to promote medication safety. Children should be included in their treatment according to their age and developmental status;
- preventive individual lifestyle education should be given to all patients and their caregivers. Further, attention should be paid to motivate children and their families to undertake physical exercise;
- the rule of "start low and go slow" should be followed.

The monitoring of SGA treatment should

- be systematic and continued throughout the SGA treatment;
- include an assessment of the overall treatment plan, including the availability and use of psychosocial treatments and other supportive measures for the child and the family;
- include a systematic assessment of efficacy and the need for continuing the medication;
- include a physical examination, including the cardiovascular and neurological status;
- include a systematic assessment of growth using growth charts at each follow-up visit. At the beginning (first 1-3 months), the weight monitoring should be performed more frequently (e.g. in co-operation with the school nurse) to detect the early changes. If weight gain of 4-5% or a zBMI increase of 0.5 is detected during the first month of treatment, re-evaluation of the medication, lifestyle, and monitoring is needed. Weight monitoring should be continued through the follow-up, even if the change in weight is smaller;

- include a regular follow-up of metabolic parameters, BP and ECG. Special attention should be paid to detecting adverse tendencies. In glucose monitoring, a cut point of ≥ 5.6 mmol/l should be used instead of > 6.1 mmol/l. HOMA-IR as a part of systematic monitoring may benefit the early detection of metabolic adverse effects and the identification of children who need additional monitoring and care.

Further, If the patient's aggression or agitation or other symptom emerges after SGA initiation or dose increase, the possibility of a neurological adverse effect, such as akathisia, should be considered.

During child psychiatric SGA treatment, liaison between paediatrics, school health care and child psychiatry should be encouraged with a low threshold.

Furthermore, all the above-mentioned should be well documented in the medical records.

3. During the present study, the systematic monitoring protocol was well followed in a clinical setting. Implementation of an SGA monitoring protocol in a child psychiatric unit can promote SGA medication safety. Monitoring should be promoted and enabled at the organisational level and made as easy as possible to perform in the child psychiatric unit.

8 IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

8.1 Clinical application – Child psychiatric medication unit at TAUH

Previous studies show that monitoring may improve if the organisation is committed and the intervention is tailored to local structures (Melamed et al., 2021). As a clinical application of this study, at TAUH the child psychiatric medication unit was set up in February 2021. The medication unit serves children who are treated at TAUH child psychiatric unit and who take psychotropic medication. Patients can be referred to the medication unit by their attending physicians in TAUH, who stay in charge of the overall treatment. The attending physician can request the monitoring of medication safety and efficacy from the medication unit during a transitional period after a diagnostic process or after an in-patient treatment, or concomitant with a therapeutic process. The unit aims to address the barriers of monitoring shown in previous studies, such as timetables, sufficient equipment and systematic training of staff. Further, emphasis has been placed on multidisciplinary teamwork, which is considered beneficial for monitoring practices (Coughlin et al., 2018; Jazi et al., 2020; Melamed et al., 2019). In the medication unit, child psychiatric residents (in rotation) work in co-operation with trained nurses. The two experienced and trained nurses work regularly in the unit, and aside from patient encounters, they oversee all practical matters, such as scheduling the follow-up visits, ordering laboratory tests, and offering lifestyle counselling and psychoeducation. Pre-scheduled monitoring routines, checklist and rating scales systematise the work. Further, a prescheduled easy-to-order set of laboratory tests is available. Reminders and concrete tools benefit the prescribers (Melamed et al., 2019; Melamed et al., 2021; Ronsley et al., 2021).

Good practical skills in psychotropic medication practices are essential for the child psychiatrist (Hutchison et al., 2020). Even though the main aim of the medication unit is to make psychotropic medication monitoring practices systematic, the other important aim is to offer child psychiatric residents clinical education and experience in psychotropic medication during their training. A recent study by

Hutchison et al. (2020) showed that the progression of training increased the confidence of child psychiatric residents in psychotropic medication practices. However, complex situations involving polypharmacy, drug interactions, off-label medication, and the reassessment of medication (de-prescribing) seemed often to remain subjects of discomfort or uncertainty (Hutchison et al., 2020). These complex skills can be enhanced with guidance (Hutchison et al., 2020). A consultation hour between a senior specialist and the resident is a fixed part of the medication unit schedule. After the university hospital training, child psychiatric residents locate to various places in the Finnish health care system. With proper education during their residency, systematic prescription and monitoring practices may become common child psychiatric practice.

8.2 Future research

SGAs are prescribed for various indications, often off-label, to children with various diagnoses and psychosocial situations. International guidelines point out the importance of SGA monitoring, but further, they highlight the general quality of care and availability of adequate psychosocial treatments (Dinnissen et al., 2020; Kealey et al., 2014; Pringsheim et al., 2011b). More studies on the quality of SGA treatment in children – including off-label treatment practices – using a multicentre approach are needed. Furthermore, the present outcome measures are various and often dependent on the target symptom. Systematic measures to assess SGAs' effects on general functioning, school performance and social relations are needed and should be evaluated. During the monitoring protocol presented in this study, outcome, functional capacity, and the child's self-report of medication benefits and adverse effects were assessed at each follow-up visit. The results of his part of the study will be reported later. More studies concerning SGA treatment response are needed. During the systematic monitoring protocol, ECGs were also regularly monitored. Analyses of this part of the study are still ongoing in co-operation with a paediatric cardiologist.

More studies concerning the development of metabolic adverse effects and effective ways to detect, prevent and to treat them during long-term SGA treatment in children are needed. Furthermore, more studies on SGA-induced neurological adverse effects and systematic methods to improve their detection in children are required.

Most importantly, the reasons behind the continuing growth of psychotropic medication prescriptions in children need to be studied and addressed.

9 ACKNOWLEDGEMENTS

This study was carried out between 2013 and 2019 at the child psychiatric unit of Tampere University Hospital and Tampere University's Faculty of Medicine and Health Technology.

I wish to express my deepest gratitude to my supervisors, Professor Tuula Tamminen, MD, PhD, Professor Kaija Puura, MD, PhD, and Raili Salmelin, Msc, PhD. I thank Professor Tuula Tamminen for helping me to find my own scientific interests. She guided me with wisdom, warmth and patience, and her contribution during the planning and first years of this study was priceless. Professor Kaija Puura successfully continued as my supervisor. I am grateful to Kaija for always being a supportive and encouraging mentor, and for helping me to find my own strengths. I cherish our many joyful conversations concerning clinical work, science, and life in general. Tuula and Kaija are both outstanding teachers who have shared with me their knowledge on child psychiatry and science and helped me to find my own path as a clinician, teacher, and researcher. I am also deeply grateful to Raili Salmelin, Msc, PhD, for her excellence in statistics and for all the time and effort she invested in me and this study. I thank her for her endlessly patient and kind help, guidance and support. Raili managed to change my aversion to statistics into a genuine interest, and she helped me to find the joy in numbers and science.

I wish to express my gratitude to the official reviewers of this dissertation, Docent Päivi Santalahti, MD, PhD, and Professor Harri Niinikoski, MD, PhD, for their in-depth corrections and valuable comments that improved this dissertation substantially.

I thank my dear, wise, and warm-hearted friend, research colleague and co-author Leena Pihlakoski, MD, for always believing in me and sharing with me the enthusiasm towards this study already from its beginning. During this process we grew to be friends and shared many joyful moments. As a clinician and researcher, Leena is a true inspiration to me.

I warmly thank my co-author Docent Päivi Keskinen, MD, PhD, for her expertise and for all the help and guidance in the field of paediatric endocrinology. With her warm attitude she also encouraged me to test my own limits and to exit my comfort zone, being always ready to help when needed.

I wish to express my gratitude to Docent Tuija Poutanen, MD, PhD, for her expertise and guidance in paediatric cardiology. I am grateful for her support and for the valuable comments that improved this dissertation. I am also thankful for the yet unpublished work that she has done in examining the ECGs of the prospective study. Our research work continues together.

I thank my dear sister and co-author Docent Kaija Järventausta, MD, PhD, who has always been in my life and with whom I have shared everything from Barbie-shoes to science. She has walked beside me during this scientific journey as my sister, but also during the last years, as my mentor and co-author. During the last crazy months when this dissertation was finalised, her sisterhood and support was irreplaceable, and it shall not fall into oblivion.

I warmly thank my co-author Nina Bjelogrlic-Laakso MD, PhD, for sharing her knowledge on intellectual disability and paediatric psychopharmacology.

I thank my co-author Docent Kai Lehtimäki, MD, PhD, for introducing me to neuroimaging and the possibilities of neurosurgery in psychiatry (just perfectly, not too deeply). Special thanks to Kai for the excellent figure in our article.

I am very grateful to Sari Miettinen, RN, for her precious help in the co-ordination of the prospective part of this study and for our friendship during my years in child psychiatry.

I wish to thank Professor Tomi Rantamäki, PhD (Pharm.), for his kind and therapeutic advice in the field of neuropsychopharmacology. He helped me to focus my thinking and writing and encouraged me not to enter all the rabbit holes that I encountered in the field of neurotransmitters.

I am most grateful to all the patients and families who participated in this study. I also wish to express my gratitude to all my dear colleagues at the TAUH child psychiatric unit who invested their time and effort for the study purposes and helped to collect the research data during the years 2015-2019.

The years of clinical work at TAUH child psychiatric unit have been a privilege. I wish to express my gratitude to the chief of the department, Reija Latva, MD, PhD, for her kind support and her belief in me and my ideas. With her effort, the clinical application of this study became possible. I also want to thank all my dear, skillful, and warm-hearted colleagues, co-workers, and friends at TAUH child psychiatric unit. Especially warm thanks to Anne-Mari Borg, MD, PhD, for her friendship and support during this process. I am also grateful to Niina Tiili, RN, MNSc, and to Mervi Keskinen, RN, and Jonna Välimäki, RN, whose commitment has laid the foundations for the child psychiatric medication unit.

I warmly thank all my inspiring teacher and research colleagues, co-workers and friends at Tampere University Faculty of Medicine and Health Technology for their friendship and support.

I wish to express my gratitude to Matthew James who has been responsible for the English-language editing of the original publications and this dissertation.

I thank all my dear friends for always being there for me and bringing so much joy to my life. I thank my friends from the Medical School who have been beside me from the green couches of BIO onwards to this day, and the whole Chickens and Roosters bunch: Noora, Ilkka, Aino, Seppo, Anniina, Juhani, Sami and Ani. I also thank Virve, Raine, Jampe, Susanna, Jussi and Jenny for being such close friends to me and to my family for over half of my life. I also thank dear Miia for our friendship and all the support during this process. Our conversations concerning everything from beautiful shoes to the structure of the amygdala are special to me. I also thank my "study group" – Tarja and Maija – for their friendship and loving support.

I am grateful to my father- and mother- in-law Tapio and Merja Kakko for their love and support. I also thank my dear brother-in-law Kari-Petteri, his wife Tanja and precious little Eero, and my brother-in-law Kristian for being there for me and my family.

I thank my parents Kari and Pirkko Järventausta for their unconditional love and support, and for providing me with the important values in life: kindness, equality, and persistence in pursuing one's dreams. I also thank them for all the meatballs that prevented my family from starving during this writing process. I thank my dear siblings Kaija, Petri and Risto who have lovingly trained me in debate and defence from my childhood onwards. I also thank their families for all the joyful moments, love and support: thanks to Jari, Elias, Karoliina, Atte, Katariina, Riitta, Teemu, Saara and Topias (and, of course, Peppi and Tipsu, the Dogs). Special thanks to Atte and Karoliina for helping me to edit the reference section of this dissertation.

Finally, I thank my beloved husband Kimmo for being beside me and for sharing his life with me. During this scientific journey he celebrated every little milestone with me and believed in me even when I was not able to. However, our most important achievement together, and the most important thing in my life, is our family. I thank our beloved children Oskari, Eemeli and Anna (and, of course, Muru the Cat) for being so special and for bringing so much love and joy to our everyday life.

This dissertation was financially supported by grants from the Finnish Brain Foundation, the Foundation of Paediatric Research, the Medical Research Fund of Tampere University Hospital and the Finnish Medical Foundation.

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Appendix 1

TAY

LÄÄKÄRIN KÄSIKIRJA

Lasten antipsykoottisen lääkehoidon seurantaa varten

Alkuperäisteoksen pohjalta muokattu 2014

LL Kirsi Kakko, LL Leena Pihlakoski, LT, FT Raili Salmelin, LT, dosentti Päivi Keskinen,

LT, dosentti Kaija Puura, Professori Tuula Tamminen

Alkuperäisteos:Panagiotopoulos C, Davidson J, Raghuram K. A Physician Handbook for Metabolic Monitoring for Youth with Mental Illness treated with Second-Generation Antipsychotics. Copyright Drs. C. Panagiotopoulos and J. DavidsonVersion July 21, 2010

Sisällysluettelo

BC= British Columbia

1. Johdanto

Tämä ohjekirja perustuu Kanadassa Vancouverin kunnan lasten ja nuorten mielenterveyspalvelujen (BC Ministry for Child and Family Development (MCFD) ja kahden tällä alueella toimivan lastensairaalan osaston (lasten- ja nuorisopsykiatria ja endokrinologia ja diabetes) yhteistyöohjelmana toteutettuun ”The Why Weight Program”-ohjelmaan. Ohjelman tarkoituksena on ollut arvioida toisen polven antipsykoottien (SGA) vaikutuksia painonnousuun, insuliiniresistenssiin, metaboliseen oireyhtymään ja glukoosi-intoleranssin/ tyypin II diabeteksen kehittymiseen mielenterveyshäiriöistä kärsivillä nuorilla. Tutkimuksen tärkeimpiä tavoitteita on ollut edistää täsmällisiä kliinisiä seurantakäytäntöjä luomalla koulutuksellisia apukeinoja lääkäreille ja psykiatrista työtä tekeville. Yhtenä näistä apukeinoista on kehitetty käsikirja, johon myös tämä suomalaisiin olosuhteisiin ja käypähoitosuosituksiin sopivammaksi muokattu ohjeistus perustuu. Suomalaisessa versiossa on pyritty metabolisten vaikutusten lisäksi kiinnittämään huomiota myös muihin toisen polven antipsykoottisten lääkkeiden mahdollisiin sivuvaikutuksiin.

