



Metabolic Syndrome Among Adolescents Using Second-Generation Antipsychotics for Treatment of Conduct Disorder

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Abbreviations

| | |
|-------------------|---|
| 5-HT | 5-hydroxytryptamine (Serotonin) |
| ACE | Angiotensin Converting Enzyme |
| ACTH | Adrenocorticotrophic hormone |
| ADHD | Attention-Deficit/Hyperactivity Disorder |
| AIMs | Abnormal Involuntary Movements |
| AL | Allostatic Load |
| ARBs | Angiotensin Receptor Blockers |
| ATP III | Adult Treatment Panel III |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CAS-P | The Children's Aggression Scale – Parent |
| CAS-T | The Children's Aggression Scale - Teacher |
| CATIE | Clinical Antipsychotic Trials of Intervention Effectiveness |
| CD | Conduct Disorder |
| CERT T-MAY | The Center for Education and Research on Mental Health Therapeutics: Treatment of Maladaptive Aggression in Youth |
| CRH | Corticotrophin-releasing hormone |
| CVD | Cardiovascular Disease |
| DALYs | Disability Adjusted Life Years |
| DM | Diabetes Mellitus |
| DSM-V | Diagnostic and Statistical Manual of Mental Disorders-5 |

List of Abbreviations

| | |
|-----------------|--|
| EPS | Extrapyrarnidal syndrome |
| FBG | Fasting blood glucose |
| FDA | Food and Drug administration |
| FGAs | First-generation antipsychotics |
| fMRI | Functional Magnetic Resonance Imaging |
| GABRA2 | Gamma-aminobutyric acid receptor subunit alpha-2 |
| GBD | Global Burden of Disease study |
| HDL-C | High density lipoprotein cholesterol |
| HPA axis | Hypothalamic-Pituitary-Adrenal axis |
| HR | Heart Rate |
| HRV | Heart Rate Variability |
| IDF | International Diabetes Federation |
| IFG | Impaired Fasting Glucose |
| IL-1,6,8 | Interlukin-1,6,8 |
| IR | Insulin resistance |
| LDL-C | Low Density Lipoprotein – Cholesterol |
| MCP | Monocyte Chemotactic Protein |
| MOAS | The Modified Overt Aggression Scale |
| MPM | Metabolic Parameter Monitoring |
| MST | Multisystemic Therapy |
| NCBRF | The Nisonger Child Behavior Rating Form |
| ODD | Oppositional defiant disorder |
| OGTT | Oral Glucose Tolerance Test |
| PEP | Pre-Ejection Period |

List of Abbreviations

| | |
|---------------------------------|--|
| PMT | Parent Management Training |
| PSST | Problem-Solving Skills Training |
| RAAPP | The Rating of Aggression Against People and/or Property scale |
| RSA | Respiratory Sinus Arrhythmia |
| SAM axis | Sympathetic-Adrenal-Medullary axis |
| SATIETY | Second-generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth study |
| SGAs | Second generation antipsychotics |
| TG | Triglycerides |
| TNF- α | Tumor necrosis factor-alpha |
| TOSCA | Treatment of Severe Childhood Aggression study |
| WHO | World Health Organization |
| YLDs | Years Lived with Disability |
| YLLs | Years of Life Lost |
| WC | Waist Circumference |

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Introduction

The introduction of antipsychotic drugs has greatly improved the management of severe mental illnesses (e.g. schizophrenia, bipolar disorder). Second-generation (atypical) antipsychotic drugs are generally better tolerated than the first-generation (conventional) antipsychotics largely because of a lower incidence of extrapyramidal symptoms. Consequently, these agents are recommended for first-line treatment of severe mental illness; however, some patients treated with second-generation antipsychotics have experienced significant weight gain and changes in metabolic variables, as well as increased risks for diabetes mellitus and dyslipidemia. In addition to having a potentially deleterious effect on physical health, being overweight or obese may also adversely affect a patient's self-esteem and desire to comply with treatment, which may in turn lead to disease relapse (*Citrome et al., 2011*).

