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

Thesis

Submitted for Partial Fulfillment of the Master Degree in Neuropsychiatry

By

Mai Mahmoud AbdelKader Zahran

M.B.B.Ch, Faculty of Medicine, Ain Shams University

Under Supervisors

Prof. Dr. Afaf Mohamed Abd El Samei

Professor of Neuropsychiatry
Faculty of Medicine – Ain Shams University

Prof. Dr. Doha Moustafa ElSerafy

Professor of Neuropsychiatry
Faculty of Medicine – Ain Shams University

Assist. Prof. Dr. Hanan Hany ElRassas

Assistant Professor of Neuropsychiatry
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2018

سورة البقرة الآية: ٣٢

ACKNOWLEDGEMENT

First of all, thanks to **Allah** whose magnificent help was the main factor in completing this work.

I wish to express my sincere gratitude to **Professor. Afaf Mohamed Abd El Samei,** Professor of Neuropsychiatry at Ain Shams University, she has always believed in this study, even during the hard moments, and given me the support I needed, and without her enthusiastic support and encouragement, this work would have never been completed. My deepest thanks for her guidance and advice regarding every step of this research.

I am also most grateful to **Professor. Doha Elserafy,** Professor of Neuropsychiatry at Ain Shams University. She has been supportive since this research was just an idea until it was completed. I really learned a lot from her supervision. For that I would like to express my deepest appreciation.

I want to express my most sincere and special thanks to **Assist. Prof. Dr. Hanan Hany ElRassas,** Assistant Professor of Neuropsychiatry at Ain Shams University. Her excellent knowledge of scientific research and her rational advice have been an essential part of carrying out this study.

I would also like to express thanks to my friends and colleagues who helped me all through this work.

Last, but not least, I would like to express my gratitude to the patients and volunteers without whose participation I wouldn't have been able to accomplish this work.

Contents

List of Abbreviations

5-HT	5-hydroxytryptamine (Serotonin)
ACE	Angiotensin Converting Enzyme
ACTH	Adrenocorticotropic 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

EPS	Extrapyramidal 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

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

.

List of Figures

List of Tables

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