Alkuperäisessä käsikirjassa lääkkeiden käyttöä koskevat tiedot perustuvat kanadalaislapsia ja -nuoria koskeviin tutkimustuloksiin, joissa on havaittu selkeä lisääntyminen antipsykoottisen lääkkeiden määräämisessä huolimatta vähäisestä näiden lääkkeiden tehoon liittyvästä tutkimusnäytöstä ja vähäisestä arvioinnista potentiaalisten metabolisten sivuvaikutusten suhteen. Myös Euroopassa ja Suomessa havainnot ovat samansuuntaisia.

Tämän seurantaohjelman käyttöönoton myötä on tarkoitus kehittää yhtenäisiä käytäntöjä toisen polven antipsykoottisten lääkkeiden haittavaikutusten tunnistamiseen ja ennaltaehkäisemiseen lapsilla, joilla on käytössä antipsykoottinen lääkitys ja näin vähentää pitkän aikavälin sairastavuutta näillä potilailla.

2. Toisen polven antipsykootit

Verrattaessa ensimmäisen polven psykoosilääkkeisiin toisen polven antipsykooteille on tyypillistä

1. D2 (dopamiini 2)/5HT2 (serotoniini) – reseptorisalpaus
2. Selvästi vähäisemmät ekstrapyramidaaliset sivuvaikutukset (EPS)
3. Vaikutus sekä negatiivisiin että positiivisiin psykoosin oireisiin

Keskushermostossa on viidentyyppisiä dopamiinireseptoreita. Antipsykoottisten lääkkeiden vaikutuksen katsotaan välittyvän pääasiassa keskushermoston mesolimbisen alueen D2-tyyppisten dopamiinireseptorien salpauksen välityksellä. Toisen polven lääkkeet ovat ensimmäisen polven lääkkeisiin verrattuna selektiivisempiä juuri D2-tyyppisille dopamiinireseptoreille. Lisäksi toisen polven psykoosilääkkeet salpaavat ensimmäisen polven lääkkeisiin verrattuna myös keskushermoston 5HT2-reseptoreita. Tämä vähentää D2-reseptoreiden salpaukseen liittyviä haittavaikutuksia. Antipsykoottisilla lääkkeillä on myös muuta mahdollista farmakologista aktiivisuutta, joka voi välittyä dopaminergisten-, noradrergisten-, serotonergisten-, histaminergisten- ja kolinergisten-reseptorien kautta. Antipsykoottien vaikutusta ei myöskään pystytä kohdentamaan vain yhden aivoalueen reseptoreihin, joten systeemivaikutuksesta voi seurata myös ei-toivottuja vaikutuksia. Liitteenä olevasta taulukosta (taulukko 1) käy esille eri reseptorityyppien salpaukseen liittyviä vaikutuksia. (Rang ym 2012, Correll ym 2008, Partonen ym 2012)

Toisen polven antipsykooteista Suomessa ovat tällä hetkellä saatavilla sertindoli, tsiprasidoni, klotsapiini, olantsapiini, ketiapiini, asenapiini, risperidoni, aripipratsoli ja paliperidoni

2.1 Mitkä ovat toisen polven antipsykoottien viralliset käyttöaiheet alle 13 -vuotiaille?

Duodecimin lääketietokannan mukaan Suomessa alle 13-vuotiaiden lasten hoitoon hyväksyttyjä antipsykoottisia lääkkeitä ovat risperidoni ja tsiprasidoni. Risperidoni on tarkoitettu käytöshäiriöihin liittyvien pitkäkestoisten aggressioiden lyhytaikaiseen (korkeintaan 6 viikkoa) oireenmukaiseen hoitoon älyllisesti jälkeenjääneillä ja kehitysvammaisilla yli 5-vuotiailla lapsilla ja nuorilla, joille on vahvistettu DSM-IV-kriteerien mukainen diagnoosi ja joilla on merkittävää

aggressiivisuutta ja muuta tuhoavaa käyttäytymistä, joka edellyttää lääkehoitoa. Tsiprasidonilla voidaan hoitaa yli 10-vuotiaiden lasten ja nuorten kaksisuuntaisen mielialahäiriön keskivaikeita maanisia tai sekamuotoisia sairausjaksoja. Aripipratsoli on hyväksytty tyypin I kaksisuuntaisen mielialahäiriön kohtalaisen tai vaikean maniavaiheen hoitoon 13-vuotiaille tai sitä vanhemmille nuorille enintään 12 viikon ajan. Näin ollen suuri osa psykoosilääkkeiden käytöstä lapsilla on siis virallisten indikaatioiden ulkopuolista ns ”off-label” käyttöä.

Lasten ja nuorten antipsykoottisen lääkityksen kohdeoireita ovat yleisimmin:

1. Aggressio
2. Matala pettymyksen sietokyky (frustration tolerance)
3. Tunne-elämän säätelyn häiriöt (Affect dysregulation)
4. Impulsiivisuus

Antipsykooteilla lääkittyjen lasten ja nuorten diagnooseja tyypillisesti ovat:

1. Psykoosi
2. Mielialahäiriöt
3. Ahdistuneisuus
4. Eksternalisoivat oireet
5. Laaja-alaiset kehityshäiriöt

2.2 Minkälaisia ovat toisen polven antipsykoottien haittavaikutukset?

Koska lasten ja nuorten fyysinen ja psyykkinen kypsymisprosessi on vielä kesken, lääkkeiden terapeuttiset vaikutukset ja haitat voivat erota aikuisten vastaavista (Correll 2008). Tutkimuksissa on kuitenkin havaittu lasten ja nuorten olevan aikuisia alttiimpia saamaan antipsykoottihoidon yhteydessä sivuoireita (Ben Amor 2012, Correll 2008, Doyle ja McDougle 2012, Pringsheim ym. 2011).

2.21 Metaboliset haittavaikutukset

Aikuisten osalta on olemassa kasvavaa näyttöä siitä, että toisen polven antipsykootit aiheuttavat merkittävää painonnousua ja ei-toivottuja metabolisia vaikutuksia kuten hyperlipidemiaa ja insuliiniresistenssiä. Toisen polven antipsykoottien käyttö yhdistyykin täten metabolisen oireyhtymän ja tyypin 2 diabeteksen ilmaantumiseen. Tyypin 2 diabetekseen liittyvät pitkän aikavälin mikro- ja makrovaskulaariset komplikaatiot vaikuttavat merkittävästi sairastavuuteen ja kuolleisuuteen. Nuorilla potilaille on havaittu samansuuntaisia metabolisia häiriöitä, mutta näyttö perustuu vähäisempään tutkimustietoon ja yksittäisiin potilastapauksiin (case reports)

Tutkimustiedon mukaan antipsykoottien käyttö kaksinkertaistaa riskin painonnousuun ja kolminkertaistaa riskin heikentyneeseen glukoosinsietoon nuorilla. Suurin osa painonnoususta tapahtuu ensimmäisen 6-kk aikana antipsykoottihoidon aloittamisen jälkeen, ja siitä suurin osa ensimmäisten viikkojen aikana.

Hyperprolaktinemia on yksi mahdollinen haittavaikutus psykoosilääkkeitä käytettäessä. Hyperprolaktinemiaa on havaittu usein risperidonihoitoon liittyen ja välillä myös muihin antipsykootteihin, kuten tsiprasidoniin, klotsapiiniin ja olantsapiiniin liittyen. Hyperprolaktinemian oireina voi esiintyä kuukautiskierron häiriöitä, seksuaalisen toiminnan häiriöitä ja maitovuotoa (galaktorrea), joka voi olla erityisen häiritsevä oire nuoruusikäiselle.

Metabolinen oireyhtymä ja lasten ylipaino

Metabolinen oireyhtymä (MBO) on kasauma riskitekijöitä, jotka suurentavat ateroskleroottisten verisuonisairauksien ja diabeteksen vaaraa. MBO:n osatekijät ovat keskivartalolihavuus, kohonnut verenpaine, dyslipidemia (suuri plasman triglyseridi- ja pieni HDL-kolesterolipitoisuus) ja häiriintynyt glukoosiaineenvaihdunta. Lasten ja nuorten kohdalla erityistä määritelmää metaboliselle oireyhtymälle ei ole olemassa. Suomessa on 10/2013 julkaistu lasten lihavuuden Käypä Hoito – suositus, jossa määritellään haitallinen ylipaino ja annetaan hoitosuosituksia sen hallintaan.(www.duodecim/kaypahoito.fi)

Kliiniseen käyttöön soveltuvat suomalaisten lasten ylipainon ja lihavuuden kriteerit Käypä Hoitosuosituksen mukaan.

	Ylipaino	**Lihavuus**
Pituuspaino < 7 v	10–20 %	> 20 %
Pituuspaino ≥ 7 v	20–40 %	> 40 %
ISO-BMI (≥ 2 v)*	25–30 kg/m^2	> 30 kg/m^2

Yli 2-vuotiailla lapsilla ISO-BMI (aikuista vastaava painoindeksi) kuvaa painoindeksiä, joka lapsella on tulevaisuudessa aikuisena, jos hänen painoindeksinsä pysyy ikätovereihin verrattuna samalla tasolla. ISO-BMI lasketaan samoin kuin aikuisen painoindeksi ja se muutetaan iänmukaisella kertoimella aikuista vastaavaksi. Lasten aikuista vastaavan painoindeksi arvo saadaan laskurista, joka löytyy esim. Terveysportista. ISO-BMI:tä käytettäessä voidaan soveltaa aikuisten ylipainon ja lihavuuden rajoja 25 kg/m^2 ja 30 kg/$m^{2.}$

On tärkeää havaita muutos lapsen painokäyrässä. Jatkuva nousu viittaa lihomiseen ja ylipainon rajan ylittäneillä ennakoi lihavuutta.

2.22 Kardiovaskulaariset haittavaikutukset (skitsofrenian Käypä Hoitosuosituksen mukaan)

1. hypotensio
2. QTc-johtumisajan piteneminen
3. kääntyvien kärkien takykardia

2.23 Neurologiset haittavaikutukset (skitsofrenian Käypä Hoitosuosituksen mukaan)

(termien selitykset lääkärin käsikirjasta ja Seppo Kaakkolan artikkelista Dystoniat on hyvä osata tunnistaa, Suomen Lääkärilehti 2012;67(45):3289 - 3294)

Ekstrapyramidaaliset haittavaikutukset

1. akuutti dystonia: okulogyyrinen kriisi (silmälihas dystonia)
    - Dystoniat eli lihasjänteyshäiriöt ovat liikehäiriösairauksia, joille on tyypillistä tahdosta riippumaton jatkuva tai ajoittainen lihasten supistuminen, joka aiheuttaa vääntäviä liikkeitä ja epänormaaleja kehon asentoja
2. opistotonus
3. leukalukko, lihaskouristukset ja kurkunpäänspasmi
4. lääkeaineparkinsonismi (hypo- ja akinesia eli liikkeiden väheneminen, vapina)
5. akatisia
    - Akatisialla tarkoitetaan lääkkeen aiheuttamaa motorista levottomuus, lähinnä liikkumispakkoa
6. tardiivi dyskinesia
    - Tardiivi dyskinesia on hankalin psykoosilääkkeisiin liittyvä liikehäiriö, koska se voi olla pysyvä. Tyypillisin ilmenemismuoto ovat suun seudun pakkoliikkeet, mutta häiriö voi ilmetä myös raajoissa ja vartalolla.

Muut neurologiset haittavaikutukset

1. väsymys
2. pahanlaatuinen neuroleptioireyhtymä
3. epileptiset kohtaukset
4. kognitiiviset häiriöt

3. Seuranta

Määrättäessä antipsykootteja tulee jo alkuvaiheessa selvittää potilaan metabolinen tilanne ja mahdolliset riskitekijät. Arviointi tulee toistaa seurannan aikana säännöllisesti mahdollisen metabolisen oireyhtymän, II tyypin diabeksen tai muiden aineenvaihdunnan häiriöiden tai niiden riskin havaitsemiseksi, sekä muiden mahdollisten haittavaikutusten havaitsemiseksi.

3.1 Alkuvaiheen toimenpiteet antipsykoottista lääkehoitoa aloitettaessa.

Esitietojen tarkoituksena on tunnistaa 2 tyypin diabeteksen, metabolisen oireyhtymän ja muiden metaboliset seurausten riskitekijöitä. Myös mahdolliset sydän- ja verisuonisairauksien riskitekijät tulee kartoittaa.

Esitiedot ja riskitekijöiden arviointi:

Tavallisen anamneesin lisäksi antipsykootteja määrättäessä tulee selvittää:

- Suvussa esiintyvät somaattiset sairaudet
  - diabetes (myös raskausdm)
  - sydän- ja verisuonisairaudet (sydänkohtaukset, aivoinfarktit, erityisesti alle 50 v iässä)
  - lihavuus
  - korkea kolesteroli
  - korkea RR
  - metabolinen oireyhtymä.

Suvussa esiintyvät psykiatriset sairaudet

  - erityisesti skitsofrenia ja bipolaarihäiriö

- Mahdolliset tämänhetkiset endokrinologiset tekijät (kilpirauhanen, murrosikä)
- Muut lääkkeet
- Allergiat
- alkoholinkäyttö, huumeet, tupakka
- Fyysinen aktiivisuus ja ruokavalio

- Kuinka paljon liikuntaa/päivä/vko?
- Paljonko ruutuaikaa/ päivä?
- Sokeripitoisten juomien määrä/ päivä?
- Kuuluvatko karkit tai "roskaruoka" päivittäiseen ruokavalioon? Kuinka paljon/ päivä?

Somaattinen status

- pituus
- paino
- kasvukäyrä/ BMI
- RR
- sydämen auskultaatio
- Ihon pigmentaation muutokset (Acanthosis Nigricans)

Laboratoriokokeet

Seuraavat laboratoriokokeet suositellaan otettavaksi kaikilta potilailta ennen lääkkeen aloitusta ja seurantalomakkeen ohjeiden mukaan.

1. Maksa-arvot (P-ALAT) **ja**
2. Kilpirauhanen (P-TSH, P-T4-V)
3. Verenkuva (B-PVK)**,** tarvittaessa TVK
4. Elektrolyytit (P-Na, P-K)
5. Kreatiniini (P-krea)
6. Paastosokeri (fP-gluk)

→Jos paastosokeri on >6mmol/l, suositellaan oraalista glukoosirasitusta (Huom, varmista että kyseessä on paastoarvo).

