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Comparing tolerability profile of second generation antipsychotics in schizophrenia and affective disorders: a meta-analysis

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Résumé

Les antipsychotiques de deuxième génération (ADG) sont de plus en plus employés dans le traitement de troubles psychiatriques. Selon de nombreuses observations cliniques, les effets secondaires reliés à la prise d'ADG diffèrent chez les patients atteints de schizophrénie (SCZ) et de maladies affectives (MA) éprouvent divers. Ainsi, il s'avère nécessaire d'étudier la fréquence et l'intensité des effets secondaires induits par les ADG qui pourraient différer selon le diagnostic. Pour ce faire, nous avons effectué une revue systématique de la littérature afin d'identifier l'ensemble des études rapportant les effets secondaires de cinq ADG (aripiprazole, olanzapine, quétiapine, rispéridone et ziprasidone) dans le traitement de la schizophrénie ou des maladies affectives. Les effets secondaires métaboliques et extrapyramidaux ont été recueillis séparément pour les deux groupes de patients, puis ont été combinés dans une méta-analyse. Des méta-régressions ainsi que des sous-analyses ont également été effectuées dans le but de regarder l'effet de différents modérateurs (i.e. âge, genre, et dose). Dans la présente méta-analyse, 107 études ont été inclues. Les résultats montrent que le traitement avec l'olanzapine a occasionné une plus importante prise de poids chez les patients SCZ comparativement aux patients MA. De plus, le traitement à la quétiapine a amené une hausse significative du taux de LDL et de cholestérol total dans le groupe SCZ par rapport au groupe MA. Selon nos résultats, les symptômes extrapyramidaux étaient plus fréquents dans le groupe MA, excepté pour le traitement à l'olanzapine qui a induit davantage de ces symptômes chez les patients SCZ. Également, nos résultats suggèrent que les patients SCZ seraient plus vulnérables à certains

effets métaboliques induits par les ADG dû à une possible susceptibilité génétique ou à la présence de facteurs de risque associés au style de vie. D'autre part, les patients MA en comparaison aux SCZ étaient plus enclins à souffrir de troubles du mouvement induits par les ADG. Bref, les ADG semblent exacerber certains types d'effets secondaires tout dépendant de la maladie dans laquelle on les utilise.

Mots-clés : Antipsychotiques de deuxième génération, Maladies affectives, Schizophrénie, Syndrome métabolique, Symptômes extrapyramidaux, Méta-analyse.

Abstract

Second generation antipsychotics (SGAs) are extensively prescribed for psychiatric disorders. Based on clinical observations, schizophrenia (SCZ) and affective disorders (AD) patients experience different SGAs side effects. The expanded use of SGAs in psychiatry suggests a need to investigate whether there is a difference in the incidence and severity of side-effects related to diagnosis. A comprehensive literature search was conducted to identify studies reporting side effects of five SGAs (aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone) in the treatment of SCZ or AD. The metabolic and extrapyramidal side effects were collected separately for each group, and then were combined in a meta-analysis. Meta-regression and sub-analyses were also performed to investigate the role of different moderators (e.g., age, dose and gender). One hundred and seven studies were included in the analysis. Olanzapine induced a body weight gain significantly higher in SCZ patients than in AD patients. In addition, quetiapine treatment led to significantly higher LDL and total cholesterol mean change in the SCZ group relative to the AD group. Based on our results, the incidence of extrapyramidal side effects was more frequent in the AD group, except for olanzapine that caused more parkinsonism in SCZ patients. Our results suggest that SCZ patients may be more vulnerable to some SGA-induced metabolic disturbances, in which lifestyle risk factors and a possible inherent genetic vulnerability may play a role. Most of the studied SGAs caused more movement disorders in AD patients than in schizophrenics. It might be that an antipsychotic induces severity of side effect according to the phenotype.

Keywords: Second generation antipsychotics, Affective disorders, Schizophrenia, Metabolic syndrome, Extrapyramidal symptoms, Meta-analysis.

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Liste des abréviations

5-HT_{1A}	5-hydroxytryptamine (serotonin) receptor $_{1A}$
5-HT_{2A}	5-hydroxytryptamine (serotonin) receptor $_{2A}$
5-HT_{2B}	5-hydroxytryptamine (serotonin) receptor $_{2B}$
5-HT_{2C}	5-hydroxytryptamine (serotonin) receptor $_{2C}$
5-HT_{1D}	5-hydroxytryptamine (serotonin) receptor $_{1D}$
5-HT_{3}	5-hydroxytryptamine (serotonin) receptor $_{3}$
5-HT_{6}	5-hydroxytryptamine (serotonin) receptor $_{6}$
5-HT_{7}	5-hydroxytryptamine (serotonin) receptor $_{7}$
α_1	Alpha-1 adrenergic receptor
α_2	Alpha-2 adrenergic receptor
AD	Affective Disorders
ADG	Antipsychotiques de Deuxième Génération
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BDNF	Brain-Derived Neurotrophic Factor
BP	Bipolar Disorder
CI	Confidence Interval
CMA	Comprehensive Meta-Analysis
CVD	Cardiovascular Diseases
CYP1A2	Cytochrome P450 1A2
CYP3A4	Cytochrome P450 3A4
CYP2D6	Cytochrome P450 2D6
D_1	Dopaminergic receptor D_1
D_2	Dopaminergic receptor D_2
D_3	Dopaminergic receptor D_3
D_4	Dopaminergic receptor D_4
D_5	Dopaminergic receptor D_5
DA	Dopamine

DHEA	Dehydroepiandrosterone
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DT	Diagnostic Type
EMBASE	Experta Medica dataBase
EPS	Extrapyramidal Symptoms
FDA	US Food and Drug Administration
FGA	First generation antipsychotic
H_1	Histaminergic receptor H_1
HPA	Hypothalamo-pituitary-adrenal
HTR2A	Serotonergic receptor 2A coding genes
HTR2C	Serotonergic receptor 2C coding genes
kg	Kilogram
M_1	Muscarinic acetylcholine receptor M_1
M_2	Muscarinic acetylcholine receptor M_2
M_3	Muscarinic acetylcholine receptor M_3
M_4	Muscarinic acetylcholine receptor M_4
M_5	Muscarinic acetylcholine receptor M_5
MAOI	Monoamine Oxidase Inhibitors
mg/dl	Milligrams per deciliter
N	Number of articles
n	Number of patients
NMDA	N-methyl-D-aspartate
PCP	Phencyclidine
QT_C	QT interval corrected
QUOROM	QUality Of Reporting Of Meta-analysis
RCT	Randomised Controlled Trials
SCZ	Schizophrenia

SGA	Second Generation Antipsychotic
SREBP	Sterol Regulatory Element Binding Protein
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic Antidepressants

Dédicace

To my Mom and Dad
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For their endless love and encouragement
&
To my husband
Ali
For all he is

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1. INTRODUCTION

1.1. Schizophrenia

1.1.1. Clinical description

Schizophrenia is a severe, chronic and debilitating psychiatric disorder. Ranking among the ten most frequent causes of disability in developed countries (Rossler et al., 2005), it affects around 0.3% to 0.7% of the world's population at some point in their life (van Os and Kapur, 2009). Schizophrenia is characterized by disordered thinking, hallucinations, delusions, bizarre behaviour and inappropriate emotional responses. The disorder can appear at any age, although symptoms most commonly appear in late adolescence or early adulthood; however, cognitive disturbances are often evident earlier (Carpenter and Buchanan, 1994, Tamminga and Holcomb, 2005). Based on epidemiological studies, men and women are affected equally often, but women are generally diagnosed at a slightly later age; in addition, some gender differences in the course of this disorder exist (Brown and Estoup, 2005, Meyer and Quenzer, 2005). Schizophrenia is estimated to be the seventh most costly and disabling disease affecting the age group between 20 and 45 years old, because of the high frequency of hospitalizations, the need for psychosocial services and lost productivity (Arguello et al., 2010, Goeree et al., 2005, Ibrahim and Tamminga, 2011, McIntyre et al., 2010).

1.1.2. Symptoms

According to the definition in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) (APA, 1994), in order to make the diagnosis of schizophrenia, continuous signs of illness, which may include symptoms from the prodromal and residual phases of the illness that are not psychotic, must be evident for at least 6 months, accompanied by a decrease in functioning from the premorbid level. Schizophrenia is diagnosed in patients who have two or more of the following symptoms for more than one month (during the last 6 months): hallucinations, disorganized speech and behaviour, delusions, affective flattening, alogia and avolition. In addition, patients' social functioning must have deteriorated (Smith et al., 2010).

Individuals with schizophrenia experience different kinds of symptoms: positive, negative and cognitive. Positive symptoms include delusions (beliefs that have no basis in reality); hallucinations (auditory or visual), for example hearing voices that are not there; or communicating in a way that is difficult to understand, such as disorganized speech and behaviour. For many schizophrenia patients, emotions are absent or inappropriate to the situation; speech and thoughts are also disrupted and may shift from one subject to a totally unrelated subject.

Negative symptoms are characterized by a decline in regular functioning, including reduced speech (alogia), loss of motivation (avolition), loss of pleasure in normally pleasurable activities (anhedonia), inhibition of facial expressions and decline in emotional responsiveness (flattened affect).

Cognitive symptoms relate to thought processes and include difficulty with planning and structuring activities, learning and memory problems, difficulty maintaining attention, loss of insight and impaired judgment (Meyer and Quenzer, 2005, Smith et al., 2010).

1.1.3. Etiology and pathophysiology

The precise cause of schizophrenia is widely debated. Multiple factors, including genetic susceptibility variations, viruses, toxins, birth injuries, neurological disorders and psychological experiences, among others, have been argued to be possible factors leading to schizophrenia.

