



PhD Thesis

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Cardiac and metabolic adverse events during treatment with quetiapine ER versus aripiprazole in children or adolescents with psychosis – the TEA trial



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1 Preface

This dissertation is based on results from the Tolerance and Efficacy of Antipsychotics (TEA) trial, and none of this research would have been possible without the effort and support (and unlimited patience) from my supervisor and all the members of the TEA team, not to mention my wife, family and friends.

This journey has been a long and arduous one – as emphasized by the occasional bald patches on my head – but also the best training one could hope for, both in terms of psychiatry, research and life itself.

2 Summary in English

The impact of mental disorders on somatic health is an issue of major importance. Youths with psychotic disorders suffer from debilitating symptoms, stigmatization from peers and social isolation, and their disabilities have major consequences for their level of daily functioning. To add insult to injury, both the abovementioned problems as well as the pharmacological treatment of the psychotic symptoms significantly increase the risk of developing metabolic and cardiovascular diseases, which, in turn, is a major contribution to the decrease in life expectancy of up to twenty years that patients with psychotic disorders face.

Nonetheless, antipsychotic medications are essential in the treatment of these patients, even though the efficacy is limited and youths endure more severe adverse effects than adults. Balancing the beneficial and harmful effects of these drugs is adamant for optimal treatment, but we still know too little concerning the cardiometabolic risk of most antipsychotic agents when prescribed to this age group.

In the present PhD study, we have examined the cardiometabolic risk factors in 113 youths with psychosis before and during treatment with quetiapine extended release (ER) versus aripiprazole in the setting of an independently funded, multi-center, randomized, controlled trial (RCT). We found that patients already at entry into the trial had significantly higher waist circumference (WC) and plasma lipids than the matched, healthy controls. We also found that a family history with type 2 diabetes or dyslipidemia was associated with higher cardiometabolic risk in psychotic youth. Our results from the 12 week intervention period revealed statistically and clinically significant increases in weight, WC, body mass index (BMI), insulin resistance, plasma lipids and corrected QT interval during treatment with quetiapine ER, while aripiprazole was associated with smaller, yet still clinically relevant, increases in weight, BMI and WC.

3 Summary in Danish

Det er velkendt at psykiske lidelser har betydende negativ effekt på det somatiske helbred. Unge med psykotiske tilstande lider under invaliderende symptomer, stigmatisering fra jævnaldrende og social isolation, og deres vanskeligheder har store konsekvenser for det daglige funktionsniveau. Derudover kan den farmakologiske behandling af psykotiske symptomer væsentligt betydeligt øge risikoen for udvikling af metaboliske og kardiovaskulære sygdomme, og dette bidrager i betydelig grad til, at den forventede levetid med skizofreni er op til tyve år kortere end i baggrundsbefolkningen.

Ikke desto mindre spiller antipsykotisk medicin en afgørende rolle i behandlingen af disse patienter, selv om effekten er begrænset og unge risikerer flere og mere alvorlige bivirkninger end voksne. For at opnå optimal behandling er det nødvendigt at finde en balance mellem effekt og bivirkninger, men vi stadig ved for lidt om den cardiometaboliske risiko ved de antipsykotika, der anvendes til denne aldersgruppe.

I denne ph.d. har vi undersøgt de kardiometaboliske risikofaktorer i 113 unge med psykose før og under behandling med quetiapin extended release (ER) versus aripiprazol i et uafhængigt finansieret, randomiseret, dobbeltblindet, kontrolleret multicenter forsøg. Vi fandt, at inkluderede patienter havde signifikant højere taljeomfang og plasmalipider end de matchede raske kontrolpersoner. Vi fandt også, at tilstedeværelsen af type 2-diabetes eller dyslipidæmi blandt forældre eller søskende var forbundet med højere kardiometabolisk risikohos patienterne. Data fra den 12 uger varende interventionsperiode viste statistisk og klinisk signifikante stigninger i vægt, taljeomfang, body mass index (BMI), insulinresistens, plasmalipider og korrigeret QT-interval blandt patienter i behandling med quetiapin ER, mens aripiprazol var forbundet med mindre, men stadig klinisk relevante, stigninger i vægt, BMI og taljeomfang.

4 List of papers

Paper 1: Corrected QT Changes During Antipsychotic Treatment of Children and Adolescents: A Systematic Review and Meta-Analysis of Clinical Trials (J Am Acad Child Adolesc Psychiatry. 2015 Jan;54(1):25-36)

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Paper 2: Pre-treatment cardiometabolic status in youth with early-onset psychosis: baseline results from the TEA trial (revised manuscript re-submitted in Journal of Clinical Psychiatry, March 13, 2016)

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Paper 3: Cardiometabolic adverse effects in children and adolescents during treatment with quetiapine ER versus aripiprazole – 12-week results from the TEA trial (manuscript in preparation)

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Paper 4: QTc change during treatment with quetiapine ER versus aripiprazole in children and adolescents with first-episode psychosis: Results from the TEA trial. (manuscript in preparation)

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5 Abbreviations

ADHD: Attention Deficit/Hyperactivity Disorder

AgRP: Agouti-Related Peptide

AIMS: Abnormal Involuntary Movement Scale

AOS: Adult Onset Schizophrenia

AP: Action Potential

BACS: Brief Assessment of Cognition in Schizophrenia

BARS: Barnes Akathisia Rating Scale

BMI: Body Mass Index

BRIEF: Behavioral Rating Inventory of Executive Functions

CART: Cocaine- and Amphetamine-Regulated Transcript

CCK: Cholecystokinin

CGI: Clinical Global Impression (-I: Improvement - S: Severity -E: Efficacy)

CI: Confidence Interval

cm: Centimeters

COS: Childhood Onset Schizophrenia

CRF: Case Report Form

CRH: Corticotropin Releasing Hormone

CTU: Clinical Trial Unit

CVD: Cardiovascular Disease

DIP: Dimensions of Psychosis Instrument

DNA: DeoxyriboNucleic Acid

DSM-5: Diagnostic and Statistical Manual of mental disorders, 5th edition

DSM-IV: Diagnostic And Statistical Manual Of Mental Disorders, 4th edition

ECG: Electrocardiogram

EOP: Early Onset Psychosis

EOS: Early Onset Schizophrenia

EPS: Extrapyrarnidal Side Effects

ER: Extended Release

FDR: First-Degree Relatives

FE: First-Episode

FGA: First Generation Antipsychotics

FPG: Fasting Plasma Glucose

GAPD: Global Assessment of Psychosocial Disability

GLP-1: Glucagon-Like Peptide 1

HDL: High-Density Lipoproteins

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

HRQoL: Health related quality of life

ICD-10: International Classification of Diseases, 10 Edition

IDF: International Diabetes Foundation

IR: Insulin Resistance

kg: Kilograms

KIDCREEN-52: Health related quality of life questionnaire for children and young people and their parents

K-SADS-PL: Kiddie-SADS-Present and Lifetime Version

LDL: Low-Density Lipoproteins

LQTS: Long QT Syndrome

MCH: Melanin-Concentrating Hormone

mg/dl: Milligrams per deciliter

mg: milligrams

mmol/l: Millimoles per liter

ms: milliseconds

MS: Metabolic Syndrome

NCEP: National Cholesterol Education Program

NPY: Neuropeptide Y
OR: Odds Ratio
PANSS: Positive and Negative Syndrome Scale
POMC: Pro-Opiomelanocortin
PYY: Peptide YY
QTc: Corrected QT interval (-B: Bazett, -F: Fridericia, -H: Hodges)
REE: Resting Energy Expenditure
SCoRS: Schizophrenia Cognition Rating Scale
SD: Standard Deviation
SGA: Second Generation Antipsychotics

SQTS: Short QT Syndrome
T1DM: Type 1 Diabetes Mellitus
T2DM: Type 2 Diabetes Mellitus
TdP: Torsade de Pointes
TEA: Tolerability and Efficacy of Antipsychotics
TRH: Thyrotropin Releasing Hormone
UKU: 'Udvalget for Kliniske Undersøgelser' Side Effect Rating Scale
WC: Waist Circumference
WMD: Weighted Mean Difference

6 Introduction

6.1 Early onset psychotic (EOP) disorders

6.1.1 Definition

Psychosis is a mental state defined by distortion of reality, often characterized by the presence of hallucinations and/or delusions.¹⁻³ According to the diagnostic manuals DSM-IV⁴, DSM-5⁵ and ICD-10⁶, the diagnostic definitions of psychosis do not differ between adults and children/adolescents. In children, however, it may be difficult to distinguish between delusions and common misconceptions, and hallucinations are a relatively common feature in children, not necessarily indicative of the development of a psychotic disorder later in life.⁷ However, if hallucinations persist over time, cause grievance or are linked to delusions (for example “*the shadows I can see are ghosts – they control my thoughts*”), this could indicate that the person has difficulties in distinguishing these experiences from reality and may thus be prone to developing a psychotic disorder. The prevalence of early psychotic symptoms has been investigated in a cross-sectional study of 3,870 schoolchildren aged seven to eight years. Here, it was found that auditory hallucinations occurred in 9%; of these, 15% reported serious suffering and 19% experienced substantial interference with thinking.⁷ In a subsequent 5-year follow-up of 337 children from this cohort, persistence of auditive hallucinations was at 23.5%. Children who experienced persisting hallucinations, or acquired hallucinations during the follow-up period, had generally more severe difficulties than the children who did not, both in terms of cognitive disabilities and psychological problems.⁸ Similar results have emerged from other studies.⁹

The clinical concept of early onset psychosis (EOP), i.e. psychotic disorder with onset before age of 18 years, is rare before the age of 13 years, but the prevalence increases during adolescence.^{10,11} As for adults, psychosis in children and adolescents occur in a range of psychiatric disorders, such as major depressive disorder, bipolar disorder with psychotic symptoms or schizophrenia spectrum disorders, such as early onset schizophrenia (EOS) or schizoaffective disorder. Psychotic disorders may also evolve in more transient forms in connection to other psychiatric disorders or somatic conditions affecting the central nervous system.¹²

6.1.2 Epidemiology

For schizophrenia, the lifetime prevalence is about 1%, and about 4% of these arise before the age of 15 years,¹³ equivalent to 400 persons in a population of 1 million. Studies have found an incidence of EOS (narrowly defined schizophrenia with early onset) aged 0-18 years of 5.15 versus for all ages 15.2 per 100.000 person years.¹⁴ In contrast to the equal male-female in adult schizophrenia, studies have found a higher preponderance of males in EOS.^{15,16} However, a recent Danish study found a shift in the gender distribution over time, with a higher incidence rate of EOS in males than females in the period 1971-1993 (males 65%) and an equal distribution in the later period 1994-2010 (males 48%).¹⁰

The prevalence of more broadly defined EOP is less studied, but up to one third of patients with psychotic illness in adulthood have an onset of psychosis in childhood or adolescence.^{11,17-20}

6.1.3 Phenomenology, clinical diagnosis, course and prognosis

Schizophrenia in both youths and adults is characterized by symptoms clustered into four main dimensions: 1) the positive dimension (psychotic symptoms, i.e. delusions, hallucinations, formal thought disorder and disorganized behavior); 2) the negative dimension (i.e. alterations in drive and volition); 3) the cognitive

symptom dimension (alterations in neurocognition) and 4) affective dysregulation (manic and depressive symptoms).¹⁴

The presentation of psychotic symptoms is related to the underlying psychiatric disorder. In schizophrenia, bizarre delusions or hallucinations without affective content (for instance paranoid delusions) are often accompanied by *negative symptoms*, such as passivity, lack of initiative, blunted affect and social withdrawal.²¹ In the context of a major depressive disorder, delusions and hallucinations may reflect underlying anxiety or self-derogatory ideas, and diminish when the underlying mood disorder is treated appropriately.

The diagnosis of psychotic disorders relies on a comprehensive medical and psychiatric history, somatic examination and description of the psychotic symptoms. As these often are highly subjective, screening instruments, diagnostic interviews and ratings scales focusing on specific symptoms as well as general psychopathology are useful. The validity of the schizophrenia diagnosis is the subject of continuous debate, as exemplified by the major diagnostic changes seen in the replacement of DSM-IV by DSM-5.²²

Although children presenting psychotic symptoms may have several underlying disorders, a diagnosis of bipolar disorders or schizophrenia tends to remain stable over time.²³ In a two-year follow-up study by Fraguas *et al.* of 24 patients (mean±SD 15.7±1.6 years, 75% males) with first-episode psychosis (FEP), authors showed a diagnostic stability of psychotic disorders of 54.2% during the first year and 95.7% during the second year.²⁴ In this sample, the diagnostic stability of schizophrenia was high (100%) but much lower for other diagnoses (range: 16.7% for psychosis NOS to 71.4% for bipolar psychosis). In another study – in a two year follow-up study of 83 patients (mean±SD 15.5±1.7 years, 67.5% males) with FEP – the diagnostic stability was 63.9%, ranging from 0% for brief psychotic disorder to 92.31% for bipolar disorder.²⁵

In EOS, symptoms are often vague, poorly defined and overlapping. Is an expression such as “*the other girls in class are talking about me*” a teenage phenomenon, a self-derogative thought or a paranoid delusion? Did the depressive symptoms appear before or after the patient started hearing voices? Youths often ignore or underrate their symptoms, making them difficult to place on a timeline.

Untreated, psychotic symptoms, which occur as a reaction to a psychological trauma or as part of a mood disorder may subside spontaneously over time or when the underlying disorder is treated. Other cases require psychosocial and/or psychopharmacological treatment. In EOS, psychotic schizophrenic symptoms are more persistent and may require long-term treatment to diminish their impact on daily functioning. Trajectories of symptom response and/or relapse are highly individual, although authors of a recent assessment of adult patients with psychosis have established that the longer duration of untreated psychosis predicts poorer outcome,²⁶ and in a two year follow-up study of early-onset FEP, clinical assessments could be used to predict functional outcome.²³

EOP and EOS are associated with a poorer prognosis than when symptoms emerge in adulthood.^{9,13,27} In a very recent 8-year follow-up study by Remberk *et al.* on 158 EOS patients from Warsaw, Poland (mean age at follow-up 24.5 ± 3.0 years),²⁸ authors found that 77.3% declared current psychiatric treatment and 68.0% received antipsychotic treatment. As many as 57.3% of the patients obtained a disability pension. These numbers – and the latter in particular – demonstrate how these disorders have a severe impact on the lives of young patients.

6.1.4 Etiology

As in Adult Onset Schizophrenia (AOS), EOS patients demonstrate cognitive and other neurodevelopmental abnormalities^{14,29} that point to a neurobiological substrate of schizophrenia. In a very rigorous NIMH study³⁰

aiming at investigating schizophrenia in its most homogeneous form, patients showing signs of childhood onset schizophrenia (COS, onset before the age of 13 years) were admitted to a psychiatric ward, tapered off all medications and observed by individually assigned staff members for 3 weeks. For almost 40%, COS was ruled out. For the children in whom the COS diagnosis was maintained, there was a high degree of premorbid impairments (55% had premorbid academic impairments, 50% had premorbid language impairments, 72% had premorbid social/behavioral impairments, 44% had premorbid motor impairments and 20% were screened positive for comorbid pervasive developmental disorder). Prospective longitudinal imaging studies show progressive gray matter cortical loss in patients with COS as compared to healthy controls.^{31,32} Taken together, the premorbid impairments and the deviating trajectories of brain development indicates that schizophrenia is a neurodevelopmental disorder, affecting the development of gray matter in the brain, which begins early in life, presumably prenatally.³

An overwhelming amount of research in many diverse fields converges to show that the etiology of schizophrenia spectrum disorders is multifactorial, including extremely complex genotype-phenotype combinations. As recently stated by Arnedo et al: "...schizophrenia comprises several distinct clinical syndromes associated with many disjoint genotypic networks."³³ There is continued support to the notion that schizophrenia is a neurodevelopmental disorder³⁴ which arises early in life, and this, combined with the differences in prognosis between EOS and AOS, emphasizes the connection between number of risk factors (genetic and environmental), age at onset and degree of severity. Even so, no anatomical or functional abnormality has been identified which is specific to schizophrenia, reflecting the complexity and heterogeneity both of the underlying mechanisms and symptom presentations.³

Although the validity of the current definition of schizophrenia may be uncertain, and the underlying etiology is still too complex to fully understand, it is still mandatory to be able to offer symptomatic treatment that can relieve the burden of suffering from psychosis. The primary focus of antipsychotic treatment is to diminish or eliminate the psychotic symptoms, not only in order to reduce illness severity, but also because a common perception of reality is required for other therapeutic approaches to work.

The dopamine hypothesis of schizophrenia emerged in the late 70s as antipsychotic drugs were found to change the dopamine metabolism.³⁵⁻³⁷ The dopamine hypothesis of schizophrenia, linking the development of schizophrenia to increased levels of dopamine in the brain, was modified by Davis et al. in 1991³⁸ and further refined in 2009³⁹ to reflect the vast number of developments in the field of neuroscience. Howes and Kapur, in their update on the dopamine hypothesis from 2009, links striatal dopamine elevation to the clinical feature of psychosis rather than to the diagnosis of schizophrenia. As Shitij Kapur stated in 2003 – "*Psychosis is a dopamine-mediated state of aberrant salience.*"^{40,41, a} While the antipsychotic action of antipsychotic medications is primarily mediated through blockade of dopamine D2 receptors, whereby this aberrant assignment of salience is attenuated, it is also hypothesized that this route of action attenuates the normal assignment of salience and thereby exacerbates pre-existing negative symptoms. Furthermore, it has been suggested that these agents cause a compensatory increase in the presynaptic dopamine synthesis, making treatment, dose regulation and discontinuation of antipsychotics even more challenging.⁴²

^a The term *salience* refers to a "high-order mental process that allows certain objects, mentally perceived or represented, to attract the spotlight, thus being incorporated into thoughts and behaviors."

6.1.5 Treatment options

The focus of treatment of psychotic disorders – in both adults and younger patients – is to improve the quality of life of affected individuals, i.e. diminishing both their psychosocial difficulties and the primary symptoms of their disorder. The psychotic symptoms may be primary (the main underlying mediator of the other symptoms) or secondary (occur as a consequence of other social or psychological problems), but most frequently it is a combination of both scenarios. For this reason, it is obvious that psychopharmacological treatment cannot stand alone, and successful treatment of these patients involves a wide variety of professions, e.g. social workers, psychologists, nurses, physicians, and physiotherapists. Psychosocial interventions, such as cognitive behavioural therapy, are frequently used in EOP, but there is inconclusive evidence regarding their efficacy.⁴³ Antipsychotic treatment unequivocally decreases the severity of the positive^{43,44} (and to some extent, but less unequivocally, also the negative⁴⁵) symptoms. The relief of symptoms most often facilitates the benefits of psychosocial interventions, leading to an overall improvement, making antipsychotic medications a cornerstone in the treatment of patients with psychotic disorders.

The first antipsychotic agent, chlorpromazine, was discovered in 1951^{46,47} and was originally introduced as a sedative, but was soon found to have direct effect on psychotic symptoms. Shortly after, a large number of antipsychotics were developed. A major disadvantage of these medications was their association with severe side effects, in particular neuromotor or “extrapyramidal” side effect (EPS) such as tremor, bradykinesia, involuntary movements, rigidity, chronic tardive dyskinesia and the feared and life-threatening malignant neuroleptic syndrome. As a group, the later emerging second-generation antipsychotics (SGAs) was thought to cause less motor side effects but, partly due to the wider receptor profile, they also caused more weight gain and metabolic disturbances.⁴⁸

Despite the wide range of adverse effects and highly variable effect of antipsychotics – the result of major differences across medications in receptor affinity, absorption, distribution and elimination – they remain the presently most effective available treatment for psychotic symptoms when non-pharmacological interventions fail to eliminate them.⁴⁹ The prescription rate of antipsychotics has increased steadily over the years, also in children and adolescents, and SGAs are often used off-label as the number of efficacy and tolerability studies in this age group is still low.⁵⁰⁻⁵³ Presently, a network meta-analysis of efficacy and safety of antipsychotic therapies in EOS is underway.⁵⁴ As many of these disorders are chronic or recurrent, young patients may face many years of pharmacological treatment. Nonetheless, knowledge regarding the long-term adverse effects of antipsychotics in EOP is very limited, and larger and more long-term studies are needed of antipsychotic treatment is needed.⁴³

6.2 Somatic health in patients with psychotic disorders

6.2.1 Morbidity and mortality in patients with psychotic disorders

The mortality rate in patients with schizophrenia is up to 20% higher than in the background population, their life expectancy being up to 16 to 18 years shorter.⁵⁵⁻⁵⁸ Although there are multiple explanations to this increased mortality (including increased prevalence of substance abuse and higher suicidality rates)⁵⁹, a major reason is an increased prevalence of cardiovascular disease (CVD).⁶⁰⁻⁶³ The background for the increased propensity towards developing CVD in this population is multi-factorial^{64,65} and stems both from genetic factors,⁶⁶ lifestyle factors (such as unhealthy diet and lack of exercise⁶⁷) and adverse effects from the pharmacological treatment of psychotic symptoms.⁶⁸ For this reason, the importance of weighing the beneficial effects of antipsychotic agents on psychotic symptoms (and, indeed, on quality of life) against their adverse effects, is unquestionable.

In the following, the two major risk factors involved in the increased mortality in schizophrenia due to diseases of the circulatory system are described: i) cardiometabolic changes and ii) arrhythmogenic effects.

6.2.2 Cardiovascular disease in schizophrenia

Obesity, in childhood as well as in adults, is associated with increased risk of developing type II diabetes mellitus (T2DM), dyslipidemia and hypertension, as well as a wide range of other disorders.⁶⁹ As obesity and associated diseases in childhood often persists into adulthood,⁷⁰⁻⁷³ it is an important marker of the later development of metabolic disorders and cardiovascular disease – i.e. disorders of the heart and blood vessels, including heart attacks, stroke and pulmonary embolism – and CVD is one of the leading causes of the excess mortality in adults with schizophrenia.

In a survey of 1,825 Australian patients with psychotic disorders aged 18-64 years (mean age 38.36 ± 11.15 years), three-quarters were overweight or obese and 82% had abdominal obesity. Almost half were hypertensive. Two-thirds were current smokers and 81% had a lifetime history of smoking. Levels of physical activity were very low. About 30% reported a diagnosis of hypertension or high cholesterol, 20% knew they had diabetes or elevated blood sugar and 18% had cardiovascular disease.⁷⁴ In the AusDiab population cohort of 11,247 adults from 42 districts in Australia, authors found prevalence rates for overweight or obesity at approximately 60% using either BMI or waist circumference as indicator.⁷⁵ In the same study, the prevalence of hypertension was 28.6%. The fraction of adult tobacco smokers in Australia is 24.8% (2005 estimate⁷⁶).

6.2.2.1 Metabolic syndrome

Metabolic Syndrome (MS) is a constellation of biomarkers which, when present, *“confers a 5–6-fold increase in the risk of developing type 2 diabetes mellitus and a 3–6-fold increase in the risk of death from coronary heart disease”*.⁷⁷ In a review by Paul Huang from 2009,⁷⁸ the four most commonly used definitions are described: The World Health Organization definition from 1998,⁷⁹ the European Group for the Study of Insulin Resistance definition from 1999,⁸⁰ the definition by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III from 2002,⁸¹ and finally the definition by the International Diabetes Foundation (IDF) from 2007.⁷⁰ All of the above require that at least three criteria are fulfilled but focus on different items; as such, the first two definitions require the presence of elevated insulin/insulin resistance, the NCEP definition requires that any three of five criteria are fulfilled, while the IDF criteria require that abdominal obesity is present. Furthermore, the cut-off values for waist circumference in the IDF definition are population-specific. For the purpose of the present PhD thesis, the IDF definition was chosen, as this definition is the most recently updated and has a separate set of criteria for children.

MS in both adults and children, as defined by the IDF, requires the presence of abdominal obesity plus two or more of the following: elevated blood pressure, elevated triglycerides, decreased high density lipoproteins (HDL), and elevated fasting plasma glucose (FPG, see Table 1).⁸² In a population-based survey in eight European countries, including 18,745 children aged 2.0 to 10.9 years, authors found that 0.4% fulfilled the IDF criteria for MS.⁸³ As is the case for obesity, MS is more prevalent in adult patients suffering from schizophrenia than in the background population. De Hert et al. examined the prevalence of MS in 430 patients with schizophrenia aged 36.5 ± 11.8 years. They found that the prevalence of MS was up to twice as high, while the prevalence of diabetes was three times higher than in the background population.⁸⁴ Furthermore, in a cross-sectional study of 367 adults (mean age 42.9 ± 15.3 years) treated with SGAs, Correll et al. found a frequency of MS of 37.3% using the NCEP criteria.⁸⁵

Even though the association between childhood obesity and diseases emerging in adulthood is more obscure, it is certain that childhood obesity is associated with adverse effects in different organ systems even in this

age group. For instance, in a study of 150 children (mean age 10.4 ± 3.1 years) referred to a pediatric clinic, Miniello et al. found that metabolic parameters were correlated to abnormal endothelial function, as measured by flow-mediated dilatation, carotid intima-media thickness and antero-posterior diameter of infra-renal abdominal aorta.⁸⁶

The IDF established criteria for diagnosing MS in children in order to “*expand on the IDF recommendations for managing type 2 diabetes in the young and to provide a useful and unified tool for identifying those at risk.*”⁷⁰ One of the obvious challenges in defining the cardiovascular risk in childhood is the variability of anthropometric measures (i.e. height, weight etc.) between age groups; for this reason, references need to be adjusted to percentiles for different age groups. Numerous studies address this issue by establishing age adjusted reference ranges for height, weight, waist circumference and BMI, and the IDF criteria for children enables the definition of MS based on ethnic-specific percentiles (Table 1). Recently, the Department of Growth and Reproduction at Rigshospitalet, Denmark, published updated growth charts for height, weight and BMI,⁸⁷ while a Norwegian study from 2011 described waist circumference data for children of 4 to 18 years of age.⁸⁸ These updated norms allow for precise evaluations of growth parameters in clinical populations.

Table 1: Definition of metabolic syndrome (MS) in children and adolescents by the IDF⁷⁰

Age group (years)	Obesity (WC)	Triglycerides	HDL	Blood pressure	Glucose
6 to <10	≥ 90th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.			
10 to <16	≥ 90th percentile or adult cut-off if lower	≥ 1.7 mmol/L (≥ 150 mg/dL)	< 1.03 mmol/L (< 40 mg/dL)	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM
≥ 16 (adult criteria)	WC ≥ 94 cm for Euroid males and ≥ 80cm for Euroid females, with ethnic-specific values for other groups	≥ 1.7 mmol/L (≥ 150 mg/dL) or specific treatment for high triglycerides	< 1.03 mmol/L (< 40 mg/dL) in males and < 1.29 mmol/L (< 50 mg/dL) in females, or specific treatment for low HDL	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM

BP: blood pressure; cm: centimeters; HDL, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; IDF, International Diabetes Federation; mg/dl: milligrams per deciliter; mmol/l: millimoles per liter; T2DM, type 2 diabetes mellitus; WC, waist circumference.

6.2.2.2 Insulin resistance

Insulin and glucagon – both secreted by the pancreas – are the main regulators of plasma glucose levels. After food consumption, blood glucose and triglyceride levels increase, stimulating insulin secretion and inhibiting glucagon secretion. Insulin stimulates the production of glycogen in the liver and the uptake of glucose in fat and muscle tissue, thus lowering the circulating plasma glucose level. A decreased sensitivity to insulin in these tissues is termed *insulin resistance* (IR) and is thought to be the main mechanism leading towards T2DM. In IR, the blood levels of both insulin and glucose is increased, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is a mathematical approach, which combines these measures to increase sensitivity of the evaluation of IR. While some studies encourage the use of HOMA-IR as marker for increased risk of developing T2DM,⁸⁹⁻⁹¹ a consensus meeting in 2010 stated that “... screening for insulin resistance is not justified in the clinical setting for children, including those with obesity. The mere presence of obesity should call for intervention to lower weight and consequently improve insulin sensitivity without a need to measure

insulin levels."⁹² For research purposes, however, the use of biomarkers as a measure of insulin sensitivity is required.

6.2.3 Factors related to increased risk of cardiovascular diseases in schizophrenia

6.2.3.1 Hereditary factors

Genetic variations associated with both schizophrenia and metabolic derangements have been the focus of intense research during the last decade. A recent review comparing association studies of genes implicated in the development of MS in patients with schizophrenia found evidence for several genetic variants associated with MS.⁹³

However, it has long been postulated that schizophrenia in itself is associated with an increased risk of developing diabetes.⁹⁴ In 2003, Ryan et al⁶⁶ presented a cross-sectional study of 26 drug-naïve, first-episode patients with schizophrenia (mean age 33.6 ± 13.5 years) who were matched to healthy controls by age, exercise, diet, smoking, body stature, ethnic background and alcohol intake, and neither patients nor controls had a history or family history of diabetes. They found that, compared to controls, patients had higher incidence of impaired glucose tolerance as well as higher levels of fasting blood glucose, insulin and cortisol.

In a study from 2009,⁹⁵ Verma et al. compared 160 drug-naïve, first-episode patients with schizophrenia to 200 age-, gender- and ethnicity-matched controls. They found that patients had lower BMI and lower levels of plasma cholesterol and LDL, but the prevalence of diabetes in patients was higher nonetheless.

These studies suggest that IR – and thereby increased susceptibility of MS and T2DM – may be a genetic trait in patients with schizophrenia. However, not all agree with these findings.⁹⁶ In a Canadian study by Sengupta et al. in 2008,⁹⁷ no differences in glucose or lipid metabolism were found between first-episode patients diagnosed with schizophrenia spectrum disorder and healthy controls (a significant difference in waist-hip-ratio was found, which is in concordance with previous studies⁹⁸). And in a Finnish birth cohort study of 5,410 adolescents,⁹⁹ no differences in cardiometabolic variables were found between subjects who later developed a psychotic disorder (first-time episode in the age range 16-20 years, n=21) to those who did not.

Finally, in a large cross-sectional population-based study, including 224,254 individuals from 52 countries, the presence of medical conditions, health problems, and access to healthcare was examined through questionnaires and compared between the following groups: Subjects with psychotic symptoms within the last 12 months and a lifetime diagnosis of psychosis, subjects with psychotic symptoms but no lifetime diagnosis, and subjects with neither psychotic symptoms nor diagnosis.¹⁰⁰ In this study, the presence of psychotic symptoms was associated with a significantly higher risk of hospitalization due to somatic disorders, having health problems or medical conditions, even in the absence of a psychotic diagnosis. However, as this was a cross-sectional study, the direction of causality could not be determined, but the study emphasizes that patients with psychotic symptoms are at higher risk of developing somatic disorders at a very early stage. Interestingly, the odds ratio (OR) for angina pectoris was second highest in both groups compared to subjects with neither psychotic symptoms nor diagnosis, surpassed only by tuberculosis. In a second study based on the same sample, authors showed an association between the number of psychotic symptoms and the risk of having diabetes (OR 1.27, confidence interval (CI) 1.24-1.30), independently of having a psychosis diagnosis.¹⁰¹

6.2.3.2 Lifestyle factors

Patients with schizophrenia are more prone to substance abuse, smoking, they exercise less and eat more unhealthy food than the background population,^{63,102} all substantial risk factors for CVD. Also, an increased level of stress is thought to be related to an increased activity in the hypothalamic-pituitary-adrenal axis,

leading to elevated levels of glucocorticoid hormones, which in turn leads to increased visceral fat and subsequently a higher risk of developing IR.¹⁰²

In 1999, Brown et al.¹⁰³ examined the lifestyle of 102 adult patients with chronic schizophrenia. Patients ate more fat and less fibers than the background population, although the difference was only significant in males. Exercise levels were generally low in the patient group. Smoking was 2-3 times more prevalent in patients than in the background population. Interestingly, obesity was not more prevalent in the patient group.

In the RICAVA study by Bernardo et al. in 2009¹⁰⁴, the cardiometabolic risk factors of 753 adult patients with schizophrenia were charted. In their sample, 71% were smokers, 66% had hypercholesterolemia, 17% had hypertension, 6% had hyperglycemia or diabetes, 27% had elevated triglycerides, 70% showed lack of exercise and 24% were either overweight or obese (i.e., BMI ≥ 25 kg/m²). Nineteen percent of patients had established MS.

Finally, in a population-based Danish cohort of 2,450,812 persons between 15 and 52 years of age, the prevalence of 18 out of 19 *a priori* selected somatic diseases was found to be increased in patients with schizophrenia or bipolar disorder, and chronic somatic diseases accounted for half of the excess mortality in these patients.¹⁰⁵

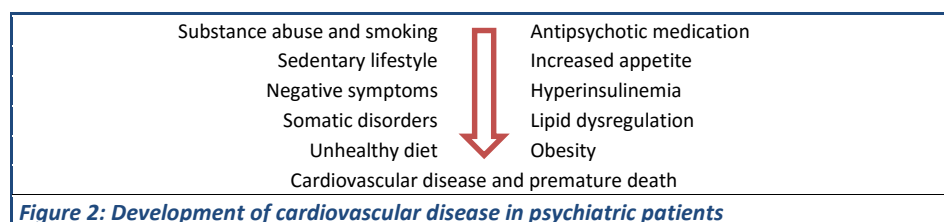
Of note, patients with mental illnesses are often insufficiently treated for their somatic disorders. Baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trials demonstrated rates of non-treatment from 30.2% for diabetes, to 62.4% for hypertension, and 88.0% for dyslipidemia.¹⁰⁶

Unfortunately, data on lifestyle habits (e.g. smoking, substance abuse and exercise pattern) in children and adolescents with mental disorders are close to none. Focus on this aspect in future research, providing detailed knowledge of lifestyle factors, could help tailor and improve treatment strategies, lowering the number of patients developing CVD.

6.3 The cardiometabolic harms of antipsychotics for treatment of psychosis in children and adolescents

6.3.1 Metabolic adverse events of antipsychotics

First-generation antipsychotics (FGAs) and especially SGAs increase the risk of developing MS, T2DM and CVD.^{68,107-114} Combined with the previously mentioned cardiac risk factors that these patients endure, patients suffering from psychotic disorders, who are treated with SGAs, are at serious risk of developing CVD (Figure 2).



Patients who present with psychotic symptoms at younger age have increased risk of developing side effects.¹¹⁵ It is important to acknowledge that these are patients often exposed to antipsychotic treatment for significantly longer time than if the condition is diagnosed later in life – and thereby an increased cumulative exposure of the adverse effects.

In a recent review by Leucht et al, comparing 15 FGAs and SGAs in a Bayesian-framework meta-analysis, across 212 trials and 43,049 patients treated for schizophrenia, authors found that, with the exception of haloperidol, ziprasidone, and lurasidone, all drugs produced more weight gain than placebo.⁴⁴ This effect has also been demonstrated in children and adolescents.¹¹⁶⁻¹¹⁹

In a cohort register study by Bobo et al.,¹²⁰ the risk of developing T2DM in youths (6-24 years of age) treated with antipsychotics was examined. In this study, patients with diagnoses that are typically treated with antipsychotics alone were excluded, and the control group consisted of psychiatric patients receiving other psychotropic drugs, matched based on a propensity score related to antipsychotic use and type II diabetes (including obesity). 28,858 antipsychotic users and 14,429 controls were included. In this study, antipsychotic drug users had a threefold increased risk of developing T2DM. The risk was already apparent after one year of treatment, and was significantly dose-related.

As part of the SATIETY cohort study, Correll et al.¹²¹ performed a prospective study on 338 antipsychotic-naïve patients aged 4 to 17 years assigned to mono-therapeutic treatment with aripiprazole, olanzapine, quetiapine or risperidone. At follow-up (after a median of 10.8 weeks of treatment), all four SGAs caused significant increase in weight, BMI, fat mass, and waist circumference, compared to the untreated control group. Olanzapine and quetiapine were significantly associated with increased plasma levels of cholesterol, non-HDL cholesterol and triglycerides. Olanzapine had largest effect on all glucose- and lipid-related metabolic parameters.

In a systematic review from 2011,¹²² Foley et al. found that the risk of developing CVD in drug-naïve, first episode adult patients with psychosis was not distinguishable from healthy controls, but the risk increased rapidly after introduction to antipsychotic medication. The authors state that the lack of rigorous monitoring for cardiometabolic risk is an *“important failure of care”*.

This tendency of antipsychotics to induce weight gain, leading to increased risk of somatic co-morbidity and early death, is an overwhelming challenge in the care of patients with psychotic disorders. It is of highest importance that the choice of medication is evidence-based and that the patients are monitored throughout their treatment period. Accordingly, a number of trials (such as the IMPACT trial¹²³) focus on attempting to diminish the cardiometabolic influence of antipsychotic drugs. It is essential that physicians and other caregivers are attentive to the many adverse effects of psychopharmacological treatment, and that they exert a continued effort to balance the effect on psychopathology with weight gain and metabolic changes.

6.3.1.1 Mechanisms of metabolic adverse effects to use of second-generation antipsychotics

The possible mechanisms underlying SGA-induced cardiovascular risk factors are numerous and incompletely understood, even though this has been the focus of intense research for decades. Metabolic effects during antipsychotic treatment appears to be associated with increased visceral fat, which is associated with IR, MS and CVD.¹²⁴ Overall, the pathways leading towards increased cardiovascular risk arise from various sites in the body, as receptors affected by antipsychotic drugs are present in various organ systems, and may be divided into i) SGA induced weight gain and ii) SGA induced IR. The regulation of satiety and food intake is the result of a complex interaction between orexigenic (appetite stimulating) and anorexigenic (appetite suppressing) factors. The most important orexigenic mediators include Ghrelin, Neuropeptide Y (NPY), Agouti-Related Peptide (AgRP), Orexin-A and Melanin-Concentrating Hormone (MCH). The anorexigenic mediators include Insulin, Leptin, Cholecystokinin (CCK), Glucagon-Like Peptide 1 (GLP-1), Peptide YY (PYY), Pro-Opiomelanocortin (POMC), Cocaine- and Amphetamine-Regulated Transcript (CART), Thyrotropin Releasing Hormone (TRH), Corticotropin Releasing Hormone (CRH) and Oxytocin.¹²⁵ Figure 3 describes the main peptides

and neurotransmitters involved in appetite regulation (as described in Steiner et al¹²⁵), while Table 2 summarizes key receptors involved in antipsychotic drug actions and their effect on metabolic changes induced by SGAs.

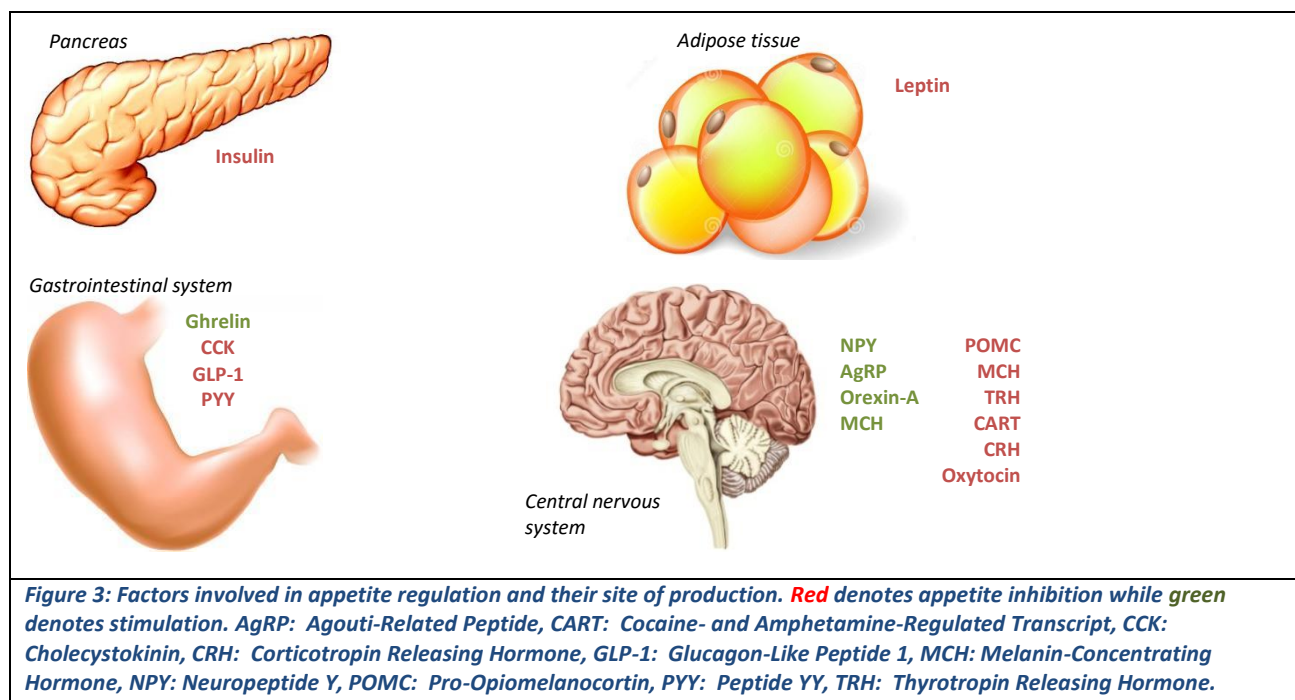


Table 2: Key receptors involved in metabolic SGA side effects.¹²⁶

Receptor	Side effect	Mechanism
Serotonin 5-HT 2C	Diabetes	Antagonists disrupt sympathetic regulation of peripheral glucose metabolism; also inhibit skeletal muscle and hepatic glucose uptake
	Weight gain	Antagonists disinhibit hypothalamic NPY neurons (resulting in elevated NPY) and inhibit POMC neurons (resulting in decreased α -MSH); may also play a role in leptin resistance
Serotonin 5-HT 1A	Diabetes	Antagonists inhibit skeletal muscle and hepatic glucose uptake and downregulate pancreatic β -cell sensitivity to glucose
	Weight gain	Agonists increase food intake; partial agonists may mitigate 5-HT _{2C} antagonism; partial agonists may also decrease carbohydrate craving
Histamine H1	Weight gain	Antagonists cause increased hypothalamic AMPK activity, mimicking depletion of cellular energy stores and causing increased appetite
	Diabetes	Antagonists disrupt sympathetic regulation of adipose tissue
	Sedation	Antagonists inhibit cholinergic neurons of basal forebrain and serotonergic neurons of dorsal raphe
Dopamine D2	Weight gain	Antagonists cause overall decrease in limbic dopaminergic activity, possibly leading to increased engagement reward-seeking behaviors such as food intake; agonists (psychostimulants, cocaine) are appetite suppressants
	Extrapyramidal side effects	Antagonists disinhibit indirect descending motor pathway in basal ganglia
	Endocrine effects	Antagonists disinhibit prolactin release from posterior hypothalamus, also contributing to weight gain
Muscarinic M1	Anticholinergic effects	Antagonists cause dry mouth, urinary retention, cognitive dysfunction, urinary retention, and constipation
Muscarinic M3	Diabetes	Antagonists cause impaired glucose tolerance and reduced insulin secretion from pancreatic β cells

α -MSH, α -melanocyte-stimulating hormone; AMPK, AMP-related kinase; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

6.3.1.2 Serotonin receptor blockade

Blocking of the 5-HT_{2A} receptor results in hyperphagia through an increase in the orexigenic neuropeptide Y¹²⁷. Studies indicate that inhibition of 5-HT_{2A} activity attenuates insulin sensitivity, affecting the risk of developing

insulin resistance. Both satiety and food intake are related to the 5-HT_{2C} receptor,^{126,128} and receptor mutations in mice have been associated to hyperglycemia, hyperinsulinemia and hyperleptinemia.¹²⁹

6.3.1.3 Dopamine receptor blockade

The dopamine receptors (particularly the D2 receptor, which is the *sine qua non* of antipsychotic drug effect) have been shown to be involved in SGA-associated weight gain through increased appetite and food intake,^{128,130} but presumably also through an increase in plasma-prolactin.¹³¹ Finally, inhibition of the D2 receptor function is also associated with disruption of the reward system, which may lead to a diminished inhibition of food intake.¹³¹

6.3.1.4 Histamine H₁ receptor blockade

Of the four subtypes of histamine receptors, H₁ is most closely related to feeding. Histaminergic neurons emanating from the tuberomammillary body project to various brain regions, including the hypothalamus, and increases in histamine signaling here leads to reductions in food intake and weight.¹³² Therefore, antipsychotic blockade of H₁ leads to increased appetite and weight gain.