7. Paasto-insuliini (P-insu)

→Jos insuliinin paastoarvo on > 25 mU/l, suositellaan oraalista glukoosirasitusta.

8. Rasva-arvot (fP-kol-LDL, sisältää kokonaiskolesteroli, triglyseridit, HDL ja LDL)
9. Prolaktiini (S-PRL)

10. EKG

Lisäksi tarvittaessa:

11. Amylaasi (P-amyl) **Huom!** suositellaan tarkistettavaksi ketiapiinihoidon aikana. (Ketiapiinihoidon yhteydessä on havaittu joitain pankreatiittitapauksia.)

3.2 Seuranta

Seuraavat asiat tulisi selvittää antipsykoottihoidon seurantakäynneillä:

Anamneesi

- Painon muutokset
- ruokahalun ja energiatason muutokset
- virtsamäärien lisääntyminen? Lisääntynyt jano/ yöllisen virtsaamistarpeen lisääntyminen? Väsymys?
- Mahdolliset prolaktiinivaikutukset? Maitovuoto/ kuukautishäiriöt?
- muut kysymykset sivuvaikutuksiin liittyen, kardiologiset? neurologiset? Kilpirauhanen? Puberteetti, muutokset kuukautiskierrossa?

Somaattinen status ja laboratoriokokeet

Tällä hetkellä ei ole olemassa kliinisiä hoitosuosituksia antipsykoottisen lääkityksen seurantaan liittyen. Tämän kirjan liitteenä on seurantaohjelma (muokattu kanadalaisesta seurantaohjelmasta), jota voidaan käyttää seurannan sisällön ja taajuuden ohjenuorana. Seurannassa kaikkia laboratorioarvoja tulisi verrata normaaliarvoihin.

4. Liitteet

Taulukko 1. Antipsykoottien reseptorivaikutukset (Mukaillen Correll 2008)

Reseptori	Reseptorisalpauksen vaikutukset:
D2	antipsykoottinen, antimaaninen, antiaggressiivinen, EPS/akatisia, tardiivi dyskinesia, prolaktiinin nousu
5-HT1a (part. agonismi)	anksiolyyttinen, antidepressiivinen, anti-EPS/akatisia
5HT2a	anti-EPS/akatisia, mahdollinen antipykoottinen
5HT2c	Mahdollinen ruokahalun /painon lisääntyminen
Alfa1	posturaalinen hypotensio, huimaus, pyörtyminen
Alfa2	antidepressiivinen, lisääntynyt valppaus, verenpaineen nousu
H1	anksiolyyttinen, sedatiivinen, painon nousu, anti-EPS/akatisia
M1(sentraaliset)	muisti, kognitio, suun kuivuminen, anti-EPS
M2-4(perifeeriset)	ummetus, virtsaretentio, näön hämärtyminen, takykardia, hypertensio

Correll C. U. J Clin Psychiatry 2008;69 (supl 4): 26-36. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents.

Taulukko 2. Toisen polven antipsykoottien haittavaikutukset

Tavalliset sivuvaikutukset	**Harvinaiset sivuvaikutukset**
Painonnousu	Hepatotoksisuus, pankreatiitti
Sedaatio, uneliaisuus	Agranulosytoosi
Dyslipidemia (matala HDL, korkea LDL, korkea TG, korkea kokonaiskolesteroli)	Kardiovaskulaariset haitat (QT-ajan piteneminen)
Diabeteksen esioireet, häiriintynyt sokeriaineenvaihdunta	Kohtausoireet
Hyperprolaktinemia	Lisääntynyt syljeneritys
	Ekstrapyramidaalioireet, tardiivi dyskinesia
	Kilpirauhashormonin (T4) väheneminen

Taulukko 3. Lasten verenpaineen seulontarajat

Ikä (v)	**Seulontaraja (mmHg)**
< 1	110/65
1–5	115/75
6–10	125/85
11–18	140/90

Jokinen E. Lapsen verenpaine, Lääkärin käsikirja 3.8.2013, Viimeisin muutos 27.5.2013

Taulukko 4. Lihavan lapsen tutkiminen perusterveydenhuollossa

Löydös	Toiminta
Vaikea lihavuus tai hyvin nopea lihominen	Harkitse erikoissairaanhoidon konsultaatiota mahdollisen paikallisen hoitoketjun mukaan.
Hidastuva pituuskasvu ja samanaikainen lihominen ennen murrosiän loppuvaihetta	Määritä tyreotropiinin ja vapaan tyroksiinin pitoisuudet ja konsultoi erikoissairaanhoitoa.
Imeväisiässä alkanut vaikea lihavuus	Kyseessä voi olla geenimutaatiosta johtuva lihavuus. Konsultoi erikoissairaanhoitoa.
Unenaikaiset hengityshäiriöt (voimakas, lähes jokaöinen kuorsaus tai epäsäännöllinen hengitys kuorsatessa)	Konsultoi erikoissairaanhoitoa (unirekisteröinti).
Epäsäännölliset kuukautiset, vaikea akne tai hirsutismi murrosikäisellä tytöllä	Munasarjojen monirakkulatauti (PCOS) on mahdollinen. Konsultoi erikoissairaanhoitoa.
Henkisen kehityksen viive tai poikkeavia kasvojen tai raajojen piirteitä	Konsultoi erikoissairaanhoitoa (oireyhtymät).
Kohonnut verenpaine (neljä peräkkäistä kaksoismittausta): • yli 115/75 mmHg alle kouluikäisellä • yli125/85 mmHg alakouluikäisellä • yli 140/90 mmHg murrosikäisellä	Konsultoi erikoissairaanhoitoa.
Dyslipidemia (kokonaiskolesterolipitoisuus ≥ 5.0 mmol/l, LDL-kolesterolipitoisuus ≥ 3.0 mmol/l, HDL-kolesterolipitoisuus < 1.0 mmol/l, triglyseridipitoisuus ≥ 2 mmol/l). Lipidiarvotutkitaan lihavilta lapsilta.	Järjestä elintapaohjaus ja seuranta. Kokonaiskolesterolipitoisuus ≥ 6 mmol/l tai LDL-kolesterolipitoisuus ≥ 4 mmol/l on aihe lähetteelle erikoissairaanhoitoon.
Poikkeava glukoosiaineenvaihdunta (viitearvon ylittävä HbA_{1C}-, paastoglukoosipitoisuus tai 2 tunnin glukoosipitoisuus glukoosirasituskokeessa). Tutkitaan vaikeasti lihavilta ja sellaisilta lapsilta, joiden lähisuvussa on tyypin 2 diabetesta tai joilla on acanthosis nigricans.	Konsultoi erikoissairaanhoitoa.
ALAT > 40 U/l	Suurentunut arvo viittaa maksan rasvoittumiseen. Järjestä elintapaohjaus ja seuranta. Jos arvo on kontrolloidusti > 80 U/l, konsultoi erikoissairaanhoitoa.

Lasten endokrinologin konsultaatio/lähete indikaatiot:

1. Pituuspaino >+ 60%
2. Lihavuuteen liittyvä insuliiniresistenssi (paastoinsuliini ≥ 25 mUl/l tai acanthosis nigricans)
3. Polykystiset munasarjat-epäily (kliininen epäily: epäsäännölliset kuukautiset tai amenorrhea, joihin liittyy hyperandrogenismin löydöksiä tai oireita, kuten hirsutismi, akne, kohonnut testosteronitaso)
4. Dyslipidemia
5. Heikentynyt glukoosinsieto tai 2 tyypin diabetes (ks. Laboratorio-ohjekirjasta rajat)
6. Koholla olevat maksa-arvot (2 x normaaliarvon yläraja) tai rasvamaksalöydös ultraäänitutkimuksessa
7. toistuva hypertensio (asianmukaisilla välineillä) ks. viiterajat
8. Toistetusti koholla oleva prolaktiinitaso (800-1000) tai hyperprolaktinemian kliiniset oireet, jotka eivät korjaannu lääkehoidon lopettamisella tai muutoksilla (maitovuoto, kuukautisten epäsäännöllisyys, amenorrhea)

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Appendix 2

Antipsykoottisen lääkityksen arviointi- ja seurantalomake: *aloituskäynti*

Potilaan nimi _____ **Henkilötunnus** _____

Arviointipäivämäärä *(pp.kk.vvvv)* _____

Arvioinnin tekijä _____

1 Sukupuoli

1 poika; *siirry kysymykseen 3*

2 tyttö

2 Kuukautiset?

1 kyllä

2 ei

3 Kohdeoireet *(ympyröi kaikkien niiden oireiden numero, jotka ovat vaikuttaneet antipsykoottisen lääkityksen käyttöönottoon)*

1 mania

2 mielialavaihtelut/ tunne-elämän labiilius

3 uhmakkuus

4 psykoosi

5 itsetuhoinen käytös

6 motoriset/vokaaliset tic-oireet

7 aggressio

8 muun lääkkeen tehon lisääminen, minkä lääkkeen (esim antidepressantti, ahdistuneisuuden lääkehoito, mielialan tasaaja, stimulantti)?

_____

10 sedaatio/ uni

11 muu, mikä? _____

4 Diagnoosit *(merkitse viiva, jos jotain diagnoosityyppiä ei ole)*

primaaridg _____

liitännäissairaudet _____

muut sairaudet _____

5 Onko lapsen kognitiivinen taso tutkittu?

1 kyllä

2 ei; *siirry kysymykseen 7*

6 Onko lapsen kognitiivinen kehitys ikätasolla?

1 kyllä

2 ei

7 Lapsen hoidosta vastaavat vanhemmat

1 lapsen biologiset vanhemmat
2 biologinen äiti yksin
3 biologinen äiti ja hänen uusi puolisonsa
4 biologinen isä yksin
5 biologinen isä ja hänen uusi puolisonsa
6 sijaisvanhemmat
7 perhetukikeskus/ lastenkoti
8 muu, mikä? _____

8 Montako lasta, potilaan lisäksi, kotona asuu? _____

9 Työtilanne

Äiti tai äidin asemassa oleva tai (kys. 5, kohdissa 7-8 tarkoitettu) **muu hoitaja**	**Isä tai isän asemassa oleva**
1 kokopäivätyössä	1 kokopäivätyössä
2 osapäivätyössä	2 osapäivätyössä
3 pääasiassa kotona (kotiäiti, työtön tms.)	3 pääasiassa kotona (koti-isä, työtön tms.)
4 muu, mikä (esim. perhetukikeskuksen ohjaaja)? _____	

10 Onko lapsen kasvu edennyt normaalisti?

1 kyllä
2 ei; kuvaile, minkälaisia ongelmia on ollut _____

_____

11 Suvun riskitekijät *(ympyröi kultakin riviltä sekä riskitekijän olemassaoloa tai puuttumista koskeva kohta että tieto läheisimmästä sukulaisesta, jolla riskitekijä esiintyy; 1. ast. sukulainen = äiti, isä, sisarus, 2. ast. sukulainen = isoäiti, isoisä, serkku, täti, setä)*

	Esiintyminen			Minkä asteen sukulaisella?		
	kyllä	ei	ei tietoa	1. ast.	2. ast.	ei tietoa
diabetes						
tyyppi 1	1	2	3	1	2	3
tyyppi 2	1	2	3	1	2	3
raskausdiabetes	1	2	3	1	2	3
hyperlipidemia	1	2	3	1	2	3
sydän- ja verisuonisairaudet	1	2	3	1	2	3
päihteiden käyttö	1	2	3	1	2	3
skitsofrenia	1	2	3	1	2	3
psykoosi	1	2	3	1	2	3
bipolaarihäiriö	1	2	3	1	2	3

12 Yksilölliset taustatekijät *(ympyröi kultakin riviltä taustatekijän olemassaoloa tai puuttumista koskeva kohta ja, jos tekijä esiintyy, tieto sen määrästä)*

	ei	kyllä	määrä
tupakointi	1	2	_____ savuketta/pv
päihteiden käyttö	1	2	mitä päihteitä, paljonko? _____
			_____
ulkoilu/arkiliikunta	1	2	_____ tuntia/pv
liikuntaharrastukset	1	2	_____ tuntia/vko
ruutuaika (aika joka käytetään tietokoneella tai TV:n äärellä)	1	2	_____ tuntia/pv
sokeripitoisten juomien (limsa tai mehu) käyttö	1	2	_____ krt/vko
karkin syönti			_____ krt/vko
sydänsairaus	1	2	mikä? _____

muita kommentteja _____

_____

13 Aloitettava lääke *(merkitse lääkkeen nimi ja annostus, mg, krt/vrk)*

_____

14 Muut käytössä olevat lääkkeet *(merkitse lääkkeen nimi ja annostus, mg, krt/vrk)*

_____

_____

15 Kommentteja

_____

_____

_____

16 Metaboliset mittarit

a) Somaattinen status

paino	kg	_____
	%	_____
pituus	cm	_____
	SD	_____
verenpaine	systol. (< 130)	_____
(mmHg)	diastol. (< 85)	_____

b) Laboratoriotutkimukset

Liitä tuloste labratoriokokeista ja ekg:stä.

Antipsykoottipaketista löytyvät seuraavat laboratoriokokeet, jotka oletaan aloitus- ja seuranta-käynneillä (1 kk aloituksesta sekä 3 kk, 6 kk ja 6 kk edellisestä):
PVK, paastosokeri, -insuliini, kokonais-, LDL-, HDL-kolesteroli, triglyseridit, ALAT, Na, K, Krea, TSH, T4V, prolaktiini, EKG.

Laboratoriopaketti löytyy, kun WebFimlabin tutkimusten tilausvalikon alaosassa olevaan valintanäyttöön kirjoittaa plpneu.

17 HoNOSCA *(täytä erillinen lomake)*

18 Interventiot

keskustelu

1 metaboliset riskitekijät

2 diabetesoireet

3 elintavat (tupakoinnin vähentäminen, ruokavalio, fyysinen aktiivisuus)

4 muu, mikä? _____

ohjattu

5 ravitsemusterapeutille

6 somaattisiin jatkotutkimuksiin, syy _____

_____

Appendix 3

Antipsykoottisen lääkityksen arviointi- ja seurantalomake: *seurantakäynti*

Seurantaa suositellaan ensimmäisen vuoden jälkeen vuosittain tai tarvittaessa tiheämmin yksilöllisen arvion mukaan.