Atypical or second-generation antipsychotics (SGAs) have been proven to be effective for treating several conditions in children and adolescents. As of March 2010, aripiprazole, olanzapine, quetiapine, and risperidone are Food and Drug Administration (FDA)-approved medications for bipolar mania in children and adolescents (aged 10-17 years; except olanzapine, aged 13-17 years) and for adolescent schizophrenia (aged 13-17 years). In addition, aripiprazole and risperidone are also FDA-approved medications for behavioral disturbances (irritability and aggression) associated with autism and/or intellectual disabilities

in children and adolescents (aged 6-17 years). Second-generation antipsychotics were developed to limit the frequency of extrapyramidal syndrome (EPS) (*Olfson et al., 2006*).

Disruptive behavior disorders include conduct disorder, oppositional defiant disorder and disruptive behavior not otherwise specified. The difficulties associated with disruptive behavior disorders are demonstrated through aggression and severe behavioral problems. These often result in presentation to psychiatric services and may be treated with medications such as atypical antipsychotics. There is increasing evidence of a significant rise in the use of atypical antipsychotics for treating disruptive behavior disorders in adolescent populations (*Loy et al, 2017*).

With steadily rising trends in prescription of antipsychotic medications, particularly in adolescents, these drugs are among the most significant risk factors for type II diabetes, weight gain and metabolic syndrome in this population (*Pramyothin & Khaodhiar, 2015*).

Six SGAs are now commonly prescribed to adolescents both in the United States and in Europe. The risk of adverse effects (weight gain, somnolence, and EPS) with olanzapine was reported to be significantly increased in young patients compared with adults, leading to concerns about the use of SGAs in adolescents. Emerging findings indicate that adolescents are more vulnerable

to weight gain and cardiometabolic effects (increase in glucose, triglyceride, and cholesterol levels) (*Cohen et al., 2012*).

Among Egyptian healthy adolescents 10 to 18 years of age, the overall prevalence of the metabolic syndrome was 7.4% with no sex or area of residence predilection. Results showed that adolescents with the full criteria of metabolic syndrome constituted nearly one-fourth of those exhibiting high values of different components, except for systolic blood pressure, where they were 42%, and TG, where they were 31% (*Sliem et al, 2012*).

Although some guidelines have been developed for the monitoring of these adverse events, adherence to these guidelines by practitioners has been suboptimal. In addition, there have been few evidence-based approaches developed to manage these side effects (*Krill & Kumra, 2014*).

In 1988, Gerald Reaven reintroduced the concept of syndrome X for the clustering of cardiovascular risk factors like hypertension, glucose intolerance, high triglycerides, and low HDL cholesterol concentrations. The syndrome is, however, much older, having been already observed in 1923 by Kylin, who described the clustering of hypertension, hyperglycemia, and gout as a syndrome. Subsequently, several other metabolic abnormalities have been associated with this syndrome, including obesity, microalbuminuria, and abnormalities in fibrinolysis and coagulation. The syndrome has also been given several other

names, including the metabolic syndrome, the insulin resistance syndrome, the plurimetabolic syndrome, and the deadly quartet. The name “insulin resistance syndrome” has been widely used and refers to insulin resistance as a common denominator of the syndrome. The prevalence of the metabolic syndrome has varied markedly between different studies, most likely because of the lack of accepted criteria for the definition of the syndrome. In 1998, WHO proposed a unifying definition for the syndrome and chose to call it the metabolic syndrome rather than the insulin resistance syndrome. This name was chosen primarily because it was not considered established that insulin resistance was the cause of all the components of the syndrome (*Isomaa et al., 2001*).

In 2005, the International Diabetes Federation (IDF) published its definition of the metabolic syndrome in adults. The intention was to rationalize the existing multiple definitions of the syndrome and to have a single, universally accepted diagnostic tool that is easy to use in clinical practice and that does not rely upon measurements only available in research settings. Additionally, the use of a single unified definition makes it possible to estimate the global prevalence of metabolic syndrome and make valid comparisons between countries (*Alberti et al., 2005*).

The new IDF definition of metabolic syndrome in children and adolescents is inspired, in part, by the IDF worldwide definition of metabolic syndrome in adults. It builds on previous