It is now generally recognized the neurotransmitter hypotheses (dopamine, glutamate and others) are the consequence of previous neurodevelopmental alterations that occurred in utero or around birth. The neurodevelopmental abnormalities remain relatively silent during brain maturation because of the extraordinary plastic capacity of the neural tissue. But, at adulthood, these abnormalities (principally related to synaptic function) generate brain neurochemical imbalances, which are associated with symptoms expression (Lewis and Levitt, 2002). The most widely accepted hypotheses to explain the etiology and pathophysiology of schizophrenia disorders are discussed below, based on work by Meyer and Quenzer (2005), Miyamoto et al. (2002) and Smith et al. (2010).

1.1.3.1. Genetic and environmental factors

The importance of heredity is demonstrated by linkage studies, genetic epidemiological investigations, DNA microarrays and twin studies. Research in molecular genetics is

currently focusing on the identification of the specific genes that predict susceptibility to schizophrenia. Multiple gene abnormalities may be responsible for a given variation in the appearance and intensity of symptoms between two individuals. Drug use, endocrine diseases, malnutrition, stress and brain hypoxia during pregnancy and delivery may increase the probability of schizophrenia (Tsuang, 2000).

1.1.3.2. Neurodevelopmental hypothesis

Another hypothesis concerning the pathology of schizophrenia concerns abnormal brain structure. Brain abnormalities and cell disorganization found in schizophrenia patients include enlarged ventricles, decreased hippocampal volume, decreased grey matter volume, decreased activity in the frontal lobe, failure of the prefrontal cortex and asymmetrical hemispheres (Rubesa et al., 2011).

1.1.3.3. Dopaminergic hypothesis

One hypothesis that has gained a good deal of support is that dopamine levels are abnormal in schizophrenia patients. After more than three decades, this assumption is still dominant in the pathophysiology of schizophrenia and is believed to explain the genesis of positive symptoms in particular. The concepts underlying this hypothesis came from the seminal work of Carlsson and Lindqvist (1963) describing the presence of dopamine in the brain and the effects of neuroleptics on monoaminergic indices. The dopaminergic hypothesis of schizophrenia proposes that hyperactive dopamine transmission in mesolimbic dopaminergic neurons is associated with positive symptoms episodes. This has been confirmed by Laruelle in schizophrenia patients using brain imaging (Laruelle et al., 1996).

In addition, increased numbers of D_2 receptors in the nucleus accumbens, basal ganglia and substantia nigra of post-mortem schizophrenic brains confirm the involvement of dopamine in developing this disorder. The work of Glenthoj et al. (2006) showed a positive correlation between the activity of D_2/D_3 dopamine receptors in the frontal cortex and positive psychotic symptoms.

The classical dopamine hypothesis has received further support from other studies (Creese et al., 1976, Levin et al., 1989, Nakajima and Baker, 1989, Seeman and Lee, 1975) which found a positive correlation between clinical doses of antipsychotic drugs and their potency in blocking D_2 dopamine receptors. Atypical antipsychotics are therapeutic agents that increase dopamine in mesocortical areas and simultaneously decrease the activity of dopamine in the mesolimbic dopamine pathway (Takahashi et al., 2006). Further investigations showed that, after exposure to certain psychostimulants, such as amphetamine and cocaine, the increase in dopamine release is greater in schizophrenia patients than in healthy volunteers (Breier et al., 1997, Laruelle and Abi-Dargham, 1999). In addition, psychostimulants increase dopaminergic neurotransmission and induce psychosis similar to schizophrenia in some healthy subjects (Depatie and Lal, 2001). Psychostimulants also exacerbate psychosis in some schizophrenia patients (Harrison et al., 2008, Zhornitsky et al., 2011).

1.1.3.4. Glutamatergic hypothesis

Glutamate is the most widely distributed transmitter in the central nervous system and is known to interact with the central dopaminergic system in many ways. Glutamate acts via

large families of receptors: ionotropic (NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) and kainite) and metabotropic receptors (mGluRs). The idea of a glutamatergic abnormality in schizophrenia was first suggested by Kim et al. (1980), based on their findings of low cerebrospinal fluid glutamate levels in schizophrenia patients. Grace (1991) proposed a glutamate-dopamine model, which emphasizes that cortical glutamate can regulate sub-cortical release of dopamine neurotransmitter. Therefore, the loss of glutamate inputs to the subcortical dopamine centre should lead to excess dopamine activity and produce the positive symptoms of schizophrenia.

Antagonists of glutamate receptors such as ketamine and PCP (phencyclidine) can produce positive, negative and cognitive symptoms of schizophrenia in healthy volunteers (Grace, 1991, Javitt and Zukin, 1991, Lahti et al., 1995, Polimeni and Reiss, 2002). This glutamatergic theory is supported by post-mortem studies showing that levels of glutamate and NMDA receptors have changed in schizophrenia patients (Konradi and Heckers, 2003, Ulas and Cotman, 1993).

Hypofunction of NMDA receptors in schizophrenia has been indicated based on various clinical, neuropathological and genetic findings (Bennett and Gronier, 2005, Conley et al., 2005, Scarr et al., 2005).

1.1.3.5. Role of other neurotransmitters

Further studies discovered that other neurotransmitters, such as serotonin and acetylcholine, may also be involved in the pathophysiology of schizophrenia. An increased number of 5-

HT_{2A} and 5-HT_{1A} cortical receptors has been observed in the brains of schizophrenia patients. The polymorphism of the 5-HT_{2A} receptor gene has also been verified; this may indicate insufficient 5-HT_{2A}-receptor-mediated activation of the prefrontal cortex (Aghajanian and Marek, 2000). Post-mortem and neuroimaging studies in schizophrenia patients have shown a reduced number of M_1 and M_4 muscarinic receptors in crucial loci, such as the caudate nucleus, hippocampus, putamen and prefrontal cortex, as well as the anterior and posterior cingulate cortex (Raedler et al., 2003).

The pathophysiology of schizophrenia is complex; no one model seems to fit perfectly, and schizophrenia researchers continue to strive to learn more. Most experts believe that schizophrenia is the result of a combination of genetic and environmental factors, as well as psychological and neurobiological abnormalities.

1.1.4. Diagnosis

The diagnosis of schizophrenia is not a simple matter, even though the symptoms described above seem relatively easy to distinguish. At present, due to a lack of clear biological markers for the disorder, the only diagnostic approach is based on symptoms. However, the symptoms vary from one individual to another; they also change over time, which can lead to a change in diagnosis. The lack of diagnostic tests and biological markers to define the illness's onset and follow its progression makes treatments primarily symptomatic (Ibrahim and Tamminga, 2011, Meyer and Quenzer, 2005). Schizophrenia has been further sub-classified, according to the most significant characteristics present in each patient. Consequently, each person may be diagnosed with different schizophrenia sub-types during

the course of the illness. Based on the DSM-IV-TR, these sub-classes include catatonic, paranoid, disorganized, undifferentiated and residual types (APA, 2000).

1.1.5. Pharmacological treatments

The aims of the pharmacological treatment of schizophrenia include the improvement of symptoms and quality of life, the rehabilitation of patients, and the prevention of relapse and re-hospitalization.

Because of the nature of schizophrenia (which appears to be a combination of thought, mood and anxiety disorders), the medical management of this disorder often requires a combination of antipsychotic, antidepressant and anxiolytic medications. Antipsychotic medications help to normalize the biochemical imbalances that occur in schizophrenia. Many medications are included in the antipsychotic group, and they are commonly divided into two major classes: typical (or first-generation) antipsychotics and atypical (or second-generation) antipsychotics.

1.1.5.1. First-generation antipsychotics (FGAs)

The first-generation or typical antipsychotic medications such as chlorpromazine and haloperidol have been available for schizophrenia treatment since the 1950s. Conventional antipsychotics, previously named neuroleptics, serve as antagonists for major neurotransmitters such as the dopamine receptor family (D_2, D_3 and D_4), muscarinic cholinergic receptors (M_1), α-adrenergic receptors (α_1 and α_2) and histaminic receptors (H_1) (Wilkaitis et al., 2006). The different antipsychotic potencies of FGAs are related to

their affinity for blocking D_2 dopamine receptors or inhibiting dopamine release (Smith et al., 2010). Many typical antipsychotics are available in both oral and intramuscular formulations. They are effective in treating positive symptoms including hallucination and delusion. However, these agents are less efficacious for negative symptoms including anhedonia, avolition and social withdrawal, as well as cognitive symptoms such as memory deficit. The majority of FGAs are metabolized by cytochrome P450 2D6 (CYP2D6) and CYP3A4. Typical antipsychotics are used in schizophrenia, schizoaffective disorder, affective disorder, Tourette's syndrome, nausea, emesis and hiccups. Shortly after chlorpromazine started to be used extensively, clinicians observed parkinsonian signs and symptoms in some treated patients. Neuromuscular central nervous system side effects, such as extrapyramidal symptoms (EPS) and tardive dyskinesia, are common during FGA treatment and happen due to D_2 antagonism in the nigrostriatal dopaminergic pathway (Wilkaitis et al., 2006). EPS are most frequent with high-potency FGAs, such as haloperidol. These movement disorders cause lack of compliance and relapse. The antagonist action of FGAs on dopaminergic, histaminic, adrenergic and muscarinic receptors induces cognitive deficits such as sedation, dizziness and disturbed concentration, and many other undesirable side effects such as drowsiness, weight gain, QTc prolongation, dry mouth, ocular side effects and hyperprolactinemia (Wilkaitis et al., 2006).

1.1.5.2. Second-generation antipsychotics (SGAs)

In contrast to first generation antipsychotic, second-generation antipsychotics (also called atypical antipsychotics) are agents that have been available only since the early 1990s.

Clozapine the first drug approved in this class introduced in 1971 and marketed in the United States of America in 1990. During the 1990s, olanzapine, risperidone and quetiapine were introduced, followed by ziprasidone and aripiprazole in the early 2000s (Hasnain et al., 2009). According to the treatment guidelines, SGAs include drugs such as amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine. In addition to dopamine D_2 receptor blocking, SGAs show broad-spectrum binding to other receptors, including dopamine (D_1, D_3, D_4), norepinephrine (α_1 and α_2), serotonin (5-$HT_{1A, 2A, 2C, 3, 6, 7}$), muscarinic cholinergic (M_1) and histamine receptors (H_1) (Stahl, 2008).