Potilaan nimi _____ **Henkilötunnus** _____

Arviointipäivämäärä *(pp.kk.vvvv)* _____

Arvioinnin tekijä _____

1 Mikä seurantakäynti on kyseessä?

1 1 kk aloituksesta/ edell. käynnistä
2 4 kk aloituksesta/ 3 kk edell. käynnistä
3 10 kk aloituksesta/ 6 kk edell. käynnistä
4 16 kk aloituksesta/ 6 kk edell. käynnistä
5 muu, mikä? _____

2 Käytössä oleva antipsykootti *(merkitse lääkkeen nimi ja annostus, mg, krt/vrk)*

_____

3 Muut käytössä olevat lääkkeet *(merkitse lääkkeen nimi ja annostus, mg, krt/vrk)*

_____

_____

4 Onko antipsykootti vaihdettu?

1 ei
2 kyllä Milloin vaihto tapahtui, miksi vaihto tehtiin, mikä oli aiempi ja mikä nykyinen lääke ja sen annostelu?

_____

_____

_____

5 Metaboliset mittarit: potilaille, joilla käytössä toisen polven antipsykoottinen lääkitys
a) Somaattinen status

paino	kg	_____
	%	_____
pituus	cm	_____
	SD	_____
verenpaine	systol. (< 130)	_____
(mmHg)	diastol. (< 85)	_____

b) Laboratoriotutkimukset

Liitä tuloste labratoriokokeista ja ekg:stä.

Antipsykoottipaketista löytyvät seuraavat laboratoriokokeet, jotka oletaan aloitus- ja seuranta-käynneillä (1 kk aloituksesta sekä 3 kk, 6 kk ja 6 kk edellisestä):
PVK, paastosokeri, -insuliini, kokonais-, LDL-, HDL-kolesteroli, triglyseridit, ALAT, Na, K, Krea, TSH, T4V, prolaktiini, EKG.

Laboratoriopaketti löytyy, kun WebFimlabin tutkimusten tilaus -valikon alaosassa olevaan valintanäyttöön kirjoittaa plpneu.

6 HoNOSCA *(täytä erillinen lomake)*

7 Lapsen arvio antipsykootin hyödyistä *(kysy lapselta käyttäen visuaalista asteikkoa)*

1 paljon hyötyä
2 jonkin verran hyötyä
3 ei osaa sanoa
4 ei juurikaan hyötyä
5 ei yhtään hyötyä

8 Lapsen arvio antipsykootin haitoista *(kysy lapselta käyttäen visuaalista asteikkoa)*

1 ei yhtään haittaa
2 ei juurikaan haittaa
3 ei osaa sanoa
4 jonkin verran haittaa
5 paljon haittaa

9 Havaitut/raportoidut kliinisesti merkittävät haittavaikutukset *(ympyröi kaikkien havaittujen haittavaikutusten numero)*

1 painonnousu
2 rintarauhasoireet
3 kuukautishäiriöt
4 neurologiset oireet
5 muu, mikä? _____

10 Interventiot

keskustelu

1 metaboliset riskitekijät
2 diabetesoireet
3 elintavat (tupakoinnin vähentäminen, ruokavalio, fyysinen aktiivisuus)
4 muu, mikä? _____

ohjattu

5 ravitsemusterapeutille
6 somaattisiin jatkotutkimuksiin, syy _____

PUBLICATION I

Clinical use of second-generation antipsychotics in children

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Scandinavian Journal of Child and Adolecent Psychiatry and Psychology (2017) vol. 5(2), pp. 77-88.
https://doi.org/10.21307/sjcapp-2017-009

SJCAPP

Scandinavian Journal of Child and Adolescent Psychiatry and Psychology
Vol. 5(2):77-88 (2017) DOI 10.21307/sjcapp-2017-009

Research Article **Open Access**

Clinical use of second-generation antipsychotics in children

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Abstract

Background: The use of second-generation antipsychotic (SGA) medication among child and adolescent psychiatric patients has increased worldwide in recent years. The increase appears to have been more extensive in the USA than in European countries, but the tendency is similar. However, after a peak the use seems to have declined in the USA. Simultaneously with the increasing numbers, the duration of SGA use has lengthened, indications have broadened, and off-label use has increased. Despite existing follow-up recommendations and evidence for the metabolic adverse effects of SGAs in children, research evidence has not translated into clinical practice.
Objective: The aim of this study was to assess the clinical use and follow-up practices of SGA medication among child psychiatric patients of one university hospital in Finland.
Method: This retrospective patient report-based study was conducted at the Child Psychiatric Clinic of Tampere University Hospital, Finland. The study sample consisted of 133 patients who were younger than 13 years when initiating SGA treatment and had an ongoing SGA medication during the study period. The study sample was divided into two groups according to diagnosis to examine whether there were differences between patients with an autistic or a developmental disorder (F83-84) and patients with other psychiatric diagnoses.
Results: This study showed that SGA use in children younger than 13 years was mainly off-label. Irrespective of diagnosis, the most common indication was aggression. Especially children with psychiatric diagnoses other than developmental disorders had multiple socio-demographic risk factors and adverse life experiences in their background. The follow-up practices were diverse and partly irregular.
Conclusions: A need for systematic SGA monitoring practices and dialogue between the medical specialities treating children and their families is evident.

Keywords: antipsychotic medication; second-generation antipsychotic; children; follow-up practices; adverse life events

Introduction

The use of second-generation antipsychotic (SGA) medication among child and adolescent psychiatric patients has increased worldwide in recent years (1-5). The increase appears to have been more extensive in the USA than in European countries, but the tendency is the same (3,6). However, after a peak, SGA use seems to have declined in the USA (7,8). At the same time, the duration of SGA use in children has lengthened, indications have broadened, and off-label use has increased (3,9,10). The use of SGAs in children and adolescents seems to be increasing from the age of 7 to 8 years onwards, predominantly in male patients (2-5).

In Finland, the prevalence of antipsychotic use among children and adolescents under the age of 18 years has increased from 4.3 to 6.7/1000 between 2008 and 2015 (5). Simultaneously, the proportion of children and adolescents in this age group using antipsychotic medication and having a diagnosis of a psychotic disorder or psychotic symptoms decreased from 19% to 11% (5). According to the statistics of

the Social Insurance Institution of Finland, during the same period, prevalence of use among children younger than 13 years increased from 1.7 to 2.8/1000. The three most commonly used SGAs in this age group were risperidone, aripiprazole, and quetiapine. The number of children younger than 13 years using these drugs in Finland has steadily increased in recent years, and the increase is most apparent for aripiprazole (14-fold) and risperidone (1.5-fold). However, the proportion of children younger than 13 years among all SGA users in Finland has remained quite steady (1.4% to 1.6%) as the number of all users has also increased (Figure 1). According to a recent Finnish study, SGAs were the most common medication among child psychiatric urgent-care in-patients at Kuopio University Hospital, and the use was mostly off-label (11).

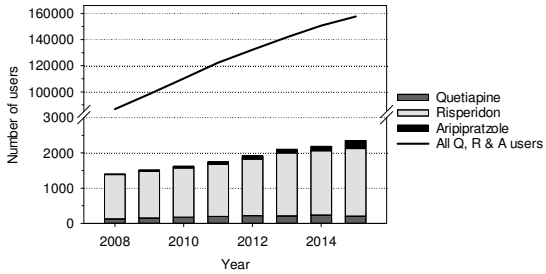

FIGURE 1. Second-generation antipsychotic use of 0 to 12-year-old children and all users in Finland (2008 to 2015)

The official criteria for SGA use by children younger than 13 years vary to some extent among countries. In the USA, the Food and Drug Administration (FDA) approves aripiprazole, quetiapine, and risperidone for the treatment of bipolar disorder among children older than 10 years (12). Aripiprazole and risperidone are also approved for the treatment of irritability associated with autism (12). In Finland, only risperidone and ziprasidone are approved for children younger than 13 years. Ziprasidone is approved for manic episodes of bipolar disease in children older than 10 years and risperidone for short-term use (≤6 weeks) in the treatment of conduct problems in children older than five years with developmental disorders or mental retardation. As official indications for SGA use are scarce, use among children is mostly off-label (2).

Children and adolescents with autism spectrum disorders and intellectual disability represent an increasing population treated with SGAs (13). SGA use is also common among children with attention deficit hyperactivity disorder or disruptive behaviour disorders (2,3). SGA medication is also used for children and adolescents with various other diagnoses – such as psychosis, mood and tic disorders, and obsessive compulsive disorder – and in symptomatic treatment for aggressive behaviour despite the primary diagnosis (1,2,8,10,14).

When looking at the socio-demographic background factors of paediatric patients using SGAs in the USA, studies show that the increase in SGA use has occurred disproportionately more often among publicly than privately insured patients (1,7). Those in foster care seem to be especially prone to antipsychotic prescriptions among publicly insured children (7). Children in foster care have often experienced traumatic life events, which are, among other individual and environmental factors, known risk factors for several mental health disturbances (15-17). These kinds of experiences are probably more common in children and adolescents treated by psychiatric services than in the general population. For example, adverse life events were frequent among adolescent-aged psychiatric in-patients suffering from bipolar disorder type I (58%) and catatonia (57%) (18). In a study by Ford et al. (19), in a clinical sample of child psychiatry out-patients aged four to 18 years, one in three participants had a history of exposure to interpersonal violence.

There is some evidence of the benefits of SGA use in children. SGAs, particularly risperidone and aripiprazole, have shown to be efficient in the treatment of irritability, aggression, self-injury, and possibly stereotypic behaviour in autism (20-24). SGAs also appear to reduce challenging behaviour in the short term among children with intellectual disabilities (25). There is some evidence that risperidone has an effect on disruptive and aggressive behaviour in the short term even among children and adolescents with a normal IQ (26,27). Risperidone and aripiprazole appear to be promising for treating tic symptoms in children with Tourette syndrome (28,29). With psychosis or schizophrenia, the efficacy of SGAs appears to be similar in children, adolescents, and young adults (30-32). Aripiprazole also appears to be effective in paediatric bipolar disease (30,33). However, the available studies mostly cover only the short-term use of SGAs, which seldom fits the clinical reality.

In children, the therapeutic profile and adverse effects of SGAs seem to differ from those in adults, and children also appear to be more vulnerable than adults to some SGA-induced adverse effects (34). Sedation, hyperprolactinemia, and metabolic disturbances, such as weight gain, dyslipidaemia, and hyperglycaemia, are known SGA adverse effects that

can have far-reaching consequences through metabolic, endocrinological, cardiovascular, and psychological effects (34-38). We also know very little about the long-term effects of SGAs on the developing central nervous system.

The detected increase in SGA use has induced attempts to monitor and improve SGA prescription practices around the world (7,39,40). All monitoring recommendations emphasize on the appropriate use of psychosocial interventions and the regular monitoring of metabolic and other adverse effects (41). The guidelines of the American Academy of Child and Adolescent Psychiatry (AACAP), the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA), and the National Institute for Health and Care Excellence (NICE) in the UK include recommendations for monitoring and managing the adverse effects of SGA in children (Table 1) (39,40,42). In Finland, there are national clinical guidelines for the treatment of schizophrenia in adults, but not for children. Psychotropic medications are however, recommended to be initiated for children in specialist-level health care services (5), with the exception of attention deficit hyperactivity disorder medication (methylphenidate).

TABLE 1. Recommendations for monitoring second-generation antipsychotic treatment according to National Institute for Health and Care Excellence (NICE), American Academy of Child and Adolescent Psychiatry (AACAP), and Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) (39,40,42)

		Follow-ups			
Issued by	**Baseline**	**1**	**2**	**3**	**4**
NICE		Weekly (first 6 weeks)	12 weeks	Every 6 months	
	Growth chart*, WHC, RR, pulse, fb-gluc, HbA_{1c}, lipids, prolactin, MD, nutritional status, diet, physical activity	Growth chart, MD, efficacy, side-effects	Growth chart, MD, RR, pulse, fb-gluc, HbA_{1c}, lipids, prolactin, physical health, efficacy, side effects	Growth chart, MD, WHC, RR, pulse, fb-gluc, HbA_{1c}, lipids, prolactin, physical health, efficacy, side effects	–
AACAP		Regular intervals			
	Family history, BMI, WC, RR, pulse, fb-gluc, lipids, MD	BMI, RR, pulse, fb-gluc (HbA_{1c} if needed), lipids†, MD	–	–	–
CAMESA		1, 2, 9 months	3 months	6 months	1 year
	Growth chart, BMI, WC, RR, NEU, fb-gluc, insulin, lipids, ASAT, ALAT, TSH (with quetiapine), prolactin	Growth chart, BMI, WC, RR, NEU	Growth chart, BMI, WC, RR, NEU, fb-gluc, insulin, lipids, prolactin	Growth chart, BMI, WC, RR, NEU, fb-gluc, insulin, lipids ASAT, ALAT, TSH (with quetiapine)	Same as baseline

Note. ECG recommendations are not included

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; fb-gluc, fasting glucose; HbA_{1c}, glycosylated hemoglobin; lipids, blood lipid profile; MD, movement disorders; NEU, neurological examination; TSH, thyroid-stimulating hormone; RR, blood pressure; WC, waist circumference; WHC, waist and hip circumference

*Includes weight and height

†If significant weight changes and/or a family history indicating risk

Recommendations and follow-up protocols seem to be helpful in clinical work and appear to increase monitoring and possibly have an effect on prescribing practices (7,43,44). Despite the already existing recommendations, there has been a lag in the translation of research evidence into clinical practice (39,45). Rates of metabolic monitoring of SGA have been low according to several studies. Rodday et al. (46) found that 66% of psychiatrists reported routinely asking about the patient's medical history, 92% reported monitoring the patient's growth, 81% reported monitoring the patient's plasma glucose and lipids, 23% reported measuring the patient's waist circumference, and 12% reported monitoring the patient's ECG. Being able to measure vital signs, height, and weight on site was associated with a higher probability of monitoring height and weight (46). In an audit performed in the UK, Pasha et al. (44) discovered that for in-patients at a child and adolescent mental health unit, the parameters measured most often before SGA initiation included BMI and hip-to-waist circumference; however, the monitoring rate of these measurements was only 60%. In the USA, many monitoring initiatives have taken place in the foster care system, and as a result, SGA-treated children in foster care are now more likely than other publically insured children to receive metabolic monitoring, and, in addition, psychosocial interventions (7). Nevertheless, both glucose and lipid monitoring failed in 72% of these foster children and in 82% of others (7).