6.3.1.5 Insulin resistance

While it is obvious that weight increase and obesity will lead to insulin resistance and diabetes over time, there are reports of a more direct antipsychotic-induced glucose intolerance and diabetes also in the absence of obesity.¹³¹ These findings suggest that there is also a more direct mechanism by which antipsychotics induce insulin resistance. One of these suggested mechanisms is through blockade of the muscarinic M₃ receptor in the pancreas. The M₃ receptor is involved in maintaining glucose homeostasis and beta-cell insulin secretion. As antipsychotics with high affinity for this receptor carry a high risk of diabetic side-effects, it seems possible that blockade of the M₃ receptor is an underlying mechanism for the occurrence of insulin resistance and diabetes during antipsychotic treatment.¹³³

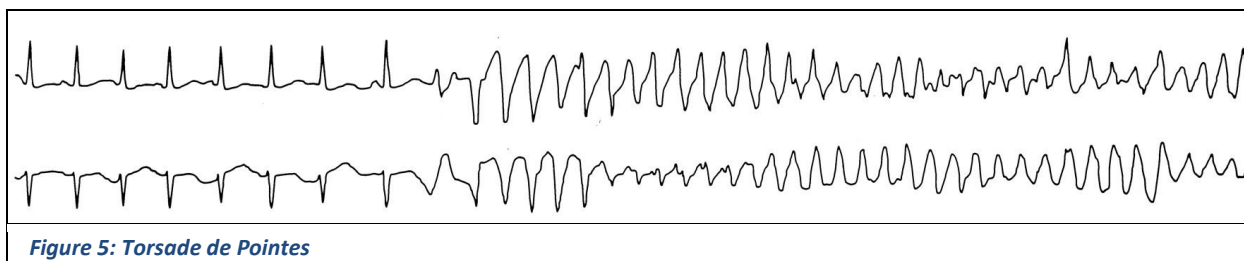
6.3.1.6 Decreased resting energy expenditure

The term Resting Energy Expenditure (REE) refers to the amount of energy that the body uses while inactive. This amounts to 68-80% of the body's energy expenditure¹²⁴, and is related to various factors including fat-free mass (FFM). In a study of 61 antipsychotic-naïve patients initializing treatment with risperidone, olanzapine or quetiapine and followed for one year the mean body weight increased. Although REE remained constant, REE/FFM ratio increased due to decreased FFM, suggesting that patients became hypometabolic during treatment¹²⁴. However, results from various trials are conflicting. In a review of 14 studies of subjects taking SGA, some studies reported decreased REE during treatment while other reported no change. As such, it is not yet possible to determine if decreased REE is a result from or a cause of weight gain.¹³⁴ In a study of REE differences between healthy controls versus patients with schizophrenia – of whom 11 were antipsychotic-naïve – authors found a decreased REE in patients, regardless of antipsychotic treatment.¹³⁵

6.3.2 Cardiac adverse effects of antipsychotics

Antipsychotic treatment may have more direct effects on the cardiovascular system. Common adverse effects include tachycardia and postural hypotension, presumably caused by alterations in the autonomic nervous system through blockade of the adrenergic and cholinergic receptors and increased sympathetic activity.^{136,137} Another factor increasing the risk of cardiac death in patients receiving antipsychotic treatment is delayed repolarization of the muscle fibers in the heart. This is seen in the electrocardiogram (ECG) as a prolongation of the QT interval, a feature shared by the effect of drugs from several pharmacological groups. QT

prolongation can lead to the life-threatening condition Torsade de Pointes (TdP), a malignant ventricular tachyarrhythmia where the normal impulse propagation in the heart is replaced by oscillating ventricular fibrillations. On the ECG, this condition is characterized by ventricular tachycardia appearing in a “party-streamer” like pattern, where the wave amplitude oscillates (see Figure 5). This condition may be self-limiting, but can also lead to sudden death within minutes if not recognized and treated.



Many factors may affect the cardiac impulse propagation – somatic conditions, concomitant medications, structural alterations of the heart, and medications. Therefore, the risk of developing clinically significant QTc prolongation during treatment with antipsychotics, as well as the risk that prolongation will induce TdP, increases with age and disease duration.

6.3.2.1 The QT interval

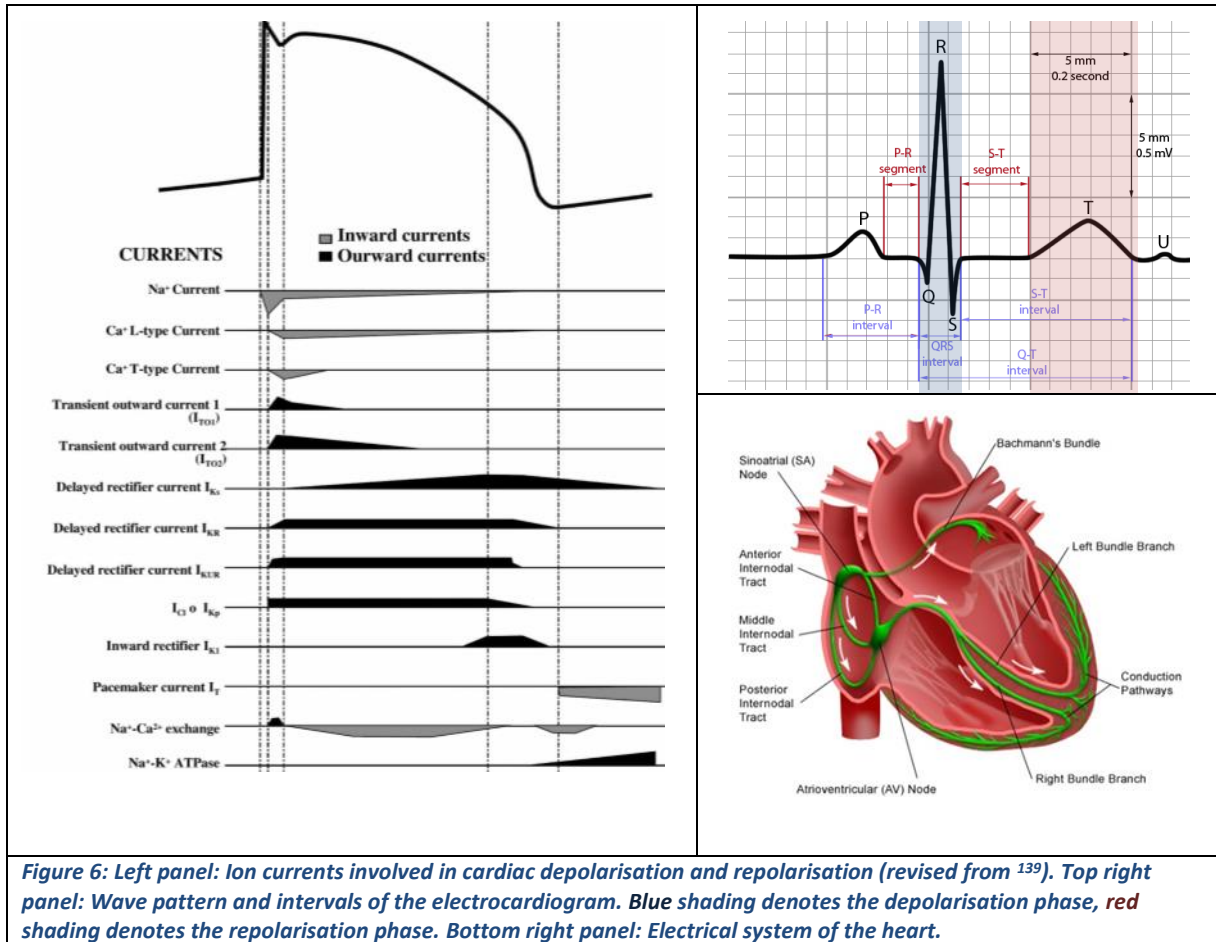
The characteristic normal pattern of the ECG (Figure 6, top right panel) is the result of a variety of ion currents moving through the myocardium. Figure 6, left panel depicts a number of the ion currents responsible for the cardiac action potential (AP). While most of the upward stroke of the AP is caused by the sodium current, the repolarization phase is the result of a complex interplay of various ion currents. The principal role of the repolarization, however, is played by the potassium currents, mediated by various potassium channels.¹³⁸

The depolarization begins in the sinoatrial node and spreads rapidly through the atria, before it reaches the atrioventricular node. The impulse then propagates through the bundle of His and continues down through the left and right bundle branch; the Purkinje fibers and finally spreads through the ventricle walls (see Figure 6, bottom right panel).

Each electrode in the electrocardiograph registers the vector sum of the ion currents between the heart and itself, so that all the leads in combination describe the various amplitudes and directions of electrochemical currents taking place in the heart. The major “waves” on the ECG – denoted P, Q, R, S and T (see Figure 6, top left panel) – represent the re- or depolarization of larger structures. The P-wave represents the depolarization of the atria, the QRS complex represents the depolarization of the ventricles, and the T wave represents the repolarization of the entire myocardium. The QT interval represents the time from the beginning of the depolarization of the myocardium until the entire myocardium has been repolarized – this is also known as the refractory period; myocytes that are not repolarized cannot be triggered by a new impulse.

6.3.2.2 Heart rate correction

At higher heart rates, the repolarization phase (and thus the refractory period) needs to be shorter, allowing for quicker repolarization of the myocardium, so the QT interval shortens at higher heart rates. Thus, in order to compare the QT interval, one must correct for the heart rate, and the resulting corrected QT interval is called the *QTc interval*. The QTc interval is a construct that describes the duration of the repolarization of the myocardium, given that the heart rate is 60 beats per minute.



Various formulae have been constructed to achieve this, the first was coined by H.C. Bazett in 1920 in the paper "An analysis of the time-relations of electrocardiograms"¹⁴⁰ and this formula is suitably known as the Bazett formula: $QTcB = \frac{QT}{\sqrt{RR}}$, RR being the interval between two R waves. However, it soon became clear that this formula is not very precise but tends to over-estimate the QTc at higher heart rates, and a large number of correction formulae emerged, one of these was the Fridericia formula $QTcF = \frac{QT}{\sqrt[3]{RR}}$, which also was published in 1920.¹⁴¹ This latter formula is generally considered more accurate; nevertheless, the Bazett formula is by far the most used and known.

The reason for the difficulty in establishing a single formula for QT correction is that the *relation* between the QT and the RR intervals differs substantially between individuals.¹⁴² In a meta-analysis of pre-treatment ECG data from seven clinical trials for attention deficit/hyperactivity disorder (ADHD), involving 2,288 children from 6 to 17 years (mean 10.8 ± 2.6 years)¹⁴³, the most accurate correction formula was $QTcH = \frac{QT}{RR^{0.38}}$. This was also the conclusion made by Hodges in 1997¹⁴⁴ and Malik in 1996.¹⁴⁵

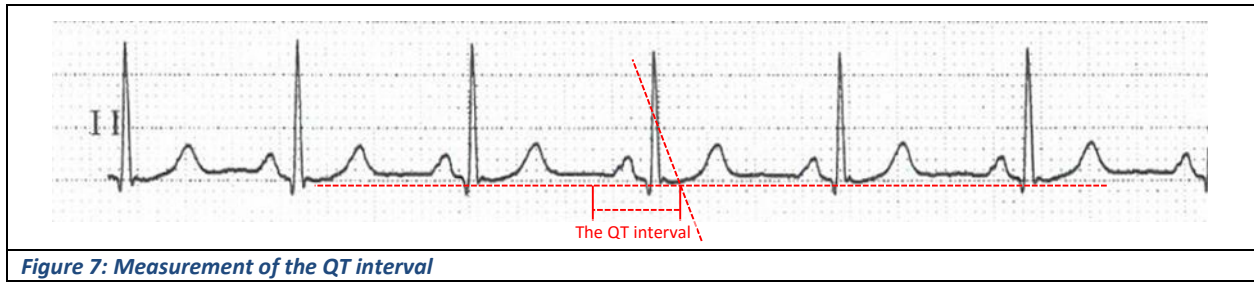


Figure 7: Measurement of the QT interval

6.3.2.3 Measurement of the QT interval

Measurement of the QT interval on the ECG is shown in Figure 7. The QT interval begins at either the first downstroke of the Q-wave or, if the Q wave is absent, the beginning of the upstroke of the R-wave. The end of the T-wave is defined as where the steepest downward tangent to the T wave intersects with the isoelectric line. The latter line represents the resting potential of the myocardium, and is drawn between the PQ (or PR) segment of two adjacent complexes. To get the optimal result, QT interval should be averaged over three to five complexes.¹⁴⁶ The QT interval may be measured in whichever lead where the Q- and T-waves are most discernable, this is usually lead II or V5. The length of the QT interval may differ across different leads, because the entire myocardium does not repolarize instantaneously – different parts of the myocardium will repolarize at different time points. This phenomenon, which is called *QT dispersion*, has in some studies been shown to correlate with the risk of TdP (i.e. that a higher dispersion = larger variability in QTc as measured by different electrodes is associated with a higher risk of TdP), although the usefulness of this parameter is still debated.¹⁴⁷

Further, it has been shown that there is a lag in the adaption of the QT interval to changed heart rate – if QT is measured both at exercise and shortly after stopping the exercise, the QT interval is different even for two complexes with equal RR intervals.¹⁴⁴ This phenomenon is termed *heart rate hysteresis*, and for this reason, it is clear that an ECG must be obtained after a resting period in supine position of at least 3 minutes. Also, the heart rate noted on the output from the ECG machine should be used, rather than entering the RR interval into the formula. This is also the method suggested by Nielsen et al. (2011),¹⁴⁶ in which the authors state that “Studies suggest that it takes up to 3 minutes for the QT interval to completely adapt to a new heart rate, with significant inter-individual variation”. The corresponding correction formula is then $QTc = \frac{\overline{QT}}{(60/HR)^\alpha}$, where α is 0.50 for Bazett, 0.33 for Fridericia and 0.38 for Hodges.

In clinical settings, the Fridericia formula will suffice for QTc evaluation during antipsychotic treatment, but the Bazett formula should be avoided.¹⁴⁸ For research purposes, more refined methods should be used: The QT interval should be averaged across several complexes and across several leads, and results from different formulae should be presented, including, if possible, individually derived correction formulae.

Measurement of the QT interval is subject to a high degree of inter- and intrarater variability, in particular when the ECG printout is dominated by background noise, which can challenge proper identification of the Q and T waves.¹⁴⁹

6.3.3 QTc prolongation and Torsade de Pointes

Long QT Syndrome, or LQTS, is the term for a condition in which the QTc interval is longer than the “normal” duration with or without clinical implications. There are various suggested cut-off values for the “normal” QTc duration in the literature. In their pediatric guidelines from 2004, Blair et al. suggested that in children, clinicians should pay particular attention to a QTc interval >450 msec,¹⁴⁹ after puberty, however, the average

QTc interval in men is up to 20 ms shorter than that in females, probably due to the QT shortening effect of testosterone.¹⁵⁰ Women are also more sensitive to the QTc prolonging effects of medications blocking the IKr current,¹⁵¹ which is why female gender is noted as a risk factor – subsequently, this probably is not relevant in prepubertal children. A large number of genetic variations have been associated with LQTS,¹⁵² which is then termed *congenital LQTS*, which in some cases is only latent, i.e. the QTc interval is normal until the patient is subject to other risk factors, for instance pharmacotherapy. Alternatively, the LQTS may be *acquired*, meaning that QTc prolongation occurs as a result of exogenous factors. The combination of genetic abnormalities and exogenous factors increase the risk of developing clinically relevant QTc prolongation.

A large number of conditions may affect the QTc interval, such as electrolyte disturbances, interactions related to polypharmacy and structural heart diseases.¹⁵³ CVD, a very common long-term comorbidity in patients with psychotic disorders,^{58,70,154-162} is an important risk factor for QTc prolongation and TdP.^{163,164} A large number of pharmaceutical agents can also affect the QT interval, causing drug induced QT prolongation, hereunder various antibiotics, anti-convulsants, antiarrhythmics and antipsychotics (a comprehensive and updated list can be found at www.qtdrugs.com). The realization that medications can induce QTc prolongation has led to the development and implementation of so-called *thorough QT/QTc* studies, which are conducted in healthy individuals under standardized settings, in order to identify new drugs which prolong the QTc interval by 10 ms or more.¹⁶⁵ The mechanism for drug-induced QT prolongation is that the offending drug interferes with an ion channel involved in the repolarization of the myocytes, most commonly the ion channel Kv7.1, coded by the human ether-a-go-go (hERG) gene^b, and often, this channel is simply referred to as the hERG channel.¹⁶⁶ Agents such as ziprasidone, which is known as a potent inducer of QTc prolongation, binds to the Kv7.1 channel and blocks the potassium current (IKr, see figure 6, left panel). Interestingly, the sympathetic hyperactivity associated with antipsychotic use has also been associated with the development of arrhythmias and QTc prolongation.¹³⁶

A delay in the repolarization will result in prolongation of the QT interval. A brief delay normally does not cause problems, but if a new impulse reaches the ventricles through the bundle of His before the myocardium is fully repolarized, some parts of the myocardium may depolarize again (e.g. initiate a new contraction), while other parts of the myocardium are still in the refractory period. The impulse will then continue to oscillate between repolarized and depolarized parts of the myocardium. As this action does not result in contractions, the blood flow is effectively stopped and death ensues, unless normal impulse propagation is restored – either spontaneously or through defibrillation. As such, the QTc interval is best visualized as a *constructed indication of the propensity towards developing Torsade de Pointes*.¹⁶³

Increased risk of developing TdP has been established for a number of antipsychotic agents, including haloperidole, sertindole and thioridazine,¹⁶⁷ and almost all pharmacological agents known to cause TdP block the Kv7.1 channel.¹⁶⁸ As the risk of sudden death increases with age, the risk of specific antipsychotic agents should be seen in the backdrop of the incidence in the general population, which ranges from 2-3 per 100.000 person-years in children and young adults to 179 per 100.000 in persons aged 30-74 years.¹⁶⁹ Thus, a relative increase in the risk of sudden death may have little significance in otherwise healthy patients but may dramatically increase the absolute risk in at-risk patients. The risk of sudden death associated with antipsychotic agents was investigated in a meta-analysis of observational studies.¹⁷⁰ Authors found an OR

^b The hERG gene is the human homolog of the Ether-à-go-go gene found in the *Drosophila* fly. The gene was named in the 1960s by William D. Kaplan, now at the City of Hope Hospital in Duarte, California. When flies with mutations in the Ether-à-go-go gene are anaesthetised with ether, their legs start to shake, like the dancing then popular at the Whisky A Go-Go nightclub in West Hollywood, California (Wikipedia, November 13 2014)

ranging from 0.06 (95% CI: 0.00–6.00) (flupheniazin) to 9.40 (95% CI: 0.21–420.75) (flupentixol). This being said, the relationship between QTc and TdP is “neither linear nor straightforward.”¹⁷¹ Patients may develop TdP despite normal QTc duration, while others may have QTc interval exceeding 550 ms and never develop TdP. This, combined with the many factors affecting the reliability of QTc measurement, underlines that the clinical evaluation of a patients’ risk of developing cardiac events should take all risk factors into account and not only rely on the QTc.

In 2000, the term *short QT syndrome* (SQTS) emerged in the literature and has been a subject of increasing attention. As in LQTS, congenital SQTS can be associated with a variety of genetic variations and SQTS may also arise as an adverse effect to pharmacological treatment.¹⁷² The author of the referenced review states that, based on available data, “360 ms is probably a reasonable value for the lower limit of normal QTcF interval.” SQTS may also be pro-arrhythmogenic and in a two-year follow-up study of 6693 patients, the relative risk of sudden death was elevated not only in patients with a QTcB $\geq$ 440 ms, but also in patients with QTcB $<$ 400 ms.¹⁷³ As aripiprazole has in fact been associated with shortening of the QTc interval,¹⁷⁴ it seems plausible that aripiprazole should be used with caution in patients with congenital SQTS.

6.3.3.1 Managing the QTc interval in psychotic patients

Before initiating antipsychotic treatment in young patients, it is important to establish if the patient is at increased risk of developing prolongation of the QTc interval. As there are many factors, which may increase this risk, the following factors (with non-exhaustive suggestions in *italic*) should always be considered:

- Genetic risk factors: *Are there any family members with known QTc prolongation or known cardiac rhythm disturbances? Are there any cases of sudden death or drowning in the family?*
- Cardiac risk factors: *Does the patient have any structural heart disease, such as atrial or ventricular hypertrophy or cardiomyopathy? Is the QTc interval prolonged ($\geq$ 450 msec) or shortened ($<$ 360 ms) a priori?*
- Metabolic risk factors: *Is the patient clinically obese? Does the patient suffer from electrolyte derangement (as may be seen in anorexia nervosa)?*
- Clinical risk factors: *Does the patient occasionally suffer from loss of consciousness (particularly during exercise), palpitations or shortness of breath?*
- Co-medications: *Is the patient under treatment with any arrhythmogenic medications?*

The existence of one or several risk factors does not, by itself, exclude the patient from antipsychotic treatment, but may indicate that a more thorough examination of the patients’ cardiometabolic status, and/or co-operation with a specialist in pediatric cardiology, is required.

6.4 Summary

Both clinicians, parents and caregivers have the desire to alleviate the debilitating symptoms present during a psychotic episode in a child or adolescent. A plethora of clinical trials has shown that antipsychotics can help achieve this goal, but the use of these pharmacological agents may impose a serious threat to the patients’ cardiovascular health, especially in the long term. How this risk affects youths is under continuous scrutiny, yet much is still to be learned. Furthermore, there are very few studies comparing antipsychotics with regard to the effect on the QTc interval in this patient group. This information generally receives little focus in clinical trials, and is often summarized in a single sentence.

Based on trials primarily in adults, health authorities lay down guidelines to ensure a high probability that the benefits outweigh the risks, but extrapolating from adults is insufficient, and there is an urgent need for large-

scale, randomized and blinded head-to-head trials to ensure that the highest quality of antipsychotic treatment in children and adolescents with psychosis is achieved.

7 Objectives of the present Ph.D. study

The increased risk of developing cardiac arrhythmias and metabolic disturbances associated with antipsychotic treatment has been thoroughly demonstrated in numerous adults studies, reviews and meta-analyses. Studies show that the risk of cardiometabolic adverse effects varies between drugs and appears associated with the varying receptor affinity profiles. Unfortunately, the current knowledge of cardiac and metabolic adverse effects of antipsychotics in children and adolescents is limited. It has been found that children and adolescents generally tend to be inflicted by adverse reactions to antipsychotics to a larger degree than adults. Furthermore, patients with psychotic disorders, such as schizophrenia, carry an increased risk of cardiometabolic morbidity and mortality. Many children and adolescents with psychosis will, due to their early onset and poor prognosis, need antipsychotic treatment for several years, either continuously or intermittently. In addition, the metabolic effects tend to accumulate over time and it has been shown that metabolic disturbances in childhood carry over into adulthood. Finally, the risk of arrhythmias may increase over time as underlying heart diseases and polypharmacy may occur with increasing age. Therefore, there is a need for careful evaluation of the risk of cardiometabolic effects associated with different antipsychotic drugs in children and adolescents, already from the initiation of such interventions.

The overall objective of the present Ph.D. study is thus to extend the existing evidence base concerning cardiometabolic adverse effects of antipsychotic treatment in children and adolescents with psychosis, drawing on data from a state-of-the-art RCT comparing quetiapine ER and aripiprazole, and by reviewing the existing literature on antipsychotic-induced QTc prolongation, meta-analyzing data from relevant trials.

The main *hypotheses* are:

- 1) That the effect on QTc varies significantly between antipsychotic agents, e.g. that the majority of antipsychotics, when used in children and adolescents, demonstrate little effect on the QTc while ziprasidone may cause clinically significant QTc prolongation.
- 2) That children and adolescents with psychotic disorders have increased occurrence of metabolic disturbances compared to healthy controls, already before treatment with antipsychotics is initiated.
- 3) That quetiapine ER causes significantly more weight gain and increased markers of metabolic syndrome than does aripiprazole in children and adolescents with psychosis.
- 4) That quetiapine ER causes significant QTc prolongation in children and adolescents with psychosis, while aripiprazole does not.

8 Methods of the present Ph.D. study

8.1 Paper 1 – Corrected QT Changes During Antipsychotic Treatment of Children and Adolescents: A Systematic Review and Meta-Analysis of Clinical Trials

8.1.1 Inclusion and Exclusion Criteria for Literature Search

Trials fulfilling the following characteristics were included: prospective study, randomized or not, with or without a comparator; patients aged <18 years; any antipsychotic treatment; treatment indication was a psychiatric condition; and numerical QTc change data. Primary outcome was change in QTc interval from baseline to last follow-up. Secondary outcomes were events of study-defined QTc prolongation (440–470 milliseconds), events of QTc >500 milliseconds, and events of prolongation >60 milliseconds. Studies were identified by searching the electronic database PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) from database inception. The search was performed on May 14, 2014.

8.1.2 Search Strategy

Search terms were as follows: (child OR children OR childhood OR adolescent OR adolescence OR youth); and (antipsychotic* OR neuroleptic* OR amisulpride OR aripiprazole OR asenapine OR blonanserin OR chlorpromazine OR clothiapine OR clozapine OR droperidol OR flupenthixol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR mesoridazine OR molindone OR mosapramine OR olanzapine OR paliperidone OR perphenazine OR perospirone OR pimozide OR prochlorperazine OR remoxipride OR risperidone OR sertindole OR sulpiride OR thioridazine OR thiothixene OR tiapride OR trifluoperazine OR quetiapine OR ziprasidone OR zuclopenthixol). The resulting papers were filtered by “English language” and “Abstract available.” The asterisk after “antipsychotic” and “neuroleptic” served to produce all iterations of the search term.

8.1.3 Study Selection

Records that could be excluded at the title and abstract level were discarded. Papers that were not available online were requested through the library service at the University of Copenhagen. In papers mentioning that ECG was performed at baseline and follow-up but QTc values or QTc changes were not reported, these data were requested from the authors by e-mail.

8.1.4 Statistics

Demographic population, illness, and treatment data were analyzed using descriptive statistics. QTc data were entered into and meta-analyzed using Comprehensive Meta-Analysis Version 3.0 (<http://www.meta-analysis.com/>), Biostat, Englewood, USA. To pool and compare change in QTc from baseline to last assessment across treatment groups, weighted mean difference (WMD) 95% CI was used. For comparison across categorical outcomes, odds ratios (ORs) with 95% CIs were used. Categorical outcomes included number of patients with the following: study defined QTc prolongation (i.e., >440, >450, >460, >470 milliseconds); QTc >500 milliseconds; and QTc change from baseline to last assessment >60 milliseconds. We performed analyses using 2 different sets of studies: single group analyses of all available study arms with a given treatment arm, namely, specific antipsychotic or placebo; and pairwise analyses of antipsychotic–placebo comparisons in placebo-controlled trials. There were too few active controlled trials to run antipsychotic versus antipsychotic treatment analyses. In the study arm–based data set, all outcomes were compared both within treatment group and comparing individually pooled antipsychotic groups against the pooled placebo arms. In addition,

exploratory meta-regression analyses were performed, assessing the following moderator variables: study duration, mean age, percentage of females, and medication dose. Heterogeneity of outcomes was studied using the I^2 statistic, with $I^2 \geq 50\%$ indicating significant heterogeneity, as well as the X^2 test for heterogeneity. All tests used random effects models and were 2-sided, and α was set at 0.05. We used funnel graphs (trial effect against trial size) to investigate the likelihood of publication bias.

8.1.5 Risk of bias

Risk of bias was assessed for each trial using the methods outlined in the Cochrane Handbook.¹⁷⁵

8.2 Paper 2-4 – Baseline metabolic characteristics from the TEA trial and cardiac and metabolic outcomes from the 12 week intervention period

8.2.1 Study design

The present Ph.D. study is part of the TEA trial (Tolerability and Efficacy of Antipsychotics), a 12-week, investigator-initiated, randomized, double-blinded multicenter trial of aripiprazole and quetiapine in psychotic children and adolescents (aged 12-17 years). The primary outcome was change in the Positive and Negative Syndrome Scale (PANSS) positive score, and the four key adverse outcomes were weight change, insulin resistance, akathisia, and sedation. The present Ph.D. study focuses on a detailed analysis of cardiometabolic changes and QTc changes in enrolled subjects during the intervention period. The trial, which has been approved by the Danish National Committee on Health Research Ethics, was commenced in May 2010 and inclusion of patients ended on 1st of February 2014. Nine child and adolescence psychiatric centers across Denmark, representing all four university clinics, participated in the trial. In the following, a brief outline of the design and methods is presented; a detailed protocol for the TEA trial has been published.¹⁷⁶ The same three investigators assessed all patients in the three major sites and repeatedly instructed and supervised personnel on the remaining sites. Whenever possible, each patient would be examined by the same investigator throughout the participation.

A comprehensive manual, describing the procedures and details regarding conduction of the trial, was used by the assessors, and all registered information was noted in each participants' case report form (CRF).

8.2.2 Subjects

Physicians at the University Hospital clinics referred youth who were deemed potentially eligible for the trial, i.e., who suffered from psychotic symptoms to a degree where antipsychotic treatment was warranted. Inclusion criteria were: 1) Children and adolescents aged 12-17 years, both sexes; 2) in- or outpatients; 3) meeting the criteria for ICD-10 F20 (Schizophrenia), F22 (Persistent delusional disorders), F23 (Acute and transient psychotic disorders), F24 (Induced delusional disorders), F25 (Schizoaffective disorders), F28/F29 (Other/Unspecified nonorganic psychosis), F30.2 (Mania with psychotic symptoms), F31.2 (Bipolar affective disorder, current episode manic with psychotic symptoms), F31.5 (Bipolar affective disorder, current episode severe depression with psychotic symptoms), F32.3 (Severe depressive episode with psychotic symptoms), or F33.3 (Recurrent depressive episode, current episode severe with psychotic symptom); 4) clinical indication for antipsychotic treatment; 5) presence of psychotic symptoms scoring ≥ 4 on ≥ 1 of the following Positive And Negative Syndrome Scale (PANSS)¹⁷⁷ items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content); as well as a total PANSS score >60 points; 6) antipsychotic-naïve or limited exposure (i.e., not exceeding the past 12 months for psychosis, or no more than 1 week lifetime for any non-psychotic indication), and 7) written and signed

informed consent by caregivers (and assent from patients) Exclusion criteria included: 1) Compulsory treatment; 2) drug-induced or organic psychosis; 3) severe chronic somatic illness or a history of severe head trauma; 4) pregnancy or lactation; 5) substance dependence (ICD-10 F1X.2 dependence syndrome) within the last year; 6) allergy towards the investigational drugs or known lactose intolerance; 7) lack of informed consent/assent. At week 4, participants and their parents underwent a Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL)¹⁷⁸ interview to establish their final diagnosis. Screening involved physical examination, blood samples, ECGs and urine samples. Furthermore, patients were interviewed using the PANSS. To participate in the TEA trial, a total score of 61 or above on PANSS, as well as a score of 4 or more on either of the “positive” symptoms was required. If they fulfilled the inclusion criteria and if written consent could be obtained from their parents, they were included into the trial.

The control sample consisted of 60 psychiatrically and somatic healthy youths (as per screening with K-SADS-PL (both subjects and parents) and standard somatic history and examination at study entry), who were recruited based on a random data extraction from the Danish Centralized Civil Register. Controls were matched 1:2 to the enrolled patients on sex, age and parental education (parents were interviewed regarding level of education, and their answers were rated on a 3-item scale, e.g., high, medium or low level of education).

8.2.3 Trial medication

Included patients were randomized to treatment with either aripiprazole or quetiapine ER. By default, patients followed a standardized titration schedule (as an exception, titration could be modified individually if, for instance, a previous exposure to antipsychotics had resulted in significant side effects). During the treatment period, the dosage could be up- or down-titrated to optimize effect and minimize side effects. The intervention period was 12 weeks; however, patients could withdraw from the study at any time if symptoms persisted in severity or aggravated during treatment, or if side effects could not be quelled by dose adjustment or side effect medications (such as orphenadrin or biperiden for parkinsonistic adverse events).

8.2.4 Concomitant medications

During the intervention period, the use of antipsychotic drugs was not allowed. If a subject experienced serious clinical symptoms to a degree where the treating physician found need for the use of *pro re nata* antipsychotic treatment, this was registered as a protocol violation. All other concomitant medications were allowed as long as the underlying condition was not a reason for exclusion. All co-medications were registered in the patient's CRF during the entire observation period.

8.2.5 Blinding procedures

Randomization was performed at the Copenhagen Clinical Trial Unit (CTU). The Capital Region Pharmacy delivered blinded capsules containing either aripiprazole or quetiapine ER for each treatment level. The randomization was stratified for age (< or ≥15 years) and symptom severity (PANNS positive score < or ≥20). Both patients and caregivers, clinical physicians and trial investigators were blinded to the treatment allocation. When the double-blinded treatment ended, the treating physicians in the clinics were contacted directly by the CTU who informed them to which treatment arm the patient had been allocated. This was done for the purpose of being able to provide the best possible continued treatment in the individual patient. The trial investigators were not informed about the results of the individual unblinding. Furthermore, in every case

it was insured that all assessment data were entered in the CRF before the individual unblinding took place in order to reduce bias.

8.2.6 Assessments

Upon inclusion, and before starting trial medications, patients underwent a comprehensive examination program. Patients were re-examined after 2, 4 and 12 weeks (see table 3). 52 weeks after inclusion, a naturalistic follow-up examination was performed (these data are not reported in the present thesis or papers).

Table 3: TEA RCT, schedule for outcome assessments during 12 weeks of blinded intervention

Assessments	Inclusion (week 0)	Follow-up (week 2)	Follow-up (week 4)	Follow-up (week 12)
Psychopathology and adverse reactions rating scales PANSS, DIPI, CGI-S, CGI-I, CGI-E, GAPD, UKU, AIMS, SAS, and BARS	X	X	X	X
Suicidal ideation K-SADS-PL specific items	X	X	X	X
Cognition, cognitive daily and executive function BACS, SCORS-DK and BRIEF	X			X
Standard clinical examination, blood pressure, pulse, weight, height, BMI, and abdominal circumference.	X	X	X	X
Health-related quality of life Questionnaire: KIDSCREEN-52	X			X
Laboratory tests (see list below)	X		X	X

AIMS = Abnormal Involuntary Movement Scale; BACS = Brief Assessment of Cognition in Schizophrenia; BARS : Barnes Akathisia Rating Scale; BMI : Body Mass Index; BRIEF : Behavioural Rating Inventory of Executive Functions; CGI : Clinical Global Impression (-I : Improvement -S : Severity -E : Efficacy); DIPI : Dimensions of Psychosis Instrument; GAPD: Global Assessment of Psychosocial Disability; HRQoL: Health related quality of life; K-SADS-PL: Kiddie-SADS-Present and Lifetime Version; KIDSCREEN-52: Health related quality of life questionnaire for children and young people and their parents; PANSS: Positive and Negative Syndrome Scale; SCORS-DK: Schizophrenia Cognition Rating Scale – Danish version; UKU: 'Udvalget for Kliniske Undersøgelser' Side Effect Rating Scale.

Blood tests relevant for this study include: (fasting) triglycerides, total cholesterol, HDL, LDL, glucose, insulin. Also assessed were: prolactin, creatinphosphokinase, hemoglobin, leukocyte cell and differential count, thrombocyte cell count, sodium, potassium, creatinine, aspartate amino transferase, alkaline phosphatases, thyroid stimulating hormone, vitamin D, omega 3 fatty acids and genetic material (DNA). Blood samples to analyze serum values of antipsychotics are drawn at week 4 and 12, and saved for later analysis. Urine tests: pregnancy test (at baseline and at follow-up if suspicion of pregnancy), screening for medication and substance abuse (at baseline and at follow-up if suspicion of substance use). ECG: Standard leads. The prescence of orthostatic dizziness and/or palpitations/tachycardia were assessed on UKU¹⁷⁹ at follow-up visits by the investigator (a score of at least 1 on UKU items 3-9 and 3-10 *and* rated probably related to study drug).

8.2.7 Statistical analyses

All patients who received at least one dose of trial medication comprised the Intention-To-Treat (ITT) cohort. For changes in metabolic outcomes, (paper 3) the modified ITT cohort included all patients with available data at follow-up assessments, regardless of whether they were still taking the investigational drug or not. For the analyses of QTc changes (paper 4), the modified ITT cohort consisted of all patients who had a baseline ECG and at least one follow-up ECG. All statistical analyses were conducted using IBM SPSS® version 21 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY). Patient characteristics between groups were compared using descriptive statistics and Mann-Whitney's U test. Baseline differences were examined using linear or logistic regression, including sex, age, smoking status and level of parental education as covariates. Differences in body composition, blood pressure, QTc and metabolic outcomes from baseline to each follow-

up point for each group were examined using paired t-tests for continuous outcomes, and Wilcoxon ranked sum test for ordinal outcomes. In analysis of metabolic outcomes (paper 3), number needed to harm (NNH) were calculated using an online calculator (<http://www.graphpad.com/quickcalcs/index.cfm>). Differences between the two groups in metabolic outcomes from baseline to each follow-up point were examined using the mixed models approach¹⁸⁰: outcomes were modelled by a longitudinal linear model including follow-up visit (three levels for body composition, two levels for laboratory values) treatment, the interaction between the two, as well as the baseline measurement as fixed effects. An unstructured matrix was used for residual correlations within subjects over visits. The model was fitted using the linear mixed models procedure in SPSS and inference was based on maximum likelihood. As the TEA trial was powered based on a different primary outcome, post-hoc power calculation was made. All statistical analyses were performed blinded, i.e. before treatment allocation was revealed to investigators.

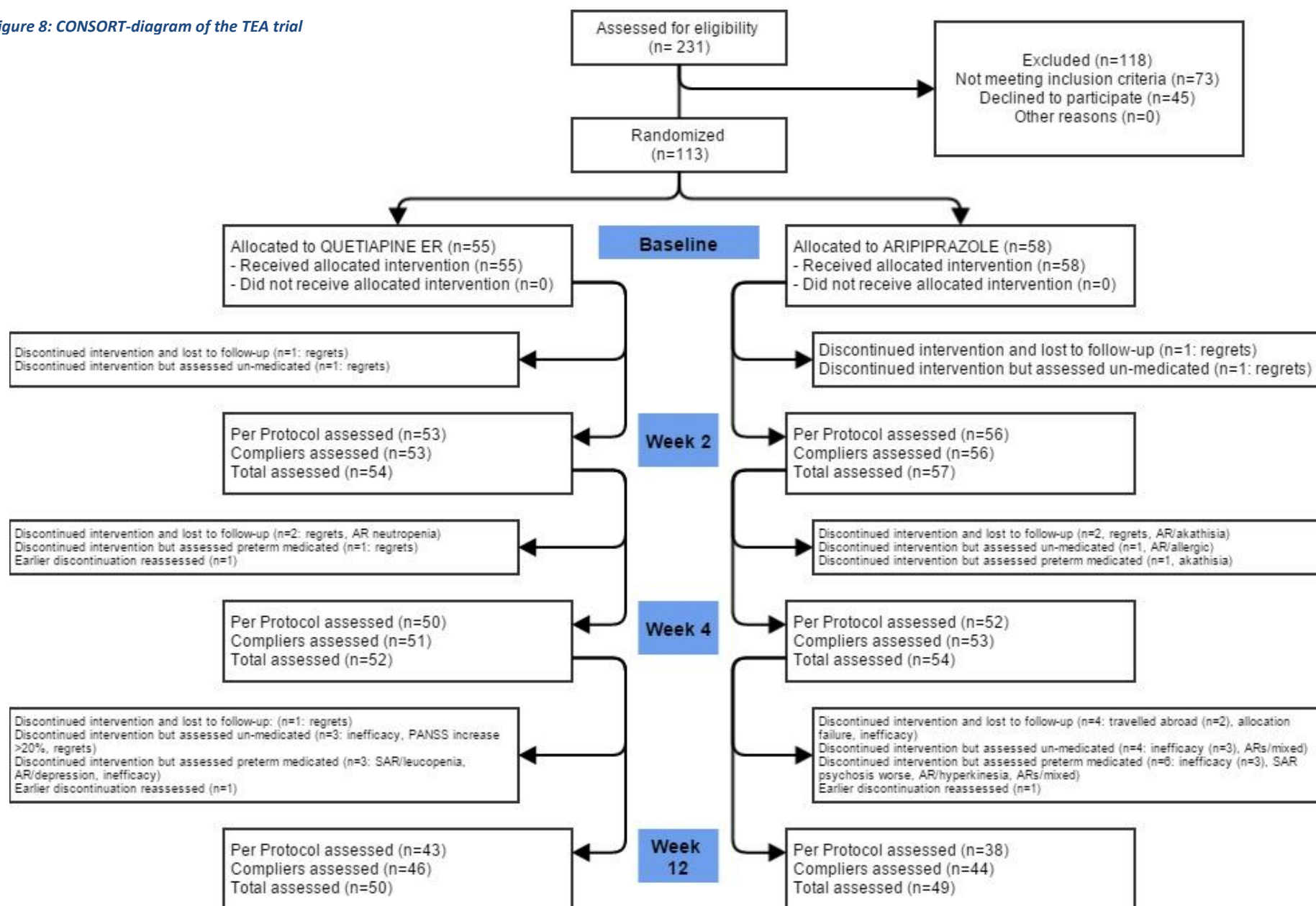
8.2.8 Main results from the TEA trial

The overall report from the TEA trial summarizes the main beneficial and harmful effects of quetiapine ER versus aripiprazole (Pagsberg et al. Quetiapine extended release versus aripiprazole in children and adolescents with first episode psychosis: results from the randomised, double-blind Tolerability and Efficacy of Antipsychotics (TEA) trial, in submission). The results from the trial showed the following: Of 231 eligible patients, 113 were included into the trial while 118 were screening-negative (see CONSORT-diagram in Figure 8). Mean±SD age was 15.74±1.36 years, males: 30.1%, schizophrenia-spectrum disorders: 92.9%, mood-spectrum disorders: 7.1%, antipsychotic-naïve: 50.4%. Patients were randomized to quetiapine ER (n: 55) or aripiprazole (n: 58). Mean±SD dosages: Quetiapine-ER: 433.1±168.9 mg/day; aripiprazole: 13.3±4.3 mg/day. There was no significant difference on PANSS-positive decline, while weight gain and metabolic parameters were significantly higher with quetiapine-ER than aripiprazole. Initially, akathisia was more common with aripiprazole than quetiapine-ER, but no longer at week 12. Sedation frequencies were not significantly different. There were no group differences on additional beneficial outcomes, including treatment response, which was modest (quetiapine ER: 20.4%; aripiprazole: 23.4%). Aripiprazole was associated with lower prolactin levels, but more anticholinergic use.

As can be seen from the above, the overall report focused on both benefits and harms associated with the two drugs in the treatment of youth with psychosis, and concluded that there were no significant differences in antipsychotic efficacy between quetiapine ER vs aripiprazole, while side-effect profiles differed with quetiapine ER being associated with more cardiometabolic adverse reactions, and aripiprazole with more initial akathisia.

This present PhD thesis elaborates on the findings from the main report of the TEA trial and expands the perspectives of the results by 1) addressing the question as to whether youth with psychosis compared to healthy controls are already at increased cardiometabolic risk before initiation of antipsychotic treatment; 2) scrutinizing the cardiometabolic and body composition data from the RCT in detail by evaluating the intermediate risk factors for cardiovascular disease including the use of standardized population reference values, analyzing the timing of occurrence of cardiometabolic adverse events, investigating the associations between the different cardiometabolic measures, and analyzing the predictors of anthropometric changes; 3) performing a meticulous analysis of ECG parameters including the use of three correction methods for QTc measurement and an analysis of possible predictors of QTc change.

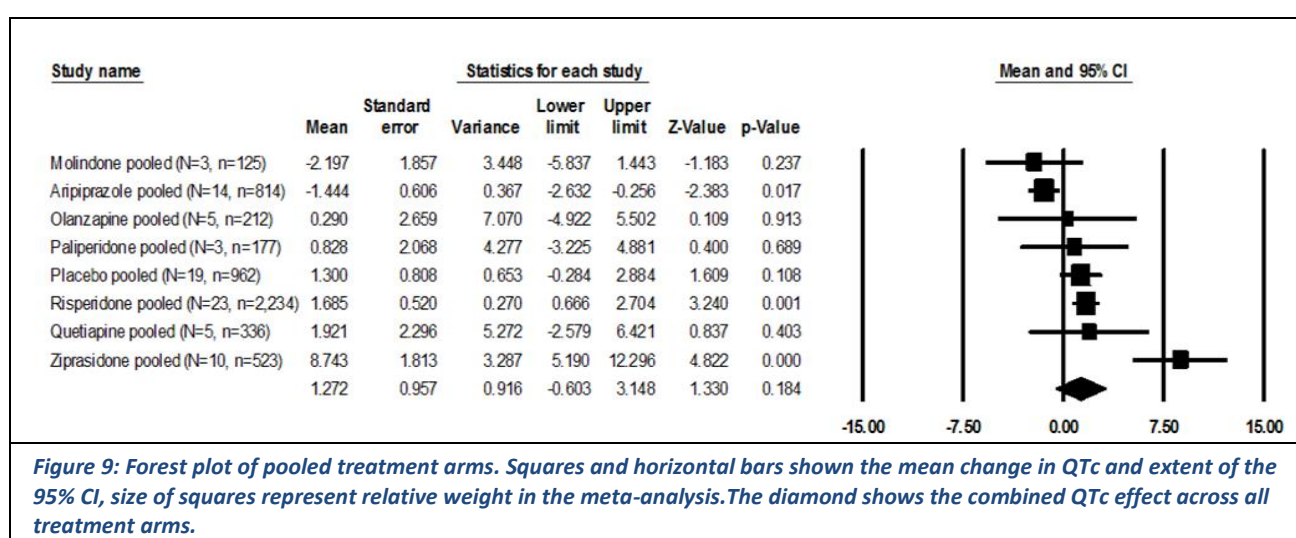
Figure 8: CONSORT-diagram of the TEA trial



9 Summary of the results

9.1 Paper 1: Corrected QT Changes During Antipsychotic Treatment of Children and Adolescents: A Systematic Review and Meta-Analysis of Clinical Trials

A total of 55 trials of antipsychotic treatment in children and adolescents were meta-analyzed, evaluating 108 treatment arms covering 9 antipsychotics and including 5,423 patients with QTc data (mean age: 12.8 ± 3.6 years, female: 32.1%), covering a range of both psychotic and other psychiatric diagnoses.¹⁷⁴ We found that aripiprazole significantly shortened the QTc interval (-1.44 ms, CI = -2.63 to -0.26 , $p = .017$), while risperidone and especially ziprasidone caused a significant increase in QTc duration ($+1.69$ ms, CI = $+0.67$ to $+2.70$, $p = .001$ and $+8.74$ ms, CI = $+5.19$ to $+12.30$, $p < .001$, respectively) (see Figure 9).