SGAs are characterized as reducing schizophrenic symptoms, while having a lower tendency to cause EPS and tardive dyskinesia than FGAs. They also show a low potency to induce hyperprolactinemia (except for risperidone and amisulpride) (Svestka et al., 2007). Over the past decade, they have become the first-line treatment for schizophrenia due to this more favourable safety profile than FGAs. Furthermore, SGAs raise hopes of superior effects in a number of areas, including improving negative symptoms, compliance, cognitive functioning, movement disorders, depression and quality of life (Leucht et al., 2009a, Leucht et al., 2003a, Rosenheck et al., 2003). Some studies have suggested that some SGAs (clozapine, olanzapine, amisulpride and risperidone) are more efficacious than FGAs (Davis et al., 2003, Leucht et al., 2009b, Leucht et al., 1999, Leucht et al., 2003a). Nevertheless, the lack of significant superiority in efficacy observed in large trials has indicated that the first and second generation antipsychotics are generally similar in terms

of efficacy (Geddes et al., 2000, Jones et al., 2006, Lieberman et al., 2005, Wahlbeck et al., 2001). Clinicians and researches have different opinions about the comparative effectiveness of first- and second-generation antipsychotics (Leucht et al., 1999, Lieberman et al., 2003).

Two reasons have been proposed to explain the differences between typical and atypical antipsychotics. First, atypical antipsychotics have a lower affinity for the dopaminergic receptors and a high degree of occupancy of the 5-HT_{2A} receptors (Meltzer et al., 1989). Meltzer et al. (1989) provided evidence that atypical antipsychotics combine $5HT_{2A/D2}$ antagonistic actions with greater relative potency at the 5-HT_{2A} receptor. Second, atypical antipsychotics have the ability to rapidly dissociate from D_2 receptors (Kapur and Seeman, 2000); therefore, SGAs help patients by transiently occupying D_2 receptors, and then they rapidly dissociate to allow normal dopamine neurotransmission. A lower affinity, a faster dissociation, and a higher off-rate for the D_2 receptors have been proposed as the mechanisms of SGAs (Stahl, 2008).

It is important to mention that problems associated with specific atypical antipsychotic treatments include metabolic effects such as weight gain, lipid dysregulation, hyperglycemia and cardiovascular abnormalities (American Diabetes Association, 2004, Correll et al., 2009). Weight gain and metabolic issues are even greater concerns in the treatment of children and adolescents (Maayan and Correll, 2011).

In section 1.3, we will discuss the mechanism and safety profiles of SGAs in more detail.

1.2. Affective disorders

1.2.1. Clinical description

Mood or affective disorders represent a large and heterogeneous group of clinical syndromes and, along with anxiety disorders, they are the most common psychiatric problems. The DSM-IV (APA, 1994) describes two general classes of affective disorders: *major depression* and *bipolar disorder*. Major depression (unipolar depressive disorder) is characterized by severe depression and by recurring episodes of negative thinking and anhedonia that are also reflected in behaviour. Bipolar disorder (historically known as manic-depressive disorder) is characterized by mood alteration from depression to mania over time. Both of these general classes of affective disorders are described as excessive and inappropriate exaggerations of moods. As mentioned above, affective disorders are among the most common forms of mental illnesses. The estimated incidence of depression varies widely; however, some studies have reported that 15% to 20% of the general population experiences depression at one point during their lifetime. Moreover, according to epidemiological studies, women are twice as likely to develop certain mood disorders, such as major depression. Based on the DSM-IV diagnostic criteria (APA, 1994), the prevalence of bipolar disorder is approximately 0.5% to 1% in the general population. Equal numbers of men and women are diagnosed with bipolar disorder (Yatham and Kusumakar, 2009, Yatham and Malhi, 2011).

1.2.2. Symptoms

During depressive episodes of bipolar disorder, patients feel the essential elements of depression including helplessness, hopelessness, fatigue and lack of interest and energy to do even the fun activities they normally enjoy. In the manic phase, patients are full of energy and more talkative than usual, and they feel incapable of making mistakes (Yatham and Kusumakar, 2009, Yatham and Malhi, 2011).

1.2.3. Etiology

Heredity and environmental stress as well as physiological factors and altered biological rhythms such as cortisol secretion and neurotransmitter levels are known risk factors for affective disorders. Serotonin, dopamine and norepinephrine are the most important neurotransmitters related to mood disorders. Family studies, linkage studies and twin studies have demonstrated the role of genetics in the etiology of both major depression and bipolar disorder. Family studies and neurobiological studies have found a strong association between anxiety and depression (Yatham and Kusumakar, 2009, Yatham and Malhi, 2011).

1.2.4. Diagnosis

A mood disorder is more than the occasional blues or depressive feelings that most people feel sometimes. A mood disorder is actually a manifestation of a mental illness and needs to be correctly diagnosed and treated. Proper diagnosis of clinical depression is the key to its successful treatment. Misdiagnosis or delayed diagnosis has negative consequences such as

inappropriate treatment, increased suicide rate and decreased quality of life for patients. Laboratory tests cannot be used to diagnose affective disorders. All diagnostic tests for mood disorders contain a questionnaire that is able to determine whether or not an individual has a mood disorder (Newman, 2002 , Yatham and Kusumakar, 2009).

1.2.5. Pharmacological treatments

Antidepressants such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), anxiolytic medications, mood-stabilizing drugs (e.g., lithium carbonate) and some SGAs (e.g., olanzapine and quetiapine) have been successfully used for the treatment of affective disorders. Nowadays, the use of atypical antipsychotics in affective disorders is increasing. SGAs are effective at reducing agitation and aggressive behaviour (Citrome, 2002, Zeller and Wilson, 2011). They also improve psychotic signs and behaviour disorders related to bipolar disorder and unipolar depression (Vieta, 2004). The U.S. Food and Drug Administration (FDA) has approved aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone for the treatment of manic and mixed bipolar episodes (Tohen and Vieta, 2009). Two large international, randomized, double-blind, placebo-controlled studies reported that quetiapine monotherapy is effective in bipolar mania (Bowden et al., 2005, McIntyre et al., 2005). In addition, quetiapine has FDA approval for the treatment of acute bipolar depression. Recent studies have revealed that some SGAs may have antidepressant properties (Calabrese et al., 2005, Tohen et al., 2003). Monotherapy and adjunctive therapy with SGAs showed greater efficacy in the

treatment of major depressive disorders than placebos (Chen et al., 2011, Yatham and Malhi, 2011).

1.3. Atypical antipsychotics

As mentioned above, we will discuss the pharmacological and safety properties of the five most commonly used SGAs. A brief description of each medication considered in our meta-analysis is presented here. Because of the chronic nature of the disorder, most individuals diagnosed with schizophrenia require continuous and comprehensive care; therefore, pharmacotherapy with antipsychotic medications is an essential component of a treatment plan for the majority of patients with this illness.

1.3.1. Pharmacological properties of atypical antipsychotics

1.3.1.1. Olanzapine

Olanzapine is a thienobenzodiazepine derivative and is chemically similar to clozapine. Olanzapine has a high affinity for serotonin (5-HT_{2A}, 5-HT_{2C} and 5-HT_6), dopamine ($D_{2\text{-}4}$), histamine (H_1) and α_1-adrenergic receptors. It also has a moderate affinity for muscarinic receptors ($M_{1\text{-}5}$), 5-$HT_{3,7}$, $D_{1,5}$ and α_2-adrenergic receptors. This atypical antipsychotic binds approximately twice as much to 5-HT_{2A} as to D_2 receptors (Bhana and Perry, 2001). Olanzapine treatment is currently available in oral formulations (tablets and orally disintegrating tablets) and intramuscular preparations. Olanzapine is well absorbed after oral administration; mean half-life is 36 hours and the compound is approximately 93%

protein-bound. It is primarily metabolized by the hepatic enzymes CYP1A2 and CYP2D6 (Deeks and Keating, 2008, Schulz et al., 2006). It is prescribed for acute mania (Tohen et al., 2000, Tohen et al., 1999), bipolar depression (Keck, 2005), schizophrenia and bipolar mania (Bhana and Perry, 2001, Frampton, 2010). Dystonic reactions and parkinsonism are uncommon and olanzapine produces fewer treatment-emergent neurological adverse events than haloperidol. Based on olanzapine's higher affinity for 5-HT_{2A} than D_2 receptors, a lower risk of EPS with clinical doses is predictable (Deeks and Keating, 2008). The main problems regarding the safety of this antipsychotic are weight gain and metabolic disturbances including hyperlipidemia and hyperglycemia that can lead to other complications such as diabetes mellitus, cardiovascular diseases (CVD) and metabolic syndrome (Deeks and Keating, 2008, Meyer and Quenzer, 2005, Parsons et al., 2009, Sechter et al., 2002).

1.3.1.2. Quetiapine

Quetiapine is a dibenzothiazine derivative and has a pharmacological profile similar to that of clozapine but with an improved safety profile regarding metabolic side effects. Quetiapine has an antagonist affinity for D_1 and D_2 receptors, serotonin 5-HT_{2A}, α-adrenergic and histamine receptors. It is also a partial agonist for 5-HT_{1A} receptors. Norquetiapine, an active metabolite of quetiapine, is a potent inhibitor of norepinephrine transporter, which may explain quetiapine's antidepressant effects (Cutler et al., 2009, Garakani et al., 2008). Its mean half-life is approximately six hours, which suggests twice-daily dosing. However, in some cases, once-daily dosing is an effective option to improve

medication adherence. Quetiapine is approximately 83% protein-bound. It is metabolized primarily by CYP3A4 and to a much lesser extent by CYP2D6 (Meulien et al., 2010, Potkin et al., 2005, Printz and Lieberman, 2006a).