Some children appear to be more vulnerable than others in developing metabolic adverse effects, and an important goal of an SGA monitoring procedure should be to identify as early as possible those children who are at particular risk for adverse effects (36,47). Some specific genes have already been linked with the increased risk of adverse effects with SGAs, but there are no gene tests available yet in everyday clinical work (47,48). In the light of current evidence, screening and monitoring practices should thus be emphasized.

Aims of the study

The aim of this study was to assess the clinical use, indications, and follow-up practices of SGA medication among child psychiatric patients at Tampere University Hospital (TAUH), Finland. This study also aims to describe the medical and socio-demographic background factors of SGA-treated children as well as the possible benefits and adverse effects of SGA medication.

Method

This study was conducted at the Child Psychiatric Clinic of TAUH and was based on patient reports. With a catchment area of approximately half a million people, TAUH is one of five university hospitals in Finland offering specialist-level health care services. The Child Psychiatric Clinic gives in-patient and out-patient services for children aged 0 to 12 years. Children aged 13 to 18 years are taken care of in adolescent psychiatry, which in Finland is a separate speciality. Children with a diagnosis of mental retardation are referred to separate services. Children are referred to TAUH by the health care centres and community hospitals of the district. Guidelines are available for the referral practices to specialist-level child psychiatric services. During the study period (1 October 2013 to 1 October 2014), 1633 children were treated at the clinic.

The inclusion criteria for the study were that the patient was younger than 13 years when initiating SGA treatment, that the medication was initiated at the TAUH clinic, and that the SGA medication was ongoing during the study period. These criteria were met by 133 patients, whose patient reports were examined until the date the medication was discontinued, the patient was referred to another clinic, or until 31 May 2015, whichever came first.

The first author (K.K.) collected information from the patient reports and recorded them. Selected patient reports were reviewed by the second author (L.P.), who also offered second opinion on request from the first author. The data collected from patient reports consisted of the patient's age, the conclusion of the cognitive evaluation, and other socio-demographic and medical factors at the SGA initiation phase. The conclusions of cognitive evaluations were dichotomized as intelligence within normal variation or below, based on patient report markings of either the attending physician or a psychologist. Information on SGA medication use (generic name, duration, reasons for discontinuing or changing medication) and other psychotropic medications as well as information on the patient's diagnoses and indications (or main symptoms) attached to the SGA initiation were collected or deduced from the patient reports. The reasons for discontinuation or changing the SGA were categorized for analyses by the first author as: adverse effect, no benefits, adverse effects more significant than possible benefits (unfavourable risk–benefit ratio), symptoms diminished so that the medication was no longer needed, and no information. In addition, information on the psychiatric and other medical history of the patient and his/her family was recorded. The possible benefits and adverse effects of SGA medication were extracted from the physicians' evaluations recorded in the patient reports. The available information of possible benefits was classified as: considerable

benefit, some benefit, uncertain, no benefit, and no information. The adverse effects, such as weight gain, and neurological, endocrinological (e.g., gynecomastia, menstruation disturbances), and other mentioned effects were recorded separately. Information concerning the follow-up protocols, such as medical evaluations made during the follow-up period (physical status, weight, and height) and possible consultations made by child psychiatrists to other medical specialties (e.g., cardiology or paediatrics) were recorded. The patient's age-adjusted BMI score was calculated at the analysis phase from the existing weight and height data (if both measurements were available from the same time point) using the tables of the new Finnish growth references (49).

To examine whether there were any differences between patients having an autism spectrum or developmental disorder diagnosis and patients with other psychiatric diagnoses, the study sample was divided into two groups based on diagnosis using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) (50). The first group (the PDD/DD group) consisted of 40 (30%) children with a pervasive developmental disorder (F84) diagnosis and seven (5%) patients with a diagnosis of mixed specific developmental disorders (F83). The second group (the non-PDD/DD group) consisted of 86 (65%) patients with various other diagnoses. Results for the groups where there are statistically significant differences are reported separately; otherwise, the results are reported for the entire sample.

The results of categorized variables are reported as frequencies (percentages or number of cases, as appropriate). For normally distributed continuous variables, means (M) and standard deviations (SD) are given, and for other continuous variables, medians and quartiles (Md, Q_1, Q_3) are reported. For testing the significance of differences between the PDD/DD and non-PDD/DD group, Pearson's chi-squared test, Fisher's exact test, or the Mann–Whitney U-test were used, as appropriate. A p-value of less than 0.05 is considered significant, and a value between 0.05 and 0.10 is considered indicative; values up to 0.10 are reported. SPSS v.23 was used for all statistical analyses.

Results

Eighty-one percent of the study sample were boys. The mean age at the time of SGA initiation was 9.3 years (SD, 2.1 years). In the PDD/DD group, the children were younger at the time of SGA initiation than the children in the non-PDD/DD group (M 8.6 years, SD, 2.0; and M, 9.7 years, SD, 2.0, respectively; $p = .002$). The age distribution of the patients showed two peaks, one during the early years of school (6 to 8 years) and the second at pre-puberty (11 to 12 years). Cognitive evaluation was performed for 85% of the children, and a conclusion about intelligence status was available for all but three of them. Eighty-one percent of those evaluated had an intelligence profile within normal age variation. One patient had a diagnosis of mental retardation. Information on whether the cognitive evaluation was performed or not was lacking in four patient reports. Cognitive evaluation was performed more frequently in the PDD/DD group than in the non-PDD/DD group (96% vs. 78%, $p = .010$), but there were no statistically significant differences between groups in the results of the evaluations. Seventy-nine percent of the study patients had been treated at least once in their lifetime at a psychiatric in-patient ward.

The most common SGA drug at initiation was risperidone (93%). Quetiapine (6%) and aripiprazole (2%) were less common. Risperidone was indicatively more common than other SGAs in the PDD/DD group than in the non-PDD/DD group (98% vs. 90%, $p = .097$). Sixteen percent of the patients had their medication switched to another SGA once, 6% twice, and two patients three times. The most common reasons for switching the SGA were adverse effects (52%) and an unfavourable risk–benefit ratio – that is, the attending physician had judged that adverse effects were more significant than possible benefits (48%). Thirty-two percent of the patients who had their SGA switched had no benefits from the initiation drug. In the PDD/DD group, there were fewer alterations in SGA medications than in the non-PDD/DD group (17% vs. 34%, $p = .035$), and the reason for switching was less frequently an adverse effect (31% vs. 73%, $p = .032$).

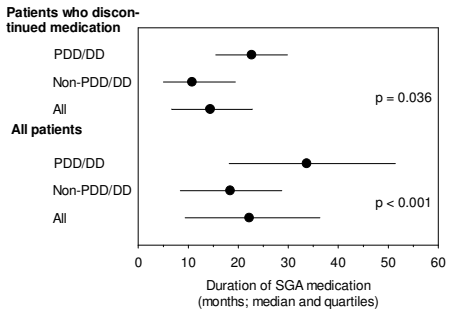

FIGURE 2. Duration of second-generation antipsychotic (SGA) medication. Figures in the "all patients" group do not describe the genuine duration of SGA medication because the duration after the endpoint of the follow-up is not known

Figure 2 shows the duration of SGA medication in this study. Almost one-fifth of the patients discontinued medication completely during the study period. The median duration of SGA medication among these patients was 14.4 months. In the PDD/DD group, the duration of SGA treatment was longer than in the non-PDD/DD group (Md, 22.7 vs. 10.8 months, $p = .036$). The most common reasons for discontinuation were that the patient's symptoms had diminished to a level where medication was no longer needed (52%) or that the risk–benefit ratio was considered unfavourable (30%). When taking all study patients into account, the median duration of SGA medication by the end of the study period was 22.2 months. In the PDD/DD group, the duration was longer than in non-PDD/DD group (Md, 33.7 vs. 18.4, $p < .001$). However, this figure does not describe the actual duration of SGA medication in this group because the duration after the end of follow-up is not known.

TABLE 2. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, diagnoses of second-generation antipsychotic (SGA)-treated children (n=133)

Diagnoses	ICD-10 class	%
Hyperkinetic disorders	F90	50
Conduct/mixed conduct and emotional disorder	F91-92	40
Pervasive developmental disorders	F84	30
Obsessive compulsive disorder	F42	13
Disorders of social functioning with onset specific to childhood and adolescence*	F94	13
Reaction to severe stress/adjustment disorders	F43	10
Tic disorders	F95	8
Emotional disorder with onset specific to childhood	F93	7
Disorders of psychological development	F80-82	7
Depressive episode	F32	6
Bipolar affective disorder	F31	5
Psychotic disorders	F23, F29	5
Mixed specific developmental disorders	F83	5
Other mood (affective) disorders	F38	5
Phobic and other anxiety disorders	F40-41	3
Dissociative (conversion) disorders	F44	3
Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence†	F98	2
Eating disorders	F50	1
Unspecified mental retardation	F79	1

Note. Each child could have more than one diagnosis
ICD-10, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
*Reactive attachment disorder F94.1 (n=5), other childhood disorders of social functioning F94.8 (n=12)
†Non-organic enuresis F98.0 (n=1), non-organic encopresis F98.1 (n=1)

Polypharmacy was common among the patients in the study. Nine patients were simultaneously using another antipsychotic medication, most commonly (five patients) levomepromazine. The actual rate of simultaneous use of two different antipsychotic agents was higher due to cross-titration periods when switching from one medication to another. Sixty-eight percent of the study patients had undergone at least a short-term treatment trial with some other psychotropic medication (not including melatonin) in addition to SGA during their treatment at the Child Psychiatric Clinic. Fifty-three percent had used one medication other than SGA and 14% two or three. The use of methylphenidate was more common in the PDD/DD group than in the non-PDD/DD group (79% vs. 58%, $p = .022$). Twenty-five percent had had at least a trial with atomoxetine and 16% with selective serotonin reuptake inhibitors. Fourteen percent of the study patients had had benzodiazepines as requisite medication at some point of their treatment. Almost two-thirds (63%) of the patients had undergone at least a short-term melatonin treatment for sleep problems.

All of the study children had at least one ICD-10 F-category psychiatric diagnosis (50) at the time of SGA initiation and 75% had at least two F diagnoses, the maximum being four (Table 2). Children in the PDD/DD group had more often comorbid disorders, 55% of them having two F category diagnoses and 38% having three or four, while the respective numbers in the non-PDD/DD group were 47% and 19% ($p = .001$). The most common diagnoses in the non-PDD/DD group were F91-92 (conduct/mixed conduct and emotional disorder; 49%, n = 42) and F90 (hyperkinetic disorders; 44%, n = 38). F91-92 and F31 (bipolar affective disorder) diagnoses were more common in the non-PDD/DD group than in the PDD/DD group (49% vs. 23%, p

= .005, and 8% vs. none, p = .051, respectively). Thirty-nine percent of the patients had also at least one ICD-10 Z diagnosis (factors influencing health status and contact with health services), implying multiple environmental factors influencing the patient's mental well-being.

The indication for SGA initiation was clearly stated in 61% of patient reports. In general, indications and symptoms were diverse, and 92% of the patients had two or more indications or main symptoms. The most common indications or core/main symptoms for SGA initiation were aggression (in 75% of the patients) and behaviour problems (74%) independent of diagnosis. Mood swings were a more common indication in the non-PDD/DD group (24% vs. 9%, p = .035) and sleep problems as indication indicatively associated with the PDD/DD group (17% vs. 6%, p = .063). The officially approved criteria for SGA medication (here risperidone, which was the most commonly used SGA in this study) use in Finland is short-term treatment of conduct problems of children older than 5 years with developmental disorders or mental retardation. None of the SGA-medicated children in this study fulfilled all these criteria. With loose interpretation, the 47 (35%) patients in the PDD/DD group fulfilled the official criterion for diagnosis of developmental disorders or mental retardation. Forty-five of these patients also fulfilled the criterion for age (> 5 years) and 34 fulfilled the indication criterion of aggression/aggressive behaviour, but in none of the study patients was the medication short-term.

TABLE 3. Family background of the second-generation antipsychotic-treated children

	All (%)	PDD/DD (%)	Non-PDD/DD (%)	*p*
Family status (n=133)				<.001
Biological parents	37	57	26	
Parental separation	40	36	42	
Foster home	18	6	24	
Other (e.g. adoption)	5	0	8	
Number of siblings (n=126)				NS
None	21	23	20	
One	38	40	37	
Two or more	41	36	43	
Mother's working status (n=133)				.018
Working at least part time	53	68	45	
Other or not known	47	32	55	
Father's working status (n=133)				NS
Working at least part time	57	64	54	
Other or not known	43	36	47	
Alcohol/drugs (n=83)	60	44	71	.021
Psychiatric history of first-degree relatives				
Schizophrenia, bipolar disease or other psychosis (n=67)	33	15	45	.016
Depression (n=88)	67	61	72	NS
Suicide (n=133)				NS
Committed	2	2	2	
At least one attempt	7	2	9	
Child exposed to violence (n=133)	41	30	48	.065
Exposed to domestic violence	11	4	15	
Been object of physical punishment or other domestic violence	12	13	12	
Both exposed and been object	11	6	13	
Other kind of violence exposure (e.g. war experiences)	8	6	8	

Note. In variables concerning suicide and exposure to violence, missing information was categorized as "no". In all other variables missing information was separated. Therefore, the total number of cases vary by variable

The study patients had diverse social stress factors and adverse life events in their past (Table 3). Less than 40% of the patients had both biological parents as caregivers at the time of SGA initiation. Parental separation was common (40%), and 18% of the patients were in foster care. There was parental substance abuse in more than half of the families. A family history of psychiatric disorders was recorded for 84% of the patients (whereas a family history of somatic diseases was recorded for 53% of the patients). There was a first-degree family member who had a diagnosis of schizophrenia, bipolar disease, or other psychosis in one-third of the families. Over a half of the patients had a depressed family member and about one-tenth had a family member who had attempted or committed suicide. Exposure to some kind of violence was mentioned in 41% of the patient reports.

The everyday functioning of the patient's parents in the PDD/DD group appeared to be better than that in the non-PDD/DD group. About half of the mothers and fathers of the study patients were working at least part time. However, the employment of mothers was statistically significantly more common in the PDD/DD group than in the non-PDD/DD group, and children in the PDD/DD group also had both biological parents as caregivers more often. In the PDD/DD group, out-of-home placements were rarer than in the non-PDD group, and there was significantly less parental substance abuse and fewer first-degree relatives with bipolar or other psychoses. Exposure to violence was also indicatively less common in the PDD/DD group than in the non-PDD/DD group (see Table 3).