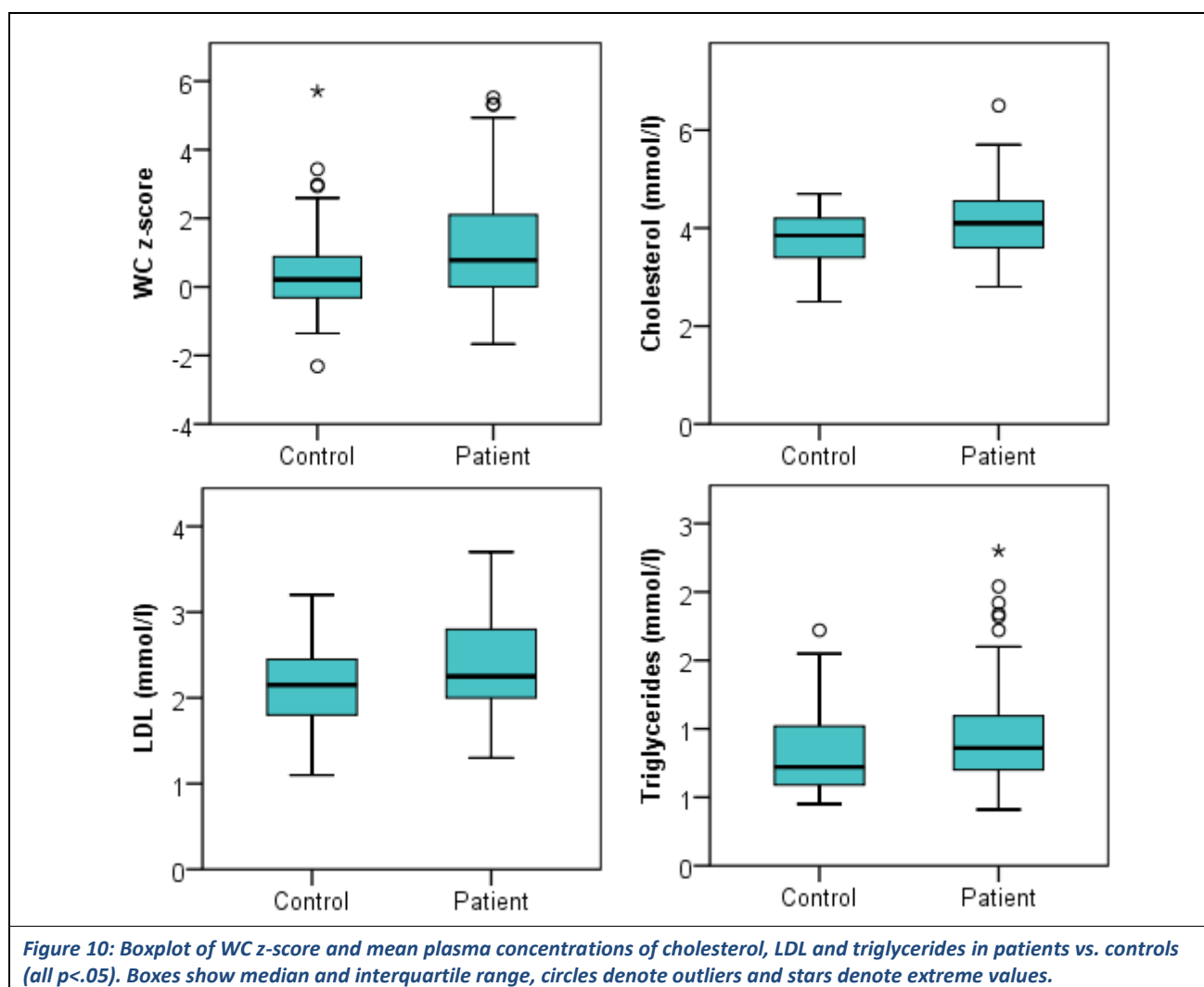


Compared to pooled placebo arms, only the effect of aripiprazole ($p = .007$) and ziprasidone ($p < .001$) remained significant. Using meta-regression analysis, we found a significant inverse dose-relationship ($p < 0.001$) for quetiapine, and an inverse relationship to age ($p < 0.001$) and ratio of females ($p = 0.001$, i.e. the more females, the smaller the QTc change). We further found a significant positive association between duration of treatment and QTc increase for risperidone ($p = 0.012$), and there was a trend towards an inverse dose-dependency for aripiprazole ($p = 0.059$), indicating that higher doses were associated with greater QTc decrease. We found no significant increase in number of events of study-defined QTc prolongation for either drug, although the frequency of an increase > 60 ms was threefold higher for ziprasidone than for placebo (non-significant). Finally, regarding study quality, we generally found very few instances of high risk of bias in any of the domains outlined by the Cochrane Handbook¹⁸¹.

We concluded that, across the 9 studied antipsychotics (aripiprazole, haloperidol, molindone, olanzapine, paliperidone, pimozide, quetiapine, risperidone and ziprasidone), treatment of children and adolescents appears safe with respect to QTc prolongation, although both medication and patients factors need to be considered before making a choice of antipsychotic medication initiation.

9.2 Paper 2-4: Baseline metabolic characteristics from the TEA trial and cardiac and metabolic outcomes from the 12 week intervention period

When comparing baseline characteristics in patients and matched healthy controls included in the TEA trial, we found that while BMI z-scores did not differ significantly between patients ($n=113$, age= 15.74 ± 1.36 years, males=30.1%, schizophrenia-spectrum disorders=92.9%, mood-spectrum disorders=7.1%, antipsychotic-naïve=57) and matched controls ($n=60$), patients had significantly higher WC z-scores (1.13 ± 1.65 vs. 0.42 ± 1.27 , $p=.018$). Patients also had significantly higher mean levels of circulating cholesterol (4.10 ± 0.71 vs. $3.79\pm.49$ mmol/l, $p=.014$), LDL (2.37 ± 0.56 vs. 2.13 ± 0.51 , $p=.012$) and non-high density lipoproteins (non-HDL) (2.58 ± 1.60 vs. 2.52 ± 0.52 , $p=.018$). More patients than controls (42.9% vs. 20.3%, $p=.019$) and antipsychotic-naïve vs -exposed (51.9% vs. 34.0%, $p=.023$) had a WC >90th percentile. Hypercholesterolemia (34.0% vs. 12.5%, $p=.015$) was more frequent in patients, while decreased HDL was more frequent in controls (32.5% vs. 19.0%, $p=.032$). Of the included patients, 17.7% were in treatment with melatonin (10.7% of antipsychotic-naïve patients and 25.0% of antipsychotic-exposed patients, $p=.038$), 13.3% with antidepressants, 2.7% with anxiolytics and 0.9% with mood stabilizers, stimulants or antihistamines (for sedation), with no significant difference between groups. With respect to illicit drug use, 12.0% of patients tested positive for benzodiazepine use while 2.8% tested positive for tetrahydrocannabinol. None of the healthy controls tested positive on drug tests or were in psychopharmacological treatment.



In the patient group we found that obesity in first-degree relatives (FDRs) was significantly associated with both a higher mean patient BMI z-score ($p=.003$) and WC z-score ($p=.034$), and that T2DM in FDRs was associated with both higher patient BMI z-score ($p<.0001$) and WC z-score ($p=.001$), as well as with higher patient FPI and HOMA-IR. In the patient group there was also a significant association between dyslipidemia in FDRs and higher patient LDL-cholesterol ($p=.041$), and between T1DM in FDR and higher patient HDL-cholesterol ($p=.029$). There was no statistically significant difference in any metabolic parameters between patients with FDRs with ($n=9$) and without ($n=104$) a history of psychotic illness. Finally, in a post-hoc analysis, we found that lower level of parental education in healthy controls was significantly correlated with higher BMI z-score (Pearson's $R: -.321$, $p=.012$), WC z-score (Pearson's $R: -.263$, $p=.040$), triglyceride level (Pearson's $R: .399$, $p=.013$) and triglyceride/HDL ratio (Pearson's $R: .347$, $p=.018$), but these correlations were not seen in the patient group.

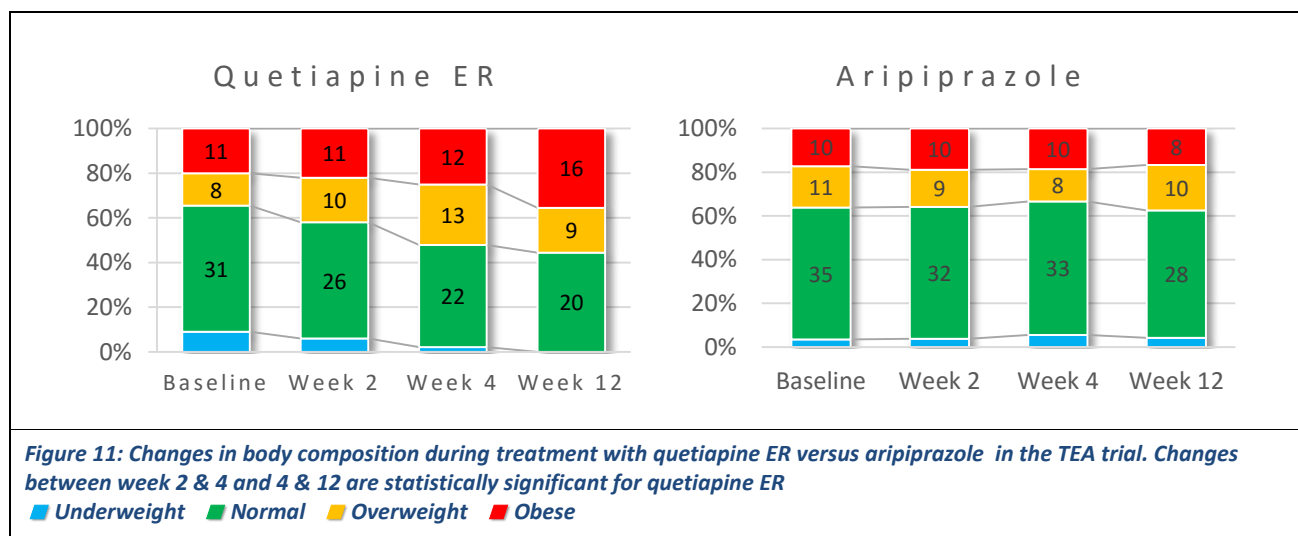
Patients were randomized to quetiapine ER ($n=55$) or aripiprazole ($n=58$). In both treatment groups, there was a significant increase in weight; however, the increase observed in patients treated with quetiapine ER was greater (mean $\pm$ SD, 5.22 ± 3.97 kg, $p<.001$) after 12 weeks compared to the aripiprazole group (1.73 ± 3.52 kg, $p<.001$, group difference significant at $p<.001$). Weight gain occurred very early with quetiapine ER, increasing by 1.42 ± 1.55 kg already after 2 weeks of treatment ($p<.001$, group difference: $p<.001$, see Table 4). BMI, BMI z-score, BMI percentile, WC and WC z-score all increased significantly in this group already after two weeks and continued to increase throughout the intervention period. Furthermore, in the quetiapine ER group, we observed significant metabolic disturbances, which occurred already at the first laboratory follow-up assessment at week 4, and their metabolic status continued to deteriorate throughout the intervention period. FPG remained stable in both treatment groups, fasting insulin increased in the quetiapine ER group by 25.42 ± 51.37 mmol/l ($p=.004$) after 4 weeks and by 22.84 ± 51.23 ($p=.008$) after 12 weeks. HOMA-IR increased in the quetiapine ER group (0.83 ± 1.69 , $p=.006$ after 4 weeks and 0.73 ± 1.99 , $p=.027$ after 12 weeks), changes being non-significant for aripiprazole. In the quetiapine ER group, lipids were significantly increased after 4 weeks: triglycerides increased by 0.34 ± 0.74 mmol/l ($p=.006$), triglyceride/HDL ratio by 0.29 ± 0.70 ($p=.015$). After 12 weeks, total cholesterol increased significantly by 0.35 ± 0.63 mmol/l ($p=.001$), triglycerides by 0.46 ± 1.09 ($p=.014$), LDL by 0.20 ± 0.48 ($p=.015$) and triglyceride /HDL ratio by 0.57 ± 1.41 ($p=.018$). No significant changes were observed in blood lipids in the aripiprazole group. Systolic and diastolic blood pressure changes with quetiapine ER were non-significant, whereas in the aripiprazole group, systolic blood pressure decreased after 4 weeks by -3.06 ± 10.70 mmHg ($p=.041$) and after 12 weeks by -2.96 ± 11.43 mmHg ($p=0.076$), and diastolic blood pressure decreased by -4.89 ± 8.30 mmHg after 4 weeks ($p<.001$) and -4.12 ± 9.50 mmHg after 12 weeks ($p=.004$). With quetiapine ER, heart rate increased 11.06 ± 16.01 bpm after 2 weeks ($p<.001$), by 14.23 ± 13.28 bpm after 4 weeks ($p<.001$) and by 10.28 ± 14.97 bpm after 12 weeks ($p<.001$). With aripiprazole, a significant increase in heart rate was observed after 2 weeks 5.95 ± 10.70 bpm ($p<.001$), but this increase was no longer significant after week 4 or 12.

We compared the changes from baseline between the two treatment groups using mixed-model analysis, the results are shown in Table 4, demonstrating significant between-group differences in anthropometric and metabolic outcomes, with the exception of changes in FPG and HDL.

Table 4: Between-group comparison of change in metabolic parameters in the aripiprazole group (n=58) (mixed models analysis in intention-to-treat population) using quetiapine ER (n=55) as the reference

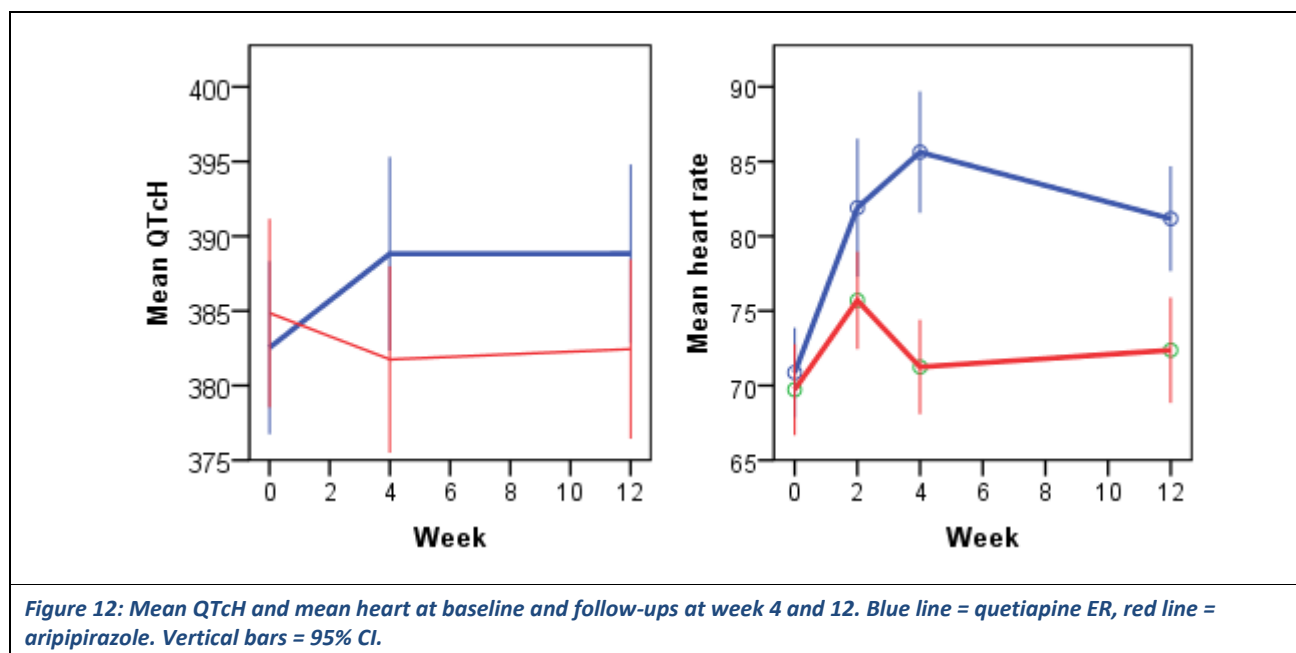
	Time	Mean	CI Lower	CI Upper	p
Anthropometrics					
Weight (kilograms)	Week 2	-1.11	-1.67	-.55	.000
	Week 4	-1.91	-2.62	-1.21	.000
	Week 12	-3.58	-5.11	-2.05	.000
BMI	Week 2	-.38	-.59	-.18	.000
	Week 4	-.67	-.93	-.41	.000
	Week 12	-1.23	-1.77	-.68	.000
BMI z-score	Week 2	-.12	-.19	-.05	.002
	Week 4	-.22	-.30	-.13	.000
	Week 12	-.35	-.51	-.19	.000
BMI percentile	Week 2	-1.73	-3.76	.30	.095
	Week 4	-4.42	-6.98	-1.87	.001
	Week 12	-5.69	-10.46	-.91	.020
WC	Week 2	-4.01	-7.56	-.46	.027
	Week 4	-4.10	-7.73	-.47	.027
	Week 12	-5.53	-9.52	-1.53	.007
WC z-score	Week 2	-.48	-.82	-.15	.005
	Week 4	-.49	-.85	-.13	.009
	Week 12	-.76	-1.19	-.32	.001
Glucemic					
Glucose (mmol/l)	Week 4	.07	-.12	.26	.459
	Week 12	-.03	-.21	.15	.762
Insulin (pmol/l)	Week 4	-38.1	-57.9	-18.4	.000
	Week 12	-17.6	-37.2	2.00	.078
HOMA-IR	Week 4	-1.31	-2.00	-.62	.000
	Week 12	-.65	-1.32	.01	.053
Lipids					
Total cholesterol (mmol/l)	Week 4	-.40	-.70	-.09	.011
	Week 12	-.62	-.91	-.33	.000
LDL (mmol/l)	Week 4	-.30	-.53	-.07	.010
	Week 12	-.38	-.63	-.13	.003
HDL (mmol/l)	Week 4	.03	-.10	.16	.636
	Week 12	-.01	-.14	.13	.929
Triglycerides (mmol/l)	Week 4	-.41	-.65	-.17	.001
	Week 12	-.43	-.76	-.10	.012
Non-HDL (mmol/l)	Week 4	-.43	-.72	-.14	.004
	Week 12	-.61	-.89	-.32	.000
Triglyceride/HDL ratio	Week 4	-.43	-.71	-.16	.003
	Week 12	-.52	-.94	-.10	.016
Blood pressure (BP)					
Systolic BP (mmHg)	Week 2	-1.07	-4.65	2.51	.554
	Week 4	-5.21	-9.14	-1.27	.010
	Week 12	-6.11	-10.11	-2.12	.003
Diastolic BP (mmHg)	Week 2	-.84	-3.66	1.98	.558
	Week 4	-7.18	-9.97	-4.39	.000
	Week 12	-8.08	-11.21	-4.94	.000
Heart Rate (bpm)	Week 2	-7.17	-12.06	-2.29	.004
	Week 4	-14.02	-18.33	-9.71	.000
	Week 12	-10.12	-14.62	-5.61	.000

There were also significantly more incidences of weight increase >7%, blood pressure >90th percentile, WC z-score reaching >90th percentile, insulin ≥ 138.9 pmol/l, cholesterol ≥ 4.4 mmol/l, LDL ≥ 3.4 mmol/l, non-HDL ≥ 3.4 mmol/l, triglycerides ≥ 1.2 mmol/l and events of dyslipidemia in the quetiapine ER group than in the aripiprazole group after 12 weeks. Changes in body composition were significant for quetiapine ER from week 2 to 4 ($p=.007$) and week 4 to 12 ($p<.001$, see Figure 11)



We also examined possible predictors of weight change and found that weight before randomization significantly and positively predicted weight change ($p<.003$) and change in triglycerides ($p=.001$) across all subjects. Age at onset of psychotic symptoms significantly and positively predicted change in cholesterol ($p=.043$) but of no other metabolic outcome. A post hoc power analysis was showed that the observed difference in weight gain had a power of .998 at a statistical significance level of $\alpha=.005$ (effect size: 0.93).

Baseline and at least one follow-up ECG were available for 97 patients (85.8%, age= 15.8 ± 1.4 years, males=34.0%, schizophrenia-spectrum diagnosis=68.0%). Quetiapine ER treatment ($n=48$) was associated with a significant increase in QTcH (Hodges correction) of $+7.3 \pm 20.3$ ms ($p=0.016$) from baseline to last follow-up, while the change from baseline was non-significant (-1.0 ± 18.9 ms, $p=0.716$, see Figure 12) in patients receiving aripiprazole ($n=49$) (between-group difference: $p=.039$). Mean dose of quetiapine ER during the last five days prior to obtaining the ECG was significantly correlated to the change in QTcH from baseline to week 4 (Pearson's $r=.504$, $p=.006$).



Furthermore, patients in the quetiapine ER group experienced an increase in heart rate (based on available ECGs, $+10.4 \pm 14.8$ beats per minute, $p < 0.001$), while patients in the aripiprazole group did not. However, the mean QTcH increase observed during the intervention period was too small to cause clinical symptoms in these otherwise physically healthy individuals. No patients experienced an increase in QTcH to >450 milliseconds, although some patients in the quetiapine ER group experienced an increase of more than 40 ms ($n=1$: 40.8 ms after 4 weeks and $n=3$: 40.5, 47.6 and 62.3 ms after 12 weeks). Age, sex, smoking, and body mass index were not significantly associated with QTc change. Treatment-associated orthostatic dizziness occurred in 27.3% in the quetiapine ER group and 20.7% in the aripiprazole group ($p=.509$, while palpitations/tachycardia occurred in 10.9% in the quetiapine ER group and 3.4% in the aripiprazole group ($p=.155$). At all time points, females had higher QTcH than males, mean difference was 20.2 ± 4.2 ms at baseline ($p < .001$), 23.8 ± 4.4 ms ($p < .001$) at week 4 and 16.9 ± 4.2 ms ($p < .001$) at week 12; however, there were no statistically significant differences in mean change in QTcH, even when comparing treatment arms.

10 Discussion

The objective of this thesis was to combine an overview of the existing literature regarding early onset psychosis and cardiometabolic risk, with results from a review and meta-analysis of available trials on QTc prolongation in youth treated with antipsychotics and cardiometabolic data from our randomized, double blinded pharmacological TEA trial comparing aripiprazole and quetiapine ER, two of the most commonly used antipsychotics in this age group. The aim was to extend the evidence base concerning the cardiometabolic risk of antipsychotic treatment in children and adolescents with psychosis.

10.1 Summary of findings

Our review and meta-analysis of 55 studies investigating QTc change in youth treated with antipsychotics showed that treatment with a wide range of antipsychotics overall appear safe with respect to QTc prolongation in otherwise healthy youths. We found that aripiprazole was associated with a significant decrease in QTc while significant prolongation was seen in patients treated with quetiapine and especially

ziprasidone. Data from the 12 weeks TEA trial showed that youths with FEP had significantly higher WC and lipid abnormalities at baseline than matched healthy controls, and metabolic disturbances in FDRs was associated with increased metabolic risk in patients. When comparing aripiprazole to quetiapine ER during 12 weeks of treatment, we found that the effect of quetiapine ER on mean weight, BMI and WC z-score, cholesterol, LDL and triglycerides was statistically – and clinically – significant. These changes occurred at a very early phase, and continued to increase throughout the intervention period. Even though blood glucose did not increase significantly, HOMA-IR did, suggesting that continued exposure could ultimately lead to the development of diabetes mellitus in susceptible individuals. Aripiprazole had smaller, yet clinically significant impact on weight and body composition, but not on any other cardiovascular risk factors. Indeed, aripiprazole slightly decreased blood pressure, which could indicate a protective effect against the development of metabolic syndrome. Finally, we found that quetiapine ER was associated with a statistically significant and dose-dependent mean increase in QTcH duration, which, although not dangerous in otherwise healthy patients, may be clinically relevant in at-risk individuals, while aripiprazole was associated with a small decrease in QTcH. Hypothetically, this latter phenomenon might be the result of carry-over effect from previous antipsychotic treatment in trials, even after a washout period.

10.2 Strengths and limitations

Our systematic review and meta-analysis of available trials with ECG data addressed the lack of existing consensus regarding QTc effects of antipsychotic drugs in children and adolescents. The main strengths of this study was the systematic literature search, selecting relevant studies among more than seven thousand abstracts, meta-analyzing the data on relevant outcomes to synthesize evidence, and the systematic assessment of risk of bias, which allows the reader to scrutinize the data sources included in the study.

The limitations of the review and meta-analysis were the relatively small number of studies (N=55) that fulfilled the inclusion criteria, the amount of missing data on specific outcomes from the trials and the associated publication bias. Many trials were performed or supported by manufacturers of antipsychotic medications, which could significantly affect the interpretation of their data,¹⁸² however, excluding these trials would result in a very low number of available data. In addition, different methods for QT correction and different cut-offs were used among studies, which challenged the comparability of trials. Previous and concomitant medication and whether wash-out was performed was not assessed in this review. Previous and concomitant treatment could influence on measurements, but excluding trials where patients were not naïve or not treated with other medications during the trial would have made the number of studies very low as most studies allowed for concomitant medications such as antihistamines or hypnotics. Also, the methods for titrating medications differed from trial to trial: some adjusted medications according to clinical symptoms while others had a fixed target dose. While this hampers the comparison between trials, controlling for and interpreting such data would have been challenging. It is worth mentioning that of the 55 trials included only four had QTc changes as primary outcome, which means that attention to the effect on QTc was rarely prioritized. Nevertheless, the trials were generally of high standard. Finally, searching more than one database is often done in systematic reviews and could seem desirable. However, this review and meta-analysis focused on medication effects, and we found it reasonable to assume that psychopharmacological papers are very well covered by PubMed, which is why we focused on this database. Including other databases would most likely have resulted in a very large number of duplicates and a very low yield.

The strength of the case-control baseline study, based on data from the TEA trial, was the relatively large pediatric sample with first-episode psychosis compared to a healthy control group that was recruited via a random data extraction from the Danish Centralized Civil Register and well matched (2:1) according to age and

gender. We had complete baseline data, a stringent prospective cardiometabolic risk assessment, and availability of family history data of cardiometabolic diseases. We conducted regression analyses adjusting for potential confounders. Furthermore, we were able to compare participants to the background population using updated and very precise z-scores for BMI and waist circumference, taking into consideration both age and sex in a European sample.

The main limitations of the baseline study included the inability to fully ascertain the representativeness of the enrolled patient sample. According to protocol and regulations from the authorities, assessment of clinical data besides age and sex was not permitted in patients who declined to participate. As such, it is possible that screening-negative patients had different anthropometric or cardiometabolic profiles – or socioeconomic or educational backgrounds – than the included sample. Unwillingness to participate could be linked to cardiometabolic risk of antipsychotic treatment, as some potential candidates might have refused participation due to the risk of weight gain, or refusal could be linked to severity of symptoms. Furthermore, we aimed at matching the patients and controls on level of parental education, but the difference in parental education between the healthy controls that were willing to participate and included patients reflects that some degree of selection bias in the healthy control group was unavoidable. The reason for this was that among the invited potential matched controls that we contacted, a larger proportion of families with low education refused to participate. Indeed, we also found a significant difference in level of education between antipsychotic-naïve and -exposed patients, possibly indicating that higher level of parents' education increases the clinicians' inclination towards pharmacological treatment regardless of symptom severity (as both PANSS and CGI scores were comparable in both groups). In addition, information on psychiatric illness in relatives of controls was not registered (however, presence of psychosis in FDR of healthy controls was exclusionary), and it is possible that psychiatric illness in relatives is linked to health and/or dietary patterns in the family. Finally, half of the patient sample was not antipsychotics-naïve, but had limited antipsychotic exposure prior to the baseline assessment. Prior antipsychotic treatment, and the absence of a wash out period in the trial design, cloud the interpretation of the data. In Denmark, olanzapine is often used as *pro re nata* treatment in emergency situations in psychotic patients, and this drug is associated with severe metabolic effects, even after brief treatment periods.¹⁸³ Even so, the doses were small and durations were indeed brief, and there was no significant differences in baseline metabolic profiles between antipsychotic-naïve and -exposed patients.

The main strengths of the TEA trial is the state-of-the-art design of an independently funded, randomized, multi-centre, double blinded comparative trial. Randomized, controlled trials are the cornerstone of psychopharmacological investigation, yet trials conducted in youths are scarce and often have small patient samples. Our sample of 113 patients makes the TEA trial one of the largest head-to-head pharmacological trials of active comparators in this area of research and the first to compare the effects of aripiprazole and quetiapine ER in this age group. An external collaborator performed the randomization and blinding procedures, and patients, physicians and investigators were blinded to treatment allocation during the data collection. Data analyses were done blinded, e.g. the patient allocation was not revealed until a conclusion of the data analyses was drawn. The cardiometabolic outcomes were analyzed with intention-to-treat (ITT)-analysis or modified ITT-analysis. All of the above aimed at lowering the risk of bias. Furthermore, all procedures were manualized and investigators were uniformly trained in assessments of both benefits and harms in order to ensure valid and reliable data.

The main limitation of the results from the TEA trial is that the sample size was estimated based on the primary outcome (reduction of positive symptoms on the PANSS scale) of the TEA trial, and was therefore not primarily powered according to cardiometabolic outcomes; however, the *post hoc* power analysis indicated that we had sufficient power to trust the outcomes of the present analyses. We included both in- and outpatients, and a

wide range of non-organic psychotic disorders, which could increase variability in data and impair comparability with other studies, but on the other hand, this rendered a patient group very similar to real-life conditions and thereby more representative for the clinical population than most RCTs in this field. Furthermore, co-medications, especially those violating the protocol by adding antipsychotics for rescue use, could affect cardiometabolic results, but co-medications (with the exception of anti-EPS medication, such as biperiden, which are not known to cause significant cardiometabolic side-effects (<http://www.drugs.com/cons/biperiden.html>)) were evenly distributed in the two treatment groups. Again, it would seem desirable if all included patients were completely antipsychotic-naïve before entering the trial. On the other hand, many patients are very ill at the presentation and require immediate treatment; for these patients it would be unethical to withhold acute antipsychotic medication, and excluding these patients would possibly have reduced the overall mean symptom severity of included patients. If the aim was to have exclusively antipsychotic-naïve patients, these patients would not have been eligible and achieving the required number of patients would have substantially increased the required time and cost of the study. Also, excluding these patients would have reduced the generalizability of the trial and our aim was to have a patient group that was representative of real life populations. In any case, the blinded design eliminated the differential effects of previous medication in the comparison between aripiprazole and quetiapine ER, as there were no significant difference in prior medication use between these groups.

10.3 The risk of QTc prolongation in youth treated with antipsychotics (Paper 1 & 4)

In the meta-analysis of clinical studies in children and adolescents, we found that ziprasidone was associated with a significant increase in the QTc interval both within drug comparisons and also when compared to pooled placebo or compared directly in placebo-controlled trials. This finding is consistent with findings in adults.⁴⁴ Also, in a recent 12-months naturalistic study of 216 treatment-naïve or quasi-naïve children or adolescents receiving antipsychotic treatment,¹⁸⁴ authors found no significant change in QTc from baseline during the follow-up period, and no differences between investigated drugs (risperidone, quetiapine and olanzapine). Likewise, our finding of a significant decrease of the QTc interval in patients treated with aripiprazole is comparable to results from trials of adults.¹⁸⁵

These results indicate that the risk of QTc prolongation is low in youths, and one should bear in mind that cardiac arrhythmias are rare in children and adolescents. This being said, it is important to acknowledge the fact that patients included in trials exploring QTc changes are usually physically healthy, free of major cardiac risk factors and an upper limit for baseline QTc is often used as exclusion criterion. For example, in the TEA trial, the presence of an abnormal ECG indicating a suspected cardiac disease would have excluded the patient. Therefore, these trials give little insight in the effect of antipsychotics on the cardiac impulse conduction in patients who a priori suffer from comorbidities such as underlying heart diseases, congenital QTc prolongation, metabolic disorders, anorexia with electrolyte derangement or who take other QTc prolonging medications. These effects cannot readily be investigated in clinical trials for ethical reasons, underscoring the importance of supplementing RCTs by conducting case reports, retrospective charts reviews and studies including more naturalistic samples.

As expected, in the TEA trial we found that the QTcH prolonging effect of quetiapine ER in youths was significantly larger than that of aripiprazole. The fact that QTcH change was dose-dependent in the quetiapine ER arm strongly supports the notion that quetiapine does have a direct effect on the IKr current. While the QTcH change of aripiprazole (-1.0 ± 18.9 ms) matched that observed in our meta-analysis, the mean QTcH change of 7.3 ± 20.3 ms in the quetiapine ER group was higher than the 95th percentile of the changes reported

in the trials included in our meta-analysis. The observed mean difference in risk of QTcH prolongation does not appear to have clinical implications for patients without underlying risk factors, and, as mentioned, this is especially true in this age group. Nevertheless, some patients in the quetiapine ER group did experience QTcH prolongation that could be of clinical significance, especially in the presence of other risk factors for cardiac arrhythmias. The metabolic data from the TEA trial show that quetiapine also increases the risk of diabetes and metabolic syndrome, which considerably increase the risk of heart disease, which again increases the risk of QTc prolongation and progression to TdP. As mentioned, even in small children, obesity is linked with a thickening on the intima in the carotid arteries, and obesity has also been linked to prehypertension in children as young as two to nine years.¹⁸⁶

Taken together, the results from our meta-analysis and QTc data from the TEA trial question the necessity of electrocardiographic monitoring in children and adolescents with no known prior or emerging risk factors. It is important, however, that clinicians are aware of the potential of antipsychotics to cause QTc prolongation and of the interacting cardiovascular risk factors, which are more prevalent in psychotic patients compared to the background population.¹⁸⁷ Consideration of these factors when choosing between antipsychotic treatments is especially relevant in clinical scenarios that may indicate patient-related risk factors, such as family history of long QT syndrome or sudden death, prior ECG with a QTc >450 milliseconds, palpitations at rest without anxiety, and dizziness or, especially, syncope upon exertion.¹⁸⁸ The severity of combined risk factors should also be considered during medication switches. For instance, in a patient whose QTc interval has increased by 60 milliseconds or more during quetiapine treatment, or who has suffered cardiac injury, switch to aripiprazole or another low-risk agent should be effectuated. During treatment in at-risk patients, ECG should be monitored, especially if clinical cardiovascular symptoms or risk factors emerge. Clinicians should be vigilant of severe weight change or co-medications, which may adversely affect cardiac conduction¹⁵³.

10.4 Metabolic status in first-episode (FE) EOP and the risk of metabolic harms of quetiapine ER versus aripiprazole (Papers 2 & 3)

Baseline data from TEA study demonstrated that patients with first-episode EOP, already before the initiation of antipsychotic treatment, had accumulated risk factors for development of overweight, severe metabolic disturbances and diabetes, compared to the matched healthy controls. These results contrast with findings from a prior systematic review in adults with first episode psychosis,¹⁸⁹ where authors found no difference in cardiometabolic risk between patients and healthy controls before treatment initiation. However, our findings converge with other studies in adults,⁹⁶ which link the presence of severe mental illness to an increased risk of cardiovascular risk factors, even before antipsychotic treatment is initiated. Similarly, baseline results from 394 FEP patients aged 15-40 years (mean age: 23.6±5.0 years) from the USA RAISE-ETP study¹⁹⁰ showed a percentage of overweight or obesity of 48.3%. While the present Ph.D. study has not investigated possible reasons for this elevated cardiometabolic risk, other studies have demonstrated a probable combined effect of genetic factors and lifestyle factors.^{65,130,157,191} In a recent meta-analysis of 13 clinical studies in youths, the unadjusted cumulative risk of T2DM was 2.6 fold higher in antipsychotic-exposed patients and 2.1 in unexposed patients compared to healthy controls.¹⁹² Data from the TEA trial showed that pre-treatment weight was predictive for weight gain and triglyceride elevation, suggesting that youths who are already overweight before treatment initiation are more sensitive to metabolic adverse effects. We also found that cardiometabolic diseases in FDRs were associated with elevated metabolic risk factors in patients.

When comparing the cardiometabolic effects of treatment with quetiapine ER vs aripiprazole we found that quetiapine ER was associated with significantly greater weight gain and metabolic harms than aripiprazole.

Patients in the quetiapine ER group experienced these adverse effects rapidly, with significant between-group differences apparent already after 2 weeks, and after 12 weeks, the magnitude of more than 5 kilograms on average was large enough to have a potentially profound impact on cardiometabolic health. This converges with our finding of significantly increased proportions of patients in the quetiapine ER group who had onset of hyperinsulinemia, hypercholesterolemia, dyslipidemia and metabolic syndrome during the intervention period. While almost all SGAs carry an increased risk of metabolic adverse effects, results from the TEA trial is consistent with a plethora of previous studies showing that the metabolic effects of aripiprazole are lesser compared to many other antipsychotic agents, including quetiapine^{77,85,154,189,193-195}. The findings also appear to reflect the differences in receptor binding profiles of quetiapine and aripiprazole, especially regarding histamine receptor blocking potentials, which is higher in quetiapine than in aripiprazole.^{49,196}

In addition, although levels of fasting plasma glucose did not increase in either groups, HOMA-IR increased rapidly in the quetiapine ER group, and continued exposure would presumably result in a failure to maintain normal glucose levels, resulting in the development of T2DM. Blood pressure decreased significantly during treatment with aripiprazole, suggesting a potential beneficial effect with respect to development of metabolic syndrome.

In summary, treatment with quetiapine ER has considerably more impact on the cardiometabolic status of treated patients than does aripiprazole. Youths are more sensitive than adults to the development of cardiometabolic adverse effects,¹⁹⁵ and the fact that quetiapine-treated patients had such pronounced changes suggests that this medication can cause diabetes and/or metabolic syndrome within a relatively short time span in at-risk patients, greatly increasing their risk of CVD at early age.

The finding that metabolic disturbances in the family of patients with psychosis not only appears to be associated with a higher pretreatment risk of cardiometabolic symptoms, but also with increased risk of antipsychotic induced metabolic adversities, underlines that both risk factors in the patients themselves and in their family should be taken into consideration when choosing an antipsychotic drug.

In spite of the amount of data demonstrating the metabolic impact of antipsychotic agents, we still know very little of how this occurs or why the interpersonal differences are so large.

11 Conclusion

The results from the present Ph.D. study demonstrate that youths with onset of psychosis before the age of 18 years have increased risk of developing metabolic disturbances, already before initiation of pharmacological treatment, and that this risk is further enhanced when treatment with quetiapine ER – and, to a significantly lesser extent, aripiprazole – is initiated. In the quetiapine ER group, clinically and statistically significant anthropometric and metabolic changes occurred early and increased throughout the 12 weeks intervention period, while in the aripiprazole group, metabolic changes were small. The risk of developing delay in cardiac impulse propagation was increased in the quetiapine ER group compared to the aripiprazole group. While the extent of the observed QTc increase in most cases was clinically negligible – in line with the results from our QTc meta-analysis – one must acknowledge the anticipated long duration of antipsychotic treatment, implying the need for continuous evaluation of the cardiometabolic adverse events of antipsychotics in patients with early onset psychosis.

12 Clinical implications and perspectives for future research

Treatment of psychotic episodes in children and adolescents is a challenging task that requires close cooperation between the patient and its caregivers, clinicians, nurses, psychologists and social services.¹⁴ Psychosis in youths is often accompanied by severe depression or anxiety, which may further complicate the identification of psychotic symptoms.¹⁹⁷ As has been discussed in the introduction, the prognosis for these patients is sinister with high risk of repeated hospitalizations and a likely need for many years of antipsychotic treatment. As such, treatment needs to focus not only on the elimination or depreciation of psychotic symptoms but also on improving the patients' overall quality of life. This implies close and continued communication with the patient, including clear information on expected beneficial and harmful effects of antipsychotic treatment, in order to set a common goal for the treatment, achieve a good alliance with the patient, ensure treatment adherence and to cooperate on the surveillance of harms.

Children and adolescents experience more frequent and severe adverse effects to antipsychotics than adults,^{115,155,195} and they are more sensitive to altered body image and stigmatization than adults.¹⁹⁸ Cardiometabolic side effects by no means stand alone – most SGAs have a wide range of significant side effects, including sedation, akathisia, EPS and hyperprolactinemia,¹⁹⁹ which may cause severe distress and not rarely results in discontinuation of treatment.²⁰⁰ In this age, youths are developing social contacts and networks, have a high need of not standing out from their peers, and incapacitation due to sedation or decreased concentration can severely affect their level of daily functioning.²⁰¹ One could suspect that antipsychotic-induced food craving is difficult to address and can lead to conflicts between parents and patients and reduce compliance. For some, prevention of possible side effects may be more important than elimination of psychotic symptoms, while the same symptoms in another individual is the cause of debilitating distress. It is crucial to include the patients and their relatives in the planning of treatment. However, while it is difficult to predict which patients will develop sedation or neuromotor adverse effects, our data indicate that existing cardiometabolic adversities – in the patients and/or their relatives – can predict the manifestation or aggravation of such conditions during antipsychotic treatment, and this information can thus guide the choice of medication. Also, careful questioning regarding cardiometabolic health, e.g. pre-existing cardiac conditions, arrhythmia, severe metabolic disturbances, or a family history indicating the presence of hereditary cardiac disease, should always forego antipsychotic treatment, if necessary supplemented with an ECG and discussed with a cardiologist. Taking these steps can help identify at-risk individuals.

The impact of metabolic adverse effects is aggravated by the fact that youths in antipsychotic treatment are even less likely to undergo routine weight and metabolic monitoring than adults,¹⁵⁵ although this probably differs between countries. Our data indicate that significant weight increase and lipid changes occur very rapidly after initiation with quetiapine ER, which underscores the importance of close monitoring during the first months of antipsychotic treatment. Furthermore, as results from the TEA trial found no significant difference in psychotic symptom reduction between aripiprazole and quetiapine ER, the adverse effect profiles should receive much attention when the choice stands between these two agents. This emphasis on side effect profiles is in line with the literature both concerning youths⁴³ and adults.⁴⁴ While genetic risk factors cannot be modified (as of yet), it is adamant that clinicians and parents cooperate in counteracting environmental risk factors by ensuring that patients are supported in the choice of healthy dietary habits, encouraged to exercise and that focus on the metabolic impact is a top priority in the treatment of psychoses. Furthermore, switch of medications in the event of weight gain and/or development of other harbingers of metabolic syndrome

should be considered when such events manifest themselves. Genetic testing can reveal differences in drug metabolism (by variances in the cytochrome P450 system) and further guide the choice of medication and dose.³

Finally, healthcare professionals should keep in mind the dynamics of the families when treating youths with psychosis. Parents, guardians and siblings may all have divergent opinions regarding how to prioritize treatment effect vs. adverse effects, and the opinions and priorities of healthcare professionals do not always align with those of our patients.

It is crucial that psychopharmacological intervention is conducted with caution, and that antipsychotic treatment does not stand alone. Treatment should, whenever possible, be combined with psychosocial interventions including psychotherapy and family intervention.^{12,14,202}

Equally important is careful monitoring of side effects, and the combined findings of the present Ph.D. study could hopefully support the adherence to guidelines regarding routine measurements of weight, height, BMI, WC, plasma levels of lipids, glucose, and insulin, blood pressure, ECG (in at-risk patients), and whether insulin resistance or metabolic syndrome has occurred.¹⁹⁴ In psychotic children and adolescents who have substantially elevated risk for QTc prolongation and/or an accumulation of risk factors for developing MS, our data suggests that aripiprazole should be considered as first choice – particularly when considering the equality of psychotic symptom reduction between the two agents.