Quetiapine is an FDA-approved atypical antipsychotic for treatment of schizophrenia, bipolar disorder, major depression and anxiety disorders. With its great range of potential uses, quetiapine is sometimes known as the *aspirin of psychiatry* (Stip, 2009). It has been shown to be effective against a broad range of schizophrenia symptoms, including positive, negative, cognitive and affective symptoms (Arvanitis and Miller, 1997, Emsley and Oosthuizen, 2003, Purdon et al., 2001, Sajatovic et al., 2002, Sax et al., 1998, Small et al., 1997, Velligan et al., 2002).

The most frequently reported adverse events are headache, dizziness and somnolence. Due to its low D_2 affinity compared to 5-HT_{1A} receptors, quetiapine, even at higher doses, is less likely to cause EPS than other antipsychotics used for schizophrenia (Arvanitis and Miller, 1997, Miller et al., 1998). For this reason, this medication is often preferred for treating psychosis or agitation in patients with Parkinson disease (Friedman, 2003). Nevertheless, quetiapine, like all atypical antipsychotics, bears a small yet significant risk of tardive dyskinesia. In the short term, the most common adverse event is somnolence, which generally subsides over time (Arvanitis and Miller, 1997, Miller et al., 1998). During long-term treatment, moderate weight gain and some glucose and lipid changes may occur (Brecher et al., 2007).

1.3.1.3. Risperidone

Risperidone, a benzisoxazole derivative compound, is an effective atypical antipsychotic. This agent has potent antagonist properties for central dopamine D_2 and 5-HT_2 receptors; it also blocks adrenergic receptors (α_1, α_2) and histamine receptors (H_1) (Deeks, 2010, Muller-Siecheneder et al., 1998). It is described as having no affinity for cholinergic receptors. Its half-life may exceed 20 hours. Risperidone and its active metabolite, 9-hydroxyrisperidone, are 90% and 77% plasma-protein-bound. Hydroxylation of the drug occurs primarily via CYP2D6 and CYP3A4 (Deeks, 2010, Goff, 2006).

Risperidone is increasingly being used for a number of different mental disorders, including schizophrenia (Carman et al., 1995, Claus et al., 1992, Deeks, 2010) and bipolar disorders (Bobo and Shelton, 2010, Woo et al., 2010).

Headache and dizziness are common side effects of risperidone treatment. In addition, unlike other atypical antipsychotics, risperidone can induce hyperprolactinemia. Although this agent produces slightly fewer extrapyramidal adverse effects than typical antipsychotics (Leucht et al., 1999), it has been associated with the development of metabolic disorders including obesity, dyslipidemia and diabetes (Lebovitz, 2003, Owenby et al., 2011).

1.3.1.4. Ziprasidone

Ziprasidone, a benzisothiazolylpiperazine, is an atypical antipsychotic agent with a unique chemical structure unrelated to any other SGA. It has a higher affinity for serotonin

($5HT_{2A}$) receptors than for dopamine (D_2) receptors; it also has a low affinity for adrenergic (α_1) and histaminergic (H_1) receptors. In addition, this molecule is a potent antagonist for 5-HT_{2C} and 5-HT_{1D} and a potent agonist for 5-HT_{1A} receptors. Ziprasidone may inhibit serotonin and norepinephrine re-uptake, which may explain its possible antidepressant effects (Keck et al., 2001, Komossa et al., 2009).

Ziprasidone is more than 99% bound to plasma protein and is metabolized by cytochrome P450 CYP3A4 and CYP1A2. Its half-life is seven hours (Daniel et al., 2006). It has been shown to improve schizophrenia symptoms, schizoaffective disorder, bipolar disorders and acute mania. It has a specific safety profile that predicts low liability for EPS and moderate weight gain. The most commonly reported adverse events of ziprasidone treatment are somnolence, insomnia and anxiety. Most of its side effects are dose-related. Weight gain and EPS have been reported as well; however, they are minor compared to other SGAs (Lincoln et al., 2010). The oral absorption of ziprasidone doubles when it is taken with food.

1.3.1.5. Aripiprazole

Aripiprazole, a quinolinone derivative, is an SGA with a mechanism of action that differs pharmacologically from those of other atypical antipsychotics. This agent is a potent partial agonist for dopamine D_2 and serotonin 5-HT_{1A} receptors, with antagonist activity for serotonin 5-HT_{2A}. Aripiprazole is more than 99% bound to plasma protein and is metabolized by CYP2D6 and CYP3A4. Half-lives for aripiprazole and its major metabolite, dehydroaripiprazole, are 75 and 94 hours, respectively. Aripiprazole improves negative and

positive symptoms of schizophrenia. It has also been shown to be effective in acute treatment and relapse prevention for bipolar mania, resistant major depression and anxiety disorders. Aripiprazole has been associated with only minimal EPS and weight gain; in addition, no association with modification of lipid or glucose levels has been reported (McQuade et al., 2004, Printz and Lieberman, 2006b).

1.3.2. Side effects of atypical antipsychotics

1.3.2.1. Metabolic disturbances

The life expectancy of individuals suffering from severe mental disorders is shorter than that of the general population. About 75% of all deaths in mental disorders' patients are related to physical illnesses; CVD is the most common cause of death (Brown et al., 2000). Patients with severe mental diseases are two to three times more at risk for obesity, metabolic syndrome and related morbidity and mortality than the general population (Correll et al., 2010, Holt et al., 2010). The prevalence of metabolic syndrome in patients with serious mental illness is approximately 50% (Holt et al., 2010). Factors that affect patients with severe mental illnesses and contribute to metabolic syndrome and diabetes mellitus include sedentary lifestyle, poor diet, smoking, adverse effects of SGAs and greater vulnerability to certain pathologies such as CVD and diabetes (Chacon et al., 2011).

SGAs are the first-line treatments for certain mental disorders, such as schizophrenia and affective disorders, in many countries. However, not all patients respond to SGAs and some of them remain intolerant of the drugs' side effects. As we have seen, the therapeutic

objectives of the pharmacological treatment of mental disorders include the improvement of syndromes and quality of life, prevention of relapse and re-hospitalization and rehabilitation of patients (McIntyre et al., 2010).

Although SGAs are essential for the treatment of many psychiatric disorders, these medications are significantly associated with metabolic complications (such as obesity, glucose intolerance and dyslipidemia), diabetes mellitus, metabolic syndrome, CVD and premature death. These adverse events have evident impacts on patients' quality of life and physical health; therefore, SGAs' side effects on physical health have become an important issue in the treatment of mental illnesses. The literature reveals that SGAs' liability to induce metabolic disturbances differs, often considerably, from one agent to another (Allison et al., 1999, Haddad, 2005, Newcomer, 2005).

In general, the highest risk of clinically significant weight gain has been reported for clozapine and olanzapine treatment. Treatment with quetiapine, risperidone and sertindole causes moderate weight gain. Amisulpride, ziprasidone and aripiprazole have the lowest risk of triggering weight gain. Based on the different receptor affinities of individual SGAs, it is suggested that these agents induce weight gain by different mechanisms. But, the exact nature of these mechanisms remains elusive. In addition, according to the literature, olanzapine and clozapine increase the risk of diabetes and dyslipidemia. The results for quetiapine and risperidone are controversial and need further inspection. Amisulpride, ziprasidone and aripiprazole do not seem to significantly change glucose levels or lipid

profiles (Haddad and Sharma, 2007, Leucht et al., 1999, Newcomer, 2005, Newcomer and Haupt, 2006).

In addition to its physical health risks, obesity can be embarrassing; it may be a source of distress and increased stress for patients with mental disorders. The reason why some patients show metabolic changes during antipsychotic treatment, while others do not, needs further investigation, but it is probably related to different genetics, diagnoses and lifestyle-related factors in different patients.

Both schizophrenia and affective disorders are complex, polygenic, multi-factorial disorders. Even though bipolar disorder and schizophrenia differ in their neurobiology and phenomenology (McDonald et al., 2004, Muir et al., 2001, Murray et al., 2004), these disorders share some genetic features (Huang et al., 2010, Park et al., 2004, Peerbooms et al., 2010, Purcell et al., 2009). Although the pathophysiology of both disorders remains unclear, in recent years, investigations of the factors that contribute to SGA tolerability profiles in affective disorder and schizophrenia has emerged (De Hert et al., 2011b, Stahl et al., 2009, van Winkel et al., 2008).

It is noteworthy that, as with schizophrenia patients, in many studies the need of screening for metabolic syndrome in patients with bipolar disorder, or at least those who are being treated with SGAs, has been clearly demonstrated (de Almeida et al., 2011, van Winkel et al., 2008). Patients, families and clinicians need to know the differences among these SGA agents and also, whether there are differences related to particular psychiatric disorders. Determining the relative contributions of the antipsychotic treatment, patient

characteristics, unhealthy lifestyle and type of psychiatric illness is still an open, and very pertinent, question.

1.3.2.2. Extrapyramidal side effects and movement disorders

Shortly after the first antipsychotics were prescribed in psychiatry, EPS were identified and reported (Steck, 1954). Acute EPS usually occur some days or even hours after the initiation of treatment. Common extrapyramidal syndromes include parkinsonism, akathisia, acute dystonia and tardive dyskinesia. EPS are important side effects because they can stigmatize patients, impair their quality of life, and lead to poor antipsychotic adherence and relapse (Haddad et al., 2011). Acute EPS have been reported in several studies as a major risk factor for later development of tardive dyskinesia in schizophrenia patients (Muscettola et al., 1999, Tenback et al., 2006). In general, when dopaminergic blockade in the striatum exceeds 75% to 80% of D_2 receptors, antipsychotics cause EPS (Wilkaitis et al., 2006). Drugs with a higher affinity for D_2 receptors lead to higher EPS incidence; for example, haloperidol treatment frequently causes EPS. Meta-analyses show that SGA treatment induces fewer EPS than haloperidol (Komossa et al., 2010, Leucht et al., 2009a, Rummel-Kluge et al., 2010a, Wilkaitis et al., 2006). Although SGAs have a more favourable profile of EPS than some FGAs (Komossa et al., 2010, Leucht et al., 2009a, Rummel-Kluge et al., 2010a, Wilkaitis et al., 2006), studies and meta-analyses have shown that akathisia (Kane et al., 2009) and tardive dyskinesia (Kane, 2004)are also observed after SGA treatment. Differences between individual SGAs' ability to induce EPS have been demonstrated in some studies (Gao et al., 2008, Rummel-Kluge et al., 2010a).