In 36% of the patient reports, there was no information on growth history at the time of SGA initiation. When reported, growth history was normal in 68% of the patients, while there was some deviance (e.g., overweight, slow growth) in the remainder prior to SGA initiation. Six patients were reported to have been drinking alcohol and five patients were reported to be smoking. One of the patients had voluntarily told the physician about experimental substance use. In general, information on the patient's possible substance use was missing.

In 81% of the cases, the attending physician reported either considerable or at least some benefit due to the SGA medication. Three percent had no benefits from the SGA medication. In 16% of the cases, the possible benefits remained uncertain or the information was lacking. In many cases, there was also fluctuation in symptoms despite the medication. In 28% of the cases, the attending physician reported no adverse effects. One adverse effect was reported in 32% of the patients and 40% had two or more adverse effects. The most frequent adverse effects were increased appetite and weight gain, which were reported in 36% and 35% of the cases, respectively. Somnolence, usually in the SGA initiation phase, was reported in 33% of cases and other neurological adverse effects in 10% of the patient reports. All other reported adverse effects (increased irritation, mammillary gland symptoms, disturbances in menstrual cycle, urinary symptoms, headaches, nosebleeds, abdominal pain or swelling, and loss of appetite) were each mentioned at most in 7% of the patient reports.

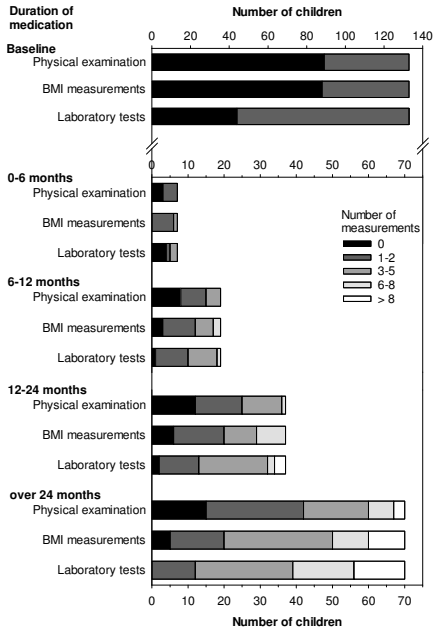

FIGURE 3. Physical examination, BMI measurements, and laboratory tests performed during the second-generation antipsychotic treatment

Figure 3 shows a summary of the frequency of physical examination, laboratory tests, and BMI measurements performed during the study period. At SGA initiation (baseline), some kind of physical examination other than measurement of height or weight was performed on 33% of the patients. Almost the same proportion of the patients (29%) had no physical examination during follow-up. Approximately one-fifth of the patients in the longest treatment category (over 24 months) had no physical examinations during follow-up. At baseline, 38% of the patients had their weight measured and 34% had their height measured. Twenty percent had

their height measured once and 69% had their height measured twice or more often during the follow-up. Weight was measured once in 16% of the patients, and 77% had at least two weight measurements during the follow-up. Ten (8%) patients had no information on weight and fourteen (11%) patients had no information on height during the follow-up. In some reports, it was mentioned that growth was followed elsewhere, but the information did not always reach the attending physician. Baseline laboratory tests were more frequent than physical examination. At baseline, some laboratory tests were performed for 67% of the patients and plasma lipids and glucose, as indicators of metabolic condition, were checked for 55% and 61% of the patients, respectively.

Twenty-five percent of the patients had one and 10% two or three consultations with a paediatric cardiologist during the study period. A consultation was most often performed as a paper consultation. Indications for consultations were diverse, but mostly involved the interpretation of an ECG if the psychiatrist considered it aberrant. The cardiologist did not find absolute obstacles for SGA use in any of the consultations. However, in two patients, cardiological adverse effects (prolonged QT interval) were mentioned as a reason for discontinuing or switching the SGA. Other paediatricians (e.g., neurologist or endocrinologist) were consulted at least once for 32% of the patients. Nine patients were referred to a nutritionist for dietary advice.

Discussion

In this study we assessed the clinical use of SGAs in 133 child psychiatric patients aged 12 years or younger. Children in the study had multiple diagnoses, and polypharmacy was common. Most (79%) of the patients had had in-patient treatment, reflecting their symptom severity and poor functional capacity. Comorbidity was common, with 75% of all children receiving more than one psychiatric diagnosis. Independently of the diagnoses, the main SGA target symptom was aggression; however, the indication was clearly stated in only 61% of the patient reports. The official indications for SGA medication for children younger than 13 years are few. Nevertheless, these medications are frequently used for varying indications in this age group (1,2,8,10,14). In this study, the data were collected from a geographically restricted area in Finland. However, the findings are in line with previous studies (2,10,11). SGA use was mostly off-label, since none of the patients fulfilled all of the official indication criteria.

Various studies show that the significant risk for metabolic and other SGA-induced adverse effects calls for appropriate monitoring (34-38). However, the content and schedule of the physical evaluations and follow-up practices of SGA medications have been diverse in child psychiatric clinical work (7,39,44-46), as was also observed in this study. Only about one-third of the study patients had undergone a physical evaluation at SGA initiation. Approximately one-fifth of the patients medicated for over 24 months had no physical examination at any of the follow-up visits. Furthermore, information on growth history was lacking of about one-third of the patients. It is also noteworthy that information on the child's family history of somatic diseases, which is of importance when assessing risk factors associated with, for example, metabolic disorders, was often incomplete and less thoroughly documented than the family history of psychiatric illnesses.

Evaluating the benefits and risks of SGA medication among children is complex. SGA treatment for children is often associated with the symptomatic treatment of developmental or other disorders with a long duration (1,2,8,14,21,22,25). The average duration of the SGA medication was long in this study as well: the median duration was almost two years. Most of the SGA-treated patients (81%) in this study had an improvement in their symptoms at least to some extent, but symptom control seemed at times insufficient. In many cases, there was fluctuation in the symptoms despite the continuous medication and the possible benefits gained at the beginning did not remain so evident in the long run. During the early years, biopsychosocial development is rapid, and many aspects affect the possible symptom development. The two peaks in the SGA initiation age observed in this study – the first school years and pre-puberty – may both reflect times of increasing environmental and social demands for the child, and these times are also challenging from a family perspective. The many other psychotropic medication trials observed in this study may also have influenced symptom improvement or deterioration. In 16% of the patients in this study, the effect of the medication remained unclear. Despite this, the medication was often continued. The use of systematic assessment methods for examining changes in patients' functioning or response to medication was not possible in this study due to the source of information being patient records, which are often incomplete and somewhat unsystematic. Further studies on the subject are needed, and systematic assessment of functional capacity at the baseline and during follow-up should be encouraged.

In this study, the majority of children medicated with antipsychotics had remarkable adverse life

events in their background. Parental psychopathology and substance use, exposure to violence, and major changes in the family environment were common, and one in every five patients was in foster care. There were, however, differences in the background factors of the two patient groups: children in the non-PDD/DD group had more social stress factors than the children in the PDD/DD group. Adverse life events are, among other individual and environmental factors, known risk factors for mental disturbances in childhood and during the whole lifetime (15-17), and emotional dysregulation is found to be more common in children exposed to repeated or multiple traumas (15,16). While psychotropic medication can diminish behavioural and emotional symptoms and function as an important aid to improve the child's functional capacity, it is apparent that psychosocial support is necessary alongside medication. If the treatment plan is sufficiently integrated, medication can be a helpful aid in learning new skills of behavioural and emotional control, and, at best, can function as a catalyst for development. However, the sufficiency of psychosocial support for children treated with SGAs is a cause for concern. In a study by Olfson et al. (8), less than one quarter of SGA-treated patients aged 1 to 13 years received psychotherapy. In a study by Crystal et al. (7) more than one-third of children in foster care receiving SGA medication failed to receive psychosocial mental health services. However, as a result of several initiatives to improve the monitoring of SGA treatments in foster care children in USA, these children now appear to receive not only more adequate metabolic monitoring, but also psychosocial mental health services at rates higher than children in the general Medicaid population (7). This encouraging finding further highlights the importance of proper monitoring practices in clinical work. In this study we did not assess the psychosocial treatment measures separately. In specialist level child psychiatric services in Finland psychoeducation and therapeutic family counselling are, however, an integral element and need for other therapeutic interventions is evaluated individually for every patient. As psychosocial support is often put into practice in homes and schools by social or educational services, multi-professional co-operation is essential. Further studies of the subject in SGA treated children are needed.

Continuous dialogue between professionals and further education concerning medications and follow-up practices is important in child psychiatric clinical work. According to recent studies, psychiatrists' attitudes towards SGAs and performing physical examinations affect their prescribing and monitoring practices (46,51). In addition, proper facilities and access to equipment for physical evaluation are of importance (46). Despite the already existing guidelines (39-42), there is still a need to standardize practices concerning antipsychotic medication use in psychiatric health care units treating children. When treating children with medications of long duration that affect both physical and mental development, liaisons should be encouraged between child psychiatry and paediatric medicine and child and adult psychiatry.

Clinical significance

Results of this study are important for future planning of the child psychiatric health care in Finland. Children suffering from severe psychiatric problems need the most efficient treatment, including SGA medication when appropriate. The need and use of medication should in all circumstances be assessed and reported systematically, targeting initiation, response, and adverse effects. To improve practice standardization, we should further develop easy-to-use follow-up protocols that are child and family oriented. When treating children with medications of long duration and influence on both physical and mental development, we should also aim to increase dialogue between the medical specialities treating children and their families.

Limitations

The data evaluated in this study were originally collected for clinical purposes at a time when there were no systematic SGA follow-up procedures available in clinical work. The results need to be interpreted with caution and more systematic research of SGA follow-up practices is needed in the future.

Ethical approval

The study was approved by the ethics committee of the Pirkanmaa Hospital District. All data were originally collected for clinical purposes. The patients and their families were not contacted and their treatment was not affected in any way by the study; hence, no informed consent was required.

Acknowledgements

This study was supported by the Foundation for Paediatric Research and the Finnish Brain Foundation.

Conflicts of interest

Dr Kakko reports grants from The Foundation for Paediatric Research and from The Finnish Brain Foundation, during the conduct of the study.

Drs Pihlakoski, Salmelin, Keskinen, Puura and Tamminen have nothing to disclose.

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Scandinavian Journal of Child and Adolescent Psychiatry and Psychology
Vol. 6(1):80 (2018) DOI 10.21307/sjcapp-2018-008

Erratum **Open Access**

Correction to: Clinical use of second-generation antipsychotics in children.

In Figure 3 on page 84 in the paper "Clinical use of second-generation antipsychotics in children" (Kirsi Kakko, Leena Pihlakoski, Raili Salmelin, Päivi Keskinen, Kaija Puura, Tuula Tamminen, Scandinavian Journal of Child and Adolescent Psychiatry and Psychology 5(2):77-88 (2017) an older version of data was used.
This figure is now updated:

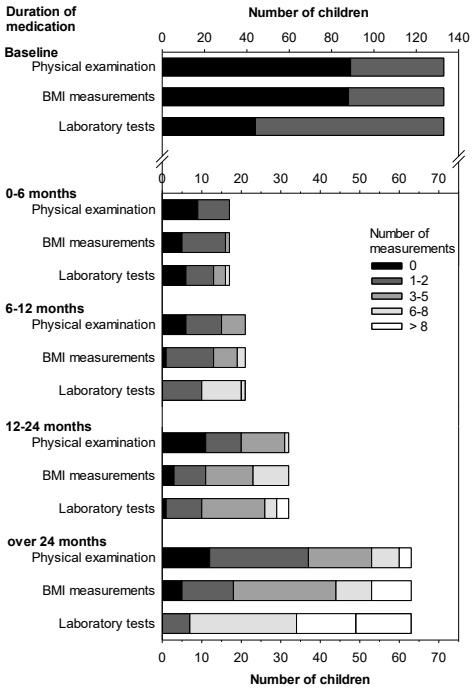

FIGURE 3. Physical examination, BMI measurements, and laboratory tests performed during the second-generation antipsychotic treatment

PUBLICATION II

Current follow-up practices often fail to detect metabolic and neurological adverse reactions in children treated with second-generation antipsychotics

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Acta Paediatrica (2020) vol. 109, pp. 342–348.
https://doi.org/10.1111/apa.14951

Received: 24 January 2019 | Revised: 10 June 2019 | Accepted: 24 July 2019

DOI: 10.1111/apa.14951

REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Current follow-up practices often fail to detect metabolic and neurological adverse reactions in children treated with second-generation antipsychotics

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Funding information
This study was supported by the Foundation for Paediatric Research and the Finnish Brain Foundation.

Abstract

Aim: This study examined the use and adverse reactions of second-generation antipsychotics (SGAs), alone or combined with other psychotropic medication, to identify areas for standardising prescribing and monitoring practices.

Methods: We conducted a retrospective study at Tampere University Hospital, Finland, involving 128 patients (81% boys) who were under 13 years old at SGA initiation and had SGA treatment between October 2013 and October 2014.

Results: The median age at baseline was 9.4 years. Weight gain was reported as an adverse reaction in 33%, but an increase in standardised body mass index, adjusted for age and sex (BMI *z*-score), was detected in 75% of patients with sufficient data. The statistically significant median changes during the study were an increase of 0.46 in BMI *z*-score, a reduction of 0.25 mmol/L in fasting plasma high-density lipoprotein and an increase of 0.28 mmol/L in triglyceride values. The weight gain was most apparent in patients treated with just an SGA or SGA plus melatonin. Patients treated with an SGA plus medication for attention deficit hyperactivity disorder were less likely to gain weight.

Conclusion: SGA-induced metabolic disturbances remained partly unrecognised in children under 13 years of age and more systematic monitoring is needed.