Clinicians should always keep in mind that initiating antipsychotic treatment is just the first step of a long journey, and the road is neither straight nor smooth. The treatment may have no effect on the primary symptoms or lose its effect over time. Infections or other conditions – both psychiatric and somatic – may interfere with the treatment or interactions with other pharmacological groups (or illicit drugs) may arise. Stressful life events may cause symptoms to fluctuate regardless of treatment,²⁰³ and genetic variations can intervene with how we believe the medications work. In short, a large number of factors can influence on the patients' mental and somatic status and clinicians must keep options open when such factors emerge. With the accumulation of knowledge of the range and scope of impact that antipsychotic treatment has on this highly vulnerable patient group, efforts to individualize treatment are essential to ensure the best possible quality of healthcare.^{155,193,199}

However, many questions remain. We still know far too little regarding the efficacy and tolerability of antipsychotic treatment in children and adolescents,^{43,54} in particular regarding long-term effects and how these effects carry over into adulthood. Medication switch may not be a good solution if the treatment has excellent antipsychotic effect in the individual patient; however, treatment of metabolic side effects in psychotic patients is a relatively new area of research. Much more knowledge is needed, for instance on the addition of metformin,²⁰⁴ GLP-1 analogues²⁰⁵ or melatonin^{206,207} as adjuvants to antipsychotic treatment in high-risk patients. Furthermore, the impact of lifestyle factors on weight gain in youths suffering from psychotic disorders – both before and during treatment – has not been sufficiently investigated. While it seems highly plausible that implementation of intense exercise regimes have the possibility of improving life expectancy, this area of research is still in its infancy. A recent study of exercise in psychiatric patients showed a significantly greater weight loss in patients subjected to an exercise regime than the control group,²⁰⁸ and a recent review of studies aiming at reducing weight gain in schizophrenic patients showed significant efficacy of all included types of intervention.²⁰⁹ Another area which lacks focus is the identification of traits which increase the risk of metabolic adverse effects in the individual patient. Subgroup analyses of those patients in the TEA trial who gained the most weight, including associations to genetic alterations in genes associated both to schizophrenia and MS⁹³, will be the next step of scrutinizing the data. Advances in pharmacogenetics

are beginning to show associations between genetic variation and the effect of antipsychotic treatment, drug metabolism and development of side-effects, but while commercial tests are already developed, the lack of experience and solid evidence in this field slows the implementation of pharmacogenetics testing in clinical settings.²¹⁰ Finally, while the effects of exercise on depression is the focus of intense research (search terms: exercise and depression: 11,806 search hits in PubMed), exercise as a part of treatment of psychosis is not (search terms: exercise and psychosis or psychotic or schizophrenia: 260 search hits in PubMed).

There is a continuous need for research and development of new antipsychotic agents with better efficacy and lesser adverse effect, but this development is impeded by the increasing cost of drug development, in particular in fields as schizophrenia where the market is relatively small.²¹¹ Nonetheless, the combination of the vast number of research projects in this area from around the world will inexorably advance our knowledge, and our hope is that this will eventually lead to better and safer treatment for both youths and adults suffering from severe mental illnesses.

13 Disclosures

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Corrected QT Changes During Antipsychotic Treatment of Children and Adolescents: A Systematic Review and Meta-Analysis of Clinical Trials

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Objective: To evaluate the effect of antipsychotics on the corrected QT (QTc) interval in youth.

Method: We searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) for randomized or open clinical trials of antipsychotics in youth <18 years with QTc data, meta-analyzing the results. Meta-regression analyses evaluated the effect of age, sex, dose, and study duration on QTc. Incidences of study-defined QTc prolongation (>440–470 milliseconds), QTc >500 milliseconds, and QTc change >60 milliseconds were also evaluated.

Results: A total of 55 studies were meta-analyzed, evaluating 108 treatment arms covering 9 antipsychotics and including 5,423 patients with QTc data (mean age = 12.8 ± 3.6 years, female = 32.1%). Treatments included aripiprazole: studies = 14; n = 814; haloperidol: studies = 1; n = 15; molindone: studies = 3; n = 125; olanzapine: studies = 5; n = 212; paliperidone: studies = 3; n = 177; pimozide: studies = 1; n = 25; quetiapine: studies = 5; n = 336; risperidone: studies = 23; n = 2,234; ziprasidone: studies = 10, n = 523; and placebo: studies = 19, n = 962. Within group, from baseline to endpoint,

aripiprazole significantly decreased the QTc interval (−1.44 milliseconds, CI = −2.63 to −0.26, $p = .017$), whereas risperidone (+1.68, CI = +0.67 to +2.70, $p = .001$) and especially ziprasidone (+8.74, CI = +5.19 to +12.30, $p < .001$) significantly increased QTc. Compared to pooled placebo arms, aripiprazole decreased QTc ($p = .007$), whereas ziprasidone increased QTc ($p < .001$). Compared to placebo, none of the investigated antipsychotics caused a significant increase in the incidence of the 3 studied QTc prolongation measures, but there was significant reporting bias.

Conclusion: Based on these data, the risk of pathological QTc prolongation seems low during treatment with the 9 studied antipsychotics in otherwise healthy youth. Nevertheless, because individual risk factors interact with medication-related QTc effects, both medication and patient factors need to be considered when choosing antipsychotic treatment.

Key Words: adolescents, antipsychotics, children, ECG, QTc

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The use of antipsychotics for children and adolescents has increased steadily over the past decades,^{1–3} although there are still many unanswered questions pertaining to the scope and magnitude of adverse events in this population, particularly regarding potential long-term harm.

Prolongation of the heart rate corrected QT interval (QTc), a condition that may progress to the malignant ventricular arrhythmia torsades de pointes (TdP) in susceptible individuals, is a known side effect associated with antipsychotics.⁴ TdP may lead to sudden cardiac death within minutes if not treated appropriately, and although the exact relationship between prolongation of the QTc interval and the risk of TdP remains elusive, QTc prolongation is still the best clinical surrogate marker for TdP risk.⁵

The QT interval on an electrocardiogram (ECG) is the period from the beginning of the Q-wave to the end of the T-wave. The QT interval shortens at higher heart rates, and should therefore be corrected for heart rate.^{6,7} Bazett's

($QTc = \frac{QT}{\sqrt{RR}}$)⁸ or Fridericia's ($QTc = \frac{QT}{\sqrt[3]{RR}}$)⁹ correction formula are most frequently used, where RR is the interval between the 2 R-waves preceding the T-wave in question.

Almost all antipsychotic agents have been associated with some degree of QTc prolongation. This happens primarily as a result of blockage of the rapidly activating delayed rectifier channel IKr, whereby the ion current responsible for repolarization is reduced.¹⁰ Other risk factors for QTc prolongation include electrolyte disturbances, drug-drug interactions related to polypharmacy, and structural heart diseases.¹⁰ Cardiovascular disease (CVD), a very common long-term comorbidity in patients with psychotic disorders,^{11–14} is an important risk factor for QTc prolongation and TdP.^{15,16} Finally, patients with inherited long QT syndrome (LQTS)¹⁷ may have no symptoms except for a higher predilection toward clinically significant QTc prolongation when exposed to other risk factors, including QTc-prolonging medications.¹⁸



This article is discussed in an editorial by Dr. Kaizad Munshi, Dr. Mark E. Alexander, and Dr. Paul Hammerness on page 9.



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Reviews and clinical trials that focus explicitly on ECG changes in children and adolescents during antipsychotic treatment are scarce.¹⁹⁻²¹ Therefore, the effect of individual antipsychotics on the QTc interval in young patients is still uncertain, and clinicians may be concerned when prescribing antipsychotics because of this uncertainty. QTc >450 milliseconds, and/or QTc prolongation >60 milliseconds, are often used as thresholds requiring increased attention in clinical settings,¹⁹ and it is recommended that physicians consider cardiovascular risk factors and status (including QTc interval) when choosing antipsychotic medications in youth and monitor QTc interval depending on patient- and treatment-related risk factors.^{22,23} To the best of our knowledge, this is the first systematic review and meta-analysis to focus on QTc changes based on clinical trials of antipsychotic treatment in this age group.

The purpose of this study was to systematically review and meta-analyze the current literature regarding effects of first- and second-generation antipsychotics (FGAs and SGAs) on the QTc interval in children and adolescents, and to use these data to help guide clinicians about the safe use of specific antipsychotics.

METHOD

Inclusion and Exclusion Criteria for Literature Search

Trials fulfilling the following characteristics were included: prospective study, randomized or not, with or without a comparator; patients aged <18 years; any antipsychotic treatment, with or without placebo arm; treatment indication was a psychiatric condition; and numerical QTc change data (reported or calculable).

Exclusion criteria were as follows: articles in other languages than English; records with no online abstract; reviews; trials not in children/adolescents; trials not in patients with psychiatric disorders; trials not using antipsychotics; studies that were not clinical trials; no reported/obtainable QTc data. Trials including both children/adolescents and adults were included, if the lower age limit was 16 years of age or below and at least 75% of participants were <18 years of age.

The primary outcome was the change in QTc interval at study endpoint compared to baseline. Key secondary outcomes included the difference between change in QTc in each antipsychotic group

compared to placebo in head-to-head trials as well as compared to all placebo groups pooled together. Additional secondary outcomes were number of events of QTc above study-defined threshold value (i.e., >440–470 milliseconds), events of QTc >500 milliseconds, and events of prolongation >60 milliseconds.

Source

Studies were identified by searching the electronic database PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) from database inception. The final search (described below) was performed on May 14, 2014.

Search Strategy

Search terms were as follows: (child OR children OR childhood OR adolescent OR adolescence OR youth); and (antipsychotic* OR neuroleptic* OR amisulpride OR aripiprazole OR asenapine OR blonanserin OR chlorpromazine OR clothiapine OR clozapine OR droperidol OR flupenthixol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR mesoridazine OR molindone OR mosapramine OR olanzapine OR paliperidone OR perphenazine OR perospirone OR pimozide OR prochlorperazine OR remoxipride OR risperidone OR sertindole OR sulpiride OR thioridazine OR thiothixene OR tiapride OR trifluoperazine OR quetiapine OR ziprasidone OR zuclopenthixol).

The resulting articles were filtered by “English language” and “Abstract available.” The asterisk after “antipsychotic” and “neuroleptic” served to produce all iterations of the search term.

Study Selection

Records that could be excluded at the title and abstract level were discarded. The remaining articles were saved. Each article was read through by the first author and discarded if ineligible. Articles that were not available online were requested through the library service at the University of Copenhagen. In articles mentioning that ECG was performed at baseline and follow-up but QTc values or QTc changes were not reported, these data were requested from the authors by e-mail.

Data Extraction

For each article, QTc measurements and other relevant data (see section “Data Items”) were entered into a database (Excel 2010, Microsoft, Redmond, USA). Change in QTc value from baseline to

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram, displaying the flowchart of the article search and selection process. Note: ECG = electrocardiogram; w/o = without.

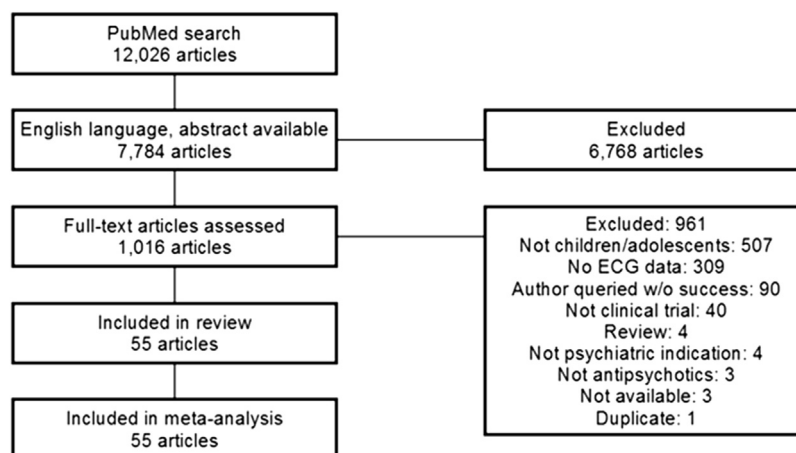


TABLE 1 Study Summary

Antipsychotics	No. of Studies and Patients	Indication, No. of Studies (%)	Design, No. of Studies (%)	Blinding, No. of Studies (%)	Patients per Study	Mean Dose (mg/d)	Duration (wk)	Mean Age (y)	% Female
Aripiprazole (ARI)	14 studies, 862 patients	TS = 3 (21.4) Irritability in AD = 2 (14.3) Any diagnosis = 1 (7.1) Aggression in CD = 1 (7.1) BD = 1 (7.1) BPI = 1 (7.1) CD = 1 (7.1) PDD-NOS and Asperger = 1 (7.1) SCZ = 1 (7.1) SCZ and acute mania = 1 (7.1) TD = 1 (7.1)	Prospective = 10 (71.4) RCT = 4 (28.6)	OL = 10 (71.4) DB = 4 (38.6)	40.2 ± 41.6	14.0 ± 3.7	15.0 ± 3.9	12.3 ± 3.5	30.2 ± 5.5
Molindone (MOL)	3 studies, 138 patients	E-O SCZ spectrum = 2 (66.7) ADHD = 1 (33.3)	RCT = 2 (66.7) RCT-E = 1 (33.3)	DB = 2 (66.7) OL = 1 (33.3)	23.0 ± 7.6	65.4 ± 8.2	15.5 ± 3.9	8.9 ± 3.0	28.4 ± 5.3
Olanzapine (OLA)	5 studies, 243 patients	E-O SCZ spectrum = 2 (40.0) Acute manic or mixed episode = 1 (20) Psychosis = 1 (20) SCZ = 1 (10)	RCT = 4 (80.0) RCT-E = 1 (10.0)	DB = 5 (100.0)	48.6 ± 36.0	10.2 ± 3.2	7.1 ± 2.7	15.4 ± 3.9	35.2 ± 5.9
Paliperidone (PALI)	3 studies, 179 patients	Autism with irritability = 1 (33.3) PDD-NOS and Asperger's = 1 (33.3) SCZ = 1 (33.3)	Prospective = 2 (66.7) RCT = 1 (33.3)	OL = 2 (66.7) DB = 1 (33.3)	29.8 ± 12.9	5.7 ± 2.4	6.4 ± 2.5	14.9 ± 3.9	31.1 ± 5.6
Placebo	19 studies, 1141 patients	SCZ = 5 (26.3) CD, ODD, DBD NOS = 4 (21.1) Acute manic or mixed episode = 2 (10.5) BD = 2 (10.5) Irritability in AD = 2 (10.5) AD = 1 (5.3) Anorexia nervosa = 1 (5.3) BPI = 1 (5.3) Overt aggressive behavior + CD, ODD, ADHD + IQ 60-91 = 1 (5.3)	RCT = 19 (100.0)	DB = 19 (100.0)	60.1 ± 34.6		10.8 ± 3.3	12.6 ± 3.5	30.8 ± 5.6
Quetiapine (QUE)	5 studies, 489 patients	Acute manic or mixed episode = 1 (20) ADHD+CD/ODD and aggression = 1 (20)	Prospective = 3 (60.0) RCT = 1 (20.0) RCTE = 1 (20.0)	OL = 3 (60.0) DB = 1 (20.0) SB = 1 (20.0)	81.5 ± 134.0	529.3 ± 23.0	22.4 ± 4.7	13.6 ± 3.7	38.9 ± 6.2

TABLE 1 Continued

Antipsychotics	No. of Studies and Patients	Indication, No. of Studies (%)	Design, No. of Studies (%)	Blinding, No. of Studies (%)	Patients per Study	Mean Dose (mg/d)	Duration (wk)	Mean Age (y)	% Female
Risperidone (RIS)	23 studies, 2,445 patients	Bipolar spectrum disorders = 1 (20) Mood symptoms other than BP-I = 1 (20) SCZ or BP-I = 1 (20) AD = 2 (8.7) Any = 2 (8.7) BD = 1 (4.3) BP-I = 1 (4.3) CD, ODD, DBD NOS = 9 (39.1) SCZ = 3 (13.0) E-O SCZ spectrum disorders = 2 (8.7) Behavioral problems in autism = 1 (4.3) Psychosis = 1 (4.3) Overt aggressive behavior + CD, ODD, ADHD + IQ 60-90 = 1 (4.3)	RCT = 13 (56.5) RCT-E = 6 (26.1) Prospective = 4 (17.4)	DB = 14 (60.9) OL = 9 (39.1)	78.9 ± 95.6	2.1 ± 1.5	29.0 ± 5.4	12.2 ± 3.5	30.0 ± 5.5
Ziprasidone (ZIP)	10 studies, 897 patients	BD = 3 (30.0) AD = 1 (10.0) SCZ = 2 (20.0) BPM, SCZ or schizoaffective disorder = 1 (10.0) Any diagnosis = 1 (10.0) TS, OCD, PDD = 1 (10.0) TS or chronic TD = 1 (10.0)	Prospective = 5 (50.0) RCT = 2 (20.0) RCT-E = 2 (20.0) PK = 1 (10.0)	OL = 8 (80.0) DB = 2 (20.0)	69.0 ± 76.9	62.7 ± 8.0	16.1 ± 4.0	14.4 ± 3.8	41.1 ± 6.4
Pimozide	1 study, 25 patients	TS	Prospective	OL	25	4.4	104.0	9.1	12.0
Haloperidol	1 study, 15 patients	Psychosis	RCT	DB	15	5.0	8.0	15.4	47.0
All trials	55 trials, 108 treatment arms, 6,434 patients	Disruptive behavior spectrum: 11 (20.0) Bipolar disorder spectrum: 10 (18.2) Schizophrenia spectrum: 10 (18.2) Autism spectrum: 7 (12.7) Tic disorder spectrum: 5 (9.1) SCZ and BD: 3 (5.5)	RCTs: 24 (43.6) Prospective trials: 21 (38.2) RCT-Es: 9 (16.3) PKs: 1 (1.8)	OL = 30 (54.5) DB = 24 (43.6) SB = 1 (1.8)	59.6 ± 72.0	ARI: 14.0 ± 3.7 MOL: 65.4 ± 8.2 OLA: 10.2 ± 3.2 PALI: 5.7 ± 2.4 QUE: 529.3 ± 23.0 RIS: 2.1 ± 1.5 ZIP: 62.7 ± 8.0	20.1 ± 4.5	12.8 ± 3.6	32.1 ± 5.7

TABLE 1 Continued

Antipsychotics	No. of Studies and Patients	Indication, No. of Studies (%)	Design, No. of Studies (%)	Blinding, No. of Studies (%)	Patients per Study	Mean Dose (mg/d)	Duration (wk)	Mean Age (y)	% Female
		Any diagnosis: 3 (5.5) Aggression in ADHD/DB: 2 (3.6) Mood disorders other than BD: 1 (1.8) Anorexia nervosa: 1 (1.8) ADHD: 1 (1.8) TS/OCD/Autism: 1 (1.8)							
Note: AD = autistic disorder; ADHD = attention-deficit/hyperactivity disorder; BPI = bipolar I disorder; BD = bipolar disorder; DB = double-blind; DBD NOS = disruptive behavior disorder not otherwise specified; E-O = early onset; N/A = not applicable (i.e. could not be summarized from table); OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; Ol = open label; PK = pharmacokinetic; RCT = randomized controlled trial; RCTE = RCT extension; SB = single-blind; SCZ = schizophrenia; TD = tic disorder; TS = Tourette syndrome.									

last follow-up (Δ QTc) was entered directly where possible; if only baseline and follow-up data were reported, Δ QTc was calculated by subtracting the baseline value from the follow-up value. When standard deviations (SDs) were missing, they were imputed using the pooled SDs from studies reporting on the same antipsychotic or placebo.

The extraction process was performed by the first author (K.G.J.) and repeated by a second author (A.K.P.) to minimize errors. In case of disagreement, a consensus was reached. If needed, a third author (C.U.C.) was involved.

Where multiple follow-up data were noted, only the last (endpoint) value was entered into the database. For articles containing data on both an acute trial and an extension trial, these data were treated as separate treatment arms. For trials reporting data for different time points pre- and post-dose (i.e., pharmacokinetic trials), pre-dose ECG at follow-up was chosen. Where QTc values using several correction formulae were reported, Bazett's formula was chosen to minimize differences between comparisons, as this correction formula is most frequently used.

There was 1 case of duplicate publication, in which the ECG results from 1 study²⁴ were re-evaluated more thoroughly in a second study.²⁵ In this case, after corresponding with the authors, we chose to include the more thorough analyses.

Different studies used different cut-off values for the term "QTc prolongation." Most studies used a cut-off value of 450 milliseconds, a few used 440 milliseconds, and even fewer used 460 or 470 milliseconds. To analyze as many events as possible, we accepted this difference and abstracted events for these slightly heterogeneously defined thresholds. However, as a number of studies by Janssen pharmaceuticals used cut-off values of QTc that were not comparable to those in the other studies (i.e., normal: females: ≤ 450 milliseconds, males: ≤ 430 milliseconds; borderline: females: 451–470 milliseconds, males: 431–450 milliseconds; prolonged: females: >470 –500 milliseconds, males: >450 –500 milliseconds; pathological: >500 milliseconds [females and males]),^{26–40} we excluded the categorical outcomes from these trials.

For 1 trial,⁴¹ QTc was calculated using Bazett's formula for children with a heart rate of <60 beats per minute (beats/min) and Fridericia's for children with heart rate ≥ 60 beats/min. As the number of patients was not provided for each of these categories, mean change in QTc and SD were merged per treatment arm based on the proportion of patients with heart rate of <60 and ≥ 60 , respectively.

Data Items

For each trial, the following data were extracted where available. Trial settings: Authors, year, type of trial, study settings, blinding procedures, duration of intervention, number of patients, whether or not missing data were handled by methods such as last observation carried forward (LOCF), method of QT assessment, QTc correction formula used, and affiliations to or contributions from the pharmaceutical industry. Intervention: antipsychotics evaluated, indication, target dose range, and mean dose ($\pm$ SD). Patient characteristics: age range, mean age ($\pm$ SD), number of patients with follow-up ECG, use of concomitant medication, and sex distribution. Outcome measures: manual versus machine reading of QTc, baseline and endpoint QTc data ($\pm$ SD), Δ QTc ($\pm$ SD) and statistics/*p* value of QTc change, number of patients with study-defined QTc prolongation, number of patients with QTc >500 milliseconds, and number of patients with QTc change >60 milliseconds.

Risk of Bias in Individual Studies

Risk of bias was examined for blinded randomized studies using the Cochrane bias method as described in the Cochrane Handbook,⁴²

where the following dimensions are evaluated: sequence generation, allocation concealment, blinding participants and personnel, blinding of outcome assessment, incomplete data, selective outcome reporting, and other sources of bias.

For the non-randomized studies, we assessed risk of bias based on the dimensions outlined by the Cochrane Collaboration.⁴² For the purpose of this review, each non-RCT was assessed using the following questions: Selection bias: Were inclusion criteria clearly defined? Was the study sample size adequate (low risk $n > 20$, unclear ≥ 15 –20, high risk < 15)? Performance bias: Were health care providers blinded? Detection bias: Was ECG assessed by non-blinded raters (high risk) or by machine (low risk) or unknown (unclear risk)? Were the methods for ECG acquisition clearly defined and identical (morning ECG, at rest, supine)? Attrition bias: Were statistical methods applied for losses to follow-up (for instance, LOCF)? Reporting bias (concerning publication biases and selective reporting of results): Was there indication of selective reporting (i.e., missing data on QTc or on number of patients with prolonged QTc)? and other sources of bias.

The purpose of this risk of bias assessment was to provide full transparency to allow readers to estimate the overall quality of the included trials; however, we chose not to exclude any trials based on this assessment.

Data Analysis

Demographic population, illness, and treatment data were analyzed using descriptive statistics. QTc data were entered into and meta-analyzed using Comprehensive Meta-Analysis Version 3.0 (<http://www.meta-analysis.com/>), Biostat, Englewood, USA.

To pool and compare change in QTc from baseline to last assessment across treatment groups, weighted mean difference (WMD) $\pm$ 95% CI was used. For comparison across categorical outcomes, odds ratios (ORs) with 95% CIs were used. Categorical outcomes included number of patients with the following: study-defined QTc prolongation (i.e., > 440 , > 450 , > 460 , > 470 milliseconds); QTc > 500 milliseconds; and QTc change from baseline to last assessment > 60 milliseconds. We performed analyses using 2 different sets of studies: single group analyses of all available study arms with a given treatment arm, namely, specific antipsychotic or placebo; and pairwise analyses of antipsychotic-placebo comparisons in placebo-controlled trials. There were too few active controlled trials to run antipsychotic versus antipsychotic treatment

analyses. In the study arm-based data set, all outcomes were compared both within treatment group and comparing individually pooled antipsychotic groups against the pooled placebo arms. In addition, exploratory meta-regression analyses were performed, assessing the following moderator variables: study duration, mean age, percentage of females, and medication dose.

Heterogeneity of outcomes was studied using the I^2 statistic, with $I^2 \geq 50\%$ indicating significant heterogeneity, as well as the χ^2 test for heterogeneity. All tests used random effects models⁴³ and were 2-sided, and α was set at 0.05. We used funnel graphs (trial effect against trial size) to investigate the likelihood of publication bias.⁴⁴

RESULTS

Search Results

The electronic search yielded 12,026 hits. After filtering for English language and abstract availability, a total of 7,784 abstracts were downloaded. Altogether, 6,768 articles were excluded at the title/abstract level. The resulting 1,016 articles were further evaluated by the first author, of which 961 met the exclusion criteria listed above. Figure 1 is the Consolidated Standards of Reporting Trials (CONSORT) diagram showing the overall search process. In total, 55 articles contained sufficient QTc data and were included. For 19 studies, authors/pharmaceutical companies shared previously unpublished data upon request.

Study, Patient, and Treatment Characteristics

A total of 55 studies^{25–41,45–82} were reviewed, evaluating 108 treatment arms including 6,434 patients on 9 different antipsychotics or placebo, of which 5,423 had QTc data (weighted mean age = 12.8 ± 3.6 years, 32.1% female). Only 4 studies examined the effect of antipsychotic treatment on cardiac conduction as their primary aim^{47,49,59,78}; in the remaining trials, ECG changes were a secondary safety assessment. Table 1 summarizes the included studies and basic characteristics across treatment arms. Details for each included study can be found in Table S1 (available online).

TABLE 2 Meta-Analysis of Corrected QT Interval (QTc) Change With Individual Antipsychotics and Placebo (All Designs)

Treatment	No. of Treatment Arms	No. of Patients	Mean Δ QTc (milliseconds)	95% CI		p vs. 0, Within Group	p Each Group vs. Placebo	Heterogeneity Within Group	
				Lower	Upper			p	I^2 (%)
Placebo	19	962	1.30	−0.28	2.88	.108		.027*	42.30
Aripiprazole	20	814	−1.44	−2.63	−0.26	.017*	.007**	.504	0.00
Molindone	6	125	−2.20	−5.84	1.44	.237	.084	.147	38.85
Olanzapine	5	212	0.29	−4.92	5.50	.913	.716	<.0001***	83.08
Paliperidone	6	177	0.83	−3.22	4.88	.689	.832	.074	50.17
Quetiapine	6	336	1.92	−2.58	6.42	.403	.799	.014*	65.01
Risperidone	31	2,234	1.68	0.67	2.70	.001**	.689	.271	12.41
Ziprasidone	13	523	8.74	5.19	12.30	<.001***	<.0001***	<.0001***	75.69
Total	106 ^a	5,383 ^a							

Note: Δ QTc = change in corrected QT interval from baseline to last follow-up.

^aOne study with haloperidol and one with pimozide were not able to be meta-analyzed.

* $p < .05$; ** $p < .01$; *** $p < .001$.

Altogether, 24 studies (43.6%) were blinded randomized controlled trials (RCTs); 19 (34.5%) were placebo controlled. Treatments included aripiprazole: studies = 14, $n = 814$; haloperidol: studies = 1, $n = 15$; molindone: studies = 3, $n = 125$; olanzapine: studies = 5, $n = 212$; paliperidone: studies = 3, $n = 177$; pimozide: studies = 1, $n = 25$; quetiapine: studies = 5, $n = 336$; risperidone: studies = 23, $n = 2,234$; ziprasidone: studies = 10, $n = 523$; and placebo: studies = 19, $n = 962$. Weighted mean doses were as follows: aripiprazole: 14.0 ± 3.7 mg/d; haloperidol: 5.0 mg/d; molindone: 65.4 ± 8.2 mg/d; olanzapine: 10.2 ± 3.2 mg/d; paliperidone: 5.7 ± 2.4 mg/d; pimozide: 4.4 mg/d; quetiapine: 529.3 ± 23.0 mg/d; risperidone: 2.1 ± 1.5 mg/d; ziprasidone: 62.7 ± 8.0 mg/d. The mean trial duration was 16.3 weeks (<12 weeks: 33 trials [60.0%]; ≥ 12 to <24 weeks: 7 trials [12.7%]; ≥ 24 weeks: 15 trials [27.3%]).

The most frequent indications were a diagnosis of disruptive behavior disorders (conduct disorder [CD], oppositional defiant disorder [ODD], and disruptive behavior disorder not otherwise specified [DBD-NOS]: 11 studies, 20.0%), schizophrenia spectrum disorders (10 studies, 18.2%), or bipolar spectrum disorders (10 studies, 18.2%).

Meta-Analysis of QTc Change

Pooling all study arms of individual antipsychotics or placebo together (Table 2, Figure 2, and Figure S1, available online), aripiprazole was associated with a significant decrease in the QTc interval (-1.44 milliseconds, CI = -2.63 to -0.26 , $p = .017$). A significant increase in the QTc duration was found with risperidone ($+1.68$ milliseconds, CI = $+0.67$ to $+2.70$, $p = .001$) and, especially, ziprasidone ($+8.74$ milliseconds, CI = $+5.19$ to $+12.30$, $p < .001$). None of the other antipsychotics or placebo were associated with a QTc change that was significantly different from 0. QTc change results were significantly heterogeneous for olanzapine ($I^2 = 83.1\%$, $p < .0001$), ziprasidone ($I^2 = 76\%$, $p < .0001$), quetiapine ($I^2 = 65.0\%$, $p = .014$), and placebo ($I^2 = 42.3\%$, $p = .027$).

The single studies with pimozide or haloperidol could not be meta-analyzed. In 1 study of pimozide versus aripiprazole,⁵⁹ the mean QTc change for pimozide was 25.20 milliseconds ($n = 25$). In 1 haloperidol study,⁷⁴ the mean QTc change was 8 milliseconds ($n = 15$).

Comparing antipsychotics to pooled placebo, the change with risperidone was no longer significant, but aripiprazole was still associated with a significantly shorter QTc ($p = .007$), whereas ziprasidone was associated with a significantly longer QTc ($p < .001$).

Across the placebo-controlled studies, only the QTc increase associated with ziprasidone ($p = .020$) was significant compared to placebo; all other antipsychotics had p values ranging from .359 to .856. Table 3 and Figure S2, available online, show the outcomes from the meta-analysis for individual medications versus placebo.

Meta-Regression Analysis of QTc Change

In meta-regression analyses, we investigated the effect of age, sex, duration of treatment, and antipsychotic dose on the relationship between individual antipsychotics and QTc (Table S2, available online). For quetiapine, we found a significant inverse dose relationship ($p < .001$) and also an inverse relationship to age ($p < .001$) and percentage of females ($p = .001$). We also found a significant association between duration of treatment and QTc increase for risperidone ($p = .012$), and there was a trend toward an inverse dose-dependency for aripiprazole ($p = .059$), indicating that higher doses were associated with greater QTc decrease.

Meta-Analysis of QTc Prolongation Outcomes

Compared to placebo, none of the investigated antipsychotics caused a significant increase in the incidence of the 3 studied QTc prolongation measures (Table 4). However, the number of events was numerically higher for ziprasidone than for any of the other antipsychotics. In particular, the percentage of patients with an increase from baseline to endpoint >60 milliseconds was 3.14% for ziprasidone, 1.02% for placebo, and 0.45% for risperidone.

FIGURE 2 Forest plot of pooled corrected QT (QTc) changes. Note: Pooled QTc changes (milliseconds $\pm$ 95% CI) are shown for each antipsychotic with data from ≥ 2 studies and placebo.

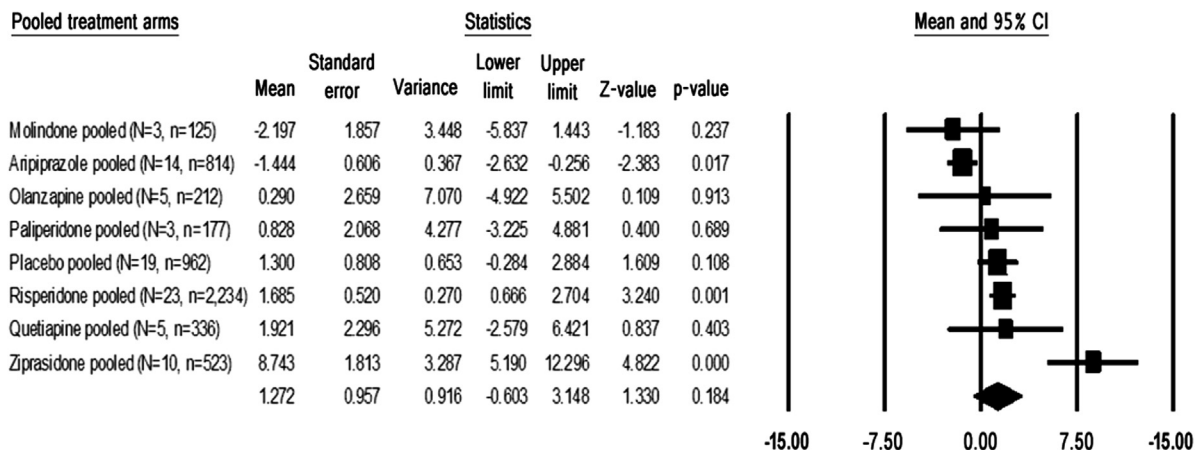


TABLE 3 Effect Size of Corrected QT Interval (QTc) Change With Antipsychotics Versus Placebo in Placebo-Controlled Trials

Treatment	No. of Treatment Arms	No. of Patients	Effect Size, Cohen's d	95% CI		p vs. Placebo	Heterogeneity Within Group	
				Lower	Upper		p	I ² (%)
Aripiprazole	8	571	−0.07	−0.21	0.08	.359	.942	0.00
Olanzapine	2	148	−0.04	−0.33	0.25	.783	.530	0.00
Paliperidone	4	139	0.03	−0.31	0.37	.850	.554	0.00
Quetiapine	1	15	−0.30	−1.02	0.42	.410	1.000	0.00
Risperidone	12	573	−0.01	−0.14	0.11	.856	.426	1.90
Ziprasidone	2	218	0.50	0.08	0.92	.020*	.083	66.78

*p < .05.

Risk of Bias Across and Within Trials

Although lack of blinding should have little or no effect on ECG-based QT interval assessments, in open trials in which QTc measurements were made manually, assessors may have been partial toward or against the investigated drug. As 78% of included studies did not describe how QTc measurements were made, it is difficult to assess the impact of this confounding effect, but most likely automated QTc measurements were used. The potential risk of bias was assessed separately for blinded RCTs (Table S3 and Figure S3, available online) and remaining open trials (Table S4 and Figure S4, available online).

Across the 24 randomized trials, we found the following risk of bias characteristics, as outlined in the Cochrane Handbook, chapter 13⁴² (see Risk of Bias in Individual Studies section in this article): sequence generation: low risk: 14 trials (58.3%), unclear: 10 (41.7%), high risk: 0 (0%); allocation concealment: low risk: 8 trials (33.3%), unclear: 15 (62.5%), high risk: 1 (4.2%); blinding participants and personnel: low risk: 6 trials (25%), unclear: 17 (70.8%), high risk: 1 (4.2%); blinding of outcome assessment: low risk: 8 trials (33.3%), unclear: 16 (66.7%), high risk: 0 (0%); incomplete data: low risk: 15 trials (62.5%), unclear: 9 (37.5%), high risk: 0 (0%); Selective outcome reporting: low risk 5 trials (20.8%), unclear: 7 (29.2%), high risk: 12 (50%), high risk mostly being due to the fact that many trials did not report all 3 relevant categorical outcomes of QTc prolongation); other sources of bias: low risk: 23 trials (95.8%), unclear: 1 (4.2%), and high risk: 0 (0%).

For the 31 nonrandomized trials, clinicians were not blinded in all studies. Except for 1 trial (3.2%), in which the exclusion criteria included baseline QTc value <425,⁶⁵ none of the studies had clearly identifiable sources of bias in the inclusion criteria. Sample size was adequate in 22 trials (71.0%). Risk of bias due to unblinded ECG assessments was low in 4 trials (12.9%), unclear in 23 (74.2%), and high in 4 (12.9%). Differences in ECG procedures: low risk in 5 trials (16.1%), unclear in 26 (83.9%), and high risk in 0 (0%). Inadequate handling of losses to follow-up: low risk: 15 trials (48.4%), unclear: 4 (12.9%), and high risk: 12 (38.7%). Selective reporting: low risk: 11 trials (35.5%), unclear: 0 (0%), and high: 20 (64.5%, high risk mostly being due to the fact that many trials did not report all 3 relevant categorical outcomes of QTc prolongation). Finally, low risk of bias by other

sources of bias was identified in 27 (87.1%) trials, unclear in 3 (9.7%), and high in 1 (3.2%).

Publication Bias

There was no discernible publication bias regarding QTc change, either by treatment group or in the head-to-head trials against placebo (data not shown). Although for risperidone and ziprasidone there were asymmetrical funnel plots, the bias was in the direction of reporting larger QTc changes (data not shown). However, regarding each of the 3 categorical outcomes relating to prolongation of the QTc, which were reported only in subgroups of the studies, there was significant publication bias indicating missing reports of QTc prolongation (data not shown). Notably, this publication bias applied to the antipsychotics and to placebo to the same degree.

DISCUSSION

In this meta-analysis, we found that ziprasidone was associated with a significant increase in the QTc interval both within drug comparisons and also when compared to pooled placebo or compared directly in placebo-controlled trials. This finding is consistent with findings in adults.^{16,83-85} Although the magnitude of change (+8.74 milliseconds, CI = +5.19 to +12.30 milliseconds) seemed higher in youth than in a recent review of ziprasidone in 4,306 adults (+3.6 milliseconds, CI = −37.2 to +44.4 milliseconds),⁸⁶ the upper bound of the 95% CI, which indicates risk for individuals with especially large QTc increases, was almost 4 times higher in the adult population. Although the incidence of QTc prolongation across the 3 categorical outcomes was highest for ziprasidone, incidences were very low and not different from pooled placebo. Nevertheless, in the largest randomized active-controlled trial that compared ziprasidone with olanzapine in more than 18,000 adults, there was no difference in cardiac mortality or all-cause mortality over a 1-year duration,⁸⁷ calling into question the clinical relevance of QTc prolongation even with ziprasidone. However, these results should be interpreted in light of the fact that participants in safety studies are usually free of many other, clinically encountered risk factors, and often a baseline QTc value exceeding 450 milliseconds is an exclusion criterion.

TABLE 4 Incidence of Corrected QT Interval (QTc) Prolongation Across Drugs

Drug	Patients With QTc			Patients With			Patients With		
	> Cut-Off, n	Total n	%	QTc > 500 ms, n	Total n	%	Δ QTc > 60 ms, n	Total n	%
Placebo	5	265	1.89	0	425	0.00	3	295	1.02
Aripiprazole	5	232	2.16	0	257	0.00	0	97	0.00
Haloperidol	ND								
Molindone	0	65	0.00	0	65	0.00	0	65	0.00
Olanzapine	ND								
Paliperidone	0	154	0.00	0	154	0.00	0	154	0.00
Pimozide	ND			0	25	0.00	ND		
Quetiapine	1	64	1.56	0	64	0.00	0	49	0.00
Risperidone	9	711	1.27	0	1,402	0.00	6	1,348	0.45
Ziprasidone	16	500	3.20	1	500	0.20	12	382	3.14
Total	36	1,991	1.81	1	2,892	0.03	21	2,390	0.88

Note: Δ QTc = change in corrected QT interval from baseline to last follow-up; ms = milliseconds; ND = no data.

Across the included antipsychotics, aripiprazole significantly shortened the QTc interval, also compared to placebo, with a trend toward dose dependency. This is comparable to results in adults. In a meta-analysis of 828 adults treated with aripiprazole, aripiprazole decreased QTc compared to baseline, but not compared to placebo (−4.16 versus −3.56 milliseconds).⁸⁸

Risperidone also increased the duration of the QTc interval, but this effect could not be differentiated from placebo, either using the pooled placebo arms or in head-to-head trials. None of the other antipsychotics assessed in this meta-analysis were significantly associated with increased QTc interval; however, the substantial QTc increase for pimozide seen in 1 single study⁵⁹ suggests that, as is the case for adults,^{4,16} pimozide should very likely be avoided in youth with relevant risk factors for cardiac conduction abnormalities.

Of note, in a large multiple treatments meta-analysis,⁸³ the effect on QTc in adults by aripiprazole was not significantly different from placebo (OR = 0.01; CI = −0.13 to 0.15), whereas risperidone (OR = 0.25; CI = 0.15–0.36) and ziprasidone (OR = 0.41; CI = 0.31–0.51) increased QTc significantly compared to placebo.

Several limitations of our study require consideration. A more comprehensive list of trials may have been achieved by searching other databases as well, such as the Cochrane Database and Medline. However, PubMed also receives data from these sources, and an extensive overlap would be suspected. Also, including only generic names and not brand names might have limited the number of trials, but it is common practice to use generic names for reports of clinical trials.

There were a number of methodological issues in the included trials on which we based our meta-analysis and conclusions. First, most studies (78.2%) lacked a description of the specific method for correcting the QT interval based on heart rate, which may explain the large heterogeneity observed, and only 12 studies (21.8%) used manual readings. Second, authors used different and often inconsistent cut-off values when reporting QTc prolongation outcomes considered clinically relevant. Third, reporting of QTc outcomes was generally sparse. Only 6 studies (10.9%) reported the

method for QT correction, baseline, endpoint, and change in QTc, each with SD, and the number of patients with prolongation events. Fourth, most studies were short-term, yet most of the QTc effect likely occurs early, as we did not find a trial duration effect on QTc change in our meta-regression analyses, except for risperidone, although these analyses may have lacked power.

Furthermore, there was generally little focus on possible ECG changes in efficacy and even in tolerability studies. Despite the widespread use of antipsychotics in youth and hundreds of prospective studies, only 55 studies had analyzable data. In fact, only 36 studies (65.5%) had published numerically reported data, and only 18 studies (32.7%) provided all 3 relevant categorical outcome data on the number of patients with QTc prolongation. The dearth of QTc data is particularly notable regarding randomized and active controlled antipsychotic trials. We were able to obtain data from 19 studies for which specific data were not reported in the published article, often simply stating that ECG findings were “normal.” The number of articles missing data on some or all categorical QTc prolongation indices may indicate a potential reporting bias, particularly when authors did not define broadly used terms, such as “no abnormality,” “no clinically significant ECG changes,” or “possible mild conduction anomaly.”³⁷

Regarding study quality, we generally found very few instances of high risk of bias in any of the domains outlined by the Cochrane Handbook.⁴² The RCTs identified by our search were generally of high standard; however, details of randomization, blinding, and allocation concealment were not always provided systematically.

Finally, the majority of RCTs on antipsychotics in children and adolescents are conducted by pharmaceutical companies, which could lead to reporting biases⁸⁹; yet, without data from these industry-sponsored trials, we would be left with only 17 studies (30.9%). Thus, investigator-initiated, randomized, and long-term controlled studies should be encouraged.

Even though sudden death is extremely rare in children and adolescents,⁹⁰ it is important that clinicians are aware of the potential of antipsychotics to prolong QTc. Risk

factors for developing QTc prolongation, as well as for the probability that QTc prolongation has clinical implications, accumulate during life and do so more rapidly in individuals with psychotic disorders who often acquire cardiovascular risk factors.⁹¹ Indeed, a very recent study of 61 youths with type 1 diabetes mellitus showed that, compared to healthy controls, patients with diabetes had a longer mean QTc duration and higher incidence of QTc prolongation.⁹² However, the association between duration of QTc interval and the risk of TdP is by no means linear, and more research is needed to shed light on the connection between the biomarker and the clinical endpoint.⁹³

Based on our findings and with respect to the impact on cardiac repolarization, first- and second-generation antipsychotics appear to confer little risk of QTc prolongation in otherwise healthy children and adolescents. Nevertheless, because individual risk factors interact with medication-related QTc effects, both medication and patient factors need to be considered when making antipsychotic medication choices. Consideration of these factors is especially relevant in clinical scenarios that may indicate higher patient-related risk factors, such as family history of long QT syndrome or sudden death, prior ECG with a QTc >450 milliseconds, palpitations at rest without anxiety, and dizziness or, especially, syncope upon exertion.⁴⁹ &

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Pre-treatment cardiometabolic status in youth with early-onset psychosis: baseline results from the TEA trial

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Abstract

Objective: The present study describes pre-treatment cardiometabolic constitution in children and adolescents with first-episode psychosis (FEP).

Method: Baseline cardiometabolic assessment was performed in youths aged 12-17 years with FEP entering the Tolerability and Efficacy of Antipsychotics (TEA) trial and matched healthy controls. Patients were included between 1st of May 2010 and 1st of March 2014. ICD-10 was used as the diagnostic classification system. Cardiometabolic risk markers were compared between patients versus (vs.) controls and antipsychotic-naïve vs. antipsychotic-exposed patients.

Results: Comparing 113 youth with FEP (age=15.74±1.36 years, males=30.1%, schizophrenia-spectrum disorders=92.9%, antipsychotic-naïve: n=57) to 60 controls, patients had higher waist circumference (WC) z-scores (1.13±1.65 vs. 0.42±1.27, p=.018), cholesterol (4.10±0.71 vs. 3.79±0.49 mmol/L, p=.014), low-density lipoproteins (2.37±0.56 vs. 2.13±0.51, p=.012) and non-high density lipoproteins (non-HDL) (2.58±1.60 vs. 2.52±0.52, p=.018). More patients than controls (42.9% vs. 20.3%, p=.019) and antipsychotic-naïve vs -exposed (51.9% vs. 34.0%, p=.023) had a WC >90th percentile. Hypercholesterolemia (34.0% vs. 12.5%, p=.015) was more frequent in patients, while decreased HDL was more frequent in controls (32.5% vs. 19.0%, p=.032). Family history of type 2 diabetes mellitus or dyslipidemia was associated with significantly increased cardiometabolic risk, while previous antipsychotic exposure was not. Early age of onset predicted increased BMI and WC z-scores, while diagnosis of schizophrenia and higher Clinical Global Impression-Severity score was associated with increased blood lipids.