With the increasing prescription of SGAs in psychiatry, it is worth examining the incidence of EPS in different phenotypes of mental disorders. Some studies have reported the same risk of EPS incidence further to SGA treatment in schizophrenia and bipolar disorder patients, while other studies have reported greater vulnerability to movement disorders in bipolar disorder patients (Cavazzoni et al., 2006, Gao et al., 2008, Nasrallah et al., 1988). However, the bipolar diagnosis as a risk factor for antipsychotic-induced EPS is still controversial.

1.4. Meta-analysis method

1.4.1. Definition of meta-analysis

Meta-analysis is a quantitative approach using statistical analysis to combine the outcomes of independent studies addressing a shared research hypothesis, in order to improve the reliability of the results. The validity of this method depends on the quality of the articles included in the meta-analysis. In order to answer a specific research question, individual studies usually report the collection of data from many participants; each participant is, therefore, a separate data-point in individual studies. In a meta-analysis, however, data from different studies that answer a single research question are collected and summarized; each *study* is, then, a separate data-point in the analysis.

Often, many of the individual trials fail to show a statistically significant difference between two treatments under study. However, significant benefits of a treatment may be shown when the results of individual studies are combined using a meta-analysis. It

increases the power of the analysis by using all of the information that is gathered in the systematic review. In addition, the accuracy of estimates of the effect size (treatment effect) increases in a meta-analysis (Borenstein et al., 2010, Borenstein.M, 2009, Sepehry, 2007).

Meta-analysis is a method that is useful for medicinal and social sciences in decision-making, resolving conflicting evidence, answering questions where the answer is doubtful, explaining variability in practice, or simply confirming the suitability of current practice. Byers and Stullenbarger (2003) recognized meta-analysis as a bridge that connects clinical practice to research.

1.4.2. Steps in meta-analysis

In general, five separate steps should be performed in conducting a meta-analysis: problem formulation, literature search, coding, effect size calculation and data analysis and finally interpretation and presentation of results (Borenstein, 2009, Borenstein et al., 2010, Sepehry, 2007).

1.4.2.1 Formulation of the problem and defining the hypothesis

A well-defined statement that theoretically connects the variables under investigation is needed; therefore, we must carefully define the inclusion and exclusion criteria when locating potential studies.

1.4.2.2. Collecting all the available studies that provide data on the relationship

A meta-analysis is only instructive if it adequately summarizes the existing literature, so a thorough literature search is critical to retrieve every relevant study. In order to gather maximum data, several search strategies are valuable: searches of the electronic databases (e.g., PubMed, PsycINFO and EMBASE), hand searching, conference proceedings, cross-referencing and looking for unpublished studies by contacting pharmaceutical companies or searching on the clinicaltrials.gov website. The authors should be contacted to collect further information if one becomes aware of missing data.

1.4.2.3. Inputting data (coding)

Coding is a method of categorizing studies with a set of priori selected criteria. Coding is done to gather empirical findings from primary studies (e.g., treatment duration, sample size, study design, etc.) and input them into a statistical database. In this step, the collaboration of the authors of the primary studies is important to avoid any bias in the study selection.

1.4.2.4. Effect size calculation and data analysis

In this step, the overall effect size is calculated and the impact of moderating variables is analyzed. There are different statistical formulas to calculate effect size and analyze whether study characteristics influence effect sizes and cause heterogeneity.

1.4.2.5. Interpretation and reporting the results

Analyzing the clinical implications, summarizing findings, discussing limitations and making recommendations are the tasks in this step (Borenstein, 2009, Borenstein et al., 2010, Sepehry, 2007).

1.4.3. Comprehensive meta-analysis

Comprehensive Meta-Analysis (CMA) software was developed by a team of experts in meta-analysis. CMA version 2 was used for our meta-analytic approach in comparing SGAs' side effects in schizophrenia and affective disorder patients.

1.5. Research objective

As mentioned above, five SGAs (olanzapine, quetiapine, risperidone, aripiprazole and ziprasidone) are considered in our meta-analysis. The steps below are followed in our study:

1. Examine SGA-induced metabolic side effects in schizophrenia and bipolar disorder groups;
2. Assess SGA-induced extrapyramidal adverse events;
3. Compare the tolerability and safety profiles of atypical antipsychotics, as prescribed for bipolar disorders and schizophrenia;
4. Assess whether moderating factors and studies' characteristics play potential roles in explaining the heterogeneity and differences in the metabolic and extrapyramidal side effects experienced by schizophrenia and affective disorder patients.

2. COMPARING TOLERABILITY OF OLANZAPINE IN SCHIZOPHRENIA AND AFFECTIVE DISORDERS: A META-ANALYSIS

Status: *Drug Safety (In Press)*

Comparing tolerability of olanzapine in schizophrenia and affective disorders: a meta-analysis

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Accord des coauteurs

1) Indentification de l'étudiant et du programme

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2) Description de l'article

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Comparing tolerability of olanzapine in schizophrenia and affective disorders: a meta-analysis

L'article a été soumis à Drug Safety et est accepté avec des révisions mineures.

3) Déclaration des coauteurs

À titre de coauteur de l'article identifié ci-dessus, je suis d'accord pour que Hoda Moteshafi inclue cet article dans son mémoire de maîtrise, qui a pour titre Comparing tolerability profile of second generation antipsychotics in schizophrenia and affective disorders: a meta-analysis.

_____ _____

Simon Zhornitsky Date

_____ _____

Dr. Sarah Brunelle Date

_____ _____

Dr. Emmanuel Stip Date

Abstract

Background: Olanzapine is prescribed for a number of psychiatric disorders including schizophrenia, bipolar mania, and unipolar and bipolar depression. Olanzapine treatment is associated with tolerability issues such as metabolic side effects (e.g. weight gain, increase in blood glucose, triglyceride and total cholesterol levels), extrapyramidal symptoms (e.g. parkinsonism, akathisia, tardive dyskinesia) and sedative side effects. Metabolic issues lead to some long-term consequences which include cardiovascular diseases and type-2 diabetes and these complications cause high rate of mortality and morbidity among patients with severe mental illnesses. The expanded indications of olanzapine in psychiatry suggest a need to investigate whether there is a difference in the incidence and severity of side effects related to category diagnosis. Are the side effects expressed differently according to phenotype? Unfortunately, there are no reported studies that investigated these differences in side effects associated with olanzapine treatment in psychiatric patients with different phenotypes.

Objective: The aim of the present meta-analysis is to separately examine olanzapine-induced cardiometabolic side effects and extrapyramidal symptoms (EPS) in patients with schizophrenia (SCZ) and affective disorders (AD).

Data sources: A search of computerized literature databases PsycINFO (1967-2010), PubMed, EMBASE (1980-2010) and clinicaltrials.gov website for randomized clinical trials was conducted. A manual search of reference lists of published review articles was carried out to gather further data.

Study selection: Randomized controlled trials were included in our study if (i) they assessed olanzapine side effects (metabolic or extrapyramidal) in adult patients with schizophrenia or affective disorders; and (ii) they administered oral olanzapine as monotherapy during study.

Data extraction: Two reviewers independently screened abstracts for choosing articles and one reviewer extracted relevant data on the basis of predetermined exclusion and inclusion criteria. It should be mentioned that for the AD group we could only find articles related to the bipolar disorder (BP).

Data synthesis: Thirty-three studies (4831 patients) that address olanzapine monotherapy treatment of adults with SCZ or BP were included in the analysis. The primary outcomes were metabolic side effects (changes in weight, blood glucose, LDL, total cholesterol and triglyceride levels). The secondary outcomes of our study were assessing the incidence of some extrapyramidal symptoms (parkinsonism, akathisia and use of antiparkinson medication). The tolerability outcomes were calculated separately for SCZ and BP groups and were combined in a meta-analysis. Tolerability outcomes show that olanzapine contributes to weight gain and elevates blood triglyceride, glucose and total cholesterol levels in both SCZ and BP patients. However, olanzapine treatment produced significantly more weight gain in SCZ patients than in BP patients. In addition, increases in blood glucose, total cholesterol and triglyceride levels were higher in the SCZ group compared to the BP group, even though these differences were not statistically significant. Based on our results; the incidence of parkinsonism was significantly higher in the SCZ group than in the

BP group. Subgroup analysis and logistic regression were used to assess the influence of treatment duration, dose, industry sponsorship, age and sex ratio on tolerability outcome.

Conclusions: Our results suggest that SCZ patients may be more vulnerable to olanzapine-induced weight gain. The findings may be explained by considering the fact that in addition to genetic disposition for metabolic syndrome in schizophrenia patients, they have an especially high incidence of lifestyle risk factors for cardiovascular diseases such as poor diet, lack of exercise, stress and smoking. It might be that an antipsychotic induces severity of side effect according to the phenotype.

Keywords: Olanzapine, Schizophrenia, Affective disorders, Bipolar Disorders, Metabolic Syndrome, Extrapyramidal symptoms, Meta-analysis.