KEYWORDS
adverse reactions, metabolic disturbances, psychotropic medication, second-generation antipsychotics, weight gain

1 | INTRODUCTION

The use of psychotropic medication and polypharmacy has increased among paediatric patients.[1-4] The use of second-generation antipsychotics (SGAs) has particularly emerged, as has the use of stimulants, other medication for attention deficit and hyperactivity disorder (ADHD) and melatonin.[4,5] Paediatric patients have been reported to be especially vulnerable to SGA-induced metabolic adverse reactions, such as weight gain, glucose and lipid abnormalities and elevated blood pressure.[2,3,6-8] The risk of type 2 diabetes has been reported to be two to three times higher in children treated with SGAs.[9] Adverse metabolic reactions have been associated with a markedly increased risk of cardiovascular disease, especially with long-term SGA treatment.[2] A study published in 2019 also showed an association between antipsychotic treatment and unexpected

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI *z*-score, standardised body mass index adjusted for age and sex; BMI, body mass index; HDL, high-density lipoproteins; IQR, lower to upper quartile; SGA, second-generation antipsychotic.

deaths in children and adolescents.[10] In the short term, SGAs have been shown to induce similar neurological adverse reactions in children and adults.[11] Longer treatment may be associated with more severe manifestations, such as tardive dyskinesia.[3,12] SGAs are sometimes used to augment methylphenidate and atomoxetine—henceforth referred to as ADHD medication—to treat comorbid aggression in ADHD.[13] ADHD medication has been reported to reduce weight, while SGA appears to have the opposite effect.[14,15] However, subjects with ADHD did gain weight when risperidone was combined with methylphenidate.[13]

These findings highlight the need for proper monitoring practices for children treated with SGAs. There are guidelines on follow-up practices, but there has been limited systematic monitoring, despite the evidence of SGA-related adverse reactions.[16-20]

The aim of this study was to find potential areas of clinical practice where prescribing and monitoring of SGA medication administered to children could be standardised. We did this by examining the use and adverse reactions of SGAs, alone or when combined with other psychotropic medication.

Key notes

- We examined the use and adverse reactions of second-generation antipsychotics (SGAs), alone or combined with other psychotropic medication, in 128 children (81% boys) under the age of 13.
- Our findings showed that statistically significant weight gain and deteriorating fasting plasma triglycerides and high-density lipoproteins were associated with SGA treatment.
- Implementing systematic prescribing and monitoring practices for SGA treatment in paediatric patients are essential, as many negative changes currently go unrecognised.

2 | PATIENTS AND METHODS

This retrospective study of medical records was conducted at the child psychiatric clinic of Tampere University Hospital, and it was approved by the ethics committee of Pirkanmaa Hospital District. We included patients who were prescribed SGA at our child psychiatric clinic when they were less than 13 years of age and received SGA treatment between 1 October 2013 and 1 October 2014. They were only included if any treatment breaks did not exceed 6 months. These criteria were met by 128 patients. We examined medical reports from SGA initiation. The study end point for each patient was whichever came first: when they discontinued SGA, when they discontinued treatment at the child psychiatric clinic or 31 May 2015. Sociodemographic factors, diagnoses and the psychiatric and any other medical history of the patient and their family were recorded. Information on SGA and other psychotropic medication use, follow-up practices, reported adverse reactions and paediatric consultations was also collected from the medical records.

If the patient's weight and height, collected from the medical records, were both measured at the same time point, the standardised body mass index adjusted for age and sex (BMI *z*-score) was calculated using Finnish national growth reference tables.[21] Based on the recommendations of the International Obesity Task Force expert panel, the BMI percentile curves passing through BMIs of 25 and 30 kg/m^2 at the age of 18 years were used to define the limits for overweight and obesity, respectively. These were the 87.8th and 98.2th percentile for the girls and the 78.2th and 95.6th percentile for the boys.[21] The minimum and maximum BMI *z*-scores were identified when at least two BMI *z*-scores were available. These were either one at baseline and at least one follow-up value or at least two follow-up values. The BMI *z*-scores were rounded to one decimal place to avoid detecting minimal changes. A maximum score occurring after a minimum score was considered weight gain during the study period and vice-versa for weight loss.

Fasting plasma high-density lipoprotein (HDL), triglyceride and glucose values were collected from laboratory reports, and blood pressure values were collected from the children's medical records. Abnormal fasting plasma values were defined as the cut-off points of the National Cholesterol Education Programme for metabolic syndrome in children and adolescents, namely HDL ≤ 1.03 mmol/L, triglycerides ≥1.24 mmol/L and glucose >6.1 mmol/L.[22,23] Elevated blood pressure was defined using the age, sex and height-specific reference tables of the American Academy of Pediatrics' *Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents*.[24] The percentile of each blood pressure measurement was set according to the guideline if a height measurement was available within 2 months of that measurement. Blood pressure was considered elevated if it was ≥90th percentile on three separate occasions, with at least a week between the readings and hypertensive if it was ≥95th percentile using the same criteria.

Because of the potential effects of ADHD medication on growth and blood pressure, the study population was initially divided into two groups for the analyses: 84 with ADHD medication and 44 without. To assess the possible effects of melatonin, similar analyses were performed for four specific patient groups based on the treatment they had received: just an SGA (n = 23), an SGA plus ADHD medication (n = 25), an SGA plus melatonin (n = 21) and an SGA plus ADHD medication and melatonin (n = 59).

The categorised variables were reported as numbers of cases or percentages, as appropriate and medians and interquartile ranges (IQR, lower to upper quartile) were reported for the continuous variables, which were mostly non-normally distributed. To test the statistical significance of the differences between the groups, we used Pearson's chi-square test, Fisher's exact test or the Kruskal-Wallis test, as appropriate. The Kolmogorov-Smirnov test was applied to examine whether the changes in BMI *z*-score, HDL and triglyceride values were statistically significant. A *P* value of less than .05 was considered significant, a value between .05 and .10 was indicative

and values up to .10 were reported. SPSS Statistics, versions 23 and 25 (IBM Corporation) were used for all the statistical analyses.

3 | RESULTS

The inclusion criteria were met by 128 patients (81% male) with a median age of 9.4 years (IQR 7.9-11.1) at baseline. The median duration of the SGA treatment was 20.4 months (IQR 9.1-34.6), but the actual duration was probably longer because of study end points other than SGA discontinuation. Selected background factors are shown in Table 1 and have previously been reported in more detail.[25] We found that 120/128 (94%) children were treated with risperidone at some point, 23 (18%) with aripiprazole and 22 (17%) with quetiapine. The SGA was changed at least once for 28 (22%) children during the follow-up period. The use of other psychotropic medication is shown in Table 1.

The follow-up practices are presented in Table 2. The most frequent metabolic test at baseline was fasting plasma glucose in 63/128 (49%) patients. The most frequently reported adverse reactions by the clinicians were increased appetite in 46 (36%) cases, weight gain in 42 (33%) and fatigue in 41 (32%). Neurological adverse reactions, such as akathisia, tics and sluggishness or stiffness were reported in 13 patients (10%). During the study period, 39/128 patients (31%) were referred to a paediatric consultation other than paediatric cardiology. The indications for consultations were diverse, but they included 10/39 (26%) who were referred to a paediatric endocrinologist due to a metabolic disturbance and 11/39 (29%) who were referred to a paediatric neurologist. None of the neurological consultations were due to adverse drug reactions.

TABLE 1 Background factors of the children treated with SGAs (n = 128)

	%
Gender	
Male	81
Female	19
Family status	
Biological parents	37
One biological parent alone or with a new partner	40
Foster home	18
Other (eg adoption)	6
Number of ICD-10 F-diagnoses[a]	
1	26
2	48
3	23
4	4
In first-degree relatives, the availability of the history of[b]	
Psychiatric disorders	84
Metabolic disorders	53
Psychotropic medication other than an SGA[c]	
Methylphenidate	65
Atomoxetine	23
Selective serotonin reuptake inhibitors	14
Benzodiazepines[d]	14
Melatonin	63

[a]F00-F99 mental and behavioural disorders.
[b]Co-occurence was possible.
[c]At least a trial during the study period.
[d]As requisite medication.

It was possible to calculate the minimum and maximum BMI *z*-scores for 97 patients (76%), and the cumulative frequency distributions are shown in Figure 1. The BMI *z*-score increased in 73 (75%) of these patients and this increase was within the normal weight category in 40 (55%) of them (Table 3). The minimum BMI was less than 25 in 74 (76%) patients, whereas the maximum BMI was less than 25 in 52 patients (54%). The number of patients who had minimum and maximum BMIs that were from 25 to less than 30 were 16 (17%) and 25 (26%), respectively, and for BMIs of 30 or more, they were seven (7%) and 20 (21%). The median BMI *z*-score change was an increase of 0.46 (IQR 0.04-0.92, $P = .005$). The number of patients for whom a BMI *z*-score could not be calculated at any point was 10/128 (8%).

The frequencies of abnormal metabolic and blood pressure measurements are presented in Table 2. At least two fasting plasma HDL and triglyceride values were available for 81/128 (63%) patients. HDL decreased in 44/81 (54%), and the reduction was within the normal range in 39 (89%). The median HDL change was −0.25 mmol/L (IQR −0.43 to −0.15, $P = .004$). Triglyceride increases were seen in 44/81 (54%) and these were within the normal range in 36 (82%). The median triglyceride change was 0.28 mmol/L (IQR 0.11-0.46, $P < .001$).

At least three blood pressure percentiles were available for 61/128 (48%) patients: two of them (3%) met the criteria for elevated blood pressure and one had hypertension. At least one blood pressure percentile was available for 104/128 patients (81%) (Table 2).

The 84 patients treated with SGA plus ADHD medication, with or without melatonin, gained weight less frequently than the 44 patients who were just treated with an SGA, with or without melatonin (Table 3). Baseline blood pressure was measured for 29/84 patients (35%) treated with SGA plus ADHD medication and 6/44 (14%) ($P = .013$) of those treated with just an SGA. At least one blood pressure value during the study period for these groups was available for 71/84 (85%) and 33/44 (75%), respectively. At least one hypertensive systolic blood pressure value was observed in 33/71 (47%) who had ADHD medication combined with an SGA and in 9/33 (27%) patients who only received SGAs ($P = .086$). We did not find any other statistically significant or indicative differences in the baseline or follow-up measurements between these two medication groups or in the reported adverse reactions.

When we compared all four medication groups, there were no statistically significant differences in the baseline or follow-up practices or in the adverse reactions reported by the clinicians. Table 3 shows the weight changes in the medication groups. In the 16 patients in the SGA plus melatonin group who had at least two BMI *z*-scores, the weight gain appeared within the normal weight

TABLE 2 Frequencies of somatic measurements and their abnormal values at the baseline and during the follow-up period (n = 128)

Type of measurement	Value considered abnormal	Baseline	During the entire study period, the proportion having at least one	
		%	Measurement %	Abnormal value[b] %
Physical examination	-	34	78	-
Body mass index	>25[a]	34	92	46
Fasting plasma high-density lipoprotein	≤1.03 mmol/L	40	86	20
Fasting plasma triglyceride	≥1.24 mmol/L	39	86	27
Fasting blood glucose	>6.1 mmol/L	49	95	7
Blood pressure	≥95th percentile	27	81	-
Systolic		-	-	40
Diastolic		-	-	21

[a]Standardised body mass index, adjusted for sex and age (BMI *z*-score) corresponding to BMI > 25.
[b]Among those who had at least one measurement.

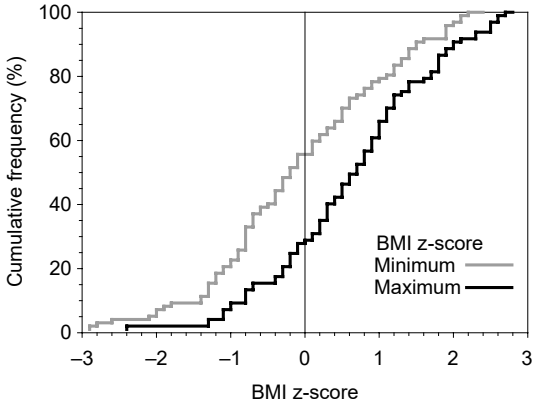

FIGURE 1 The cumulative frequency distribution of the minimum and maximum BMI *z*-score (standardised body mass index, adjusted for sex and age) in children treated with SGAs (n = 97)

category in 11 (69%) patients. The proportion was around one-third in the other groups (Table 3). There were no statistically significant differences in triglyceride and HDL values between the medication groups. The number of patients with at least one hypertensive systolic blood pressure measurement was seven (41%) out of the 17 who were treated with just an SGA and had at least one blood pressure measurement during the study period. The respective figure was 11/22 (50%) in the group treated with SGA plus ADHD medication, 2/16 (13%) in the patients treated with an SGA plus melatonin and 22/49 (45%) in the patients treated with an SGA plus ADHD medication and melatonin (P = .092). There were no statistically significant differences in diastolic blood pressure values between the medication groups.

4 | DISCUSSION

The aim of this study was to find potential areas where prescribing and monitoring practices of SGA medication for children could be standardised. Our study findings were in line with previous studies that suggested that SGA treatment poses major metabolic risks for children.[6,7,26] Despite these findings and the existing guidelines, monitoring practices have often remained irregular.[16-20] In our study, the baseline information necessary for detecting changes in growth and the laboratory test values was seldom complete. In addition, information on familial metabolic risk factors was often lacking, which complicates the evaluation of possible hereditary risks.