Conclusion: Youths with FEP had significantly greater WC and lipid abnormalities than matched controls, regardless of antipsychotic exposure. In youths with FEP, elevated metabolic risk predates antipsychotic exposure.

Key words: Early Onset Psychosis, Metabolic status, Antipsychotic naïve

ClinicalTrials.gov: NCT01119014, EudraCT: 2009-016715-38 (<https://eudract.ema.europa.eu/>)

Introduction

The shorter life expectancy in patients diagnosed with psychotic disorders, such as schizophrenia, is largely due to an increased risk of developing obesity, type 2 diabetes mellitus (T2DM)¹ and cardiovascular diseases (i.e. coronary heart disease, stroke and pulmonary embolism).²⁻⁴ In a Swedish population-based study of 9162 discharged with schizophrenia from 1973-95, cardiovascular disease was the main cause of

excess death in females, while in males suicide was the primary cause.⁵ The elevated risk results from combined effects of genetic factors, unhealthy diet, sedentary lifestyle, and adverse antipsychotic effects.⁶⁻¹⁴ Compared to adults, youth with early-onset psychotic disorders have a poorer prognosis¹⁵⁻¹⁷ and an increased risk of developing adverse effects from antipsychotic treatment.^{4,7,8,18} In addition, early introduction of antipsychotics that may be needed for several years, translates into longer lifetime exposure to

their adverse effects. Although extensively studied, the mechanisms leading to antipsychotic-related weight gain and disturbed glucose and lipid metabolism are complex and incompletely understood.^{7,19,20} As the number of antipsychotic prescriptions for children and adolescents increases,²¹⁻²³ there is an urgent need to better understand the factors associated with cardiovascular risk factors and morbidity, including factors related or unrelated to antipsychotic use.

The primary aim of this study was to compare cardiometabolic risk parameters in antipsychotic-naïve youths with first episode psychosis (FEP) to matched healthy controls in order to gain a better understanding of treatment-independent risk factors already present before antipsychotic exposure. The primary hypothesis was that youths with FEP have higher body mass index (BMI), waist circumference (WC), blood sugar and lipids than matched healthy controls. The secondary aim was to identify significant correlates of cardiometabolic risks in patients with FEP, including demographic variables, smoking, cardiovascular disease in first-degree relatives (FDR), measures of duration and severity of psychotic illness and previous antipsychotic treatment. The secondary hypothesis was that the presence of cardiovascular disease in FDR and higher severity of psychopathology predict higher risk for metabolic disturbances.

Methods

Study design

The present study refers to baseline data of the Tolerability and Efficacy of Antipsychotics (TEA) trial, a 12-week, investigator-initiated, randomized, double-blinded, multicenter trial of the effects of aripiprazole versus quetiapine ER in children and adolescents aged 12-17 years with FEP. The inclusion period ran from May 2010 to

March 2014. Seven child and adolescence mental health centers across Denmark, covering all university clinics, participated in the trial. A brief outline of the methods is presented below; the detailed TEA trial protocol has been published.²⁴ The trial is registered at ClinicalTrials.gov: NCT01119014, EudraCT: 2009-016715-38, and approved by Danish Medicines Agency: 2612-4168, The Ethics Committee of Capital Region of Denmark: H-3-2009-123 and Danish Data Protection Agency: 2009-41-3991.

Subjects

Physicians at the University Hospital clinics referred youths aged 12-17 years old who seemed eligible for the trial, i.e., who suffered from psychotic symptoms to a degree where antipsychotic treatment was warranted. Investigators screened eligible patients using the Positive And Negative Syndrome Scale (PANSS) interview to verify the presence and severity of psychotic symptoms. Inclusion criteria were: 1) Children and adolescents aged 12-17 years, both sexes; 2) in- or outpatients; 3) meeting the diagnostic criteria for ICD-10²⁵ F20 (Schizophrenia), F22 (Persistent delusional disorders), F23 (Acute and transient psychotic disorders), F24 (Induced delusional disorders), F25 (Schizoaffective disorders), F28/F29 (Other/Unspecified nonorganic psychosis), F30.2 (Mania with psychotic symptoms), F31.2 (Bipolar affective disorder, current episode manic with psychotic symptoms), F31.5 (Bipolar affective disorder, current episode severe depression with psychotic symptoms), F32.3 (Severe depressive episode with psychotic symptoms), or F33.3 (Recurrent depressive episode, current episode severe with psychotic symptom); 4) clinical indication for antipsychotic treatment; 5) presence of psychotic symptoms scoring ≥ 4 on ≥ 1 of the following PANSS²⁶ items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual

thought content); as well as a total PANSS score >60 points; 6) antipsychotic-naïve or limited exposure (i.e., up to 12 months in the past year for psychosis, or no more than 1 week lifetime for any non-psychotic indication), and 7) written and signed informed consent by caretakers. Exclusion criteria included: 1) Compulsory treatment, i.e. pharmacological treatment or hospital admission, instituted by the treating physician against the patients' will; 2) drug-induced or organic psychosis; 3) severe chronic somatic illness or a history of severe head trauma; 4) pregnancy or lactation; 5) substance abuse fulfilling the criteria of ICD-10 F1X.2 dependence syndrome within the last year; 6) allergy towards the investigational drugs or known lactose intolerance; 7) lack of informed consent.

In patients fulfilling inclusion criteria, trial interventional medication was initiated by the investigators (in collaboration with the treating physician) according to the TEA protocol.²⁴ At week 4, participants underwent a Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL)²⁷ interview covering the last 8 weeks (i.e., from 4 weeks prior to and 4 weeks after randomization) in order to precisely establish their specific diagnosis.

Healthy controls

The control sample consisted of 60 psychiatrically and somatic healthy youths (as per screening with K-SADS-PL²⁷ (both subjects and parents), somatic history and clinical examination at study entry), who were recruited based on a random data extraction from the Danish Centralized Civil Register (government-owned registry of all residents in Denmark, located in Copenhagen (<http://sundhedsdatastyrelsen.dk/da/forskerservice>)). Controls were matched 1:2 to the enrolled patients on sex, age and parental education.^{28,29}

Assessments

Before randomization, included patients underwent comprehensive physical assessments, including height, weight, WC, heart rate and blood pressure. Thyroid Stimulating Hormone (TSH), fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides were analyzed at the laboratory facilities of each site, while all fasting plasma insulin samples were analyzed with Roche Cobas e 411 (Roche Professional Diagnostics, Basel, Switzerland) at the Steno Diabetes Center, Copenhagen. The choice of insulin over glycosylated hemoglobin A1C (Hb1AC) reflects research indicating that the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is a more valid marker of the risk of developing diabetes and metabolic syndrome than Hb1AC.³⁰⁻³² TSH was assessed, as hypo- or hyperthyroidism may affect both psychopathology and metabolism. Patients and their caregivers underwent systematic interviews regarding level of parental education,²⁸ participants' smoking status and use of alcohol and illicit drugs. Clinical Global Impression (CGI) scale,³³ Global Assessment of Psychosocial Disability (GAPD)³⁴ and duration of untreated psychosis (DUP)³⁵ was determined by the investigator. Urine samples were collected and tested for presence of illicit drugs but determination of substance abuse did not lead to exclusion unless criteria for dependency syndrome during the past year were fulfilled. The presence or absence of psychotic or somatic illnesses in first degree relatives was examined through systematic questions covering heart disease, diabetes type 1 and 2, dyslipidemia, obesity and other somatic disorders (e.g., epilepsy or other neurological disorders). Any pre-existing somatic illness in included participants was registered. Information regarding patients' concomitant medication at the time of inclusion was collected.

Outcomes

We assessed intermediate risk factors for developing cardiovascular disease, including elevated blood pressure (BP), increased glucose, hyperinsulinemia, insulin resistance, dyslipidemia (i.e., increased fasting cholesterol and/or triglycerides), and overweight/obesity.³⁶

The metabolic syndrome (MS) is defined as a cluster of measurable and modifiable risk factors which significantly increases the risk of T2DM and cardiovascular disease in adults as well as in children and adolescents.³⁷ Table S1, available online, shows the age-dependent MS definition by the International Diabetes Foundation (IDF).

For the purpose of this article, WC was compared to the general population, using age-stratified means and 90th percentiles in n=5,725 adolescents from a Norwegian study,³⁸ as the dietary³⁹ and physical habits⁴⁰ of Denmark and Norway are comparable, and no recent population based Danish standards for WC were available.

In order to determine the age- and sex-adjusted z-scores for BMI $\left(\frac{\text{weight (kg)}}{(\text{height (m)})^2}\right)$ in each individual, the LMS method⁴¹ was used, which summarizes the distribution of the dependent variable at each age interval by its median (M) and coefficient of variation (S), plus a measure of skewness based on the Box-Cox power (L) required to transform the data to normality.⁴² Accordingly, the BMI was transformed to its z-score by the formula:

$$z = \frac{\left(\frac{\text{BMI}}{M}\right)^L - 1}{L \times S} \text{ for } L \neq 0$$

The age- and sex-adjusted values (at age intervals of 0.01 years) for L, M and S, were based on data from 12,671 measurements in *“The 2014 Danish references from birth to 20 years for height, weight and body mass index”*,⁴³. By using these

updated reference intervals, the global increase in obesity in this age group is taken into consideration, allowing for a contemporary comparison between patients and the background population. The following categorical definitions were applied: underweight: <5th BMI percentile, normal weight: 5th-84.9th BMI percentile, overweight: 85th-94.9th BMI percentile, obese: ≥95th BMI percentile.

HOMA-IR was calculated using the formula

$$\frac{\text{glucose (mmol/l)} \times \frac{\text{insulin (pmol/l)}}{6.945}}{22.5}$$

(μU/ml x 6,945=pmol/L being the conversion factor between mU/l and pmol/L, data supplied by Roche Professional Diagnostics). The defined cut-offs for elevated values were: HOMA-IR ≥4.39^{32,44,45}; insulin ≥138.9 pmol/L⁴⁶, plasma cholesterol ≥4.40 mmol/L, LDL ≥3.4 mmol/L, HDL <1.03 mmol/L, non-HDL >3.4 mmol/L and triglycerides ≥1.24 mmol/L⁴⁷. Hypertension was defined as systolic BP or diastolic BP above 90th percentile based on age, sex and height.⁴⁸

The IDF criteria for metabolic syndrome 1) elevated triglycerides (≥1.7 mmol/L), 2) decreased HDL (<1.03 mmol/L; <1.29 mmol/L in females ≥16 years of age) and 3) hypertension (systolic bp ≥130 mmHg or diastolic bp ≥85 mmHg)) were applied to the data of all participants.³⁷

Statistical analyses

We used descriptive statistics for patient and control characteristics. A two-sided α of .05 was considered statistically significant. For insulin, HOMA-IR, total cholesterol, HDL, LDL, non-HDL-cholesterol and triglycerides, only fasting samples were included. Groups compared were: Patients vs. controls and antipsychotic-naïve vs. antipsychotic-exposed. For demographics, Mann-Whitney U-tests and Fisher’s exact tests

were used to compare continuous variables as appropriate. Metabolic continuous and categorical outcomes were compared using linear regression and logistic regression, respectively, with age, sex, smoking status and level of parental education as covariates. The latter two covariates were included as they 1) differed between patients and controls and 2) both may have impact on food consumption. A post-hoc correlation analysis of parental education and cardiometabolic outcomes was performed. SPSS version 21 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY) was used for statistical analyses.

Results

Demographic and clinical characteristics

Of 231 patients screened in the 7 mental health centers, 113 patients were included in the TEA trial (for reasons for exclusion, see patient flowchart, Figure 1). Of these, 91 were recruited from the three centers within the Capital Region of Denmark. The screening failures consisted of 118 youths (males=37.3%, mean age=15.31±1.50 years), without significant differences in age or sex distribution between screening failures and randomized patients. All healthy controls were recruited within the Capital Region of Denmark. Of the 134 healthy controls who were willing to participate, 18 were excluded during screening, and of the remaining 116, the 60 that matched the best to patients on relevant variables were enrolled.

FIGURE 1 HERE

Participant baseline characteristics are shown in table 1. Mean age was 15.74±1.36 years for patients (34 (30.1%) males) and 15.69±1.41 years for controls (18 (30.0%) males). Differences in age and sex distribution were not significant (ns). The most frequent diagnoses among included

patients were schizophrenia (ICD-10 F20) = 66.4% and schizoaffective disorders (F25) = 20.4. Mean CGI was 4.85±0.73, mean DUP 142.25±169.44 weeks. Prior to inclusion, 56 patients (49.6%) had received antipsychotic treatment for a limited period of time (median lifetime doses for each antipsychotic are listed in Table 1), while 57 patients (50.4%) were completely antipsychotic-naïve. Of the included patients, 17.7% were treated with melatonin (10.7% of antipsychotic-naïve patients and 25.0% of antipsychotic-exposed patients, $p=.038$), 13.3% with antidepressants, 2.7% with anxiolytics and 0.9% with either mood stabilizers, stimulants, or antihistamines (for sedation), without significant between-group differences. Regarding illicit drug use, 12.0% of patients tested positive for benzodiazepines (most frequently given in the psychiatric emergency room or prescribed by the general practitioner for acute symptom reduction), while 2.8% tested positive for tetrahydrocannabinol. Among patients, 96.4% reported consuming 0-7 servings per week, 3.6% reported 8-14 servings of alcohol per week; while 2.7% did not answer the question. Among healthy controls, 98.3% reported consuming 0-7 servings of alcohol per week and 1.7% reported 8-14 servings per week ($p=.657$).

TABLE 1 HERE

As only few controls with lower parental education level consented to participate, controls had a significantly higher level of parental education than patients ($p<.001$). As matching was performed group wise (one group for each year of age and sex), the number of controls was slightly higher than half of the number of patients.

There were no significant difference between patients and controls on presence in first-degree relatives (FDR) of obesity (22.1% of patients vs. 11.7% of controls), dyslipidemia (10.6% of

patients vs. 3.3% of controls), T1DM (1.8% of patients vs. 3.3% of controls), while T2DM was significantly more frequent in FDR of 8.0% patients compared to 0.0% controls ($p=.028$).

Smoking

Patients smoked significantly more cigarettes than controls ($p<0.001$) (Table 1). Among patients 40 (35.7%) smoked cigarettes on a regular. The median number of cigarettes smoked per day among smokers was 10 (interquartile range: 6.0-16.5). Among controls, there was one smoker (1.7%), smoking two cigarettes a day (patients versus controls: $p<0.001$).

Anthropometric Parameters

To test the validity of the WC measurements, we correlated the BMI z-scores and WC z-scores in both patients and controls, and found a strong correlation between these measurements (Pearson's $r=.746$, $p<.001$ and $r=.820$, $p<.001$, respectively).

TABLE 2a HERE

Height and weight were comparable across all groups. There was no significant difference in BMI z-scores between patients vs. controls or antipsychotic-naïve vs. antipsychotic-exposed patients (Table 2a). However, mean WC z-scores were significantly higher in patients than in controls ($p=.018$); however, the standardized residuals for the patient group were not normally distributed as determined by Shapiro-Wilks test.

Although no significant differences in the frequency of overweight or obese individuals or in the distribution of BMI percentile groups existed, significantly more patients (42.9%) than controls (20.3%) had WC z-score $>90^{\text{th}}$ percentile ($p<.019$). Also, more antipsychotic naïve than -exposed patients had WC z-score $>90^{\text{th}}$ percentile (51.9% vs. 34.0%, $p=.023$) (Table 2b).

TABLE 2b HERE

Blood Pressure and Heart Rate

Both the systolic BP (118.6 ± 12.3 vs. 123.8 ± 12.0 , $p=.046$) and the diastolic BP (69.6 ± 9.2 vs. 73.8 ± 8.4 mmHg, $p=.013$) were significantly lower in patients than controls. The mean systolic and diastolic BP did not differ significantly between antipsychotic-naïve and antipsychotic-exposed patients (Table 2a). Further, patients had had a significantly higher heart rate than controls (70.3 ± 11.3 vs. 66.1 ± 11.0 bpm, $p=.012$), while, again, the two patient subgroups did not differ from each other. However, for diastolic blood pressure, the standardized residuals were not normally distributed as determined by Shapiro-Wilks test.

The frequency of systolic and/or diastolic BP $>90^{\text{th}}$ percentile for age, sex and height did not differ significantly between groups (Table 2b).

Glucose metabolism

Compared to patients, controls had slightly higher fasting glucose levels (4.94 ± 0.68 vs. 5.07 ± 0.30 mmol/L, $p=.094$), without differences between the patient subgroups ($p=.591$) (Table 2a).

There were no significant differences between patients and controls in levels of fasting insulin, but HOMA-IR was higher in patients than in controls (2.51 ± 2.92 vs. 2.41 ± 1.09 , $p=.048$, Table 2a). There were no significant differences in prevalence of hyperglycemia, hyperinsulinemia or insulin resistance between the groups (Table 2b). Two patients and no controls had fasting glucose ≥ 6.1 mmol/L ($p=1.000$), one patient and no controls had fasting glucose >7.0 mmol/L ($p=1.000$), thus one patient fulfilled the criteria for T2DM. No patients or controls had T1DM at time of inclusion.

Lipid metabolism

Compared to controls, patients had significantly higher total, LDL-cholesterol and non-HDL cholesterol levels than controls (total cholesterol: 4.10 ± 0.71 vs. 3.79 ± 0.49 mmol/L, $p=.014$; LDL-cholesterol: 2.37 ± 0.56 vs. 2.13 ± 0.51 mmol/L, $p=.012$; non-HDL-cholesterol: 2.58 ± 1.60 vs. 2.52 ± 0.52 mmol/L, $p=.018$) (Table 2a). However, for LDL- and non-HDL-cholesterol, the standardized residuals were not normally distributed as determined by Shapiro-Wilks test. Again, antipsychotic-naïve vs. antipsychotic-exposed patients did not differ on lipid levels (Table 2a).

Finally, evaluating categorical outcomes, the prevalence of total cholesterol ≥ 4.4 mmol/L was higher in patients than in controls (34.0% vs. 5.0%, $p=.015$ (Table 2b)), while decreased HDL-cholesterol was less frequent in patients than controls (19.0% vs. 32.5%, $p=.032$).

Metabolic Syndrome

There were no significant differences between the prevalence of MS in the patient (2.8%) vs. control (0.0%) groups or the antipsychotic-naïve (2.0%) and antipsychotic-exposed (3.6%) subgroups (Table 2b).

Effect of schizophrenia diagnosis

No difference in patient characteristics, DUP or PANSS and GAPD scores was found between patients diagnosed with schizophrenia vs. patients with other psychosis diagnoses. Being diagnosed with schizophrenia was associated with lower total cholesterol (3.96 ± 0.68 vs. 4.38 ± 0.69 mmol/L, $p=.004$) and lower triglycerides (0.90 ± 0.34 vs. 1.07 ± 0.39 , $p=.015$), but also lower HDL-cholesterol (1.38 ± 1.13 vs. 1.80 ± 2.18 mmol/L, $p=.047$), than in patients with other diagnoses (Table 3).

TABLE 3 HERE

Correlates of anthropometric and metabolic parameters

Using linear regression analyses, we found significant associations between younger age at onset of psychotic symptoms in patients and both higher BMI ($p=.005$) and higher WC ($p=.002$) z-score. Also, Clinical Global Impression (CGI) - severity score was positively and significantly associated with both total cholesterol ($p=.008$), LDL-cholesterol ($p=.032$) and non-HDL-cholesterol ($p=.010$) (Table 3).

TABLE 4 HERE

Mann-Whitney U-tests were run to assess if BMI and WC z-scores as well as lipid and glucose metabolism parameters were higher in patients whose first-degree relatives (FDRs, i.e., biological parents or siblings) suffered from T1DM or T2DM, overweight or obesity (Table 4). There were no significant differences in sex distribution, mean age, Tanner stage, or cigarette consumption between groups in these four categories (i.e., when comparing groups with familial -obesity vs. +obesity, -T1DM vs. + T1DM, -T2DM vs. + T2DM, and -dyslipidemia vs. +dyslipidemia). In the patient group we found that obesity in FDRs was associated with both a higher mean patient BMI z-score ($p=.003$) and WC z-score ($p=.034$), and that T2DM in FDRs was associated with both higher patient BMI z-score ($p<.0001$) and WC z-score ($p=.001$), as well as with higher patient insulin ($p=.038$) and HOMA-IR ($p=.025$). In the patient group there was also an association between dyslipidemia in FDRs and higher patient LDL-cholesterol ($p=.041$), higher patient insulin ($p=.041$) and HOMA-IR ($p=.032$) and between T1DM in FDR and higher patient HDL-cholesterol ($p=.029$).

No controls had FDRs with known T2DM. Obesity in FDR of controls was associated with increased control BMI z-score ($p=.009$) and insulin ($p=.024$).

T1DM in FDR of controls was associated with lower control WC z-score ($p=.005$).

There was no statistically significant difference in any metabolic parameters between patients with FDRs with ($n=9$) and without ($n=104$) a history of psychotic illness.

Finally, in a post-hoc analysis, we found that lower level of parental education in healthy controls was significantly correlated with higher BMI z-score (Persons R: $-.321$, $p=.012$), WC z-score (Pearsons R: $-.263$, $p=.040$), triglyceride level (Pearsons R: $.399$, $p=.013$) and triglyceride/HDL ratio (Pearsons R: $.347$, $p=.018$), but these correlations were not seen in the patient group.

Discussion

To our knowledge, this is the first study in which cardiometabolic risk status was assessed in antipsychotic-naïve or briefly exposed, early-onset, first-episode psychotic children and adolescents and compared to concurrently enrolled, matched healthy controls. Psychotic patients had higher waist circumference z-scores and increased lipids (total cholesterol and LDL-cholesterol) than the healthy controls, despite almost identical BMI-z score values. While the frequency of overweight and obesity based on BMI percentiles did not differ between patients and controls, the frequency of waist circumference above the 90th percentile – the cut-off for abdominal obesity for the metabolic syndrome – was doubled in patients compared to controls.

Taken together, our data indicate a higher occurrence of abdominal obesity and specific lipid, but not glucose metabolism abnormalities in children and adolescents with psychotic disorders in the initial phase. Our results contrast with findings from a prior systematic review in adults with first episode psychosis,⁴⁹ where

authors found no difference in cardiometabolic risk between patients and healthy controls before treatment initiation. Nevertheless, the authors found indications of a higher waist to hip ratio and more intra-abdominal fat relative to BMI in pre-medicated patients compared to controls, but that such differences did not reach significance, probably due to a lack of adequate matching with controls.⁴⁹ On the other hand, our findings converge with other studies in adults,^{50,51} which link the presence of severe mental illness to an increased risk of cardiovascular risk factors, even before antipsychotic treatment is initiated. Our data support the hypothesis that the risk of developing chronic metabolic disturbances in youths with psychotic disorders is elevated even at a pretreatment stage. When antipsychotic medication effects are added, the risk is further heightened^{3,6-14,49,52,53} Similarly, baseline results from 394 patients with first-episode psychosis aged 15-40 years (mean age= 23.6 ± 5.0 years) from the USA RAISE-ETP study⁴⁶ showed a percentage of overweight or obesity of 48.3%. This prevalence did not differ from that of the general US population of similar age, yet despite only 47 days of lifetime antipsychotic exposure several other metabolic abnormalities were observed compared to the general population controls. Nevertheless, in that sample, higher anthropometric measures were associated with overall psychotic illness duration, and antipsychotic exposure duration was associated with metabolic risk. On average, patients from the TEA trial had higher sex- and age-adjusted BMI and WC z-scores than the background population.⁴³ Our results do not allow us to speculate whether the reasons underlying this increased cardiometabolic risk is due to genetic factors or diet and lifestyle patterns, but most likely, both contribute to the observed differences.

Although seemingly counterintuitive, the finding that antipsychotic-naïve and antipsychotic-

exposed patients did not differ across almost all anthropometric and metabolic assessments is likely due to the very short mean exposure (median 6 days, IQR 1-12) to antipsychotics.

The post-hoc analysis revealed that in the healthy control group, BMI and WC z-scores were both inversely correlated with parents' level of education. This finding coincides with results from a Greek study of 1,125 children, where higher adherence to a healthy diet was associated with lower likelihood of overweight/obesity, but only among children with at least one parent with higher education.⁵⁴ This association was not seen in the patients group. It may be that in patients, the protective effect of parental education is "trumped" by effect of the psychotic disorder.

We also found that early onset of psychotic symptoms predicted both higher BMI and WC z-scores, indicating that psychotic symptoms at an early age may interfere with the adaption of healthy eating habits after the growth spurt in early adolescence. This finding could also explain the dissonance between the effect of parental education in patients and controls. However, these hypotheses are speculative and require further investigation. Also, higher CGI-S scores correlated to higher total cholesterol, LDL-cholesterol and non-HDL-cholesterol, suggesting that the severity of the psychotic disorders has a negative impact on the patient's ability to maintain a healthy diet. Nevertheless, the latter two results could also support the notion that the same genetic loading contributing to the development of psychosis might also be linked to the development of metabolic disturbances. Other studies have demonstrated that psychotic symptoms are related to higher risk of somatic health problems⁵⁵ including diabetes.⁵⁶ Finally, smoking was also much more prevalent in the patient group (35%) than among healthy controls (2%), consistent with data from a Norwegian study comparing substance abuse and smoking in

adolescents with mental disorders to the background population.⁵⁷ The healthy controls in our sample, however, had a relatively low frequency of tobacco use. According to a recent study of childhood health in Denmark, around 5% of adolescents aged 15 years are daily smokers.⁵⁸

Finally, in patients, obesity and T2DM in FDRs were both associated with increased BMI z-score and WC z-score, while T2DM and dyslipidemia in FDRs were associated with increased insulin and HOMA-IR, and dyslipidemia was associated with increased LDL. Whether or not these associations are due to shared genetic risk or shared environment/behavior requires further study. Nevertheless, these results underscore the importance of thoroughly evaluating the family history when choosing and administering antipsychotics in youths.

This study has several limitations. First, the number of patients and healthy controls is relatively modest. Even though the TEA trial is one of the largest head-to-head randomized trial of antipsychotics conducted in youth, the power estimation is based on the primary efficacy outcome measure, i.e., change in PANSS positive symptoms. Second, we cannot fully ascertain the representativeness of the enrolled sample. Also, due to very limited access to information on the non-included patients, we could not compare our sample to the screening failures beyond age and gender. Although we had a high percentage of females in our sample, there was no difference in sex distribution compared to the patients not enrolled in the study, and a similar proportion of females among first episode psychosis patients was also found in a recent Danish register study of early onset schizophrenia⁵⁹. Further, the difference between healthy controls and patients in parental education reflects that some degree of selection bias was unavoidable (only 14% out of 957 healthy controls invited by letter consented to participate). Third, we did not have information on diet and exercise in patients and

controls, which could have enriched analysis and interpretation of cardiometabolic status in FEP. Fourth, half of the patient sample had antipsychotic exposure prior to the baseline assessment. Using only truly antipsychotic-naïve patients would have increased the power of the study but would have required a twice as long recruitment period. Also, this allowed us to compared antipsychotic-naïve to -exposed patients. Fifth, the small number of healthy controls who had FDRs with metabolic/cardiovascular diseases limits the possibility to draw conclusions for the comparison between patients and controls. And finally, the very high rates of blood pressures >90th percentile in healthy controls prompted us to check for any systematic error. While all patients had blood pressure measured after five minutes of rest, we found that this resting period had not been rigorously implemented during the assessment of healthy controls. This discrepancy may explain the unexpectedly high blood pressures seen in this group, and invalidate the result.

Despite these limitations, the strengths of the present study include the comparison of patients with first-episode early-onset psychosis to a concurrently ascertained matched healthy control group, all with complete baseline data, a stringent prospective cardiometabolic risk assessment and availability of family history data of cardiometabolic diseases. The use of very recent and precise population data as basis for the z-score data allows for a contemporary comparison with the background population.

In summary, our findings demonstrate that children and adolescents with psychosis have elevated abdominal obesity and lipid abnormalities already prior to antipsychotic initiation. Therefore, clinicians must carefully consider the potential for inducing weight gain and dyslipidemia when selecting antipsychotic treatment. During treatment, routine monitoring

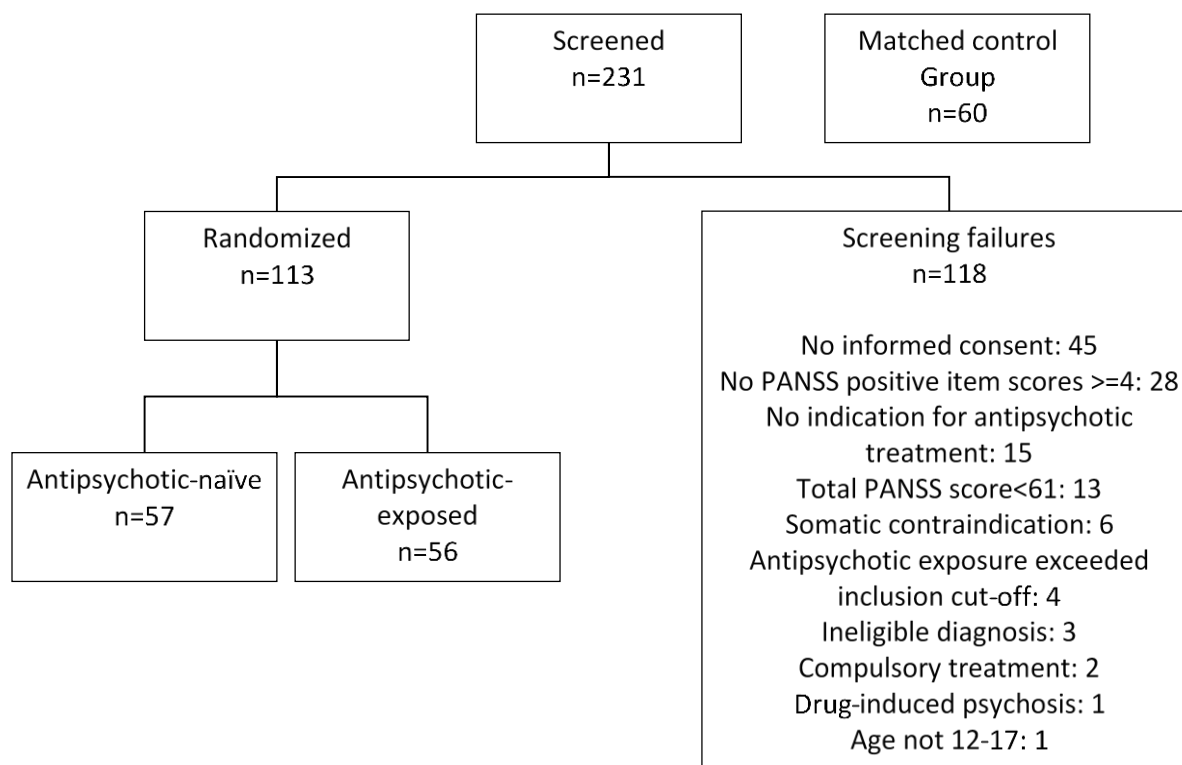
of anthropometric and metabolic parameters is essential. Furthermore interventions to minimize the impact of offending medications, either through exercise, dose reduction, dietary changes or use of medications with counter-acting potentials, such as metformin⁶⁰⁻⁶² or melatonin⁶³⁻⁶⁵ as well as interventions to prevent or stop smoking, are essential to reduce the long-term risk of cardiovascular disease in patients with early-onset psychosis.

Clinical Points

1. Few studies have examined the pretreatment cardiovascular risk in youths with first-episode psychosis, despite the documented shorter life expectancy in patients with psychosis, which appears primarily due to premature cardiovascular disease risk factors and morbidity.
2. Patients with FEP accumulate cardiovascular risk factors at an early age, even prior to antipsychotic treatment, and clinicians must be vigilant to prevent early development of obesity and metabolic syndrome.

Figures

Figure 1: Participant flowchart



Tables

Table 1: Participant characteristics

		All patients N=113	Antipsychotic- Naïve n=57	Antipsychotic- Exposed n=56	Controls n=60	Controls vs. patients	Antipsychotic- Exposed vs Antipsychotic- Naïve p-value
Demographics							
Age, years, mean±SD		15.74±1.36	15.87±1.36	15.60±1.36	15.69±1.41	.857	.469
Males, n (%)		34 (30.1%)	16 (28.1%)	18 (32.1%)	18 (30.0%)	1.000	.685
Smokers, n (%)		40 (35.7%)	22 (38.6%)	18 (32.7%)	1 (1.7%)	<.001	.558
Cigarettes per day, median (IQR)		10.0 (6.0-16.5)	7.5 (5.0-15.0)	10.0 (6.8-20.0)	2.0 (-)	<.001	.791
TSH, mean±SD		2.03±0.97	2.01±0.99	2.05±0.96	2.07±1.02	.889	.543
Tanner stage, mean±SD	Males	4.12±0.91	.321	3.94±1.11	3.94±0.80	.321	.484
	Females	4.21±0.64	.110	4.28±0.61	4.00±0.70	.110	.407
Parents' level of education, n (%)							
Low		30 (26.5%)	21 (36.8%)	9 (16.1%)	4 (6.7%)	<.001	.012
Medium		68 (60.2%)	32 (56.1%)	36 (64.2%)	33 (55.0%)		
High		13 (11.5%)	3 (5.2%)	10 (17.8%)	13 (21.7%)		
Diseases in first-degree relatives (n (%))							
T1DM in family		2 (1.8%)	1 (1.8%)	1 (1.8%)	2 (3.3%)	.610	1.000
T2DM in family		9 (8.0%)	4 (7.0%)	5 (8.9%)	0 (0.0%)	.028	.742
Familial dyslipidemia		12 (10.6%)	8 (14.0%)	4 (7.1%)	2 (3.3%)	.142	.361
Familial obesity		25 (22.1%)	11 (19.3%)	14 (25.0%)	7 (11.7%)	.103	.504
Psychopathology (mean±SD)							
PANSS positive subscore		20.26±3.52	20.23±3.64	20.29±3.44			.725

	All patients N=113	Antipsychotic- Naïve n=57	Antipsychotic- Exposed n=56	Controls n=60	Controls vs. patients Antipsychotic- Exposed vs Antipsychotic- Naïve p-value
PANSS negative subscore	20.59±5.29	20.28±5.00	20.91±5.61		.610
PANSS general subscore	37.04±6.44	36.77±6.10	37.32±6.82		.883
PANSS total	77.89±12.24	77.28±11.75	78.52±3.14		.726
Age at onset of psychotic symptoms, years	13.03±3.30	13.13±3.20	12.91±3.43		.731
DUP, weeks	142.25±169.44	142.33±154.59	142.17±185.59		.505
CGI-S score	4.85±0.73	4.77±0.73	4.93±0.73		.360
GAPD score	4.39±1.10	4.28±1.11	4.50±1.08		.320
Diagnosis (n (%))					
Schizophrenia (F20)	75 (66.4%)	40 (70.2%)	35 (62.5%)		.695
Delusional disorders (F22)	2 (1.8%)	1 (1.8%)	1 (1.8%)		
Acute and transient psychotic disorders (F23)	1 (0.9%)	1 (1.8%)	0 (0.0%)		
Schizoaffective disorders (F25)	23 (20.4%)	10 (17.5%)	13 (23.2%)		
Other psychotic disorders (F28)	4 (3.5%)	1 (1.8%)	3 (5.4%)		
Bipolar disorder (F31)	1 (0.9%)	0 (0.0%)	1 (1.8%)		
Major depressive disorders (F32)	6 (5.3%)	3 (5.3%)	3 (5.4%)		
Recurrent depressive disorder (F33)	1 (0.9%)	1 (1.8%)	0 (0.0%)		
Antipsychotic use before inclusion					
Number of antipsychotic medications used (n (%))					
1			42 (75.0%)		
2			13 (23.2%)		
3			1 (1.8%)		
Distribution of antipsychotic medications					
Aripiprazole, n (%)			3 (2.7%)		

	All patients N=113	Antipsychotic- Naïve n=57	Antipsychotic- Exposed n=56	Controls n=60	Controls vs. patients p-value	Antipsychotic- Exposed vs Antipsychotic- Naïve
Aripiprazole, median cumulated life time dose, mg (IQR)			20.00 (15.00-35.00)			
Aripiprazole, median number of days (IQR)			7.0 (6.0-8.0)			
Quetiapine, n (%)			9 (8.0%)			
Quetiapine, median cumulated life time dose, mg (IQR)			250.00 (75.00-820.00)			
Quetiapine, median number of days (IQR)			15.5 (2.5-16.0)			
Olanzapine, n (%)			23 (20.4%)			
Olanzapine, median cumulated life time dose, mg (IQR)			45.00 (10.00-115.00)			
Olanzapine, median number of days (IQR)			8.0 (1.0-16.0)			
Chlorprothixene ^a , n (%)			38 (33.6%)			
Chlorprothixene, median cumulated life time dose, mg (IQR)			75.00 (25.00-180.00)			
Chlorprothixene, median number of days (IQR)			3.0 (1.0-8.0)			
Use of other psychopharmacological agents prior to inclusion						
Melatonin	20 (17.7%)	6 (10.7%)	14 (25.0%)			.038
Antidepressants	15 (13.3%)	9 (15.8%)	6 (10.7%)			.303
Anxiolytics	3 (2.7%)	2 (3.5%)	1 (1.8%)			.507
Mood stabilizers (e.g. lamotrigin)	1 (0.9%)	1 (1.8%)	0 (0.0%)			.504
Stimulants (e.g. methylphenidate)	1 (0.9%)	1 (1.8%)	0 (0.0%)			.504
Antihistamines (e.g. phenergan ^b)	1 (0.9%)	1 (1.8%)	0 (0.0%)			.504
Alcohol use, n (%)						
0-7 servings per week	106 (96.4%)	52 (96.3%)	54 (96.4%)	59 (98.3%)	.657	1.000

	All patients N=113	Antipsychotic- Naïve n=57	Antipsychotic- Exposed n=56	Controls n=60	Controls vs. patients Antipsychotic- Exposed vs Antipsychotic- Naïve p-value
8-14 servings per week	4 (3.6%)	2 (3.7%)	2 (3.6%)	1 (1.7%)	
Positive drug tests, n (%)					
Tetrahydrocannabinol	3 (2.8%)	1 (1.9%)	2 (3.6%)		.514
Cocaine	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Opioids	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Metamphetamine	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Benzodiazepine	13 (12.0%)	7 (13.2%)	6 (10.9%)		.471
Amphetamine	0 (0.0%)	0 (0.0%)	0 (0.0%)		

^a first generation high dose antipsychotic similar to thiotixene; ^b phenergan used for sedation; BP = blood pressure; CGI-S: clinical global impression, severity; DUP: duration of untreated psychosis; GAPD: global assessment of psychosocial disability; ICD-10: international classification of diseases manual, 10th edition; IQR: interquartile range; mg: milligrams; PANSS: positive and negative syndrome scale; SSRI: selective serotonin reuptake inhibitor; SD: standard deviation.