2.1. Background

Atypical antipsychotics (second-generation antipsychotics or SGAs) are widely prescribed for the treatment of multiple psychiatric conditions such as schizophrenia, bipolar disorder, major depressive disorder and anxiety disorder.[1] Olanzapine is an atypical antipsychotic that is prescribed for acute mania,[2, 3] bipolar depression,[4] schizophrenia and bipolar mania.[5, 6] It is an antagonist with a moderate to high affinity for the dopamine ($D_{1–5}$), serotonin ($5\text{-}HT_{2A, 2B, 2C, 3, 6}$), histamine ($H_1$), α_1-adrenergic and muscarinic cholinergic ($M_{1–5}$) receptors.[5]

The main problem regarding the safety of antipsychotics, and particularly olanzapine, is weight gain and metabolic risks that lead to other complications such as diabetes mellitus and cardiovascular diseases (CVD).[7] CVD are already recognized as the leading cause of

mortality and morbidity among patients with severe mental illnesses, such as schizophrenia, major depression and bipolar disorders.[8, 9]Risk factors for CVD such as obesity, hypertension, smoking, dyslipidemia, and diabetes are more frequent in schizophrenic and bipolar disorder patients than in the general population;[10, 11] furthermore, SGAs may worsen CVD risk factors.[11-13] Diabetes and CVD can significantly increase the rate of medical morbidity and mortality, affect quality of life and produce additional health care costs.[14, 15]

Extrapyramidal symptoms (EPS) including dystonia, parkinsonism and akathisia, are other common side effects of antipsychotic treatment.[16] Although it is well known that atypical antipsychotics cause fewer EPS compared to typical antipsychotics,[17, 18] studies have shown that EPS, including akathisia[19] and tardive dyskinesia[20] are also observed with some SGAs and a meta-analysis of head-to-head comparisons by Rummel-kluge et al.[21] demonstrated differences between the SGAs in inducing EPS. Several studies have reported that acute EPS development is a major risk factor for later development of tardive dyskinesia in schizophrenia patients.[22, 23] With the increasing use of SGAs in psychiatry, it is worth examining the incidence of EPS in different mental disorders. The presence of bipolar disease as a risk factor for antipsychotic-induced movement disorders is still unconvincing. Although some reports in the literature suggest that bipolar disorder patients are more likely to develop EPS than SCZ patients,[24] the results of the pooled data analysis reported by Cavazzoni et al.[16] showed that these findings may be representative of treatment with haloperidol, but not necessarily of olanzapine treatment.

Although the pathophysiology of both disorders remains unclear, in recent years, the investigation of the factors which contribute to the different SGAs tolerability profiles between SCZ and BP has just begun.[25, 26] Given that SGAs are prescribed for different diagnoses, it would be interesting to see whether the side effects have a different expression according to phenotype.

Some authors indicate possible inherent genetic vulnerability to metabolic irregularity in schizophrenia patients,[27-29] although some other studies are not in line with this suggestion.[30, 31] Results from a comprehensive, naturalistic screening program[26] showed that the prevalence of the metabolic syndrome in schizoaffective patients was higher compared to schizophrenia and bipolar disorders patients. They suggest a possible increased inherent genetic vulnerability to metabolic syndrome in schizoaffective patients. Unadjusted odds ratio for metabolic syndrome did not statistically differ between bipolar disorder and schizophrenia patients in their study; however, the differences were statistically significant after adjustment.

If there is a difference, it could mean that a phenotype *per se* influences a medication's safety and tolerability. What might be the biological mechanism involved in these differences? What could we learn about a disease if there is such a difference? Schizophrenia is a polygenic and multi-factorial complex disorder in which a myriad of different genes are potentially involved. The phenotypic expression of the disease in conjunction with epigenetic and environmental phenomena needs to be better understood.

Bipolar disorders are also heterogeneous and share some genetic features with schizophrenia.[26, 32-34]

The objective of this research was to compare the tolerability and safety profiles of olanzapine as prescribed for bipolar disorders and schizophrenia. To the best of our knowledge, no meta-analysis has previously compared the metabolic and extrapyramidal side effects of olanzapine for different mental diseases. We therefore conducted a meta-analysis of studies in order to compare olanzapine side effects in patients with schizophrenia and bipolar disorders. We hypothesized that phenotype of disease may affect induction and severity of olanzapine side effects. With the increasing use of SGAs in psychiatry, this investigation is valuable not only to inform clinicians but also to provide clues to the pathophysiology of schizophrenia and bipolar disorders.

2.2. Methods

2.2.1. Data sources and search strategy

A systematic review of the literature on olanzapine for the treatment of schizophrenia (SCZ) and affective disorders (AD) that reported randomized controlled trials (RCTs) was performed. The keywords used for the search were *olanzapine, atypical antipsychotics* and *schizophrenia* or *bipolar disorder, bipolar depression, manic disorder, bipolar affective disorder, bipolar mania, major depression* and *unipolar disorder.* The search engines were PsycINFO (1967–2010), PubMed (MEDLINE), EMBASE (1980–2010) and

clinicaltrials.gov website. There were no limitations on language. A hand search of published review articles, as well as cross-referencing, was carried out to gather further data. Authors of the studies that met inclusion criteria were contacted to provide the unreported data. Two reporters independently checked all reports for inclusion and exclusion criteria.

2.2.1.1. Inclusion criteria

Studied were searched and divided into two groups: schizophrenia and bipolar disorder. Inclusion criteria were studies that contained (1) adult patients (18–65 years old) which had a diagnosis of schizophrenia or affective disorders; (2) randomized controlled trials, open-label or double-blind; (3) oral monotherapy treatment of olanzapine; (4) fixed- and flexible-dose studies with a duration of three weeks or longer; and (5) reported data on metabolic or extrapyramidal side effects with olanzapine treatment.

2.2.1.2. Exclusion criteria

Trials in both groups were left out if they contained (1) combination therapy of olanzapine with another agent such as an anti-manic, antidepressant or other antipsychotic medication; (2) psychotic diagnosis other than schizophrenia such as schizoaffective or schizophreniform disorders; (3) incomplete or unavailable data; (4) study groups of children or adolescents; (5) non-randomized methods; or (6) treatment with olanzapine depot injection (because no related study was found in the BP group).

2.2.2. Data extractions and outcome parameters

Two reviewers (H.M and E.S) independently checked abstracts for each diagnostic group and chose related articles, then one reviewer (H.M) extracted data to ensure that they met the inclusion criteria. Trial abstracts were screened initially, and then in the second step full texts were reviewed. Data and articles from the schizophrenia and bipolar disorders group were analyzed separately to compare the results of the two groups. The data extractions were separated along two dimensions: (a) clinically important metabolic side effects including change in weight, glucose, LDL, HDL, triglyceride and total cholesterol levels were separately assessed in each group. Weight change was reported as the change in kilograms from baseline to endpoint; the changes in other metabolic parameters were defined as the change in mg/dl from baseline to endpoint. (b) some EPS-related adverse events were chosen as second outcome. Outcome variables were the incidence of some EPS-related side effects (e.g. parkinsonism, antiparkinson medication use and akathisia), as measured by treatment-emergent adverse event data.

2.2.3. Meta-analytic calculations

Continuous outcomes were analyzed by estimating means and confidence intervals for each group of subjects: SCZ and AD. Using Comprehensive Meta-Analysis (CMA),[35] effect size estimates for continuous outcomes were calculated from the mean, standard deviation and sample size for each group of subjects. The moderator was diagnostic type (DT), which varied between studies. Dichotomous outcomes (incidence of akathisia, parkinsonism and

use of antiparkinson medication) were estimated based on events and sample size for each group of patients (SCZ and AD) and reported as event rates. Then, we compared the point estimates of each group to see whether the difference between the points was significant or not. The level of significance for the effect size estimates was set at p=0.05. For all analyses, effect size estimates were pooled with the random-effects model, which is more strict than fixed-effects model and permits population-level inferences as well.[36] We examined the heterogeneity of study with the I-squared statistic, supposing that I^2 statistics greater than 50% proposed considerable heterogeneity. Level of significance was set at $p<0.1$.

2.2.3.1. Sub-analyses and addressing potential confounding factors

Sub-analyses, including between-group differences, were carried out for potential confounding factors in age, sex ratio and daily dose. The effects of treatment duration on the results were examined by performing subgroup analyses including short-term (12≤ weeks) and longer term studies, separately. To analyze pharmaceutical company sponsorship effects, a subgroup analysis was done as well. Logistic regression analyses were used to determine association of sex ratio with the tolerability outcome.

2.3. Results

2.3.1. Study characteristics

The search strategy identified 688 articles which were related to the schizophrenia group and 255 articles were found for the affective disorders group. Among these, 910 were

discarded according to the following criteria: (1) duplicating: 317 studies, (2) type of article/study (e.g., case study, review, letter to the editor and crossover study): 313 studies; (3) type of population (e.g., non randomized, nonschizophrenia patients, age range): 108 studies; (4) treatment type (e.g., combination therapy or depot olanzapine injection): 73 studies; (5) incomplete or unavailable data: 99 studies. As a result, 33 studies[3, 37-68] (n=4831) were accepted for both groups: for SCZ patients N=19, n=2389[1] and for AD group N=14, n=2442. It should be mentioned that for the AD group we could only find articles related to the bipolar disorder (BP); we could not find related studies on other affective disorders, considering our inclusion criteria. More information on the sorting process in each group is shown in figure 1. In addition, Table 1 provides details of demographic characteristics among studies included in the meta-analysis.

2.3.2. Outcome results

2.3.2.1. First outcome measure: metabolic changes

(a) Weight gain

Thirty-one studies (n=4488), 18 for the SCZ (n=2196) and 13 for the BP group (n=2292), were accepted and checked for changes in weight (kg) in the sample. Analysis revealed an increase in weight in both groups; however, the SCZ group showed significantly more weight gain than the BP group (3.13 kg vs. 2.27 kg, respectively; p=0.020). Details are shown in Figure 2.

[1] "N" refers to the number of articles whereas "n" is the number of patients.