Three-quarters of the patients in our study gained weight and there was also a statistically significant deterioration in their triglyceride and HDL values. One of the main findings of this study was that these alterations appeared mainly within the normal reference values and seemed to remain unrecognised. For example, there was a discrepancy when we compared the BMI *z*-score findings and the frequency of reported weight gain in the medical records. Surprisingly, the clinicians only reported weight gain as an adverse reaction in one-third of the patients. Nevertheless, even a smaller increase in BMI *z*-score or alterations in metabolic parameters may, without intervention, predict future cardiovascular morbidity. Neurological adverse reactions were reported in a tenth of the study patients, and this figure was slightly lower than in previous studies.[11,17] Irregular reporting and the retrospective nature of the study may have affected this result. However, the common assumption that SGAs are less likely to cause neurological adverse reactions means that there is a risk that these reactions are not monitored and may remain unrecognised. Furthermore, misinterpreting neurological adverse reactions as worsening psychiatric symptoms may lead to overmedication and more severe adverse reactions.[3,27]

Psychiatric polypharmacy was common in our study, but it did not have a major effect on the follow-up practices. Children treated

TABLE 3 Weight changes in medication groups

	Medication group[a]					
	SGA	**SGA + ADHD**	**SGA + melatonin**	**SGA + ADHD + melatonin**	***P***	**All**
	(n = 23)	**(n = 25)**	**(n = 21)**	**(n = 59)**		**(n = 128)**
Patients who had ≥ 2 simultaneous measurements of weight and height available						
n	14	22	16	45	ns[d]	97
%	61	88	76	76		76
	(n = 14)	**(n = 22)**	**(n = 16)**	**(n = 45)**		**(n = 97)**
Patients who did not gain weight						
n	1	8	0	15	.024[c]	24
%[b]	7	36	0	33		25
Patients who gained weight within normal range						
n	5	7	11	17		40
%[b]	36	32	69	38		41
Patients who gained weight within over-weight or obesity, or moved to either of them						
n	8	7	5	13		33
%[b]	57	32	31	29		34
Change in standardised body mass index, adjusted for age and sex						
Md	0.55	0.51	0.51	0.31	ns[d]	0.46
IQR	0.22-1.08	−0.27 to 1.14	0.34-1.01	−0.12 to 0.73		0.04-0.92

Abbreviation: Md, Median; IQR, intra quartile range.
[a]SGA, second-generation antipsychotic; ADHD: methylphenidate, atomoxetine, lisdexamfetamine (n = 1).
[b]% of those who had at least two measurements available.
[c]Pearson's chi-square test.
[d]Kolmogorov-Smirnov test.

with an SGA plus ADHD medication were more likely to have their blood pressure measured at baseline compared with other patients. This was probably due to the existing national ADHD treatment guidelines which recommend repeated blood pressure measurements. Even though polypharmacy only had a minor effect on the follow-up practices, it had effects on the observed weight gain and blood pressure readings. Studies have reported that appetite loss and blood pressure elevation have been relatively common adverse reactions to psychostimulant treatment.[14,15] These reactions were also observed in our study. Patients using an SGA plus ADHD medication at some point during the study were less likely to gain weight compared with other patients. However, their systolic blood pressure values were indicatively more likely to be hypertensive.

In our study, the weight gain was most apparent in patients treated with just an SGA or an SGA plus melatonin. However, when melatonin was combined with an SGA, a weak association with more modest weight gain was observed, mostly appearing within the normal weight category. In addition, hypertensive systolic blood pressure values were indicatively less frequent in patients using an SGA plus melatonin than in patients receiving other treatment regimens. A similar tendency was observed in previous studies of adults and adolescents,[28,29] indicating that adding melatonin could reduce SGA-related metabolic effects. However, these studies had several methodological limitations, such as small sample sizes, short follow-up times and scarce information concerning children.[28,29] On the other hand, in a study by Tuomi et al[30], adding melatonin decreased insulin release and increased glucose concentrations in adults. Sleep disturbances are known comorbidities of psychiatric disorders, and quality of sleep is known to affect weight and metabolic control.[29] The finding that adding melatonin was associated with fewer SGA-induced metabolic adversities should encourage clinicians to pay special attention to the sleeping habits of these patients.

Second-generation antipsychotics treatment, on its own or to augment ADHD medication, is a major risk factor for metabolic disturbances in children. Psychotropic polypharmacy may increase the risk of adverse drug reactions or sometimes diminish it. Special attention should be paid to detecting adverse tendencies, not just to absolute reference values. It is essential that patients are monitored when they start new medication and that they are followed up regularly. Our study shows that there is still an urgent need for improvement, as inadequate monitoring can mean that adverse reactions with far-reaching consequences are missed. Early interventions and lifestyle changes are effective ways of reducing the metabolic comorbidities of SGAs. However, the most effective tool is prevention, which is not possible without systematic monitoring.

The major strengths of our research were the real-life nature of the study and long follow-up period. Our study provided an honest

perspective on the clinical reality and disclosed major targets for interventions. The relatively small sample size, retrospective nature and the lack of a control group limit the generalisability of our results and they should be interpreted with caution. However, this study has laid the foundation for a more systematic follow-up procedure for SGA treatment in children at Tampere University Hospital.

5 | CONCLUSION

Knowing the possible adverse drug reactions and being aware of the pitfalls in current practices of SGA treatment should encourage clinicians to adopt more systematic treatment procedures. The identification, follow-up and management of SGA-related adverse reactions are important activities for patient safety and all treating physicians are responsible for carrying these out.

ACKNOWLEDGEMENTS

We wish to acknowledge the contribution of Dr Tuula Tamminen to the design of this study and Dr Tuija Poutanen for providing a paediatric cardiology advice about the blood pressure measurements.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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How to cite this article: Kakko K, Pihlakoski L, Keskinen P, Salmelin R, Puura K. Current follow-up practices often fail to detect metabolic and neurological adverse reactions in children treated with second-generation antipsychotics. *Acta Paediatr*. 2020;109:342–348. https://doi.org/10.1111/apa.14951

PUBLICATION III

In search of measures to improve the detection of increased cardiometabolic risk in children using second-generation antipsychotic medications

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Nordic Journal of Psychiatry (2021). Advance online publication.
This is an Author's Original Manuscript of an article published by Taylor & Francis Group in Nordic Journal of Psychiatry available online at: https://www.tandfonline.com/doi/full/10.1080/08039488.2021.1968489

PUBLICATION IV

Tardive dyskinesia should not be overlooked

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Journal of Child and Adolescent Psychopharmacology (2019) 29(1), pp. 72–74.
https://doi.org/10.1089/cap.2018.0084

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 29, Number 1, 2019

Pp. 72–74
DOI: 10.1089/cap.2018.0084

Letters to the Editor

Tardive Dyskinesia Should Not Be Overlooked

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Introduction

Medicating the comorbid behavioral symptoms of children and adolescents with autism spectrum disorders (ASD) and intellectual disability (ID) with second-generation antipsychotics (SGA) has become accepted practice in recent years (Park et al. 2016). Although the available research data cover at most short-term use, SGAs are often used for long periods in clinical settings. There are also reports of electroconvulsive therapy (ECT) in treating aggressive and self-injurious behaviors in pediatric patients with ASD/ID, but as current evidence is based on case reports, ECT is an off-label treatment method (Sajith et al. 2017; Wachtel et al. 2018).

While SGAs are generally considered more tolerable than first-generation antipsychotics, they can still increase the risk for extrapyramidal symptoms (EPS) (Garcia-Amador et al. 2015). EPS rates in children and adolescents vary in studies (Carbon et al. 2015; Garcia-Amador et al. 2015; Pringsheim et al. 2017), but a younger age, a longer duration of treatment, and higher doses associate with more severe manifestations, such as tardive dyskinesia (TD) (Garcia-Amador et al. 2015). Patients with ID are more susceptible to EPS (Sheehan et al. 2017).

TD is probably the most feared and potentially irreversible form of EPS. TD manifests usually after months or years of medication as involuntary athetoid or choreiform movements and dystonia, often affecting the facial area and tongue (Lerner et al. 2015). Treatment options for TD include pharmacological interventions (Lerner et al. 2015), but severe TD is often permanent. There is encouraging evidence for deep brain stimulation (DBS) in treating severe, medication-resistant TD in adults (Macerollo and Deuschl 2018) and also in the treatment of dystonic cerebral palsy in children (Elia et al. 2018). To our knowledge, however, this is the first case reports (Macerollo and Deuschl 2018) describing DBS in the treatment of TD in an adolescent patient.

Case Example

Our patient is an adolescent male with a diagnosis of ASD and ID (ICD-10 diagnosis F71, moderate mental retardation). He communicates using, for example, pictures, and he understands short sentences. Risperidone (0.25 mg daily) was first initiated—with a favorable response—for aggressive behavior and tantrums when he was 8 years old. During the first 2 years, the daily dose of risperidone was increased to 0.4 mg. Higher dosages appeared to cause tics and sedation. Despite the medication, the patient's aggression and behavioral symptoms further worsened between the ages 13 and 16, and the risperidone dose was gradually increased to 3 mg daily. Melatonin (1.5 mg daily) and later chlorprothixene 25 mg daily (thioxanthene) were prescribed for transient sleep problems. Regardless of pharmacotherapy, his behavioral symptoms continued and worsened. Just before the patient turned 16, he became constantly restless, his aggressive behavior worsened, and twitching appeared in the upper limbs. Due to his aggression, the risperidone dose was further increased to 4.5 mg daily. The patient also used valproate (600–1000 mg daily) for epilepsy.

After the increase in the dose of risperidone, compulsive involuntary movements, shivering, and sweating emerged. Because of these movement symptoms, first chlorprothixene and later risperidone were discontinued. The discontinuation of risperidone immediately ameliorated the movement symptoms. However, the patient's behavioral symptoms continued to fluctuate, and quetiapine (150–200 mg daily) was initiated with no response. The movement symptoms increased again. Haloperidol 1.5 mg, clonazepam 1 mg, and diazepam 2 mg daily were introduced to relieve the symptoms, but without response. Instead, the behavioral symptoms worsened, and the movement symptoms became gradually constant; in addition to the aforementioned movement symptoms, choreoathetoid-type movements emerged in the upper limbs. The patient was distressed and his communicative abilities deteriorated.

Due to the worsening of the movement symptoms, the quetiapine and, temporarily, also the valproate were discontinued, but short-term levomepromazine (phenothiazine) medication was prescribed for aggressive behavior. The patient was temporarily hospitalized and piperidine 2 mg daily was introduced. Eventually, ~5 months after the movement symptoms had started, all antipsychotics were discontinued. Despite the discontinuation, the serious movement symptoms continued and worsened. The patient suffered from continuous involuntary choreoathetoid movements affecting the trunk, limbs, neck, facial area, and mouth. Twitching dyskinetic extensions appeared in the back and neck area. Due to the movement symptoms, the patient had insomnia and eating problems, leading to severe weight loss (12 kg in 8 months). The patient was anxious and in constant pain. Diazepam relieved these symptoms temporarily. An MRI was performed for differential diagnostics,

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Funding: This study was supported by the Foundation for Pediatric Research and the Finnish Brain Foundation.

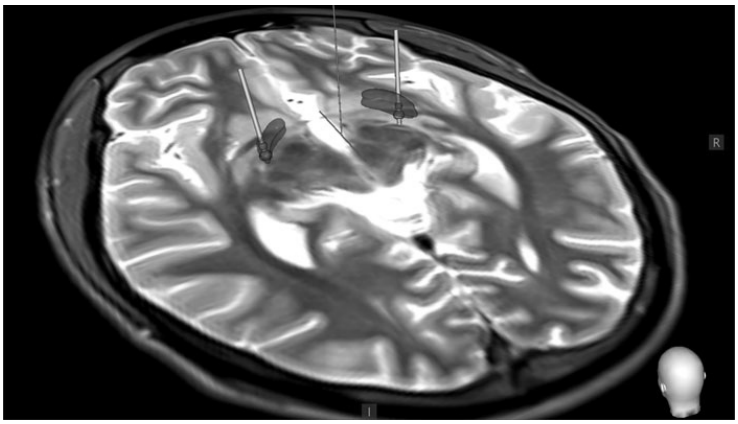

FIG. 1. Deep brain stimulation implant bilaterally in the Gpi is demonstrated. The borders of the Gpi (blue color) were manually identified from 3T MRI images, and 3D reconstruction was generated using Medtronic SureTune 3 software (red color). Gpi, globus pallidum interna. Color images available online at www.liebertpub.com/cap

and the patient was tested for Huntington's and Wilson's diseases and neuroacanthocytosis. A final diagnosis of severe TD was made when the patient was 17 years and 7 months old.

The patient's severe movement symptoms led to self-mutilation, with several lacerations and infected wounds, resulting in sepsis and treatment in an intensive care unit. Multiple conservative treatment approaches for TD failed (including medical cannabis, tetrabenazine, levetiracetam, and piperidine). Finally, at the age of 19 years, the patient was referred to a neurosurgeon for evaluation for DBS, and the decision to undertake pallidal DBS was made. At the age of 19 years and 5 months, based on a 3T MRI performed under general anesthesia, electrodes were stereotactically implanted into the visually defined globus pallidus interna target (Fig. 1). DBS ameliorated the TD symptoms remarkably. Anxiety, restlessness, behavioral symptoms, and self-destructive behavior ceased, and the patient's functional capacity and communicative skills gradually recovered to the previous level.

Discussion

Delayed diagnosis of drug-induced EPS may lead to deleterious consequences, as presented in our case. With our patient, it took too long to reach a diagnosis of TD, and even after the initial diagnosis, antipsychotics were still prescribed. There may have been several reasons for the diagnostic delay. The patient's extremely severe manifestation of movement symptoms and young age did not fit the expected picture of TD. EPS were also misinterpreted as behavioral symptoms, which possibly led to overmedication. ID and communication deficits further complicated the diagnosis.

It should be kept in mind that SGA-induced EPS, including TD, are a possibility also in children and adolescents (Carbon et al. 2015; Garcia-Amador et al. 2015; Pringsheim et al. 2017). There is not enough information available on the long-term effects of SGAs on the developing central nervous system; the studies on EPS and TD in pediatric patients cover only short time periods. Despite this, treatment periods tend to be long in clinical reality.

Patients with a diagnosis of ID do not clearly fall under any distinct medical specialty, which creates a core problem complicating the diagnosis of drug-induced adverse effects. These patients often have multifaceted health problems, and as each clinician attempts to ameliorate the symptoms, the risk of overmedication increases. To avoid serious and possibly far-reaching adverse effects related to antipsychotics, greater emphasis should be placed on the systematic follow-up of children and adolescents. Multiprofessional teamwork is essential, and specialized units for the management of neuropsychiatric disorders in ID patients are needed (Bjelogrlic-Laakso et al. 2014).

If medication fails to relieve serious behavioral symptoms related to ASD and ID, other treatment approaches, such as ECT, should be considered on a case-by-case basis. DBS should be considered in cases of severe TD.

Disclosures

K.K. has received a study grant from the Foundation for Pediatric Research and the Finnish Brain Foundation. No other conflicts of interest exist. N.B.-L. has no conflicts of interest. L.P. has received lecture fees from Biocodex, Shire Plc. and has been sponsored to travel and attend a medical congress by Biocodex, Shire Plc. K.L. has received lecture fees from Medtronic Ltd. and Abbot and has been sponsored to travel and attend a medical congress by Medtronic Ltd., Boston Scientific, and Abbot (former St. Jude Medical). K.J. has received lecture fees from Medtronic Ltd., Otsuka Pharmaceutical Ltd., and Lundbeck Ltd. and has been sponsored to travel and attend a medical congress by Medtronic Ltd.

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