Table 2a: Cardiometabolic parameters in patients versus controls

	All patients		Antipsychotic-naïve		Antipsychotic-exposed		Controls		Controls vs patients	Antipsychotic-naïve vs antipsychotic- exposed
	N	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	p-value	
Anthropometric assessments										
Weight, kg	113	62.22±12.3	57	63.43±12.77	56	60.98±11.78	60	61.55±10.09	.816	.173
Height, m	113	1.69±0.10	57	1.70±0.09	56	1.69±0.1	60	1.69±.08	.434	.362
BMI z-score	113	0.44±1.26	57	0.51±1.25	56	0.36±1.27	60	0.44±0.99	.771	.570
BMI percentile	113	0.60±0.33	57	0.62±0.32	56	0.58±0.33	60	0.61±.27	.771	.570
WC z-score	105	1.13±1.65	52	1.41±1.72	53	0.86±1.54	59	0.42±1.27	.018	.105
Heart rate and blood pressure										
Heart Rate, bpm	112	70.3±11.3	57	69.4±11.6	55	71.2±11.0	60	66.1±11.0	.012	.663
Systolic BP, mmHg	112	118.6±12.3A	57	117.7±11.1A	55	119.4±13.4 A	60	123.8±12.0B	.046	.795
Diastolic BP, mmHg	112	69.6±9.2A	57	69.5±8.2A	55	69.8±10.2A	60	73.8±8.4B	.013	.710
Glucose metabolism										
Glucose, mmol/l	99	4.94±0.68	49	4.87±0.51	50	5.00±0.81	39	5.07±0.30	.094	.519
Insulin, pmol/l	90	75.43±58.80	46	75.91±59.84	44	74.93±58.37	39	72.64±31.70	.087	.974
HOMA-IR	89	2.51±2.92	46	2.46±2.4	43	2.57±3.41	38	2.41±1.09	.048	.992
Lipids										
Total cholesterol, mmol/l	100	4.10±0.71	49	4.17±0.77	51	4.03±0.65	40	3.79±0.49	.014	.397
LDL-cholesterol, mmol/l	100	2.37±0.56	49	2.42±0.61	51	2.33±0.51	36	2.13±0.51	.012	.431
HDL-cholesterol, mmol/l	100	1.52±1.57	49	1.51±1.30	51	1.54±1.81	40	1.26±0.31	.138	.882
Non-HDL-cholesterol, mmol/l	100	2.58±1.60	49	2.67±1.51	51	2.49±1.70	40	2.52±0.52	.018	.344
Triglycerides, mmol/l	99	0.96±0.37	49	1.00±0.42	50	0.91±0.31	38	0.84±0.34	.154	.510
TG/HDL ratio	99	0.76±0.38	49	0.78±0.41	50	0.74±0.35	38	0.71±0.36	.914	.707

Bolded values: $p < .005$; ^A measured after 5 minutes of rest; ^B measured without consistent adherence to rest; BMI: body mass index; BP: blood pressure; bpm: beats per minute; HDL: high density-lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; kg: kilograms; LDL: low density-lipoprotein; m: meters; SD: standard deviation; TSH: thyroid stimulating hormone; WC: waist circumference

Table 2b: Frequency of abnormal cardiometabolic values in patients versus controls

	All patients		Antipsychotic-Naive		Antipsychotic-Exposed		Controls		Controls vs. patients	Antipsychotic-Naive vs. Antipsychotic-Exposed
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	p	
Body mass index percentile groups	113		57		56		60		.375	.566
Underweight		7 (6.2%)		2 (3.5%)		5 (8.9%)		1 (1.7%)		
Normal		66 (58.4%)		36 (63.2%)		30 (53.6%)		43 (71.7%)		
Overweight		19 (16.8%)		9 (15.8%)		10 (17.9%)		9 (15.0%)		
Obese		21 (18.6%)		10 (17.5%)		11 (19.6%)		7 (11.7%)		
Overweight or obese	113	40 (35.4%)	57	19 (33.3%)	56	21 (37.5%)	60	16 (26.7%)	.183	.893
Systolic and/or diastolic BP ≥90 th percentile	113	29 (25.7%)	57	17 (29.8%)	56	19 (33.9%)	60	36 (60.0%)	.273	.755
IDF Metabolic Syndrome										
WC z-score >90 th percentile	105	45 (42.9%)	52	27 (51.9%)	53	18 (34.0%)	59	12 (20.3%)	.019	.023
Triglycerides ≥1.7 mmol/L	99	6 (6.1%)	49	4 (8.2%)	50	2 (4.0%)	38	1 (2.6%)	.583	.709
HDL-cholesterol <1.03mmol/L, <1.29 in females >16 years	100	19 (19.0%)	49	8 (16.3%)	51	11 (21.6%)	40	13 (32.5%)	.032	.362
Systolic BP ≥130 or diastolic BP ≥85 mm Hg	112	21 (18.8%)	57	10 (17.5%)	55	11 (20%)	60	17 (28.3%)	.382	.614
Glucose >5.6 mmol/L	99	7 (7.1%)	49	5 (10.2%)	50	2 (4.0%)	39	1 (2.6%)	.360	.249
Metabolic Syndrome present	106	3 (2.8%)	51	1 (2.0%)	55	2 (3.6%)	58	0 (0.0%)	.997	.546
Glucose metabolism										
Glucose ≥6.1	99	2 (2.0%)	49	1 (2.0%)	50	1 (2.0%)	38	0 (0.0%)	1.000	.891
Glucose ≥7.0	99	1 (1.0%)	49	0 (0.0%)	50	1 (2.0%)	38	0 (0.0%)	1.000	.999
Insulin ≥138.9 pmol/L	90	7 (7.8%)	46	3 (6.5%)	44	4 (9.1%)	39	1 (2.6%)	.834	.160

	All patients		Antipsychotic- Naïve		Antipsychotic- Exposed		Controls		Controls vs. patients	Antipsychotic- Naïve vs. Antipsychotic-Exposed
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	p	
Insulin Resistance (HOMA-IR>4.39)	89	9 (10.1%)	46	3 (6.5%)	43	6 (14.0%)	39	1 (2.6%)	.402	.070
Lipid abnormalities										
Total cholesterol ≥4.4 mmol/l	100	34 (34.0%)	49	20 (40.8%)	51	14 (27.5%)	40	5 (12.5%)	.015	.209
LDL-cholesterol ≥3.4 mmol/L	100	3 (3.0%)	49	1 (2.0%)	51	2 (3.9%)	36	0 (0.0%)	.998	.688
HDL-cholesterol <1.03mmol/L	100	19 (19.0%)	49	8 (16.3%)	51	11 (21.6%)	40	13 (32.5%)	.032	.362
Non-HDL-cholesterol ≥3.4mmol/L	100	15 (15.0%)	49	10 (20.4%)	51	5 (9.8%)	40	1 (2.5%)	.114	.111
Triglycerides ≥1.2 mmol/L	99	16 (16.2%)	49	10 (20.4%)	50	6 (12.0%)	38	6 (15.8%)	.312	.367
Dyslipidemia	99	40 (40.4%)	49	24 (49.0%)	50	16 (32.0%)	38	10 (26.3%)	.284	.204

Bolded values: p <.05BMI: body mass index; HDL: high density-lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; kg: kilogram; LDL: low density-lipoprotein; SD: standard deviation; WC: waist circumference (Dyslipidemia = total cholesterol >4.4 mmol/l and/or triglycerides >1.2 mmol/L)

Table 3: Psychopathological predictors of anthropometric and metabolic outcomes

	BMI z-score	WC z-score	Glucose	Insulin	HOMA-IR	Cholesterol	LDL	Non-HDL	HDL	TG	TG/HDL ratio
Diagnosed with schizophrenia (F20)	$F(1, 111) = .002$ $p = .968$	$F(1, 103) = .007$ $p = .931$	$F(1, 97) = .082$ $p = .775$	$F(1, 88) = .080$ $p = .778$	$F(1, 87) = .111$ $p = .740$	$F(1, 98) = 8.651$ $p = .004$	$F(1, 98) = 2.142$ $p = .147$	$F(1, 96) = 3.209$ $p = .076$	$F(1, 98) = 4.043$ $p = .047$	$F(1, 97) = 6.124$ $p = .015$	$F(1, 97) = 0.320$ $p = .859$
Age at onset of psychotic symptoms	$F(1, 108) = 8.172$ $p = .005$	$F(1, 100) = 9.980$ $p = .002$	$F(1, 94) = .661$ $p = .418$	$F(1, 86) = .637$ $p = .427$	$F(1, 85) = .961$ $p = .330$	$F(1, 95) = .047$ $p = .829$	$F(1, 95) = .003$ $p = .957$	$F(1, 93) = .004$ $p = .950$	$F(1, 95) = .575$ $p = .450$	$F(1, 94) = .318$ $p = .574$	$F(1, 94) = .108$ $p = .743$
PANSS positive score	$F(1, 111) = 3.645$ $p = .059$	$F(1, 103) = .505$ $p = .479$	$F(1, 97) = .918$ $p = .340$	$F(1, 88) = .449$ $p = .505$	$F(1, 87) = .371$ $p = .544$	$F(1, 98) = 1.169$ $p = .282$	$F(1, 98) = .365$ $p = .547$	$F(1, 96) = .236$ $p = .628$	$F(1, 98) = .591$ $p = .444$	$F(1, 97) = .199$ $p = .657$	$F(1, 97) = .065$ $p = .799$
PANSS negative score	$F(1, 111) = .001$ $p = .972$	$F(1, 103) = .093$ $p = .761$	$F(1, 97) = .375$ $p = .541$	$F(1, 88) = .171$ $p = .680$	$F(1, 87) = .010$ $p = .922$	$F(1, 98) = .965$ $p = .328$	$F(1, 98) = 1.292$ $p = .258$	$F(1, 96) = 1.315$ $p = .254$	$F(1, 98) = .004$ $p = .947$	$F(1, 97) = .020$ $p = .888$	$F(1, 97) = .014$ $p = .906$
PANSS total score	$F(1, 111) = .686$ $p = .409$	$F(1, 103) = .002$ $p = .962$	$F(1, 97) = .157$ $p = .693$	$F(1, 88) = .039$ $p = .844$	$F(1, 87) = .242$ $p = .624$	$F(1, 98) = .095$ $p = .758$	$F(1, 98) = .368$ $p = .545$	$F(1, 96) = .570$ $p = .452$	$F(1, 98) = .168$ $p = .683$	$F(1, 97) = .011$ $p = .915$	$F(1, 97) = .129$ $p = .720$
CGI score	$F(1, 111) = .318$ $p = .574$	$F(1, 103) = .811$ $p = .370$	$F(1, 97) = .331$ $p = .567$	$F(1, 88) = .094$ $p = .759$	$F(1, 87) = .207$ $p = .650$	$F(1, 98) = 7.294$ $p = .008$	$F(1, 98) = 4.752$ $p = .032$	$F(1, 96) = 6.953$ $p = .010$	$F(1, 98) = .077$ $p = .782$	$F(1, 97) = 1.458$ $p = .230$	$F(1, 97) = .333$ $p = .565$
Level of parental education	$F(1, 109) = .151$ $p = .698$	$F(1, 101) = .610$ $p = .437$	$F(1, 96) = .615$ $p = .435$	$F(1, 87) = 4.930$ $p = .029$	$F(1, 86) = 3.622$ $p = .060$	$F(1, 97) = .791$ $p = .376$	$F(1, 97) = .002$ $p = .696$	$F(1, 95) = .076$ $p = .784$	$F(1, 97) = .332$ $p = .566$	$F(1, 96) = 1.296$ $p = .258$	$F(1, 96) = .096$ $p = .758$

Bolded values: $p < .05$; BMI: body mass index; BP: blood pressure; HDL: high density-lipoprotein; CGI: clinical global impression; HOMA-IR: homeostatic model assessment of insulin resistance; LDL: low density-lipoprotein; PANSS: positive and negative syndrome scale; TG: triglycerides; WC: waist circumference

Table 4: Associations between somatic conditions in first-degree relatives and metabolic disturbances in participants

Somatic condition in first-degree relatives - PATIENTS								
	Obesity (n=25)		T1DM (n=2)		T2DM (n=9)		Dyslipidemia (n=12)	
	U	p	U	p	U	p	U	p
BMI z-score	1525.000	.003	28.000	.071	845.000	.000	631.000	.816
WC z-score	1216.000	.034	48.000	.229	712.000	.001	563.500	.627
Glucose	118.500	.504	49.500	.268	429.000	.769	451.500	.717
Insulin	915.500	.068	13.000	.311	519.000	.038	516.500	.041
HOMA-IR	891.500	.086	9.000	.225	525.000	.025	517.500	.032
Total cholesterol	1089.500	.151	149.500	.233	464.000	.511	661.000	.058
LDL-cholesterol	1067.000	.210	126.000	.524	499.500	.277	674.500	.041
Non-HDL-cholesterol	1010.500	.426	125.500	.524	493.500	.311	598.000	.231
HDL-cholesterol	962.500	.682	180.500	.029	377.500	.699	537.000	.599
Triglycerides	988.000	.472	114.000	.693	452.500	.563	563.000	.379
TG/HDL ratio	872.000	.819	92.000	.911	458.000	.519	494.000	.911
Somatic condition in first-degree relatives - CONTROLS								
	Obesity (n=5)		T1DM (n=2)		T2DM (n=0)		Dyslipidemia (n=2)	
	U	p	U	p			U	p
BMI z-score	138.000	.009	57.000	.983	-	-	101.000	.081
WC z-score	209.500	.211	2.000	.005	-	-	49.000	.339
Glucose	77.000	.760	40.500	.826	-	-	56.000	.270
Insulin	138.000	.024	17.500	.243	-	-	29.000	.513
HOMA-IR	123.000	.084	21.000	.376	-	-	27.000	.579
Total cholesterol	104.500	.498	43.000	.785	-	-	44.500	.697
LDL-cholesterol	111.500	.122	38.500	.762	-	-	53.000	.229
Non-HDL-cholesterol	116.000	.261	46.000	.656	-	-	53.500	.369
HDL-cholesterol	72.000	.551	31.500	.697	-	-	26.500	.503
Triglycerides	75.500	.769	36.500	1.000	-	-	42.000	.728
TG/HDL ratio	91.000	.738	37.500	.922	-	-	41.000	.774

Bolded values: $p < .05$; BMI: body mass index; BP: blood pressure; HDL: high density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; LDL: low density lipoprotein; T1DM: type 1 diabetes; T2DM: type 2 diabetes; WC: waist circumference

Table S1: Definition of metabolic syndrome in children and adolescents by the International Diabetes Federation

Metabolic Syndrome is present if there is obesity plus two or more other criteria are fulfilled					
Age group (years)	Obesity (waist circumference)	Triglycerides	HDL-cholesterol	Blood pressure	Glucose
6 to <10	≥ 90th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.			
10 to <16	≥ 90th percentile or adult cut-off if lower	≥ 1.7 mmol/L (≥ 150 mg/dL)	< 1.03 mmol/L (< 40 mg/dL)	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM
≥ 16 (adult criteria)	WC ≥ 94cm for Europid males and ≥ 80cm for Europid females, with ethnic-specific values for other groups	≥ 1.7 mmol/L (≥ 150 mg/dL) or specific treatment for high triglycerides	< 1.03mmol/L (< 40 mg/dL) in males and < 1.29mmol/L (< 50 mg/dL) in females, or specific treatment for low HDL	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM

BP: Blood Pressure; cm: centimeters; FPG, Fasting Plasma Glucose; HDL, High Density Lipoprotein; mg/dL, milligrams per deciliter; mmol/L: millimoles per liter; T2DM, Type 2 Diabetes Mellitus; WC, Waist Circumference.

Table S2: Measurements for patients (n=3) with metabolic syndrome

	Age, years	Gender	Alcohol	Cigarettes per day	Systolic BP, mmHg	Diastolic BP, mmHg	Heart Rate, bpm	Weight, kg	Height, m	WC, cm	BMI, kg/m ²	BMI z-score	WC z-score	Tanner stage	LDL-cholesterol mmol/L	HDL-cholesterol mmol/L	Triglycerides mmol/L	Glucose mmol/L	Insulin pmol/l
1	15	M	0	0	152	95	82	82.7	1.84	88.0	24.4	1.4	2.3	4	1.90	.70	1.07	5.5	27.0
2	14	M	0	7	145	76	60	79.7	1.82	90.0	24.1	1.5	2.8	4	1.80	.80	1.00	5.1	17.0
3	15	F	0	10	118	55	78	79.3	1.65	97.0	29.1	2.7	5.3	5	2.50	.90	1.60	6.4	403.4

BMI: Body Mass Index; BP: Blood Pressure; bpm: beats per minute; cm: centimeters; HDL: High-Density Lipoprotein; kg: kilograms; LDL: Low-Density Lipoprotein; m: meters; TG: Triglycerides; WC: Waist Circumference

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Cardiometabolic adverse effects in children and adolescents during treatment with quetiapine ER versus aripiprazole – 12-week results from the TEA trial

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Abstract

Objective: To compare the cardiometabolic effects of aripiprazole vs. quetiapine extended release (ER) in youths with first-episode psychosis (FEP).

Methods: Youths aged 12-17 years old were randomized to aripiprazole or quetiapine ER in the 12-week, double-blinded, randomized Tolerability and Efficacy of Antipsychotics (TEA) trial. Patients were assessed at baseline, week 4, week 12 or premature exit visit. Primary outcome were baseline-to-endpoint change in weight, secondary outcomes were changes in body mass index (BMI) z-score and waist circumference (WC) z-score, blood pressure (BP), heart rate, lipid and glucose metabolism parameters.

Results: Altogether, 113 patients (schizophrenia-spectrum disorders=93%, age=15.7±1.4 years, males=30%), were randomized to quetiapine ER (n=55) or aripiprazole (n=58). During the 12-week treatment, patients on quetiapine ER experienced weight gain of 5.22±3.97 kilograms ($p<.001$), while BMI z-score and WC z-score increased by 0.45±0.37 ($p<.001$) and 1.00±1.08 ($p<.001$). Changes were significantly smaller in the aripiprazole group (between-group p-values were $<.001$, $<.001$ and $.007$, respectively): weight: 1.73±3.52 kilograms ($p=.001$), BMI z-score: 0.11±0.40 ($p=.069$) and WC z-score: 0.30±0.92 ($p=.039$). Lipid and glucose metabolism parameters increased statistically significantly only with quetiapine ER at 4 and 12 weeks. A slight reduction in blood pressure was observed with aripiprazole. Patients on quetiapine ER were significantly more likely to develop abdominal obesity, hypertriglyceridemia, hyperinsulinemia and metabolic syndrome. Higher pre-treatment weight in patients and metabolic diseases in first-degree relatives predicted the development of specific metabolic abnormalities during antipsychotic treatment.

Conclusion: In youths with FEP, quetiapine ER was associated with significantly greater weight gain and metabolic disturbances than aripiprazole. Cardiometabolic risk factors should be considered when choosing antipsychotic medications.

Keywords: Early Onset Psychosis, Metabolic changes, Antipsychotic treatment

ClinicalTrials.gov: NCT01119014, EudraCT: 2009-016715-38 (<https://eudract.ema.europa.eu/>)

Introduction

The life expectancy in patients with schizophrenia or other psychotic disorders is reduced, being up to 10 to 20 years shorter than in the background population.¹⁻³ This reduction is largely the result of an increased prevalence of cardiovascular disease (CVD).⁴⁻⁶ In a population study of 20 million individuals from 3 Nordic countries, the standardized mortality ratio for diseases of the

circulatory system was approximately 2 for patients with schizophrenia or bipolar disorder.²

The background for the increased propensity towards developing CVD in patients with psychotic disorders is multi-factorial⁷ and stems both from genetic factors,⁸ lifestyle factors (such as lack of exercise, unhealthy diet, smoking and substance abuse)⁹ and adverse effects from the pharmacological treatment primarily for psychotic symptoms.¹⁰ Patients who present with psychotic

symptoms at younger ages have increased risk of developing adverse effects,¹¹ and a poorer prognosis.^{12,13}

Second-generation antipsychotic (SGA) use increases the risk of developing diabetes and CVD^{10,14-20} in patients with psychotic disorders. Nevertheless, the prescription rate of antipsychotics has increased steadily over the last decades – also in children and adolescents.²¹⁻²⁴

In a Bayesian meta-analysis of 41 short-term (3-12 week) trials of SGAs in children and adolescents, Cohen et al.²⁵ found significant mean±SD weight gain during treatment with olanzapine, 3.99±0.42 kilograms, clozapine, 2.38±1.13, risperidone, 2.02±0.32 kilograms, quetiapine, 1.74±0.38 and aripiprazole 0.89±0.32 kilograms. Moreover, total cholesterol and triglycerides increased significantly with olanzapine and quetiapine, while olanzapine and risperidone treatment was associated with increased glucose levels.

As part of the SATIETY cohort study, Correll et al.²⁶ investigated 338 antipsychotic-naïve patients aged 4-17 years clinically treated with aripiprazole, olanzapine, quetiapine or risperidone. At follow-up (after a median of 10.8 weeks of treatment), all four SGAs caused a significant increase in weight, body mass index (BMI), fat mass and waist circumference (WC), compared to the untreated psychiatric control group. Olanzapine was associated with increased fasting glucose and insulin parameters, olanzapine and quetiapine were significantly associated with increased plasma levels of cholesterol, non-high density lipoprotein (non-HDL) cholesterol and triglycerides, risperidone was associated with significantly increased triglycerides, but despite 4.4 kilograms weight gain, the metabolic changes in patients treated with aripiprazole were non-significant. However, the authors note that the aripiprazole sample that contained 41 subjects was small and that a type II error could not be ruled out.

Quetiapine has been associated with weight gain in a number of studies in children and adolescents,²⁷⁻³⁰ although not all clinical studies consistently observe metabolic adverse effects during quetiapine treatment.³¹

Finally, in a nationwide Danish register study of 48,299 psychiatrically ill patients <18 years old (eating disorders excluded), Nielsen et al investigated the incidence of type II diabetes (T2DM), as defined by filling ≥1 prescription of oral antidiabetics. The authors found that exposure to antipsychotic medications significantly increased the risk of developing T2DM (Odds Ratio 1.60 (CI: 1.08-2.36)).³²

It is important to acknowledge that patients presenting with psychotic symptoms in childhood or adolescence are probably at risk of a higher cumulative exposure to antipsychotics and their adverse effects, due to early onset and poor prognosis. In a systematic review of four samples of early onset psychosis (EOP), 82% of patients were still on antipsychotic treatment after 1-2 years following treatment initiation (Submitted: Stentebjerg-Olesen M PA, Fink-Jensen, Correll C, Jeppesen P. Symptomatology, clinical characteristics and outcomes of schizophrenia-spectrum psychosis in children and adolescents: results from a systematic review and exploratory analysis of correlates) and in a similar study 81% were on antipsychotic treatment after 1 year.³³ Almost no studies have investigated the long-term use of antipsychotics in EOP, but in a follow-up study on 145 adults who were diagnosed with mental disorders in adolescence, Helgeland et al. found that all 13 patients diagnosed with schizophrenia were still on antipsychotic treatment after 28 years.³⁴

The propensity of antipsychotics to induce weight gain and metabolic disturbances, which is associated with increased risk of co-morbidities and premature death, particularly in patients with elevated risk for obesity and T2DM, underscores the

importance of evidence-based choice of medications.³⁵

Purpose

The purpose of the current study was to examine differences in the metabolic effects of 12 weeks intervention with aripiprazole versus (vs.) quetiapine extended release (ER) in children and adolescents with first-episode psychotic disorders.

Methods

Study design

The present study is part of the Tolerability and Efficacy of Antipsychotics (TEA) trial, a 12-week, independently funded, randomized, double-blinded, multicenter trial of aripiprazole vs. quetiapine ER in psychotic children and adolescents aged 12-17 years. The primary outcome of the TEA trial was changes in Positive And Negative Syndrome Scale (PANSS)³⁶ positive score; these results will be reported separately (Pagsberg et al. Quetiapine extended release versus aripiprazole in children and adolescents with first episode psychosis: results from the randomised, double-blind Tolerability and Efficacy of Antipsychotics (TEA) trial, in submission). The trial was conducted from May 2010 to May 2014. Seven child and adolescence mental health centers across Denmark, covering all university hospital clinics, participated in the trial. In the following, a brief outline of the design and methods is presented; a detailed protocol for the TEA trial has been published.³⁷ The trial is registered at ClinicalTrials.gov: NCT01119014, EudraCT: 2009-016715-38 and was approved by Danish Medicines Agency: 2612-4168, The Ethics Committee of Capital Region: H-3-2009-123, and Danish Data Protection Agency: 2009-41-3991.

Subjects

Physicians at the University Hospital clinics referred youth who were deemed potentially eligible for the trial, i.e., who suffered from psychotic symptoms to a degree where antipsychotic treatment was warranted. Inclusion criteria were: 1) Children and adolescents aged 12-17 years, both sexes; 2) in- or outpatients; 3) meeting the criteria for ICD-10³⁸ F20 (Schizophrenia), F22 (Persistent delusional disorders), F23 (Acute and transient psychotic disorders), F24 (Induced delusional disorders), F25 (Schizoaffective disorders), F28/F29 (Other/Unspecified nonorganic psychosis), F30.2 (Mania with psychotic symptoms), F31.2 (Bipolar affective disorder, current episode manic with psychotic symptoms), F31.5 (Bipolar affective disorder, current episode severe depression with psychotic symptoms), F32.3 (Severe depressive episode with psychotic symptoms), or F33.3 (Recurrent depressive episode, current episode severe with psychotic symptom); 4) clinical indication for antipsychotic treatment; 5) presence of psychotic symptoms scoring ≥ 4 on ≥ 1 of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content); as well as a total PANSS score > 60 points; 6) antipsychotic-naïve or limited exposure (i.e., not exceeding the past 12 months for psychosis, or no more than 1 week lifetime for any non-psychotic indication), and 7) written and signed informed consent by caregivers (and assent from patients). Exclusion criteria included: 1) Compulsory treatment; 2) drug-induced or organic psychosis; 3) severe chronic somatic illness or a history of severe head trauma; 4) pregnancy or lactation; 5) substance dependence (ICD-10 F1X.2 dependence syndrome) within the last year; 6) allergy towards the investigational drugs or known lactose intolerance; 7) lack of informed consent/assent. At week 4, participants and their parents underwent a Schedule for

Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL)³⁹ interview to establish their final diagnosis.

Trial interventions

Patients were randomized to double-blinded treatment with either aripiprazole or quetiapine ER. By default, patients followed a standardized titration schedule, which could be modified individually by the treating physician (see Supplementary Table S1, available online). The target doses were quetiapine ER 600 mg/day and aripiprazole 20 mg/day. During the treatment period, the dosage could be adjusted by the treating physician to optimize effect and minimize side effects (ranges: quetiapine ER: 50-800 mg/day; aripiprazole 2.5-30 mg/day). Patients could discontinue the study medication at any time during the intervention period due to lack of efficacy or aggravated symptoms, or if side effects were intolerable and could not be managed by dose adjustment or addition of medications to treat side effects (such as orphenadrin or biperiden for extrapyramidal adverse events).

Randomization and blinding

procedures

Randomization was performed at the Copenhagen Clinical Trial Unit (CTU) using a computer-generated allocation sequence with a block size unknown to the authors. The Capital Region Pharmacy delivered blinded capsules containing either aripiprazole or quetiapine ER for each treatment level. The randomization was stratified for age (<15 or ≥15 years) and symptom severity (PANSS positive score ≤20 or >20 points). Patients and caregivers, clinicians, and trial investigators were blinded to the treatment allocation until all data on the individual patient were collected. In order to ensure high quality continued treatment of the individual

patient, the treating physicians, but not the research personnel, were informed by the CTU as to which treatment arm the patient had been allocated. Before this information was provided, all investigational data were ensured in the individual Case Report Forms when the double-blinded treatment period ended.

Examination schedule

Before randomization, included patients underwent comprehensive physical assessments, including height, weight, waist circumference (WC), heart rate and blood pressure. Measurements were made once, using stadiometers and electronic weights at the in- or outpatient clinic where the patient received treatment. The same type of tape measure was used for measuring waist circumference at the level of umbilicus. Fasting blood samples including plasma glucose (FPG), total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG) were analyzed at the laboratory facilities at the clinic where the patient received treatment, while plasma insulin (FPI) samples were analyzed by Roche Cobas e 411 (Roche Professional Diagnostics, Basel, Switzerland) at the Steno Diabetes Center, Copenhagen. The choice of FPI over glycosylated hemoglobin A1C (Hb1AC) reflects research indicating that the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is a more valid marker of the risk of developing diabetes and metabolic syndrome than Hb1AC.⁴⁰⁻⁴² The investigators systematically interviewed participants and their parents regarding level of education (for details, see ^{43,44}) duration of untreated psychosis (DUP),⁴⁵ patient smoking status and use of alcohol. The presence or absence of somatic illnesses in first degree relatives was examined through systematic questioning of parents covering heart disease, diabetes type 1 and 2, dyslipidemia, obesity and other somatic

disorders. Any pre-existing somatic illness in included patients was registered.

During the 12-week intervention period, patients were re-examined after 2, 4 and 12 weeks, but blood samples and ECGs were performed only at the 4-week and 12-week visits (see supplementary table S2, available online). Thorough psychopathological examinations were performed at each visit, the results of which will be scrutinized in separate reports. If patients discontinued trial medication, they would be assessed at the time of discontinuation instead of the next follow-up. Whenever possible, all subsequent follow-ups would also be performed.

Computed outcome measures

Intermediate risk factors for CVD include elevated blood pressure, increased blood glucose, increased blood lipids, and overweight/obesity.⁴⁶ The metabolic syndrome (MS, see supplementary table S3, available online) is defined as a cluster of measurable and modifiable risk factors shown to increase the risk of developing T2DM and CVD later in life, and the use of MS as a marker for T2DM and CVD is also applicable to children and adolescents.⁴⁷ For the purpose of this study, 90th percentiles for WC in adolescents from a Norwegian study⁴⁸ were used as cut-offs, as the dietary and physical habits of Denmark and Norway are comparable (Supplementary table S4, available online). Data from “*The 2014 Danish references from birth to 20 years for height, weight and body mass index*”⁴⁹ were used as reference for age-stratified BMI. BMI was calculated using the formula $\frac{\text{weight (kg)}}{(\text{height (m)})^2}$,

HOMA-IR using the formula $\frac{\text{FPG (mmol/l)} \times \text{FPI (mU/l)}}{22.5}$

⁴⁰.

Statistical analyses

All patients who received at least one dose of trial medication comprised the Intention-To-Treat (ITT)

cohort. All statistical analyses were conducted using IBM SPSS® version 21. Patient characteristics in the two intervention groups were compared using descriptive statistics and Mann-Whitney's U test on a modified ITT population, e.g. comprising all patients in which data were collected, regardless of whether they discontinued trial medication or not. Differences in body composition, blood pressure and metabolic outcomes from baseline to each follow-up point for each group were examined using paired t-tests for continuous outcomes, and Wilcoxon signed ranked test for ordinal outcomes, for instance, number of cases with WC above 90th percentile or TG > 1.2 mmol/l. The frequency of abnormal metabolic values at baseline were evenly distributed across the two groups (Table 4, 9th column). Number needed to harm (NNH) were calculated using an online calculator (<http://www.graphpad.com/quickcalcs/index.cfm>). Numerical differences between the two groups in metabolic changes from baseline to each follow-up point were examined using the mixed models approach⁵⁰: outcomes were modelled by a longitudinal linear model including follow-up visit (three levels for body composition, two levels for laboratory values) using treatment group, the interaction between the two, as well as the baseline measurement as fixed effects. An unstructured matrix was used for residual correlations within subjects over visits. The model was fitted using the linear mixed models procedure in SPSS and inference was based on maximum likelihood. All statistical analyses were performed blinded, i.e. before treatment allocation was revealed to investigators.

Results

Patients

Of 231 eligible patients, 113 were included into the trial and randomized. The screening failures consisted of 118 youths (males=37.3%, mean

age=15.3±1.5 years, see CONSORT diagram in figure 1). The primary reasons for screening failures are listed in the CONSORT diagram. When comparing treatment groups and included vs. screening failures, we found no significant differences in age (p=.522 and p=.914, respectively) or gender distribution (p=.855 and p=.266, respectively) (see table 1).

FIGURE 1 HERE

TABLE 1 HERE

Fifty-eight patients were randomized to the aripiprazole arm (mean±SD dose: 13.3±5.4 mg) and 55 were randomized to quetiapine ER (mean±SD dose: 433.1±168.9 mg).

Fifty-seven patients (50.4%) were antipsychotic-naïve before randomization, without significant differences between the two treatment groups (table 1). There were no significant differences in the use of non-antipsychotic psychopharmacological use, nor in the occurrence of positive drug urine tests (benzodiazepines, n=20, and tetrahydrocannabinol, n=3), prior to inclusion (data not shown). There were no significant difference between treatment groups in the number of patients who discontinued trial medication prematurely or in the time difference between planned follow-up and premature follow-up. Protocol violations with patients receiving additional single doses of antipsychotics as rescue medication occurred in 41 subjects (36.3%), again without significant differences between the treatment groups. There were no differences in change in metabolic parameters between those who received additional as-needed antipsychotics during the treatment period vs. those who did not, and there were no differences in change in heart rate or BP between those who received antiarrhythmic drugs (n=1), asthma medications (n=12)

or methylphenidate (n=3) vs. those who did not (data not shown).

Outcome measures for all visits are show in table 2.

TABLE 2 HERE

Change in anthropometric values

At baseline, treatment groups did not differ significantly regarding any of the body composition, blood pressure and metabolic parameters examined prospectively in this study.

Except for BMI percentile at week 2 (p=0.095), all anthropometric changes of continuous parameters were significantly (p<.05) larger with quetiapine ER than aripiprazole from the first post-baseline assessment at week 2 and throughout the intervention period (table 3b). Patients in the quetiapine ER group experienced significant weight gain of 1.42±1.55 kilograms after 2 weeks of treatment (p<.001) and the weight gain continued through week 4 (2.24±1.89 kilograms, p<.001) and week 12 (5.22±3.97 kilograms, p<.001). Conversely, the weight gain in patients in the aripiprazole group was significantly smaller (0.26±1.35 kilograms (non-significant, NS) after 2 weeks, 0.40±1.80 kilograms (NS) after 4 weeks and 1.73±3.52, p=.001 after 12 weeks) (see table 3a and figure 2).

BMI z-score increased by 0.14±0.17 (p<.001) after 2 weeks, 0.23±0.21 (p<.001) after 4 weeks and 0.45±0.37 (p<.001) after 12 weeks in the quetiapine ER group. Corresponding changes in BMI percentile are listed in table 3a. In the aripiprazole group, increases in BMI and corresponding z-scores and percentiles were significantly smaller than in the quetiapine ER group and non-significant, except for BMI percentile change after 12 weeks (p=.025) (see Table 3a).

Likewise, changes in WC and WC z-score were statistically significant after 2 weeks (WC z-score: 0.54±0.83, p<.001), 4 weeks (WC z-score: 0.60±0.90,

$p < .001$) and 12 weeks (WC z-score: 1.00 ± 1.08 , $p < .001$) in the quetiapine ER group, but significantly smaller and non-significant in the aripiprazole group during the first 4 weeks. Only after 12 weeks were increases in WC and WC z-score significant (WC: z-score 0.30 ± 0.92 , $p = .039$) (Table 3a).

Patients in the quetiapine ER group experienced adverse changes in weight status (fewer underweight and normal, more overweight and obese, see table 4) during the course of treatment, and this change was statistically significant after 4 and 12 weeks ($p = .007$ and $p < .001$, respectively), while the distribution of patients in the aripiprazole group across these categories remained largely unchanged.

The number of patients who gained $\geq 7\%$ of baseline body weight was one (1.9%) after 2 weeks, four (8.0%) after 4 weeks and twenty-four (52.2%) after 12 weeks in the quetiapine ER group, while the corresponding numbers for the aripiprazole group were none (0%), two (3.7%) and nine (18.4%) after 2, 4 and 12 weeks, respectively (table 4). The difference in number of patients gaining $\geq 7\%$ in weight between groups was statistically significant at week 12 ($p = .001$).

Finally, patients reaching WC above 90th percentile (abdominal obesity) increased from 26 (51.0%) at baseline and week 2 to 28 (63.6%) after 4 weeks ($p = .096$) and to 30 (69.8%) after 12 weeks ($p = .035$) in the quetiapine ER group. In the aripiprazole group, the number increased from 19 (35.2%) at baseline to 23 (42.6%) after 2 weeks ($p = .157$) but then tapered off to 21 (42.0%) after 4 weeks and 17 (38.6%) after 12 weeks (table 4). The number of patients with WC $> 90^{\text{th}}$ percentile was statistically different between treatment groups after weeks 4 ($p = .041$) and 12 ($p = .005$).

Change in glucose metabolism

The between-group differences in fasting insulin and HOMA-IR were statistically significant after 4 weeks ($p < .001$) but not after 12 weeks ($p = .078$ and $p = .053$) (table 3b).

FPG remained fairly unchanged in both treatment groups (see table 3a). However, fasting insulin increased in the quetiapine ER group by 25.42 ± 51.37 mmol/l ($p = .004$) after 4 weeks and 22.84 ± 51.23 ($p = .008$) after 12 weeks, while decrease at week 4 and increases at week 12 in the aripiprazole group were small and non-significant.

Correspondingly, HOMA-IR also increased in the quetiapine ER group (0.83 ± 1.69 , $p = .006$ after 4 weeks and 0.73 ± 1.99 , $p = .027$ after 12 weeks), being non-significant for aripiprazole.

In the quetiapine ER group, the number of patients with fasting insulin ≥ 138.9 pmol/l increased from 3 (6.5%) at baseline to 12 (26.7%) after 4 weeks ($p = .020$), decreasing to 8 (19.0%) after 12 weeks ($p = .025$). The corresponding numbers from the aripiprazole group were 4 (9.1%) at baseline and 0 (0%) and 2 (4.4%) after 4 and 12 weeks, respectively (non-significant, table 4). Significantly more patients on quetiapine ER than aripiprazole had insulin ≥ 138.9 pmol/l after week 4 ($p < .001$) and 12 ($p = .045$), while insulin resistance was only significantly more common with quetiapine ER than aripiprazole at week 4 ($p = .001$).

Changes in lipids

Except for HDL, all changes in all other continuous lipid parameters were significantly larger with quetiapine ER than aripiprazole from the first post-baseline assessment at week 4 and at week 12 (table 3b).

In the quetiapine ER group, significant increases were observed after 4 weeks: Triglycerides increased by 0.34 ± 0.74 mmol/l ($p = .006$), and

TG/HDL ratio increased by 0.29 ± 0.70 ($p=.015$). After 12 weeks, total cholesterol increased significantly by 0.35 ± 0.63 mmol/l ($p=.001$), triglycerides by 0.46 ± 1.09 ($p=.014$), LDL by 0.20 ± 0.48 ($p=.015$) and TG/HDL ratio by 0.57 ± 1.41 ($p=.018$) (see table 3a). No significant changes were observed in blood lipids in the aripiprazole group.

In the quetiapine ER group, the number of patients with total cholesterol ≥ 4.4 mmol/l rose from 18 (37.5%) at baseline to 29 (67.4%) after 12 weeks ($p=.008$). The number of patients with non-HDL-cholesterol ≥ 3.4 mmol/l increased from 8 (16.7%) at baseline to 18 (38.3%) after 4 weeks ($p=.011$) and 20 (46.5%) after 12 weeks ($p=.004$). The number with triglycerides ≥ 1.2 mmol/l rose from 11 (23.4%) to 18 (40.9%) after 4 weeks ($p=.008$) and was 17 (40.5%) by 12 weeks ($p=.083$). The number with dyslipidemia rose from 22 (45.8%) to 33 (68.8%) after 4 weeks ($p=.008$) and 32 (74.4%) after 12 weeks ($p=.020$). Changes in these parameters were all non-significant with aripiprazole and the between-group differences in these proportions were significant at both 4 and 12 weeks for non-HDL-cholesterol, triglycerides and dyslipidemia (table 4).

Blood pressure and heart rate

Systolic and diastolic BP were significantly lower with aripiprazole than quetiapine ER at weeks 4 and 12; the same was true for heart rate at weeks 2, 4 and 12. Systolic and diastolic blood pressure changes with quetiapine ER were non-significant, whereas in the aripiprazole group, systolic blood pressure decreased after 4 weeks by -3.06 ± 10.70 mmHg ($p=.041$) and after 12 weeks by -2.96 ± 11.43 mmHg ($p=0.076$), and diastolic blood pressure decreased by -4.89 ± 8.30 mmHg after 4 weeks ($p<.001$) and -4.12 ± 9.5 mmHg after 12 weeks ($p=.004$) (see table 3a).

With quetiapine ER, heart rate increased 11.06 ± 16.01 bpm after 2 weeks ($p<.001$), by

14.23 ± 13.28 bpm after 4 weeks ($p<.001$) and by 10.28 ± 14.97 bpm after 12 weeks ($p<.001$). With aripiprazole, a significant increase in heart rate was observed after 2 weeks 5.95 ± 10.70 bpm ($p<.001$), but this increase was no longer significant after week 4 ($p=.272$) or 12 ($p=.162$).

The number of patients with hypertension differed significantly between the two groups only at week 12 (20 vs. 11, $p=.049$).

TABLE 3 HERE

TABLE 4 HERE

Metabolic syndrome

One patient (2.0%) in the quetiapine ER group had MS at baseline, this number increased to 6 (13.3%) after week 4 and 12 ($p=.046$). In the aripiprazole group, the corresponding numbers were 2 (3.6%) at baseline, 2 (3.8%) after 4 weeks ($p=.317$) and 4 (8.3%) after 12 weeks ($p=.157$).

Predictors of anthropometric changes

Weight before inclusion significantly and positively predicted change in weight ($p=.003$) and TG ($p=.001$) in all subjects. Also, the presence of T2DM in first degree relatives (FDR) predicted weight and WC increase, while obesity in FDR predicted weight gain (table 5).

Predictors of metabolic changes

Age at onset of psychotic symptoms significantly and positively predicted change in cholesterol ($p=.043$) but of no other metabolic outcome. Dyslipidemia in FDR predicted a decline in HDL, while obesity in FDR predicted an increase in TG and decrease in HDL (table 5).

Discussion

This randomized, 12-week, head-to-head study comparing aripiprazole with quetiapine ER in youth with EOP showed that quetiapine ER was associated with significantly larger adverse effects in all body composition parameters and almost all metabolic parameters at each post-baseline time point than aripiprazole, which despite significant increases in body composition parameters was metabolically neutral. In particular, patients treated with quetiapine ER experienced a very rapid increase (already apparent after 2 weeks of treatment) across a wide range of body composition and metabolic parameters, including weight, WC, insulin, HOMA-IR and lipids. The magnitude of these changes after 12 weeks was large enough to have a potentially profound impact on the cardiometabolic health of these patients. This clinically relevant effect was apparent by significantly increased proportions of youth in the quetiapine ER treatment arm with new-onset cases of hyperinsulinemia, hypercholesterolemia, dyslipidemia and MS. These results are consistent with observations from previous placebo-controlled trials in youth^{15,51} and we have shown that these adverse effects occur very early during the treatment with quetiapine ER. Our results are also consistent with findings from the naturalistic inception cohort SATIETY study in US youth with mixed psychiatric disorders (mean age=13.9 years)²⁶ that had less patients in the quetiapine ER and aripiprazole arms, importantly confirming the absence of significant metabolic abnormalities with aripiprazole treatment despite significant increases in all but one measured body composition parameters. Interestingly, in our European sample, the 12-week weight gain was similar to that in the US sample (5.2 Kilograms and 0.45 BMI z-score units vs. 6.1 kilograms and 0.44 BMI z-score units), but the weight gain with aripiprazole was much smaller in our sample (1.73 kilograms and 0.11 BMI z-score units vs. 4.4 kilograms and 0.37 BMI z-score units). Furthermore,

our 3-month findings for quetiapine ER differ from that reported in a 6-month Spanish inception cohort study of youth with mixed psychiatric disorders (mean age=14.6 years) that did not include aripiprazole.⁵² In that study, the weight gain with quetiapine at 3 months was very comparable to our results and those from the SATIETY study (5.7 kilograms and 0.5 BMI z score units), but, surprisingly, none of the metabolic parameters changed significantly with quetiapine. While this discrepancy to the US sample could have been potentially due to differences in diet and exercise, our findings in a European youth sample seem to rule out that possibility, showing that the significant and large weight gain with quetiapine ER translates into expected adverse metabolic effects that manifest rapidly.

While the long-term effects of antipsychotic-related cardiometabolic abnormalities have not been sufficiently investigated, it is likely that metabolic adverse effects occurring in childhood will increase the risk of subsequent comorbidity and mortality in adulthood^{53,54} For example, in a review of BMI as a predictor of cardiovascular disease in adulthood by Park et al,⁵⁵ authors found that high BMI in childhood was associated with and 40-60% increase in risk of all-cause mortality in adulthood, and also with a hazard ratio ranging from 1.53 to 5.43 for the development of CVD.

Considering baseline predictors and risk factors for adverse cardiometabolic effects of the two studied antipsychotics, we found that higher baseline weight was correlated to greater weight gain and higher triglyceride values. While this finding is inconsistent with a large body of literature that found an inverse relationship between baseline weight gain and antipsychotic induced weight change,^{7,14} this inconsistency is due to the fact that those other studies investigated chronically ill patients with prior medication-induced weight gain, which attenuates the likelihood of observing additional weight gain. Conversely, in mostly

antipsychotic-naïve youth, those with problems regulating normal body weight and appetite homeostasis seem to be at higher risk for gaining weight on medications that increase appetite. We further found that metabolic disturbances in FDR predicted increased risk for some metabolic adverse effects in patients, suggesting a common underlying genetic vulnerability or shared environmental risk, indicating that both the metabolic risk factors of a patients and of their relatives should be considered when choosing antipsychotic medications. However, these findings were exploratory and should be interpreted with caution.

Aside from the direct health consequences, youths with psychotic disorders are a highly vulnerable patient group who may already feel marginalized by their peers, so that weight gain of 5 kilograms may be yet another cause of (self-) stigmatization,⁵⁶ which may increase the risk of treatment discontinuation and which may damage the alliance between patients and healthcare providers.

While the randomized design, the relatively high number of participants (considering the small population of early onset psychosis and size of prior randomized trials in this patient group) and low drop-out rates (9 (Lost to follow-up: aripiprazole, 9 (15.5%), quetiapine ER 4 (7.2%)) are the major strengths of this trial, there are also several limitations. First, the number of included patients was based on a power calculation on the primary outcome (PANNS positive subscale score). Second, laboratory settings differed between participating centers, which may have led to small differences in laboratory values. However, insulin samples, which are characterized by extremely low concentrations and therefore prone to measurement inaccuracy, were all analyzed at Steno Diabetes Center (www.steno.dk). Third, although measures were taken to ensure smoking abstinence before blood sampling, this was not always possible. Fourth, we did not have information on diet and exercise. Fifth, it was not always possible to obtain blood samples

at the same time in the morning, but all analyzed samples were fasting. Sixth, even though measures were taken to optimize conditions for evaluation of blood pressure and heart rate, it is possible that level of anxiety or stress may have influenced these parameters. Seventh, co-medications were allowed in this study, which could have affected some of the results, but the two treatment groups did not differ significantly and the co-treatment with other medications is common clinical practice, enhancing the generalizability of our results. Finally, measurement of waist circumference was made at the level of umbilicus, and due to variations related to age, gender and level of sexual maturation, this posed some difficulties in obtaining reliable data. For similar studies, measuring at the level of smallest WC may be preferred. These potential limitations (second through fifth) may, however, be minimized due to the random allocation.

Conclusion

In youths with first-episode psychosis, patients treated with quetiapine ER developed significantly more weight gain and metabolic disturbances compared to patients treated with aripiprazole. These differences emerged early, are clinically relevant and should therefore inform treatment choice for youth with EOP, especially given the fact that in the TEA trial aripiprazole and quetiapine ER were equally effective for improving psychopathology (data not yet published).