(b) Cholesterol change

Thirteen studies (n= 2723), six for the SCZ (n=1011) and seven for the BP group (n=1712), were examined for changes in blood cholesterol levels (mg/dl). Even though the increase from baseline is clear in both groups, there was no statistically significant difference between the two groups (11.7 mg/dl in SCZ group vs. 9.9 mg/dl for BP group; p=0.771) (Figure 3).

(c) Glucose change

Fifteen studies (n=2825), seven for the SCZ (n=1105) and eight for the BP group (n=1720), were compared for changes in blood glucose levels (mg/dl). In spite of the fact that olanzapine changed the levels of glucose in both groups, the difference was not statistically significant between SCZ and BP groups (5.6 vs. 2.02 mg/dl, respectively; p=0.116) (Figure 4).

(d) Triglycerides change

Six studies (n=1165), two for the SCZ (n=551) and four for the BP group (n=614), were evaluated for changes in blood triglyceride levels (mg/dl). There was no statistically significant difference between the two groups (38.2 vs. 26.1 mg/dl, respectively; p=0.064), although the levels of triglycerides changed after taking olanzapine for both groups (Figure 5).

(e) LDL and HDL change

We could not find enough studies to compare LDL and HDL changes between the two groups.

2.3.2.2. Second outcome measure: extrapyramidal side effects

EPS-related adverse event rates and their intensity were low in both groups; however, there were some significant differences in the frequency of parkinsonism between the two groups.

(a) Incidence of akathisia

The akathisia event rate did not differ significantly between the groups. Based on eight articles included in the BP group (n=1575), the event rate was 6.3%; according to eleven articles in the SCZ group (n=1475), the incidence of akathisia was 7.8% (p=0.468) (Figure 6).

(b) Incidence of parkinsonism

The incidence of parkinsonism was significantly higher in the SCZ group. Based on seven articles included in the BP group (n=1460), the event rate was 3.1%; in six articles in the SCZ group (n=884), the incidence of parkinsonism was 13.9% (p=0.005) (Figure 7).

(c) Antiparkinson medication use

Antiparkinson medication use did not differ significantly between two groups. According to four articles included in the BP group (n=926), the event rate was 6.7%; in eight articles in the SCZ group (n=1099), the use of such medication was 13.7% (p=0.184) (Figure 8).

2.3.2.3. Heterogeneity

Heterogeneity of all outcomes (metabolic and extrapyramidal) were explored by I^2 statistic; they were all heterogeneous (I^2>50%). Sub-analyses were assessed to determine possible sources of heterogeneity in results.

2.3.3. Sub-analyses

2.3.3.1. Age

All studies reported mean age and standard deviation (SD) of participants. No significant difference was observed between the two groups: 38.9(11) and 39.7(11.9) years for studies in SCZ and BP groups, respectively. See Table 1 for more information on demographic characteristics among studies included in the meta-analysis.

2.3.3.2. Sex ratio

Sex ratio was also reported in all studies. Significantly more males participated in SCZ group studies compared to BP groups; male percentage in SCZ group: N=2389; 1612 (67%) was compared to male ratio in BP group: N=2442; 1135 (46%); p=0.000.

Considering the significant difference in sex ratio between SCZ and BP patients' groups, this variable was included in the statistical analysis as a regressor. For this meta-regression on weight gain and parkinsonism incidence, we found that in the SCZ patients' group, weight gain and parkinsonism incidence were inversely related to male ratio. As weight gain and parkinsonism incidence were significantly higher in SCZ, and male percentage was also higher in this group, outcome differences between the two groups seem not related to sex ratio.

2.3.3.3. Dose

Based on eight studies in BP and eight in SCZ groups which specified mean daily dose, no difference was observed between the two groups: SCZ group 14.6(4.9) mg/day and BP group 13.5(5) mg/day.

2.3.3.4. Company sponsorship

The studies were stratified based on industry sponsorship. By considering only the studies with industry sponsorship, 14 studies were found in the BP group and 13 in SCZ group. By running meta-analyses between the stratified BP and SCZ groups, outcomes remained the same as the main analysis for levels of blood total cholesterol levels and weight gain, and the incidence of akathisia and antiparkinson medication use. In addition, we observed significantly higher glucose levels in the SCZ group compared with the BP group (7.5 mg/dl vs. 2.6 mg/dl, respectively; p=0.01). It should be mentioned that we could not find non-sponsored studies for the BP group.

2.3.3.5. Treatment duration

We stratified the studies based on treatment duration. Short-term studies (between 3 and 12 weeks) displayed that the results of primary and secondary outcomes remained the same as the main analysis for levels of total cholesterol and glucose, and the incidence of akathisia, antiparkinson medication use and parkinsonism. The results for weight gain were, however, different. Nineteen studies, eleven for the BP (n=2231) and eight for the SCZ group (n=262), in which weight changes have been reported for short-term treatment, were

compared together. Even though weight gain was higher in the SCZ group, this difference was no longer statistically significant (2.18 vs. 2.94 kg, respectively; p=0.226). For studies more than 12 weeks, we did not have enough data in the BP group.

2.4. Discussion

Metabolic syndrome is a significant public health problem in patients with mental illnesses and particularly schizophrenia. Recently, atypical antipsychotic agents have been linked to several forms of morbidity, including obesity, hyperlipidemia and type-2 diabetes mellitus, which predict metabolic syndrome, cardiovascular morbidity and malignancy.[67, 69, 70] The mechanisms responsible for an association between schizophrenia, antipsychotic treatment and metabolic syndrome still remain unclear.[71]

The aim of our meta-analysis was to investigate the difference between olanzapine side effects in schizophrenia and bipolar disorder patients. To our knowledge, this is the first meta-analysis comparing SCZ and BP patients with regard to metabolic and extrapyramidal side effects of olanzapine in randomized controlled trials. Based on the different phenotypes of these mental illnesses and the frequent use of SGAs to treat them, studying the degree of sensitivity and tolerability to SGAs in BP and SCZ patients seems essential. Our results revealed that all metabolic parameters increased from baseline for both groups. Furthermore, these changes were statistically significant for mean weight gain in the SCZ group compared to the BP group.

As many studies indicate, SGA medications associate with weight gain, and our findings are consistent in this regard. In a meta-analysis comparing all SGAs head to head,

significantly higher weight gain was seen with clozapine and olanzapine treatment compared to other antipsychotics.[11] These results are generally similar to the findings of a systematic review reporting metabolic adverse effects among different SGAs in children and adolescents, showing that olanzapine was the most likely to lead to weight gain.[72] Another randomized comparative study[73] also reported that olanzapine produced more weight gain and glucose level increase compared to amisulpride during a 6-month trial. The mechanism of olanzapine-induced weight gain remains obscure at present; however, several factors could account for it, such as a high affinity of this medication to histamine-H_1, serotonin 5-HT_{2c} and M_1 muscarinic cholinergic receptors.[56, 74-77] Olanzapine's high affinity to these receptors is associated with appetite changes, increased food intake and sedation. Genetic data also propose a role of leptin receptor activity, G-protein signaling, cannabinoid receptor activity and promelanin-concentrating hormone signaling in the SGAs' weight gain.[78, 79]

We also examined the mean changes in lipid profile and glucose level in both patients' groups. Our meta-analysis showed increases in the mean levels of blood glucose, total cholesterol and triglycerides in both groups. The metabolic changes are higher in the SCZ group compared to the BP group; however, the differences between these groups were not statistically significant.

Even though the mechanism for olanzapine's effect on glucose level and insulin resistance is poorly understood, there is some indication that the long-term use of olanzapine may decrease insulin secretion, which may lead to hyperglycemia.[80] A

proposed mechanism for hyperglycemia is related to the drug's affinity for the H_1, M_3 and 5-HT_{2C} receptors, which is correlated with an increased risk of diabetes.[81] Another possible mechanism for the increase of insulin resistance with olanzapine treatment could be by impairing the ability of insulin to stimulate glucose uptake into peripheral tissues such as skeletal muscle and adipose tissue. There is recent evidence indicating that polymorphism in 5-HT_{2A} and 5-HT_{2C} receptor coding genes, HTR2A and HTR2C, seems to be associated with development of metabolic abnormalities such as C-peptide and insulin elevation during olanzapine and clozapine treatment.[82-84]

Some SGAs are associated with dyslipidemia, including increased levels of LDL, total cholesterol and triglycerides, which can result in CVD.[85] At present, the exact mechanism underlying changes in lipids due to certain SGA treatments is unknown. Several hypotheses have been proposed regarding biological factors such as weight gain, dietary changes and the development of glucose intolerance to explain the high frequency of dyslipidemia with specific antipsychotic medications. [86, 87]

Albaugh et al.[88] recently proposed an interesting mechanism to explain why olanzapine contributes to metabolic side effects leading to obesity and diabetes. In their animal model, they indicated that chronic administration of olanzapine has at least five effects on predisposing male rats to increased adiposity. These effects are decreased physical activity, impaired glucose and insulin tolerance, increased tendency to ^{14}C-2-deoxyglucose and free fatty acid (FFA) uptake into fat depots, increased adipose tissue lipogenesis and impaired lipolysis. Recently, results of a 3-months prospective open label

study showed a significant decline in adiponectin levels, an adipocytes-derived hormone that increases insulin sensitivity, for olanzapine-treated patients compared to risperidone-treated patients.[89] The observed reduction in plasma adiponectin levels in olanzapine-treated patients may suggest a direct effect of olanzapine on the adipose tissue and explain partially the increased metabolic risk in these patients.

As our second outcome, we examined extrapyramidal symptoms related to olanzapine treatment between schizophrenia patients and those with bipolar disorder. Most published placebo-controlled studies show that the rate of akathisia is similar for olanzapine and placebo in both schizophrenia and bipolar disorder,[19] which is consistent with our results. The difference found between the two groups of patients for the incidence of akathisia was not significant. Our results revealed that even with the low incidence of parkinsonism in patients treated with olanzapine, parkinsonism was observed significantly more often in the SCZ group compared to the BP group. The use of antiparkinson medication was also checked and it was higher in the SCZ group; however, this difference was not significant.