Tables

Table 1: Baseline demographic and clinical characteristics, and concomitant medication in 113 subjects with early onset psychosis

All participants	All patients (n=113)	Quetiapine ER group (n=55)	Aripiprazole group (n=58)	p
Age, total, mean (SD) (years)	15.7±1.4	15.8±1.4	15.7±1.3	.522
Males, n (%)	34 (30.1%)	17 (30.9%)	17 (29.3%)	.855
Smokers, n (%)	40 (35.7%)	20 (26.4%)	20 (34.5%)	1.000
Cigarette consumption /day, median (IQR)	10 (6.00-16.50)	10 (6.25-13.75)	9 (5.25-19.25)	.922
Tanner stage, males, mean (SD)	4.1±0.9	4.1±1.0	4.2±0.8	.865
Tanner stage, females, mean (SD)	4.2±0.6	4.2±0.7	4.2±0.6	.949
Psychopathology, mean±SD				
PANSS positive subscore	20.3±3.5	19.9±3.3	20.6±3.7	.297
PANSS negative subscore	20.6±5.3	20.6±5.4	20.6±5.3	.931
PANSS general subscore	37±6.4	36.7±5.9	37.4±7	.683
PANSS total	77.9±12.4	77.2±11.1	78.6±13.6	.823
Age at onset of psychotic symptoms, years	13±3.3	13±3.7	13±2.9	.647
DUP, weeks	142.3±169.4	145.2±192.2	139.5±146.9	.881
CGI-S score	4.7±0.8	4.7±0.7	4.8±0.9	1.000
GAPD score	4.4±1.1	4.3±1.1	4.4±1.1	.757
ICD-10 diagnoses, n (%)	Patients (n=113)	Quetiapine ER group (n=55)	Aripiprazole group (n=58)	p
F20, schizophrenia	75 (66.4%)	33 (60%)	42 (72.4%)	X ² =7.092, p=.419
F22, delusional disorders	2 (1.8)	2 (3.6%)	0 (0.0%)	
F23, acute and transient psychotic disorders	1 (0.9%)	0 (0.0%)	1 (1.7%)	
F25, schizoaffective disorders	23 (20.4%)	14 (25.5%)	9 (15.5%)	
F28, other nonorganic psychotic disorders	4 (3.5%)	2 (3.6%)	2 (3.4%)	
F31, bipolar affective disorders	1 (0.9%)	0 (0.0%)	1 (1.7%)	
F32, depressive episode	6 (5.3%)	3 (1.8%)	3 (5.2%)	
F33, recurrent depressive disorder	1 (0.9%)	1 (3.6%)	0 (0.0%)	
Antipsychotic treatment prior to inclusion				
Antipsychotic naive, n (%)	57 (50.4)	28 (50.9)	29 (50.0)	.923

All participants	All patients (n=113)	Quetiapine ER group (n=55)	Aripiprazole group (n=58)	p
Not antipsychotic naive, n (%)	56 (49.6)	27 (49.1)	29 (50.0)	.923
Number of antipsychotic drugs prior to inclusion				
0	57 (50.4%)	28 (50.9%)	29 (50.0%)	.917
1	42 (37.2%)	19 (34.5%)	23 (39.7%)	
2	13 (11.5%)	8 (14.5%)	5 (8.6%)	
3	1 (0.9%)	0 (0.0%)	1 (1.0%)	
Prior antipsychotic treatment				
Aripiprazole, n (%)	3 (2.7%)	1 (1.8%)	2 (3.4%)	1.000
Aripiprazole, median cumulated life time dose, mg (IQR)	20.00 (15.00-35.00)	15.00 (-)	27.50 (20.00-35.00)	.667
Aripiprazole, median number of days (IQR)	7.0 (6.0-8.0)	6.0 (-)	7.5 (7.0-8.0)	.667
Quetiapine, n (%)	9 (8.0%)	4 (7.3%)	5 (8.6%)	1.000
Quetiapine, median cumulated life time dose, mg (IQR)	250.00 (75.00-820.00)	138.00 (13.00-535.00)	675.00 (150.00-1250.00)	.286
Quetiapine, median number of days (IQR)	15.5 (2.5-16.0)	8.0 (1.0-23.0)	25.0 (3.0-27.0)	.393
Olanzapine, n (%)	23 (20.4%)	12 (21.8%)	11 (19.0%)	.816
Olanzapine, median cumulated life time dose, mg (IQR)	45.00 (10.00-115.00)	50.00 (17.50-242.50)	20.00 (10.00-110.00)	.525
Olanzapine, median number of days (IQR)	8.0 (1.0-16.0)	13.0 (1.0-25.0)	6.0 (1.0-11.0)	.235
Chlorprothixene, n (%)	38 (33.6%)	20 (36.4%)	18 (31.0%)	.558
Chlorprothixene, median cumulated life time dose, mg (IQR)	75.00 (25.00-180.00)	58.00 (20.00-195.00)	98.00 (40.00-160.00)	.874
Chlorprothixene, median number of days (IQR)	3.0 (1.0-8.0)	2.5 (1.0-9.0)	6.0 (1.0-8.0)	.478
Concomitant psychiatric medications				
Antipsychotics (acute), n (%)	41 (36.3%)	19 (34.5%)	22 (37.9%)	.845
Aripiprazole, n (%)*	3 (2.7%)	0 (0.0%)	3 (5.2%)	.244
Aripiprazole, median cumulated dose in assessment period, mg (IQR)	132.50 (25.00-240.00)		132.50 (25.00-240.00)	-
Aripiprazole, median number of doses (IQR)	8.0 (4.0-12.0)		8.0 (4.0-12.0)	-
Quetiapine, n (%)*	9 (8.0%)	3 (5.5%)	6 (10.3%)	.491

All participants	All patients (n=113)	Quetiapine ER group (n=55)	Aripiprazole group (n=58)	p
Quetiapine, median cumulated dose in assessment period, mg (IQR)	11050.00 (3125.00-29250.00)	3125.00 (350.00-6600.00)	23325.00 (11050.00-32950.00)	.095
Quetiapine, median number of doses (IQR)	48.0 (15.0-62.0)	15.00 (14.0-23.0)	51.0 (48.0-82.0)	.167
Olanzapine, n (%)	18 (15.9%)	12 (21.8%)	6 (10.3%)	.125
Olanzapine, median cumulated dose in assessment period, mg (IQR)	60.00 (20.00-155.00)	37.50 (20.00-155.00)	60.00 (10.00-440.00)	.884
Olanzapine, median number of doses (IQR)	12.0 (3.0-21.0)	15.0 (3.0-21.0)	9.0 (2.0-61.0)	1.000
Chlorprothixene, n (%)	28 (24.8%)	10 (18.2%)	18 (31.0%)	.131
Chlorprothixene, median cumulated dose in assessment period, mg (IQR)	210.00 (75.00-450.00)	187.50 (30.00-465.00)	210.00 (105.00-435.00)	.494
Chlorprothixene, median number of doses (IQR)	9.0 (4.0-29.0)	7.0 (2.0-31.0)	11.0 (7.0-29.0)	.146
Antidepressants (SSRI), n (%)	28 (24.8%)	13 (23.6%)	15 (25.9%)	.784
Mood stabilizers, n (%)	1 (0.9%)	1 (1.8%)	0 (0.0%)	.302
Benzodiazepines, n (%)	32 (28.3%)	11 (20%)	21 (36.2%)	.056
Methylphenidate, n (%)	3 (2.7%)	2 (3.6%)	1 (1.7%)	.527
Antihistamines for sedation, n (%)	5 (4.4%)	2 (3.6%)	3 (5.2%)	.691
Melatonin, n (%)	43 (38.1%)	19 (34.5%)	24 (41.4%)	.455

* acute treatment with aripiprazole or quetiapine only occurred after discontinuation of trial medication. BP = blood pressure; CGI-S: clinical global impression, severity; DUP: duration of untreated psychosis; GAPD: global assessment of psychosocial disability; ICD-10: international classification of diseases manual, 10th edition; IQR: interquartile range; mg: milligrams; PANSS: positive and negative syndrome scale; SSRI: selective serotonin reuptake inhibitor; SD: standard deviation.

Table 2: Mean observed anthropometric and metabolic measurements across treatment groups, modified intention-to-treat population

	Quetiapine ER group								Aripiprazole group							
	Baseline		Week 2		Week 4		Week 12		Baseline		Week 2		Week 4		Week 12	
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
Anthropometrics																
Weight (kilograms)	55	63.21±13.8	52	65.48±14.08	50	66.65±14.31	46	69.65±15.96	58	61.27±10.72	54	61.39±10.7	54	61.81±10.66	49	63.14±11.78
BMI (kilograms/m ²)	55	21.85±3.38	50	22.38±3.62	48	23.05±3.45	45	23.7±3.93	58	21.53±3.48	53	21.58±3.5	54	21.59±3.42	48	21.88±3.57
BMI z-score	55	0.48±1.27	50	0.65±1.25	48	0.87±1.19	45	1.01±1.21	58	0.4±1.25	53	0.4±1.27	54	0.4±1.26	48	0.47±1.22
BMI percentile	55	62.01±32.35	50	65.97±31.39	48	71.86±29.49	45	73.89±28.88	58	58.72±33.26	53	59.29±33.34	54	59.17±33.43	48	61.45±32.65
WC (cm)	51	76.9±9.65	48	79.65±10.12	44	81.77±10.52	43	84.43±11.75	54	75.68±9.81	54	76.17±9.83	50	76.25±10.22	44	77.91±11.19
WC z-score	51	1.22±1.59	48	1.74±1.70	44	1.94±1.66	43	2.43±1.84	54	1.04±1.71	54	1.13±1.74	50	1.17±1.82	44	1.91±1.93
Body mass index percentile groups																
Underweight (n)	55	5	50	3	48	1	45	0	58	2	53	2	54	3	48	2
Normal (n)		31		26		22		20		35		32		33		28
Overweight (n)		8		10		13		9		11		9		8		10
Obese (n)		11		11		12		16		10		10		10		8
Glucemic																
Glucose (mmol/l)	47	4.88±0.52			47	4.91±0.57	44	5.01±0.44	52	4.98±0.8			49	4.99±0.35	45	4.98±0.41
Insulin (pmol/l)	46	78.57±60.61			45	106.14±71.9	42	99.62±58.87	44	72.15±57.35			46	65.15±24.75	45	74.34±34.29
HOMA-IR	45	2.5±2.41			44	3.37±2.43	42	3.24±2.05	44	2.53±3.39			46	2.06±0.79	44	2.38±1.15
Lipids																
Total cholesterol (mmol/l)	48	4.19±0.73			48	4.45±0.75	43	4.64±0.64	52	4.01±0.69			49	4.02±0.8	44	3.99±0.7
TG (mmol/l)	47	0.99±0.41			44	1.32±0.92	42	1.43±1.2	52	0.93±0.33			49	0.89±0.26	45	0.93±0.37
LDL (mmol/l)	48	2.45±0.57			47	2.65±0.56	41	2.75±0.58	52	2.3±0.55			49	2.3±0.63	45	2.35±0.6
HDL (mmol/l)	48	1.76±2.23			47	1.34±0.31	44	1.3±0.35	52	1.3±0.31			49	1.32±0.36	46	1.25±0.24
Non-HDL (mmol/l)	48	2.43±2.23			47	3.12±0.78	43	3.34±0.65	52	2.71±0.59			49	2.7±0.68	44	2.75±0.68
TG/HDL ratio	47	0.77±0.42			43	1.03±0.88	42	1.34±1.6	52	0.75±0.35			49	0.73±0.3	45	0.78±0.39
Blood pressure and heart rate																
Systolic BP (mmHg)	54	119.26±13.07	52	117.13±11.15	48	119.79±12.09	47	120.81±11.67	58	117.91±11.57	56	117.29±11.11	54	114.61±11.01	49	115.1±11.54
Diastolic BP (mmHg)	54	69.93±10.5	52	69.94±8.47	48	71.79±7.73	47	72.57±8.75	58	69.36±7.84	56	69.84±7.42	54	64.54±7.59	49	65.57±7.97
Heart rate (bpm)	54	70.87±11	52	81.9±16.58	48	85.63±14.01	47	81.17±11.94	58	69.72±11.63	57	75.7±12.27	54	71.24±11.6	49	72.37±12.31

BP = blood pressure; bpm = beats per minute; FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; kilograms = kilograms; LDL = low-density lipoprotein cholesterol; TG = triglycerides; WC = waist circumference.

Table 3a: Within-group comparison of change in observed metabolic parameters, modified intention-to-treat population

	Quetiapine ER group						Aripiprazole group					
	n	Week 0-2 Mean±SD	n	Week 0-4 Mean±SD	n	Week 0-12 Mean±SD	n	Week 0-2 Mean±SD	n	Week 0-4 Mean±SD	n	Week 0-12 Mean±SD
Anthropometrics												
Weight (kilograms)	52	1.42±1.55 p<.001	50	2.24±1.89 p<.001	46	5.22±3.97 p<.001	54	0.26±1.35 p=.167	54	0.40±1.80 p=.108	49	1.73±3.52 p=.001
BMI	50	0.45±0.55 p<.001	48	0.75±0.63 p<.001	45	1.59±1.26 p<.001	53	0.06±0.53 p=.395	54	0.08±0.71 p=.384	48	0.44±1.3 p=.024
BMI z-score	50	0.14±0.17 p<.001	48	0.23±0.21 p<.001	45	0.45±0.37 p<.001	53	0.02±0.22 p=.496	54	0.03±0.25 p=.407	48	0.11±0.40 p=.069
BMI percentile	50	2.99±4.79 p<.001	48	5.39±5.68 p<.001	45	9.65±11.78 p<.001	53	1.47±6.08 p=.085	54	1.74±7.26 p=.084	48	3.89±11.66 p=.025
WC (cm)	44	3.15±5.15 p<.001	42	3.71±5.83 p<.001	40	6.09±6.48 p<.001	51	0.20±3.41 p=.683	47	0.46±3.17 p=.324	42	1.89±5.20 p=.024
WC z-score	44	0.54±0.83 p<.001	42	0.60±0.90 p<.001	40	1.00±1.08 p<.001	51	0.04±0.57 p=.604	47	0.08±0.54 p=.340	42	0.30±0.92 p=.039
Body mass index percentile groups	50	p=.059	48	p=.007	45	p<.001	53	p=1.000	54	p=.180	48	p=1.000
Glycemic												
Glucose (mmol/l)			39	0.06±0.49 p=.460	40	0.06±0.41 p=.344			44	-0.05±0.74 p=.657	39	0.01±0.41 p=.938
Insulin (pmol/l)			38	25.42±51.37 p=.004	39	22.84±51.23 p=.008			35	-9.48±66.58 p=.406	33	2.75±69.70 p=.822
HOMA-IR			36	0.83±1.69 p=.006	39	0.73±1.99 p=.027			35	-0.63±3.94 p=.353	32	0.42±1.37 p=.095
Lipids												
Total cholesterol (mmol/l)			41	0.16±0.77 p=.189	39	0.35±0.63 p=.001			44	0.06±0.48 p=.388	38	0.07±0.54 p=.439
Triglycerides (mmol/l)			39	0.34±0.74 p=.006	38	0.46±1.09 p=.014			44	-0.03±0.28 p=.558	39	0.02±0.35 p=.713
LDL (mmol/l)			40	0.09±0.36 p=.114	37	0.20±0.48 p=.015			44	0.04±0.41 p=.556	39	0.11±0.40 p=.095
HDL (mmol/l)			40	-0.51±2.43 p=.189	40	-0.29±1.98 p=.364			44	0.03±0.24 p=.352	40	-0.01±0.21 p=.771
Non-HDL (mmol/l)			40	0.7±2.5 p=.086	39	0.65±2.07 p=.058			44	0.03±0.41 p=.638	38	0.08±0.49 p=.334

	Quetiapine ER group						Aripiprazole group					
	n	Week 0-2 Mean±SD	n	Week 0-4 Mean±SD	n	Week 0-12 Mean±SD	n	Week 0-2 Mean±SD	n	Week 0-4 Mean±SD	n	Week 0-12 Mean±SD
TG/HDL ratio			38	0.29±0.70 p=.015	38	0.57±1.41 p=.018			44	-0.03±0.3 p=.465	39	0.02±0.36 p=.773
Blood pressure and heart rate												
Systolic BP (mmHg)	51	-2.18±13.07 p=.240	48	0.83±13.77 p=.677	47	1.47±11.98 p=.405	56	0.77±10.82 p=.598	54	-3.06±10.70 p=.041	49	-2.96±11.43 p=.076
Diastolic BP (mmHg)	51	0.06±13.32 p=.975	48	1.21±11.60 p=.474	47	2.68±9.29 p=.054	56	0.36±7.34 p=.717	54	-4.89±8.30 p<.001	49	-4.12±9.5 p=.004
Heart Rate (bpm)	51	11.06±16.01 p<.001	48	14.23±13.28 p<.001	47	10.28±14.97 p<.001	57	5.95±10.70 p<.001	54	1.61±10.67 p=.272	49	2.18±10.75 p=.162

Bolded values = p<.05; BP = blood pressure; bpm = beats per minute; FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; kilograms =kilograms; LDL = low-density lipoprotein cholesterol; TG = triglycerides; WC = waist circumference.

Table 3b: Between-group comparison of change in metabolic parameters (mixed models analysis in intention-to-treat population) using quetiapine ER as the reference

	Time	Mean	CI Lower	CI Upper	p
Anthropometrics					
Weight (kilograms)	Week 2	-1.11	-1.67	-.55	.000
	Week 4	-1.91	-2.62	-1.21	.000
	Week 12	-3.58	-5.11	-2.05	.000
BMI	Week 2	-.38	-.59	-.18	.000
	Week 4	-.67	-.93	-.41	.000
	Week 12	-1.23	-1.77	-.68	.000
BMI z-score	Week 2	-.12	-.19	-.05	.002
	Week 4	-.22	-.30	-.13	.000
	Week 12	-.35	-.51	-.19	.000
BMI percentile	Week 2	-1.73	-3.76	.30	.095
	Week 4	-4.42	-6.98	-1.87	.001
	Week 12	-5.69	-10.46	-.91	.020
WC	Week 2	-4.01	-7.56	-.46	.027
	Week 4	-4.10	-7.73	-.47	.027
	Week 12	-5.53	-9.52	-1.53	.007
WC z-score	Week 2	-.48	-.82	-.15	.005
	Week 4	-.49	-.85	-.13	.009
	Week 12	-.76	-1.19	-.32	.001
Glucemic					
Glucose (mmol/l)	Week 4	.07	-.12	.26	.459
	Week 12	-.03	-.21	.15	.762
Insulin (pmol/l)	Week 4	-38.1	-57.9	-18.4	.000
	Week 12	-17.6	-37.2	2.00	.078
HOMA-IR	Week 4	-1.31	-2.00	-.62	.000
	Week 12	-.65	-1.32	.01	.053
Lipids					
Total cholesterol (mmol/l)	Week 4	-.40	-.70	-.09	.011
	Week 12	-.62	-.91	-.33	.000
LDL (mmol/l)	Week 4	-.30	-.53	-.07	.010
	Week 12	-.38	-.63	-.13	.003
HDL (mmol/l)	Week 4	.03	-.10	.16	.636
	Week 12	-.01	-.14	.13	.929
TG (mmol/l)	Week 4	-.41	-.65	-.17	.001
	Week 12	-.43	-.76	-.10	.012
Non-HDL (mmol/l)	Week 4	-.43	-.72	-.14	.004
	Week 12	-.61	-.89	-.32	.000
TG/HDL ratio	Week 4	-.43	-.71	-.16	.003
	Week 12	-.52	-.94	-.10	.016
Blood pressure (BP)					
Systolic BP (mmHg)	Week 2	-1.07	-4.65	2.51	.554
	Week 4	-5.21	-9.14	-1.27	.010
	Week 12	-6.11	-10.11	-2.12	.003
Diastolic BP (mmHg)	Week 2	-.84	-3.66	1.98	.558
	Week 4	-7.18	-9.97	-4.39	.000
	Week 12	-8.08	-11.21	-4.94	.000
Heart Rate (bpm)	Week 2	-7.17	-12.06	-2.29	.004
	Week 4	-14.02	-18.33	-9.71	.000
	Week 12	-10.12	-14.62	-5.61	.000

Bolded values: $p < .05$; BP = blood pressure; bpm = beats per minute; CI = confidence interval; FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density lipoprotein cholesterol; TG = triglycerides; WC = waist circumference.

Table 4: Incidence of youth with pathological values in anthropometric, metabolic and blood pressure as well as heart rate parameters

	Quetiapine ER group, n (%) p-values for change from baseline				Aripiprazole group, n (%) p-values for change from baseline				Between-group p-value, NNH (95% confidence interval)			
	Baseline	Week 2	Week 4	Week 12	Baseline	Week 2	Week 4	Week 12	Baseline	Week 2	Week 4	Week 12
Weight increase ≥7%		1 (1.9%)	4 (8.0%)	24 (52.2%)		0 (0.0%)	2 (3.7%)	9 (18.4%)		.491	.424	.001 3 (2-7)
Blood pressure >90th percentile	21 (38.2%)	16 (30.8%) p=.317	18 (37.5%) p=.782	20 (42.6%) p=.480	15 (25.9%)	17 (30.4%) p=.617	11 (20.4%) p=.593	11 (22.4%) p=.782	.225	1.000	.078	.049 5 (3-57)
Body mass index percentile groups		p=.059	p=.007	p<.001		p=1.000	p=.180	p=1.000	.578	.841	.237	.113
Underweight	5 (9.1%)	3 (6.0%)	1 (2.1%)	0 (0.0%)	2 (3.4%)	2 (3.8%)	3 (5.6%)	2 (4.2%)				
Normal	31 (56.4%)	26 (52.0%)	22 (45.8%)	20 (44.4%)	35 (60.3%)	32 (60.4%)	33 (61.1%)	28 (58.3%)				
Overweight	8 (14.5%)	10 (20.0%)	13 (27.1%)	9 (20.0%)	11 (19.0%)	9 (17.0%)	8 (14.8%)	10 (20.8%)				
Obese	11 (20.0%)	11 (22.0%)	12 (25.0%)	16 (35.6%)	10 (17.2%)	10 (18.9%)	10 (18.5%)	8 (16.7%)				
Overweight or obese	19 (34.5%)	21 (42.0%) p=.083	25 (52.1%) p=.014	25 (55.6%) p=.003	21 (36.2%)	19 (35.8%) p=.317	18 (33.3%) p=.157	18 (37.5%) p=.564	1.000	.550	.071	.098
IDF criteria for Metabolic Syndrome												
WC z-score >90 th percentile	26 (51.0%)	26 (54.2%) p=.257	28 (63.6%) p=.096	30 (69.8%) p=.035	19 (35.2%)	23 (42.6%) p=.157	21 (42.0%) p=.083	17 (38.6%) p=1.000	.118	.321	.041 5 (3-53)	.005 4 (2-9)
Triglycerides ≥1.7 mmol/L	4 (8.5%)		9 (20.5%) p=.096	10 (23.8%) p=.020	2 (3.8%)		0 (0.0%) p=.317	3 (6.7%) p=.564	.419		.001 5 (4-12)	.035 6 (4-43)
HDL-cholesterol <1.03mmol/L, <1.29 in females >16 years	10 (20.8%)		10 (21.3%) p=.480	12 (27.3%) p=.480	9 (17.3%)		11 (22.4%) p=.782	12 (26.1%) p=.480	.800		1.000	1.000
Systolic BP ≥130 or diastolic BP ≥80	13 (24.1%)		11 (22.9%) p=.782	16 (34.0%) p=.096	8 (13.8%)		5 (9.3%) p=.480	7 (14.3%) p=1.000	.226		.100	.031 6 (3-33)
FPG >5.6 mmol/L	4 (8.5%)		6 (12.8%) p=.083	4 (9.1%) p=.317	3 (5.8%)		2 (4.1%) p=.655	3 (6.7%) p=1.000	.705		.155	.714
Metabolic syndrome present	1 (2.0%)		6 (13.3%) p=.046	6 (14.0%) p=.046	2 (3.6%)		2 (3.8%) p=.317	4 (8.3%) p=.157	1.000		.139	.508
Glucose metabolism												
FPG ≥6.1	1 (2.1%)		0 (0.0%) p=.317	1 (2.3%) p=1.000	1 (1.9%)		1 (.02%) p=1.000	1 (2.2%) p=1.000	1.000		1.000	1.000
FPG ≥7.0	0 (0.0%)		0 (0.0%) p=1.000	0 (0.0%) p=1.000	1 (1.9%)		0 (0.0%) p=.317	0 (0.0%) p=1.000	1.000		-	-
Insulin ≥138.9 pmol/L	3 (6.5%)		12 (26.7%) p=.020	8 (19.0%) p=.025	4 (9.1%)		0 (0.0%) p=.083	2 (4.4%) p=1.000	.711		<.001 4 (3-8)	.045 7 (4-78)
Insulin Resistance (HOMA-IR>4.39)	5 (11.1%)		9 (20.5%) p=.414	8 (19.0%) p=.180	4 (9.1%)		0 (0.0%) p=.083	3 (6.8%) p=.317	1.000		.001 5 (4-12)	.113

	Quetiapine ER group, n (%)				Aripiprazole group, n (%)				Between-group p-value, NNH (95% confidence interval)			
	p-values for change from baseline				p-values for change from baseline							
	Baseline	Week 2	Week 4	Week 12	Baseline	Week 2	Week 4	Week 12	Baseline	Week 2	Week 4	Week 12
Lipid metabolism												
Total cholesterol ≥4.4 mmol/l	18 (37.5%)		25 (52.1%)	29 (67.4%) p=.405 p=.008	16 (30.8%)		16 (32.7%)	17 (38.6%) p=.480 p=.096	.530	.066		.010 4 (2-12)
LDL-cholesterol ≥3.4 mmol/L	2 (4.2%)		3 (6.4%)	6 (14.6%) p=1.000 p=.317	1 (1.9%)		2 (4.1%)	1 (2.2%) p=.157 p=.317	.606	.674		.050 9 (5-131)
HDL-cholesterol <1.03mmol/L	10 (20.8%)		8 (17.0%)	10 (22.7%) p=.480 p=.705	9 (17.3%)		9 (18.4%)	9 (19.6%) p=.782 p=1.000	.800	1.000	.799	
Non-HDL-cholesterol ≥3.4mmol/L	8 (16.7%)		18 (38.3%)	20 (46.5%) p=.011 p=.004	7 (13.5%)		9 (18.4%)	6 (13.6%) p=.180 p=.705	.781		.041 6 (3-44)	.001 4 (2-7)
Triglycerides ≥1.2 mmol/L	11 (23.4%)		18 (40.9%)	17 (40.5%) p=.020 p=.083	9 (17.3%)		7 (14.3%)	7 (15.6%) p=.527 p=.739	.466		.005 4 (3-11)	.015 5 (3-15)
Dyslipidemia	22 (45.8%)		33 (68.8%)	32 (74.4%) p=.008 p=.020	20 (38.5%)		19 (38.8%)	19 (42.2%) p=.763 p=.285	.544		.004 4 (2-9)	.003 4 (2-8)

Bolded values: p<.05; BP: blood pressure; FPG: fasting plasma glucose; HDL: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; LDL: low-density lipoprotein cholesterol; mmol/l: millimoles per liter; NNH: number needed to harm; WC: waist circumference.

Table 5: Predictors of metabolic change from baseline to week 12 (linear regression, intention-to-treat cohort)

Baseline value	ΔWeight	ΔWC	ΔGlucose	ΔInsulin	HOMA-IR	ΔCholesterol	ΔTG	ΔLDL	ΔHDL
Age at onset	R ² =.002 p=.695	R ² =.020 p=.209	R ² =.000 p=.983	R ² =.005 p=.543	R ² =.002 p=.720	R²=.054 p=.043	R ² =.006 p=.509	R ² =.055 p=.043	R ² =.012 p=.337
Weight	R²=.092 p=.003	R ² =.014 p=.289	R ² =.016 p=.265	R ² =.002 p=.739	R ² =.005 p=.553	R ² =.001 p=.808	R²=.147 p=.001	R ² =.012 p=.349	R ² =.010 p=.373
WC	R ² =.031 p=.097	R ² =.007 p=.460	R ² =.015 p=.287	R ² =.000 p=.991	R ² =.039 p=.111	R ² =.001 p=.831	R ² =.021 p=.216	R ² =.009 p=.419	R ² =.030 p=.132
CGI	R ² =.004 p=.546	R ² =.000 p=.935	R ² =.032 p=.114	R ² =.000 p=.875	R ² =.014 p=.324	R ² =.023 p=.184	R ² =.001 p=.746	R ² =.041 p=.079	R ² =.011 p=.357
Parental education	R ² =.001 p=.796	R ² =.000 p=.882	R ² =.024 p=.176	R ² =.002 p=.687	R ² =.002 p=.701	R ² =.011 p=.369	R ² =.000 p=.946	R ² =.023 p=.196	R ² =.002 p=.678
PANSS positive	R ² =.001 p=.777	R ² =.003 p=.640	R ² =.002 p=.717	R ² =.010 p=.400	R ² =.024 p=.201	R ² =.008 p=.434	R ² =.002 p=.705	R ² =.003 p=.613	R ² =.00 p=.930
PANSS negative	R ² =.003 p=.614	R ² =.000 p=.878	R ² =.004 p=.579	R ² =.001 p=.752	R ² =.000 p=.887	R ² =.022 p=.201	R ² =.002 p=.724	R ² =.038 p=.092	R ² =.002 p=.731
PANSS total	R ² =.001 p=.720	R ² =.011 p=.341	R ² =.009 p=.399	R ² =.006 p=.517	R ² =.006 p=.510	R ² =.018 p=.240	R ² =.003 p=.654	R ² =.027 p=.155	R ² =.001 p=.810
Diagnosis of schizophrenia	R ² =.002 p=.642	R ² =.002 p=.695	R ² =.025 p=.161	R ² =.004 p=.598	R ² =.024 p=.200	R ² =.001 p=.805	R ² =.017 p=.252	R ² =.001 p=.827	R ² =.022 p=.191
T2DM in FDR	R²=.048 p=.033	R²=.053 p=.038	R ² =.001 p=.736	R ² =.047 p=.068	R ² =.051 p=.059	R ² =.014 p=.310	R ² =.038 p=.090	R ² =.006 p=.524	R ² =.001 p=.747
Dyslipidemia in FDR	R ² =.098 p=.345	R ² =.023 p=.169	R ² =.004 p=.604	R ² =.005 p=.552	R ² =.025 p=.185	R ² =.025 p=.168	R ² =.011 p=.367	R ² =.011 p=.367	R²=.111 p=.002
Obesity in FDR	R²=.082 p=.005	R ² =.006 p=.501	R ² =.023 p=.186	R ² =.013 p=.340	R ² =.048 p=.067	R ² =.000 p=.880	R²=.065 p=.025	R ² =.022 p=.201	R²=.055 p=.036

Bolded values = p<.05; Δ: change; BP = blood pressure; CGI: clinical global impression; FRD: first-degree relatives; FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density lipoprotein cholesterol; PANSS: positive and negative syndrome scale; T2DM: type 2 diabetes; TG = triglycerides; WC = waist circumference.

Figures

Figure 1: CONSORT diagram

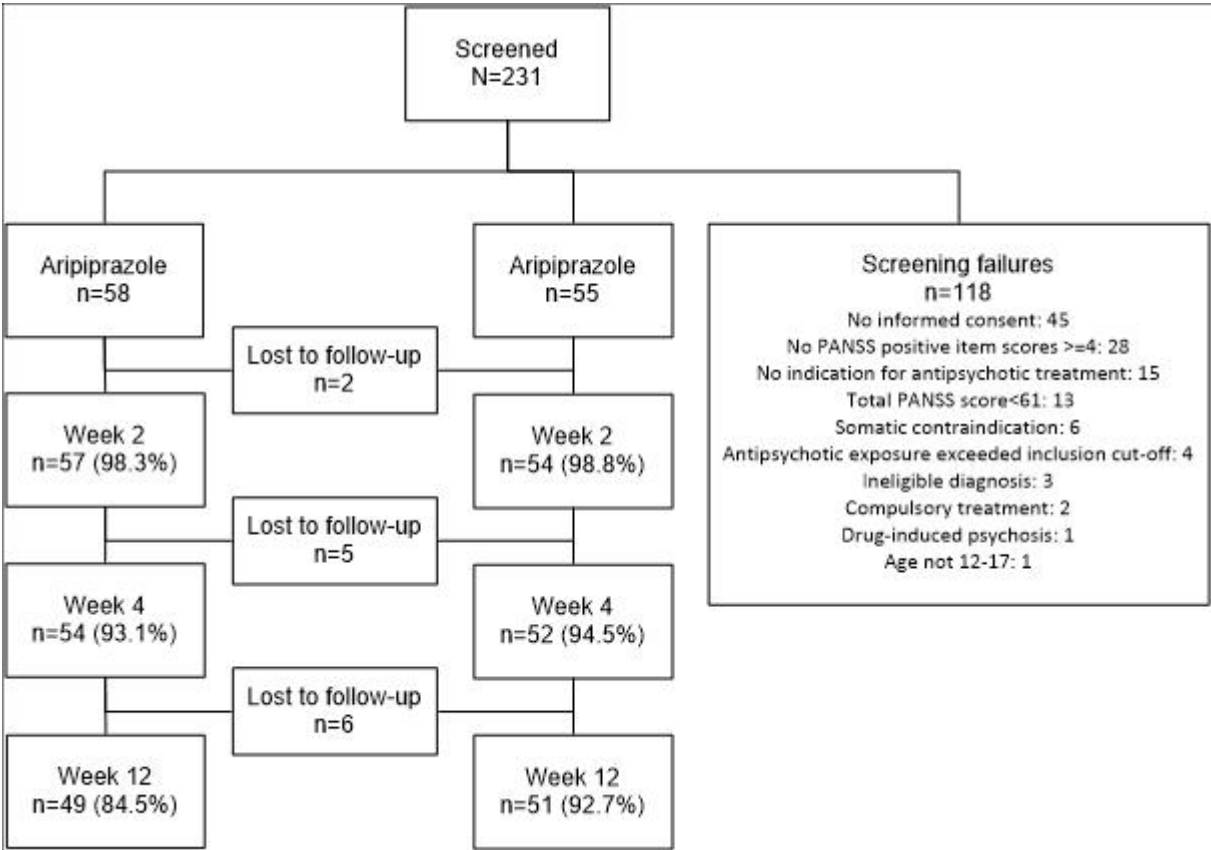
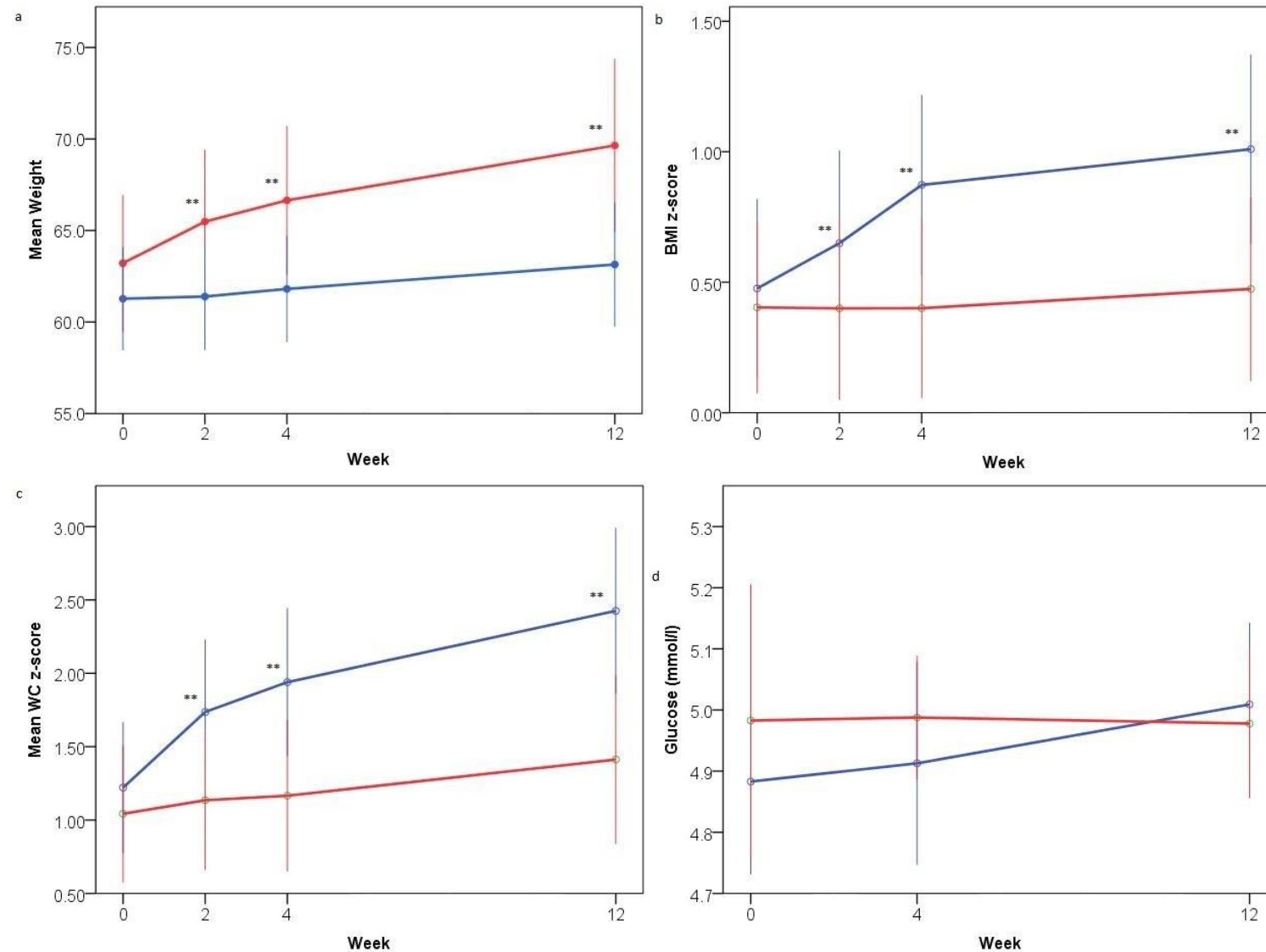
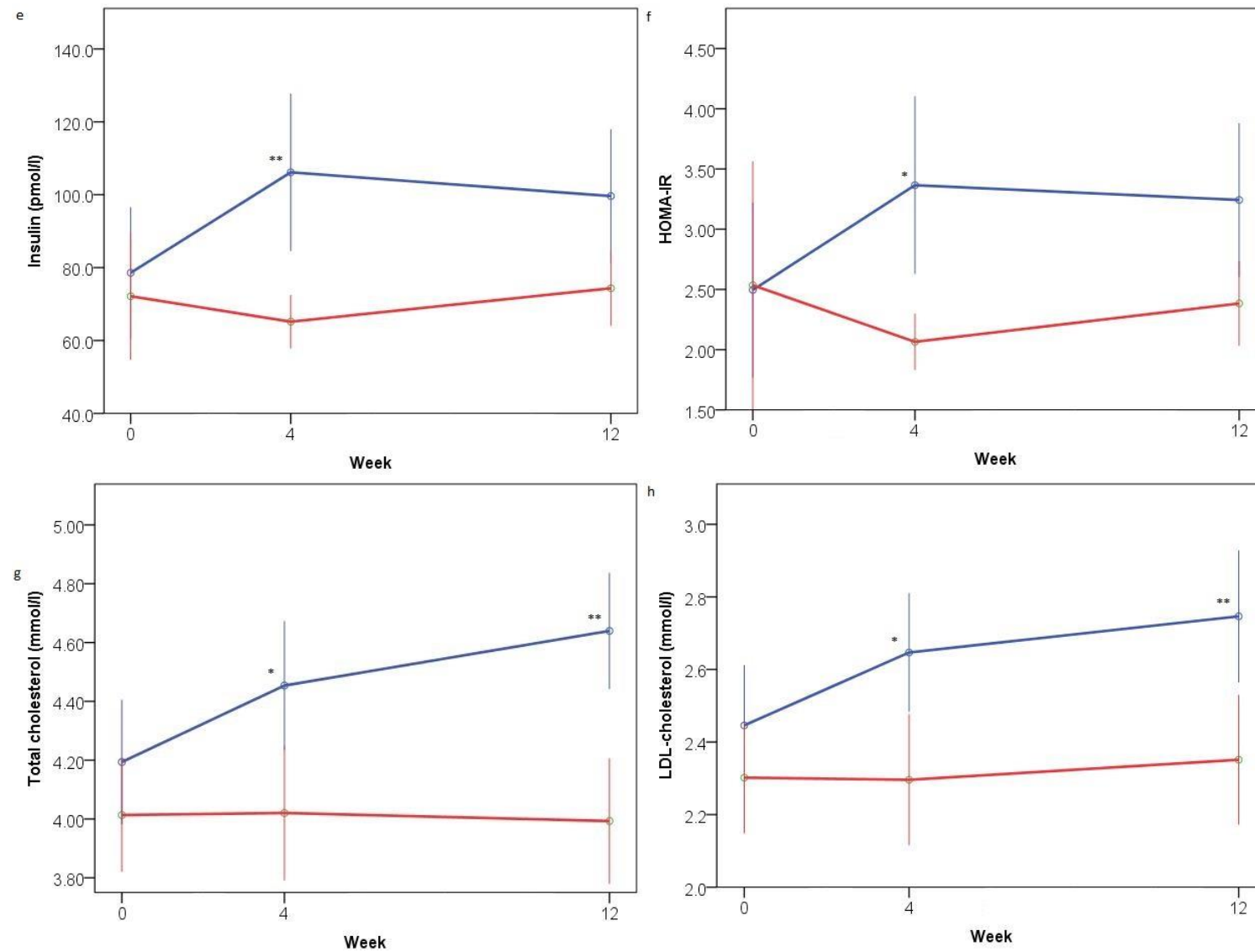
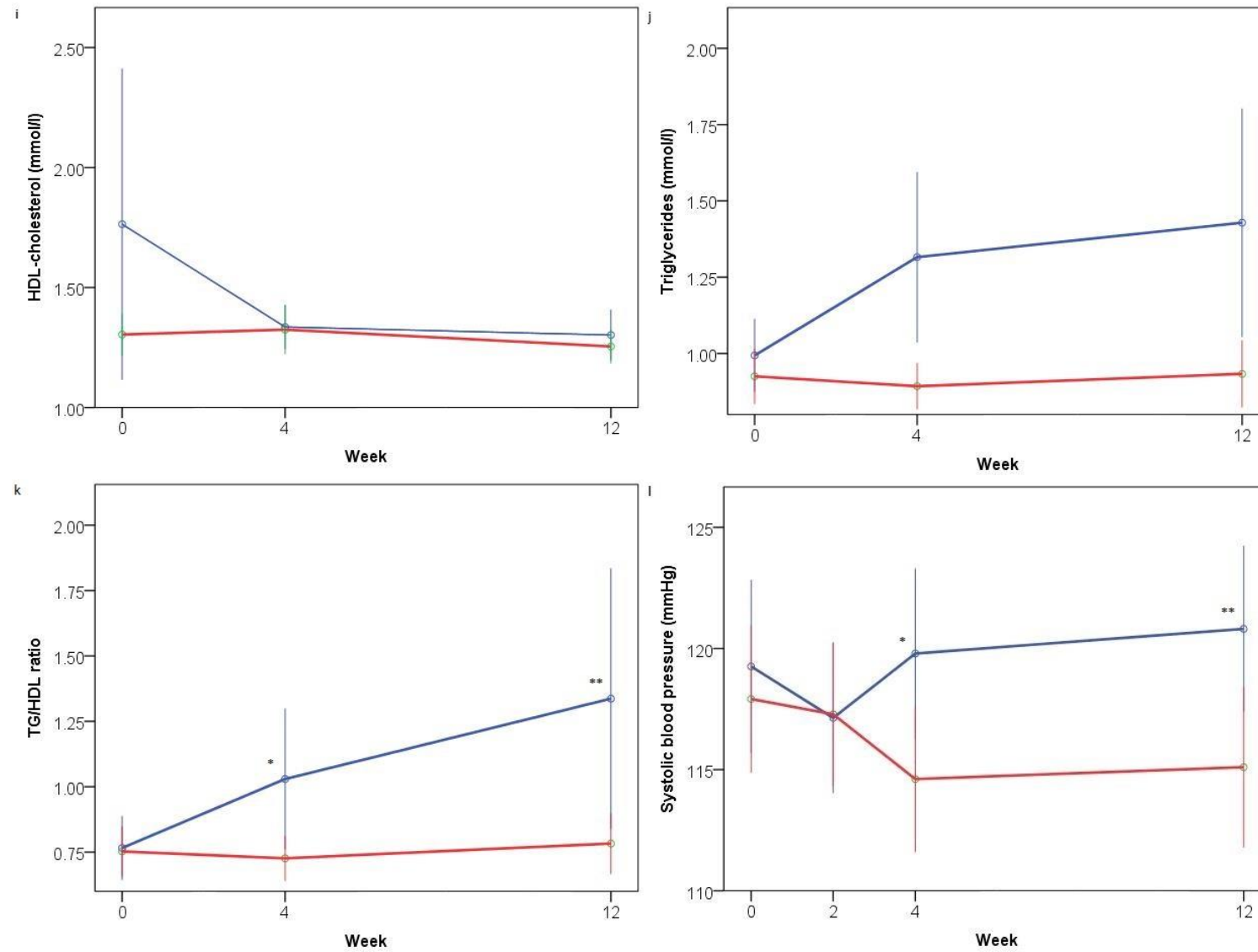
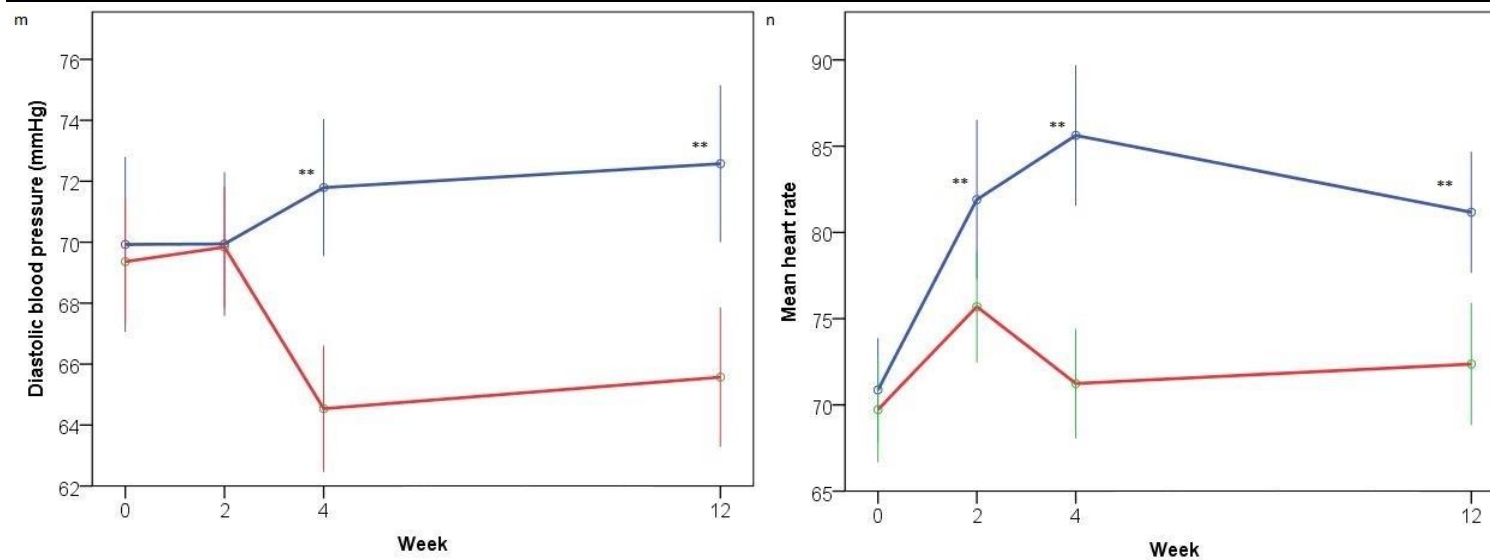


Figure 2a-n: Changes in anthropometric and metabolic outcomes (observed values). Blue line: quetiapine ER. Red line: aripiprazole. Vertical lines: 95% confidence interval. * $p < .05$ ** $p < .01$ for between-group difference in change from baseline









Supplementary tables

Table S1: Dosing and titration schedule

Day	1	2	3	4	5	6	7	8	9	Possible maximum titration
Level	1		2		3		4		5 (final)	6 (max)
Aripiprazole Daily dose, mg	2,5	2,5	5	5	10	10	15	15	20	30
Quetiapine extended release Daily dose, mg	50	50	100	100	200	200	400	400	600	800
Blinded capsules* Daily quantity, pieces	1	1	2	2	1	1	2	2	3	4

* The amount of capsules containing active preparation (quetiapine extended release and aripiprazole) is complemented with capsules containing non-active preparation

Table S2: TEA RCT, schedule for outcome assessments during 12 weeks of blinded intervention

Assessments	Inclusion (week 0)	Follow-up (week 2)	Follow-up (week 4)	Follow-up (week 12)
Psychopathology rating scales: PANSS, DIPI, CGI-S, CGI-I, CGI-E, GAPD	X	X	X	X
Adverse events rating scales: UKU, AIMS, SAS, and BARS				
Suicidal ideation K-SADS-PL specific items	X	X	X	X
Cognition, cognitive daily and executive function BACS, SCORS-DK and BRIEF	X			X
Somatic examination Standard clinical examination, blood pressure, pulse, weight, height, BMI, and abdominal circumference.	X	X	X	X
Health-related quality of life Questionnaire: KIDSCREEN-52	X			X
Laboratory tests (see list below)	X		X	X

AIMS = Abnormal Involuntary Movement Scale; BACS = Brief Assessment of Cognition in Schizophrenia; BARS = Barnes Akathisia Rating Scale; BMI = Body Mass Index; BRIEF = Behavioural Rating Inventory of Executive Functions; CGI = Clinical Global Impression (-I = Improvement -S = Severity -E = Efficacy); DIPI = Dimensions of Psychosis Instrument; GAPD = Global Assessment of Psychosocial Disability; HRQoL = Health related quality of life; K-SADS-PL = Kiddie-SADS-Present and Lifetime Version; KIDSCREEN-52 = Health related quality of life questionnaire for children and young people and their parents; PANSS = Positive and Negative Syndrome Scale; SCORS-DK = Schizophrenia Cognition Rating Scale – Danish version; UKU = 'Udvalget for Kliniske Undersøgelser' Side Effect Rating Scale.

Table S3: Definition of metabolic syndrome (MS) in children and adolescents by the IDF⁵⁷

Age group (years)	Obesity (waist circumference)	Triglycerides	HDL-C	Blood pressure	Glucose
6 to <10	≥ 90th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.			
10 to <16	≥ 90th percentile or adult cut-off if lower	≥ 1.7 mmol/L (≥ 150 mg/dL)	< 1.03 mmol/L (< 40 mg/dL)	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM
≥ 16 (adult criteria)	WC ≥ 94cm for Europid males and ≥ 80cm for Europid females, with ethnic-specific values for other groups	≥ 1.7 mmol/L (≥ 150 mg/dL) or specific treatment for high triglycerides	< 1.03mmol/L (< 40 mg/dL) in males and < 1.29mmol/L (< 50 mg/dL) in females, or specific treatment for low HDL	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension	FPG ≥ 5.6 mmol/L (100 mg/dL) or known T2DM
BP: blood pressure; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; IDF, International Diabetes Federation; T2DM, type 2 diabetes mellitus; WC, waist circumference.					

Table S4: Waist circumference in centimetres, 90th percentile ⁴⁸

Age	Girls	Boys
12	70.9	73.5
13	72.2	75.6
14	73.3	77.8
15	74.3	80.1
16	75.3	82.5
17	76.1	84.7
18	76.8	86.7

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QTc change during treatment with quetiapine ER versus aripiprazole in children and adolescents with first-episode psychosis: Results from the TEA trial.

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Abstract

Objective: To compare the effect of aripiprazole versus quetiapine on the corrected QT interval (QTc) in youths with first-episode psychosis.

Methods: Youths aged 12-17 years were randomized to aripiprazole or quetiapine ER in a 12-week, multicenter, double-blinded study and examined at baseline and after 4 and 12 weeks. The primary outcome was QTc change using Hodges formula (QTcH); secondary outcomes included QTc >450 milliseconds, QTc >500 milliseconds, QTc change >60 milliseconds, and heart rate (HR). Linear regression analyses were performed to identify correlates of QTc change.

Results: Among 113 randomized youths, ≥ 1 follow-up ECG was available for 97 patients (85.8%) (age=15.8 $\pm$ 1.4 years, males=34.0%, schizophrenia-spectrum diagnosis=68.0 %). Quetiapine ER treatment (n=48) was associated with a significant increase in QTcH of +7.3 $\pm$ 20.3 milliseconds (p=0.016), while the change from baseline was non-significant (-1.0 $\pm$ 18.9 milliseconds, p=0.716) in patients receiving aripiprazole (n=49) (between-group difference: p=.039). One patient in the quetiapine group had a QTcH change of +62.3 milliseconds. No patient had QTcH >450 milliseconds during treatment. Age, sex, smoking, and body mass index were not significantly associated with QTc change. In the quetiapine group, the potassium level at baseline and mean antipsychotic dose were correlated to change in QTcH (p<0.05). The HR increased significantly with quetiapine ER (+10.4 $\pm$ 14.8 beats per minute, p<0.001), but not with aripiprazole.

Conclusion:

QTcH and HR increased significantly with quetiapine ER, remaining unchanged with aripiprazole. Overall, QTcH changes with both antipsychotics were small and are likely not clinically significant, although individual patients may experience clinically relevant QTc changes with quetiapine ER.

Keywords: Children; Adolescents; Antipsychotics; Drug-Related Side Effects and Adverse Reactions; ECG; QTc; Heart rate

ClinicalTrials.gov: NCT01119014, EudraCT: 2009-016715-38 (<https://eudract.ema.europa.eu/>)

Introduction

In children and adolescents, the use of antipsychotic medications is increasing,¹⁻³ and so is the need for more detailed information regarding effects and adverse effects of these medications. Antipsychotics can cause prolongation of the corrected QT interval (QTc, considered normal when <440 ms⁴), and long QT syndrome (LQTS) can lead to ventricular arrhythmia, especially torsade de pointes (TdP)

tachycardia and/or ventricular tachycardia in susceptible individuals.⁵ TdP can lead to sudden cardiac death, and although the exact relationship between LQTS and the risk of TdP is elusive, QTc prolongation remains the best surrogate marker for TdP.⁵ Drug induced QTc prolongation is primarily a result of blockade of the rapidly activating delayed rectifier potassium channel IKr, whereby the ion flux responsible for repolarization is reduced.⁵⁻⁸ The effect of antipsychotic agents on the duration of the QTc interval is considered to

be related to dose and concomitant medications, and differs between antipsychotic agents⁹. Patient risk factors for QTc prolongation include age, gender, electrolyte disturbances and structural heart diseases.¹⁰ Cardiovascular disease (CVD), a very common long-term comorbidity in patients with psychotic disorders,¹¹⁻²¹ is an important risk factor for QTc prolongation and TdP.^{9,22} A recent study²³ in adults with life-threatening cardiac arrhythmias associated with drug-induced LQTS, found that a QTc interval of at least 500 ms seemed to be the major determinant of the risk of drug-induced arrhythmias.

Even though several of the risk factors for LQTS, such as older age and cardiovascular disease, have not yet occurred in children and adolescents, the risk of developing QTc prolongation must be taken into consideration also in pediatric populations when balancing efficacy and tolerability of antipsychotics. In our recent meta-analysis of 55 studies in children and adolescents,²⁴ seven out of nine antipsychotics did not have a significantly different effects on the QTc interval than placebo. Aripiprazole was shown to significantly decrease the QTc duration (mean change: -1.44 milliseconds (ms), confidence interval (CI): -2.63 to -0.26, $p=0.017$), and ziprasidone significantly increased the QTc duration (mean change: +8.74 ms, CI: +5.19 to +12.30, $p<0.001$); the effect of quetiapine on QTc duration was not different from placebo (mean change +1.92 ms, CI -2.58 to +6.42, $p=0.403$). Patients with underlying risk factors for cardiac conduction impairment may be more susceptible to the QTc prolongation exerted by some medications. For instance, patients with inherited long QT syndrome (LQTS)²⁵⁻²⁷ may have no symptoms except for a higher predilection towards clinically significant QTc prolongation when exposed to additional risk factors.²⁸ Furthermore, as youths suffering from potentially chronic mental disorders that demand long-term antipsychotic treatment move into adulthood, the added risk factors relevant for this population may

increase the propensity for cardiac adverse effects.

Aripiprazole, a partial dopamine D2 receptor agonist,²⁹ and quetiapine, a low-affinity dopamine D2 receptor antagonist,³⁰ are some of the most commonly used antipsychotics in youths with psychotic disorders. In adults, Leucht et al³¹ found that quetiapine was associated with a statistically significant increase in QTc while aripiprazole was not. Even though studies overall show that aripiprazole is probably associated with the lowest risk of QTc prolongation in both youths and adults,^{24,32} cases of TdP associated with this low risk antipsychotic have been reported.³³ Also, recent research has shed light on the short QTc syndrome, a condition with QTc interval duration <330 ms, which is more elusive and rare, but may result in potentially life-threatening arrhythmias.³⁴ Hypothetically, patients with short QTc syndrome may be vulnerable to iatrogenic negative changes in the QTc interval.

The effects of quetiapine and aripiprazole have never been directly compared in a randomized, head-to-head clinical trial in youth with psychosis. As part of a large, randomized, double-blinded, multicenter clinical trial investigating the tolerability and efficacy of aripiprazole versus quetiapine ER, the aim of this study was to investigate their effects on the QTc interval in a population of children and adolescents with first-episode psychosis. We also aimed at determining whether QTc prolongation is dose dependent in this age group and whether it might be predicted by age, sex, tobacco use, weight or serum potassium concentration at baseline. Based on the literature, we hypothesized that treatment with quetiapine would be associated with greater adverse effects on cardiac repolarization, including significant increases in QTc prolongation compared to aripiprazole.

Methods

Study design

The present study is part of the Tolerability and Efficacy of Antipsychotics (TEA) trial, a 12-week, independently funded, randomized, double-blinded, multicenter trial of aripiprazole versus quetiapine ER in psychotic children and adolescents aged 12-17 years. The trial was conducted from May 2010 to May 2014. Seven child and adolescent psychiatric departments across Denmark, covering all university clinics, participated in the trial. A detailed protocol for the TEA trial has been published,³⁵ therefore, the design and methods are only presented briefly. The trial was registered at ClinicalTrials.gov: NCT01119014, EudraCT: 2009-016715-38, and approved by Danish Medicines Agency: 2612-4168, The Ethics Committee of Capital Region: H-3-2009-123 and Danish Data Protection Agency: 2009-41-3991.

Subjects

Physicians at the university hospital child- and adolescent psychiatric clinics referred patients who suffered from psychotic symptoms to a degree where antipsychotic treatment was warranted. The subsequent screening procedure involved physical examination, blood samples, electrocardiogram (ECG) and urine samples. 12-lead ECGs were, whenever possible, recorded in the morning after fasting from midnight, supine after resting. ECG recording machines differed between participating centres. Furthermore, psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS),³⁶ as well as a series of other psychological rating scales. Inclusion criteria were: 1) Children and adolescents aged 12-17 years (both inclusive), both sexes; 2) in- or outpatients; 3) fulfilling one of the non-organic, non-drug-induced-psychosis ICD-10 criteria³⁷, i.e. F20 (Schizophrenia), F22

(Persistent delusional disorders), F23 (Acute and transient psychotic disorders), F24 (Induced delusional disorders), F25 (Schizoaffective disorders), F28/F29 (Other/Unspecified nonorganic psychosis), F30.2 (Mania with psychotic symptoms), F31.2 (Bipolar affective disorder, current episode manic with psychotic symptoms), F31.5 (Bipolar affective disorder, current episode severe depression with psychotic symptoms), F32.3 (Severe depressive episode with psychotic symptoms), or F33.3 (Recurrent depressive episode, current episode severe with psychotic symptoms). Diagnoses were subsequently verified by the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL);³⁸ 4) clinical indication for antipsychotic treatment; 5) presence of psychotic symptoms scoring ≥ 4 on ≥ 1 of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content) as well as a total PANSS score > 60 points; 6) antipsychotic-naïve or limited exposure (i.e. not extending the previous year for psychosis or maximally 1 week lifetime for any non-psychotic indication); and 7) signed, written informed consent by caregivers and by the patient. Exclusion criteria included: 1) Compulsory treatment; 2) drug-induced or organic psychosis; 3) severe chronic somatic illness or a history of severe head trauma; 4) pregnancy or lactation; 5) substance dependence (ICD-10 F1X.2 dependence syndrome) within the last year; 6) allergy towards the investigational drugs or known lactose intolerance; and 7) lack of informed consent/assent.

Trial intervention

Patients included in the trial were randomized to treatment with either aripiprazole or quetiapine ER in a double-blinded fashion. The randomization procedure is described in the published protocol.³⁵

Patients followed a standardized titration schedule using 6 levels of antipsychotic doses ranging from 50-800 mg of quetiapine ER and 2.5-30 mg of aripiprazole (Table 1), with the doses at different titration levels designed to be equivalent. During the first 9 days, the assigned antipsychotic was up-titrated in fixed dose steps, with slower up-titrations and dose adjustments if clinically indicated. The target doses were quetiapine 600 mg/day vs aripiprazole 20 mg/day. During the 12 week intervention, the dosage could be up- or down-titrated to optimize efficacy and minimize side effects.

TABLE 1 HERE

Concomitant medication

Concomitant antipsychotic medication was generally not allowed during the intervention period. If acute rescue antipsychotic use was required, this was registered as a protocol violation. Any other concomitant medications were also recorded throughout the trial intervention period (including side effect medications).

Examination schedule

Upon inclusion, and before initiating trial medication, patients underwent a comprehensive examination program (for details, see the study protocol³⁵). Patients were re-examined after 2, 4 and 12 weeks. Blood samples and ECGs were acquired by experienced laboratory technicians at inclusion and week 4 and 12, with blood test analyses being conducted at each site's laboratory. The prescence of orthostatic dizziness and/or palpitations/tachycardia were assessed on UKU³⁹ at follow-up visits by the investigator (a score of at least 1 on UKU items 3-9 and 3-10 and rated probably related to study drug).

ECG assessment

ECGs were blinded before manual assessment of the QT interval, which was performed by two clinicians trained in QT measurement (KGJ and SG) and subsequently averaged. In case of disagreements exceeding 40 ms, a pediatric cardiologist (KJ) could be consulted (although this situation never arose). The QT interval was measured from the beginning of the Q-wave (or the R-wave, if the Q wave was not discernible) to the point where the steepest tangent of the T-wave crossed the isoelectric line.⁵ The QT interval was averaged across up to 6 complexes in both the II and V5 lead of each ECG, depending on the number of readable complexes.

A large number of heart rate correction formulae exist. Bazett's formula⁴⁰ $QTcB = \frac{QT}{\sqrt{RR}}$ is most widely used and often reported in tolerability studies despite its lack of precision.⁴¹ Fridericias formula⁴² $QTcF = \frac{QT}{\sqrt[3]{RR}}$ adopts better to faster heart rates and is also used in clinical settings. However, a meta-analysis of pre-treatment ECG data in 2,288 children with attention-deficit/hyperactivity disorder aged 6 to 17 years (mean 10.8 ± 2.6 years) from seven clinical trials⁴³ found that the most accurate correction formula was $QTcH = \frac{QT}{RR^{0.38}}$, which was also suggested by Hodges in 1997⁴⁴ and by Malik in 1996.⁴⁵ We corrected for heart rate using the heart rate (HR) computed by the ECG machine.⁵ We determined the QTc with all three correction methods. Thus, the corresponding formula for use in this report is

$$QTcH = \frac{[QT]}{(60/HR)^\alpha}$$

where α is 0.50 for Bazett's correction, 0.33 for Frederica's correction and 0.38 for Hodges correction, and [QT] is the mean QT measurement.

Analyses

All statistical analyses were conducted using IBM SPSS® version 22. Investigators were blinded to treatment allocation until all statistical analyses had been performed. Patient characteristics were compared using descriptive statistics and Mann-Whitney's U test. Pearson's *r* and Cronbach's alpha were calculated to estimate the inter-rater correlation between the measured QT values. Change in QTc was normally distributed as determined by Shapiro-Wilk's test of normality. We used paired t-tests to compare the change in QTc from baseline to last follow-up (LFU), and linear regression models to compare the effect of treatment, controlling for the effect of mean trial medication dose level during the five days before obtaining the ECG.

The intention-to-treat (ITT) sample consisted of all randomized patients in the TEA trial, regardless of any events of subsequent noncompliance, protocol deviations or withdrawal.⁴⁶ In the present study, we included only those patients who had a baseline and at least one follow-up ECG (modified ITT (mITT) group). We compared baseline ECGs at both week 4, week 12 and at Last Follow-Up (LFU). To evaluate the effect of treatment in the patients never or not recently exposed to antipsychotics ("Recently unexposed" group), patients who had received antipsychotic treatment within 5 days prior to inclusion (10 days for aripiprazole due to longer half-life) were excluded in the sensitivity analysis ("Recently exposed" group).

Results

Demographic and clinical characteristics

Of 231 screened patients, 113 patients were included in the trial (see CONSORT diagram, Figure

1), whereof the mITT group consisted of 97 patients (aripiprazole: n=48, quetiapine ER: n=49). Altogether, 118 youths (males=37.3%, mean age=15.31±1.50 years) were screening failures (see reasons in Figure 1), without significant differences in age or sex distribution between screening failures and patients randomized in the trial.

FIGURE 1 HERE

Participant characteristics are shown in table 2. The most frequent diagnoses among randomized patients were: schizophrenia (ICD-10 F20.x), n=66 (68.0%), schizoaffective disorders (F25.x), n=19 (19.6%) and depressive episode (F32.x), n=4 (4.1%). Fifty-nine patients (60.8%) had received antipsychotic medication close to the time of inclusion ("Recently exposed" group), while 38 patients (39.2%) had not or were antipsychotic naïve ("Recently unexposed" group). There were no differences between treatment groups in types or doses of antipsychotics used prior to inclusion or concomitant use of psychoactive medications (see table 1). Among patients, there were 37 (37.1%) smokers. The median number of cigarettes per day among smokers was 10, interquartile range (IQR) 6-19. There were no significant differences in the use of non-antipsychotic psychopharmacological use, nor in the occurrence of positive drug urine tests (benzodiazepines, n=20, and tetrahydrocannabinol, n=3), prior to inclusion (data not shown). There were no significant differences in weight, BMI z-score or serum-potassium between treatment groups.

TABLE 2 HERE

QT measurement inter-rater reliability

The differences across all measurements of the QT interval between rater 1 and 2 are described in supplementary table S1, available online. Overall,

there was an acceptable reproducibility with a mean difference of QT measurements between rater 1 and 2 of -0.7 ± 8.0 ms (range -23.3 to 22.5 ms).

Sex differences in QTcH

At all time points, females had higher QTcH than males, mean difference was 20.2 ± 4.2 ms at baseline ($p < .001$), 23.8 ± 4.4 ms ($p < .001$) at week 4 and 16.9 ± 4.2 ms ($p < .001$) at week 12; however, there were no statistically significant differences in mean change in QTcH, even when comparing treatment arms.

Change in ECG parameters

During the 12 weeks of treatment, QTcH change in two patients in the quetiapine ER group was >40 ms and ≤ 60 ms, while QTcH change in one patient in the quetiapine ER group exceeded the cut-off value of >60 ms (change from baseline to week 12: 62.3 ms, range for all patients: -53.7 to 62.3 ms). No patient had a QTcH exceeding the often used cut-off value for QTc prolongation of 450 ms⁴⁷ (range: 340.2 to 447.9 ms). No patients had a decrease in QTcH >60 ms or a QTcH interval <330 ms.

From baseline to LFU, mean $\pm$ SD change in heart rate in the mITT sample ($n=97$) was significantly larger with 10.4 ± 14.8 beats per minute (bpm) in the quetiapine ER group compared to -0.1 ± 12.2 bpm in the aripiprazole group ($p < .001$) (Table 3). Mean $\pm$ SD change from baseline to LFU for QTcH, QTcB and QTcF were 7.3 ± 20.3 , 14.3 ± 27.1 , 4.7 ± 18.4 ms, respectively, for the quetiapine ER group, and -1.0 ± 24.4 , -1.0 ± 17.4 , -1.0 ± 18.9 ms, respectively, for the aripiprazole group. The difference between baseline and LFU was significantly different from zero for QTcB ($p = .001$), QTcH ($p = .016$) and for heart rate ($p < .001$) in the quetiapine ER group, but not in the aripiprazole group (data not shown). The difference between treatment groups in mean change from baseline

to LFU was statistically significant for QTcH ($p = 0.039$) and QTcB ($p = 0.004$), but not for QTcF ($p = 0.123$).

TABLE 3 HERE

The mean $\pm$ SD difference between treatment groups in QTcH change from week 4 to week 12 was not significant (1.1 ± 18.8 vs. 1.5 ± 16.1 , $p = .900$).

Sensitivity analysis

When pre-baseline ECG antipsychotic-exposed patients were excluded from the analysis, mean $\pm$ SD change from baseline to LFU was 8.1 ± 18.1 ms for QTcH, 16.7 ± 26.4 ms for QTcB and 4.8 ± 15.8 ms for QTcF, in treatment group 1, and -1.7 ± 19.9 for QTcH, -2.1 ± 25.9 for QTcB and -1.5 ± 18.0 for QTcF (Table 3, bottom panel). Although the crude difference between treatment groups in mean QTcH change increased when excluding antipsychotic-exposed patients, the p-value increased to .054 as a result of the smaller sample.

Effect of possible predictors

Regression analyses were performed in order to evaluate the effect of specific baseline variables (i.e., age, sex, cigarettes, BMI z-score, waist circumference z-score and potassium level) on the change in QTcH values. Potassium level at baseline predicted higher QTcH change, but only in the quetiapine ER group (Table 4).

TABLE 4 HERE

Dose-response effect

When excluding patients who had been exposed to antipsychotics just prior to inclusion, we found that the mean dose of trial drug during the last five days prior to obtaining the ECG was significantly correlated to the change in QTcH from baseline to week 4 in the quetiapine ER group (Pearson's $r = .504$, $p = .006$) but not in the aripiprazole group

(Pearson's $R=-.139$, $p=.489$). This correlation was no longer present at week 12 or when using LFU as endpoint.

Mean doses of both aripiprazole (Pearson's $r=-.517$, $p=.006$) and quetiapine ER (Pearson's $r=.588$, $p=.001$) were correlated to the change in heart rate from baseline to week 4, but these correlations were no longer present at week 12. However, the mean dose of quetiapine ER was correlated to the change in heart rate at LFU (Pearson's $r=.380$, $p=.046$).

Cardiac symptoms

Treatment-associated orthostatic dizziness occurred in 27.3% in the quetiapine ER group and 20.7% in the aripiprazole group ($p=.509$, while palpitations/tachycardia occurred in 10.9% in the quetiapine ER group and 3.4% in the aripiprazole group ($p=.155$).

Discussion

Previous studies have found that even in children and adolescents, the impact on the duration of the QTc interval differs significantly between antipsychotics.²⁴ In the present study, we found that the QTcH interval increased from baseline to last follow-up by 7.3 ± 20.3 ms in patients treated with quetiapine ER, while the change in QTcH in the aripiprazole group was not significantly different from zero (-1.0 ± 18.9 ms). Furthermore, patients in the quetiapine ER group experienced an average increase in heart rate by 10.4 ± 14.8 bpm, while the heart rate was unaffected by aripiprazole (-0.1 ± 12.2 bpm). The fact that mean antipsychotic dose was associated with higher heart rate for both groups and with higher QTcH for the quetiapine ER group only after 4 weeks, could be explained by the fact that 1) more patients had dropped out at week 12 than week 4, and 2) that the dose ranges were smaller at week

12 than at week 4 (700 mg vs. 750 mg for quetiapine, 17.5 mg vs. 27.5 mg for aripiprazole).

The change between the week 4 and the week 12 measurements were comparable across the treatment groups. As the blockade of the hERG channel occurs in a dose-dependent manner,^{48,49} our observations suggest that the effect of antipsychotic use on QTc appears shortly after reaching a stable dosage level (patients in the present trial, when following the standardized titration schedule, would reach steady-state plasma concentrations of aripiprazole after 22 days and of quetiapine after 10 days).

Our findings support data from previous studies in children and adolescents as well as in adults.³¹ Although the observed mean change in QTcH was relatively small,⁴⁷ it is important to acknowledge that five patients had QTcH changes exceeding 40 ms (-53.7 , -42.6 , 40.5 , 47.6 and 62.3 ms). While this degree of change is unlikely to cause clinical symptoms in otherwise healthy children and adolescents, patients with underlying cardiac conditions and those with elevated baseline QTc levels are more susceptible to drug-induced heart rhythm abnormalities, and it is important to acknowledge that the adverse effects of antipsychotic medications accumulate over time in chronic patients. Additionally, the somewhat arbitrary cut-off of 60 ms increase stems from studies in adults, not youths. More research is still needed to shed light on the complex interplay between various predictors and risk factors of TdP. Finally, the possibility that a negative change in QTcH, as observed with aripiprazole, may be proarrhythmic, particularly in patients with short QTc syndrome,³⁴ should be examined further. Nevertheless, with aripiprazole, there was no significant change from baseline in QTc, and no patients had a decrease in QTcH exceeding 60 ms.

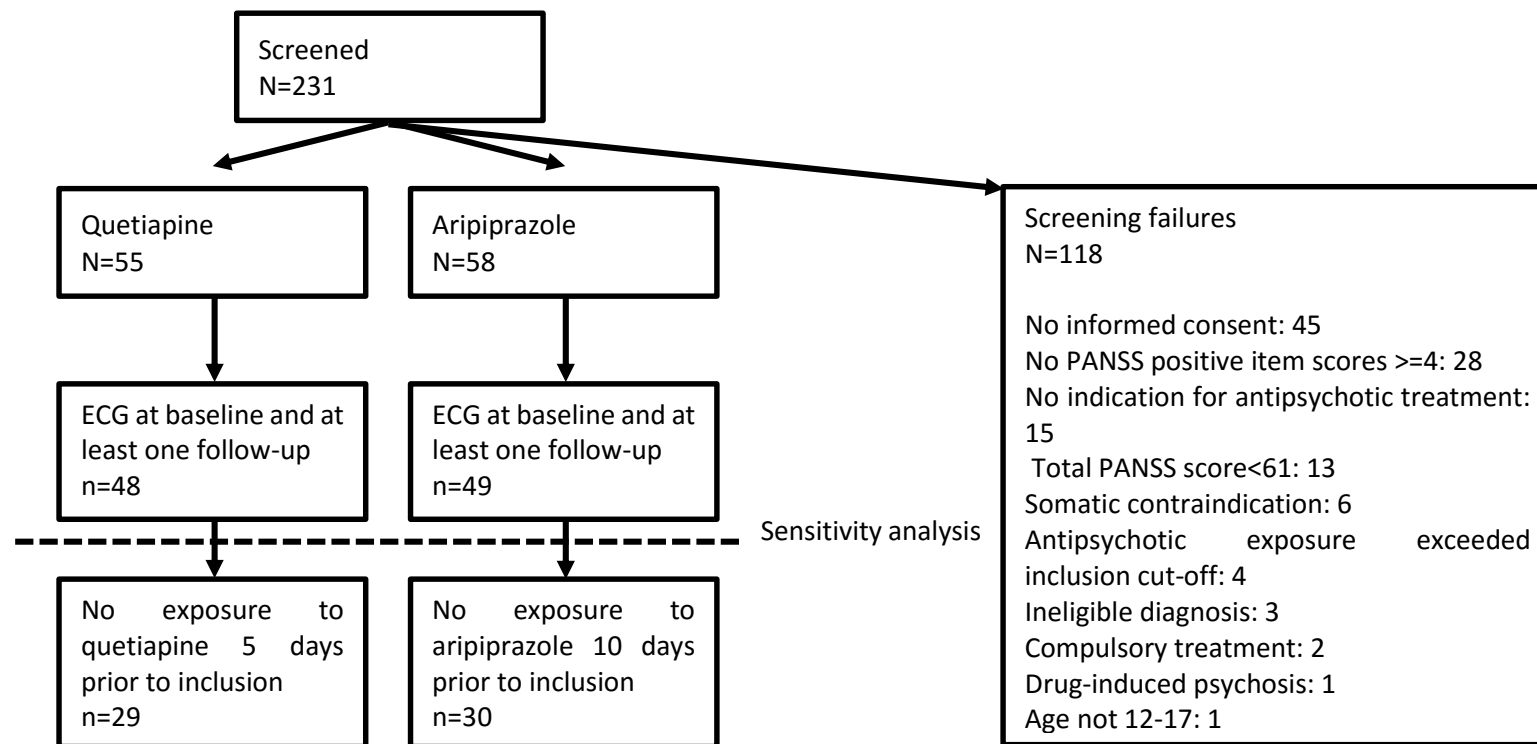
This study has several limitations. First, the sample size was relatively limited, probably explaining that the change in QTc interval did not reach

statistical significance when using Fredericia's correction. Second, one third of the patients had been briefly exposed to antipsychotic treatment to some degree shortly before inclusion into the trial, which might have affected the results, there were no differences in the use of prior antipsychotic agents between groups. Third, some patients received concomitant medications that may increase the QTc interval. However, co-medication use was evenly distributed in the two groups, doses were low, and usage was infrequent. Despite these limitations, the randomized controlled design, large number of antipsychotic-naïve patients in a pediatric sample, blinded recording and analysis of QTc, and the very low inter-rater variability are clear strengths.

In summary, our data show that already after 4 weeks of treatment, quetiapine ER significantly increased QTcH and heart rate in children and adolescents with first-episode psychosis. It is crucial that both patient- and medication factors are considered when making antipsychotic medication choices, in particular in patients with a family history of long/short QT syndrome or sudden death, prior ECG with QTc interval exceeding 450 ms, or when patients experience symptoms such as dizziness, palpitations or especially syncope during exercise.⁵⁰ During treatment, re-evaluation of the ECG may be required if the clinical status changes, such as when clinical cardiovascular symptoms emerge that should be inquired about. Furthermore, clinicians should be vigilant of severe weight change or co-medications, which may adversely affect cardiac conduction¹⁰, which both should prompt consideration of additional ECG monitoring.

Figures

Figure 1: CONSORT diagram.



ECG: electrocardiogram, PANSS: positive and negative syndrome scale

Tables

Table 1: Dosing and titration schedule

Day	1	2	3	4	5	6	7	8	9	Possible maximum titration
Level	1	2	3	4	5 (final)	6 (max)				
Aripiprazole Daily dose, mg	2.5	2.5	5	5	10	10	15	15	20	30
Quetiapine extended release Daily dose, mg	50	50	100	100	200	200	400	400	600	800

Table 2: Patients characteristics

All participants	All patients (n=97)	Quetiapine group (n=48)	Aripiprazole group (n=49)	p
Age, mean±SD	15.8±1.4	15.8±1.4	15.8±1.4	.829
Males, n (%)	33 (34.0%)	16 (33.3%)	17 (34.7%)	1.000
Smokers, n (%)	37 (37.1%)	17 (35.4%)	19 (38.8%)	.834
Cigarette consumption per day, median (IQR)	10 (6-19)	10 (7-15)	10 (5-20)	.851
Tanner stage, males, mean±SD	4.2±0.9	4.1±1.0	4.2±0.8	.958
Tanner stage, females, mean±SD	4.3±0.6	4.3±0.6	4.3±0.6	.767

All participants	All patients (n=97)	Quetiapine group (n=48)	Aripiprazole group (n=49)	p
Weight	63.1±12.5	64.5±14.0	61.8±10.9	.407
BMI z-score	0.45±1.27	0.56±1.26	0.35±1.30	.352
Serum potassium	4.0±0.3	3.9±0.3	4.1±0.3	.630
Psychopathology, mean±SD				
PANSS positive subscore	20.4±3.6	20.3±3.3	20.6±3.9	.579
PANSS negative subscore	20.5±5.4	20.8±5.4	20.3±5.4	.503
PANSS general subscore	36.9±6.4	36.7±5.7	37.0±7.1	.925
PANSS total	77.9±12.4	77.8±10.7	78.0±14.0	.636
Age at onset of psychotic symptoms, years	12.9±3.4	12.8±3.8	13.0±3.0	.710
DUP, weeks	151.1±175.0	156.7±203.4	145.9±145.4	.803
CGI-S score	4.8±0.7	4.9±0.7	4.8±0.8	.444
GAPD score	4.4±1.1	4.4±1.1	4.4±1	.961
ICD-10 diagnoses, n (%)				
Schizophrenia (F20)	66 (68.0%)	30 (62.5%)	36 (73.4%)	X ² =6.343, p=.500
Delusional disorders (F22)	2 (2.1%)	2 (4.2%)	0 (0.0%)	
Acute and transient psychotic disorders (F23)	1 (1.0%)	0 (0.0%)	1 (2.0%)	
Schizoaffective disorders (F25)	19 (19.6%)	11 (22.9%)	8 (16.3%)	
Other psychotic disorders (F28)	3 (3.1%)	2 (4.2%)	1 (2.0%)	
Bipolar disorder (F31)	1 (1.0%)	0 (0.0%)	1 (2.0%)	
Major depressive disorders (F32)	4 (4.1%)	2 (4.2%)	2 (4.1%)	
Recurrent depressive disorder (F33)	1 (1.0%)	1 (2.1%)	0 (0.0%)	
Antipsychotic use before inclusion, n (%)				
Antipsychotic-naïve	59 (60.8%)	29 (60.4%)	30 (61.2%)	X ² =0.007, p=1.000
Antipsychotic-exposed	38 (39.2%)	19 (39.6%)	19 (38.7%)	
Number of antipsychotic medications used, n (%)				X ² =1.524, p=.464
1	29 (29.9%)	14 (29.2%)	15 (30.6%)	

All participants	All patients (n=97)	Quetiapine group (n=48)	Aripiprazole group (n=49)	p
2	8 (8.2%)	5 (10.4%)	3 (6.1%)	
3	1 (1.0%)	0 (0.0%)	1 (2.0%)	
Distribution of antipsychotic usage				
Aripiprazole, n (%)	2 (2.1%)	0 (0.0%)	2 (4.1%)	.495
Aripiprazole, median cumulated life time dose, mg (IQR)	27.50 (20.00-35.00)	-	27.50 (20.00-35.00)	-
Aripiprazole, median number of days (IQR)	7.5 (7.0-8.0)	-	7.5 (7.0-8.0)	-
Quetiapine, n (%)	9 (9.3%)	4 (8.3%)	5 (10.2%)	1.000
Quetiapine, median cumulated life time dose, mg (IQR)	250.00 (75.00-820.00)	138.00 (13.00-535.00)	675.00 (150.00-1250.00)	.286
Quetiapine, median number of days (IQR)	15.5 (2.5-26.0)	8.0 (1.0-23.0)	25.0 (3.0-27.0)	.393
Olanzapine, n (%)	20 (20.6%)	11 (22.9%)	9 (18.4 %)	.623
Olanzapine, median cumulated life time dose, mg (IQR)	50.00 (12.50-132.50)	55.00 (30.00-255.00)	20.00 (10.00-110.00)	.331
Olanzapine, median number of days (IQR)	10.0 (1.0-19.0)	15.0 (1.0-28.0)	7.0 (1.0-11.0)	.152
Chlorprothixene, n (%)	31 (32.0%)	17 (35.4%)	14 (28.6%)	.518
Chlorprothixene, median cumulated life time dose, mg (IQR)	75.00 (15.00-195.00)	65.00 (15.00-195.00)	98.00 (40.00-150.00)	1.000
Chlorprothixene, median number of days (IQR)	3.0 (1.0-11.0)	2.0 (1.0-11.0)	6.0 (1.0-7.0)	.710
Concomitant psychiatric medications				
Antipsychotics (acute), n (%)	37 (38.1%)	18 (37.5%)	19 (38.8%)	1.000
Aripiprazole, n (%)*	2 (2.1%)	0 (0.0%)	2 (4.1%)	.495
Aripiprazole, median cumulated dose in assessment period, mg (IQR)	25.0 (25.0-25.0)		25.0 (25.0-25.0)	-
Aripiprazole, median number of doses (IQR)	4.0 (4.0-4.0)		4.0 (4.0-4.0)	-
Quetiapine, n (%)*	7 (7.2%)	3 (6.3%)	4 (8.2%)	1.000

All participants	All patients (n=97)	Quetiapine group (n=48)	Aripiprazole group (n=49)	p
Quetiapine, median cumulated dose in assessment period, mg (IQR)	11,050.0 (3,125.0-32,950.0)	3,125.0 (350.0-6,600.0)	31,100.0 (20,150.0-37,225.0)	.057
Quetiapine, median number of doses (IQR)	50.0 (15.0-82.0)	15.0 (14.0-23.0)	67.0 (51.0-102.0)	.057
Olanzapine, n (%)	15 (15.5%)	12 (25.0%)	3 (6.1%)	.012
Olanzapine, median cumulated dose in assessment period, mg (IQR)	60.0 (22.5-155.0)	37.5 (20.0-155.0)	60.0 (60.0-1,230.0)	.456
Olanzapine, median number of doses (IQR)	13.5 (4.0-21.0)	15.0 (3.0-21.0)	12.0 (6.0-123.0)	.769
Chlorprothixene, n (%)	25 (25.8%)	9 (18.8%)	16 (32.7%)	.164
Chlorprothixene, median cumulated dose in assessment period, mg (IQR)	195.0 (75.0-418.5)	105.0 (30.0-350.0)	210.0 (90.0-1,319.3)	.357
Chlorprothixene, median number of doses (IQR)	8.0 (3.0-27.0)	5.0 (2.0-9.0)	11.0 (6.0-51.5)	.097
Antidepressants (SSRI), n (%)	24 (24.7%)	12 (25.0%)	12 (24.5%)	1.000
Mood stabilizers, n (%)	1 (1.0%)	1 (2.1%)	0 (0.0%)	.495
Benzodiazepines, n (%)	25 (25.8%)	10 (20.8%)	15 (30.6%)	.354
Methylphenidate, n (%)	3 (3.1%)	2 (4.2%)	1 (2.0%)	.617
Antihistamines for sedation, n (%)	3 (3.1%)	1 (2.1%)	2 (4.1%)	1.000
Melatonin, n (%)	36 (37.1%)	17 (35.4%)	19 (38.8%)	.834

* Treatment with aripiprazole or quetiapine only occurred after discontinuation of trial medication. BP = blood pressure; CGI-S: clinical global impression, severity; DUP: duration of untreated psychosis; GAPD: global assessment of psychosocial disability; ICD-10: international classification of diseases manual, 10th edition; IQR: interquartile range; mg: milligrams; PANSS: positive and negative syndrome scale; SSRI: selective serotonin reuptake inhibitor; SD: standard deviation.

Table 3: Changes in heart rate and QTc intervals

	All patients 97		quetiapine 48		Aripiprazole 49		p
	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	
Baseline							
QTcH 0	344.2 to 449.7	382.6±21.9	345.8 to 445.4	382.6±21.5	344.2 to 449.7	382.6±22.4	.997
QTcB 0	335.8 to 479	388.4±26.6	335.8 to 479.0	389.2±27.6	343.1 to 455.7	387.5±25.8	.759
QTcF 0	342 to 447.4	380.5±20.9	342.0 to 433.0	380.2±20.1	342.7 to 447.4	380.8±21.8	.890
HR 0	47 to 110	68.9±14.1	47 to 110	70.3±15.6	47 to 99	67.6±12.6	.346
Week 4	91		45		46		
QTcH 4	340.2 to 447.9	385.2±22.1	347.5 to 436.0	389.1±22.0	340.2 to 447.9	381.5±21.8	.098
QTcB 4	334.4 to 466.9	394.9±28.3	344.2 to 466.9	403.0±27.9	334.4 to 462.2	387.0±26.6	.006
QTcF 4	338.4 to 442.4	381.6±20.6	341.2 to 424.6	383.9±20.5	338.4 to 442.4	379.4±20.7	.297
HR 4	48 to 111	74.8±15.5	48 to 111	81.3±15	51 to 111	68.4±13.3	.000
Week 12	83		41		42		
QTcH 12	341.7 to 436.9	385.4±20.2	348 to 436.9	389.2±19.8	341.7 to 422.7	381.7±20.1	.091
QTcB 12	334.3 to 459.3	395.0±25.9	355.7 to 459.3	403.4±24.1	334.3 to 441.4	386.8±25.3	.003
QTcF 12	344.7 to 428.5	381.8±18.8	345 to 428.5	383.9±18.8	344.7 to 421.5	379.8±18.8	.326
HR 12	50 to 104	74.5±14.5	55 to 104	81.4±12.5	50 to 102	67.8±13.2	.000
Last Follow-Up	97		48		49		
QTcH at LFU	341.7 to 436.9	385.8±20.1	348 to 436.9	390.0±19.9	341.7 to 422.7	381.6±19.6	.040
QTcB at LFU	334.3 to 459.3	395.0±26.3	355.7 to 459.3	403.6±25.2	334.3 to 441.4	386.5±24.8	.001
QTcF at LFU	344.7 to 428.5	382.3±18.6	345 to 428.5	384.9±18.7	344.7 to 421.5	379.8±18.3	.180
HR at LFU	48 to 104	74±15.2	48 to 104	80.7±14.2	50 to 102	67.5±13.4	.000
Change in values							
Week 4	91		45		46		
ΔQTcH	-53.7 to 40.8	2.0±15.7	-22.9 to 40.8	5.5±13.7	-53.7 to 32.9	-1.5±16.9	.033
ΔQTcB	-57.4 to 61.2	5.9±21.5	-20.1 to 61.2	12.2±19.4	-57.4 to 46.3	-0.3±21.9	.005
ΔQTcF	-52.3 to 33.2	0.5±14.1	-24.0 to 33.2	3.0±12.1	-52.3 to 27.7	-1.9±15.6	.098
ΔHR	-18 to 42	5.9±12.1	-9 to 34	10.1±11.1	-18 to 42	1.7±11.7	.001
Week 12	83		41		42		
ΔQTcH	-42.6 to 62.3	4.2±19.8	-42.6 to 62.3	7.8±21.4	-39.5 to 38.6	0.6±17.7	.097
ΔQTcB	-53.9 to 75.8	7.9±26.8	-48.7 to 75.8	15.3±28.2	-53.9 to 61.2	0.7±23.5	.012
ΔQTcF	-40.3 to 57.3	2.7±17.9	-40.3 to 57.3	5.0±19.5	-36.5 to 36.7	0.5±16.1	.262
ΔHR	-24 to 47	5.5±14.9	-19 to 47	11±15.3	-24 to 40	0.1±12.5	.001
Last Follow-Up	97		48		49		
ΔQTcH	-53.7 to 62.3	3.1±19.9	-42.6 to 62.3	7.3±20.3	-53.7 to 38.6	-1.0±18.9	.039
ΔQTcB	-57.4 to 75.8	6.6±26.7	-48.7 to 75.8	14.3±27.1	-57.4 to 61.2	-1.0±24.4	.004
ΔQTcF	-52.3 to 57.3	1.8±18	-40.3 to 57.3	4.7±18.4	-52.3 to 36.7	-1.0±17.4	.123
ΔHR	-24 to 47	5.1±14.4	-19 to 47	10.4±14.8	-24 to 40	-0.1±12.2	.000

All patients 97			quetiapine 48		Aripiprazole 49		p
Range	Mean±SD		Range	Mean±SD	Range	Mean±SD	
Only recently unexposed							
Last Follow-Up	59		29		30		
ΔQTcH	-53.7 to 40.5	3.1±19.5	-30.5 to 40.5	8.1±18.1	-53.7 to 36.5	-1.7±19.9	.054
ΔQTcB	-57.4 to 63.7	7.1±27.6	-42.8 to 63.7	16.7±26.4	-57.4 to 61.2	-2.1±25.9	.008
ΔQTcF	-52.3 to 37.4	1.6±17.1	-26.0 to 37.4	4.8±15.8	-52.3 to 27.4	-1.5±18.0	.156
ΔHR	-24 to 47	6.1±15.9	-19 to 47	12.9±16.4	-24 to 40	-0.5±12.5	.001

Δ=Change; HR: heart rate; LFU: last follow-up; QTcB=QT corrected by Bazett's formula; QTcF=QT corrected by Fridericias formula; QTcH=QT corrected by Hodges formula; SD: standard deviation

Table 4: Linear regression of predictors of QTcH change to LFU

Predictor	Quetiapine group	Aripiprazole group
Age	F(1,46)=3.680, p=.061	F(1,47)=.091, p=.764
Sex	F(1,46)=.264, p=.610	F(1,47)=.264, p=.610
Cigarettes (in smokers)	F(1,15)=.218, p=.647	F(1,17)=.000, p=.988
BMI z-score	F(1,46)=.376, p=.543	F(1,47)=1.517, p=.224
Waist circumference z-score	F(1,42)=.155, p=.696	F(1,44)=3.318, p=.075
Potassium	F(1,45)=5.818, p=.020	F(1,46)=.264, p=.610

Table S1: Interrater variability on QT measurement

	Mean±standard deviation (ms)
Rater 1	360.8±27.5
Rater 2	360.0±27.4
Cronbach's α	0.978
Pearson's r	0.958

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