Cavazzoni and his research group compared olanzapine-induced extrapyramidal symptoms in bipolar mania and SCZ patients in a pooled analysis.[16] They indicated the same results as us, namely that parkinsonism incidence in SCZ patients was higher than in bipolar patients; however, the use of antiparkinson medication was similar for both groups.

The reduced incidence of EPS during treatment with atypical antipsychotic agents is thought to happen because of their unique receptor-binding profiles.[90] In a review by Gao

et al.[91] it is mentioned that olanzapine did not produce more akathisia, parkinsonism or use of antiparkinson medication in bipolar groups compared to SCZ groups.

As expected, effect size estimates were heterogeneous across studies. A secondary objective was, therefore, established to identify the factors contributing to this heterogeneity. Because of concerns that socio-demographic characteristics among different studies included in our meta-analysis might have influences on our results and cause heterogeneity, we conducted logistic regression assessing the effect of various baseline characteristics (sex ratio, age, daily dose and industry sponsorship) on weight gain and parkinsonism incidence. In the BP patients' group, none of these baseline variables had any noticeable effect on parkinsonism incidence. In the SCZ group, however, parkinsonism incidence and weight gain showed a reversed dependency on the male ratio, by using a meta-regression. As weight gain and parkinsonism incidence were significantly higher in SCZ, and male percentage was also higher in this group, outcome differences between the two groups still remain significant.

As mentioned earlier, we also stratified the studies based on treatment duration. Short-term studies displayed that parkinsonism incidence was significantly higher in the SCZ group. Weight gain level was also higher in the SCZ patients; however, this difference was no longer statistically significant. For studies more than 12 weeks, data unavailability in the BP group prevented us from performing the same analysis. Conducting studies on long-term safety of antipsychotics drugs should be considered a priority in psychopharmacology,

as treatment with antipsychotics is often continued for a long period of time or even for the patients' whole life.

Taken together, these results do not suggest that population differences in sex ratio, age and daily dose significantly influenced our results. Furthermore, as no non-sponsored study was available for the BP group, we could not assess the industry-sponsorship effects in it; however, by comparing the industry-sponsored studies between the two groups of patients, weight gain, glucose level and parkinsonism incidence were significantly higher in the SCZ group. Treatment duration was also considered and discussed above. The remaining heterogeneity of effect size estimates across studies, even after performing numerous sub-analyses, raises the possibility that factors such as life style and disease phenotype in our comparison groups may contribute to these results.

Some limitations affect this meta-analysis which may confound our results and determine the necessity to interpret the current results with caution. In particular, relatively few studies were available for direct comparison of SGAs side effects among BP vs. SCZ patients; therefore, we obtained data from articles focusing on either SCZ or BP patients and then compared the results of both groups. In addition, in our comparison there was no placebo control group, which may restrict the interpretation of our results. To cope with this limitation, prospective controlled trials are required specifically to determine a possible relationship between psychiatric diagnosis and olanzapine-induced side effects. Second, due to the retrospective nature of this analysis, information on severity of psychiatric illness could not be considered in this analysis. Another limitation of this meta-analysis is

unavailability of data for depot administration of olanzapine in the BP group; in our study only oral monotherapy with olanzapine is included. Finally, we did not examine the impact of previous exposure to antipsychotic treatment, race/ethnicity and initial weight in both groups, which may impact the generalizability of our findings. These variables should be more deeply considered in future studies.

In conclusion, side effects are important to consider for prescribers because the efficacy of treatment may be reduced due to the presence of certain side effects. The results of our meta-analysis suggest that schizophrenia patients may be more vulnerable to olanzapine-induced weight gain. This meta-analysis proposes that factors such as life style and disease phenotype may contribute to this susceptibility in SCZ group. Patients with severe mental illnesses need to be informed of the different side effects induced by olanzapine treatment and they should be monitored regularly, especially for metabolic issues. In several domains, we can only conclude, based on our findings, that metabolic side effects are lower in the BP group compared to the SCZ group. However, it is unclear what that means for a patient and how it would change our follow-up.

It is also important to consider that BP patients are more prone to receive polypharmacy (a combination of mood stabilizers, antidepressants and antipsychotics) compared to SCZ patients. Therefore, clinicians should take into account the risk of metabolic side effects associated with antipsychotic drugs (which is confirmed in our meta-analysis) when prescribing atypical antipsychotics for BP patients. In a recent review, Taylor et al.[92] emphasized the necessity of respecting guidelines for screening and

monitoring metabolic side effects in patients with severe mental illnesses, since physical health problems are one of the most common causes of premature death in people with chronic mental illnesses.

Compared with the general population, people with schizophrenia and bipolar disorder have an increased risk of obesity.[79] Our results, consistent with other studies,[13, 93] indicate that weight gain and increase in blood glucose, total cholesterol and triglyceride levels are also present in BP patients' group with olanzapine treatment. Our study supports the recommendation of regular screening and accurate monitoring of these patients. Furthermore, appropriate psychoeducation on lifestyle modification programs including weight control, healthy diet and increased physical activity are important to prevent and treat the metabolic syndrome and CVD in patients with severe mental disorders.

As mentioned previously in a review article, structural and functional variations in the genome cause proteomic and metabolomic imperfections associated with the disease phenotype. [94] Genetic polymorphism may be an important factor that contributes to the difference in metabolic side effects of SGAs between SCZ and AD patients. In addition to a genetic predisposition for metabolic syndromes among schizophrenic patients, lifestyle risk factors such as stress, poor diet, lack of exercise and smoking are common in schizophrenic patients.[82, 95]

In order to achieve a mature discipline of pharmacogenomics of schizophrenia and bipolar disorder it would be relevant to promote the education of prescribers and the public for the use of genomic screening in clinical practice; pharmacogenomic protocols need to

be validated according to drug category and phenotype in order to optimize efficiency. Obviously, these findings need further investigation and the variable confounders are still to be clarified.

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Table legends

Table 1 Demographic characteristics among bipolar and schizophrenia studies included in the meta-analysis

Tables

Table 1

Diagnostic type/Study	Age (mean± SD),y	Dose(mean± SD),mg/day	Treatment duration, w	Male/Female, N
Bipolar Disorder				
McIntyre et al. Dec. 2009	39.6±11.9	5-20	12	135/94
Tohen et al. 2006	41.4±12.1	11.8±7.5	12	87/138
Tohen et al. 2008	39.5±11.9	11.4±2.49	3	99/116
Tohen et al. Nov. 2003	42.2±12.5	9.7	8	141/229
Tohen et al. 1999	39.5±11	14.9±5	3	35/35
Tohen et al. 2000	38.3±10.7	16.4±4.2	4	27/28
Sanger et al. 2003	39.1±10.9	5-20	3	10/9
Tohen et al. 2009	39.5±10.9	5-20	48	29/47
McIntyre et al. Nov. 2009	40.1±11.3	15.8±2.3	3	114/76
McIntyre et al. April 2010	38.4±10.4	15.9±2.5	3	117/88
McIntyre et al. Nov. 2010	38.7±12.4	15.7±4.1	40	68/39

Tohen et al. Dec 2003	41±13	11.4±5.3	12	86/148
NCT00510146*	35.93±11.13	5-20	6	138/205
NCT00129220*	43.12±12	5-20	6	49/55
Schizophrenia				
McQuade et al. 2004	38.2±11	16.5	26	115/46
Kane et al. 2009	38.3±10.5	16.7	28	194/87
Wu et al. 2006	34.2±10.3	10–20	6	25/11
Bhowmick et al. 2010	31.4±7.7	10-20	12	20/18
Saddichha et al. 2007	26.7±6.4	17±5	8	94/46
Beasley et al. 1996	38±9.3	10	8	16/19
Riedel et al. 2007	34.47±11.6	15.82±5.44	8	11/6
Chan et al. 2010	40.8±11.5	11.72±4.87	8	14/10
Lieberman et al. 2005	40.8±10.8	20.1	72	244/92
Sirota et al. 2006	36.2±10.9	16±3.3	11	17/4
Dollfus et al. 2005	39±9	5–15	6	11/18
Bitter et al. 2004	37.6±9.3	17.2±4.8	18	46/30
Breier et al. 2005	40.1±11.6	15.27±4.52	28	180/97
Alvarez et al. 2006	37±10.6	12.2±5.8	52	85/39
Lecrubier et al. 2006	37.25±10.75	5, 20	24	37/13
Vanelle et al. 2006	36.5±8	11.4±2.8	8	23/17
NCT00320489*	40.12±10.84	5-20	104	177/83
NCT00645099*	37.5±11.4	10-15	24	133/87
NCT00145496*	42.8±11.27	5-20	24	170/54

*Unpublished studies

Figure legends

Figure 1 Flow Diagram Describing the Search Process (Quality of Reporting of Meta-analysis (QUOROM)

Figure 2 Forest plot of the effect size estimates of weight changes (kg) in schizophrenia compared to bipolar disorder patients (p=0.020). CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder.

Figure 3 Forest plot of the effect size estimates of cholesterol changes (mg/dl) in schizophrenia compared to bipolar disorder patients (p=0.771). CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figure 4 Forest plot of the effect size estimates of glucose changes (mg/dl) in schizophrenia compared to bipolar disorder patients (p=0.116). CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figure 5 Forest plot of the effect size estimates of triglycerides changes (mg/dl) in schizophrenia compared to bipolar disorder patients (p=0.064). CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figure 6 Forest plot of the effect size estimates of akathisia incidence in schizophrenia compared to bipolar disorder patients (p=0.468). CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figure 7 Forest plot of the effect size estimates of parkinsonism incidence in schizophrenia compared to bipolar disorder patients (p=0.005). CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figure 8 Forest plot of the effect size estimates of antiparkinson medication use in schizophrenia compared to bipolar disorder patients (p=0.184). CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figures

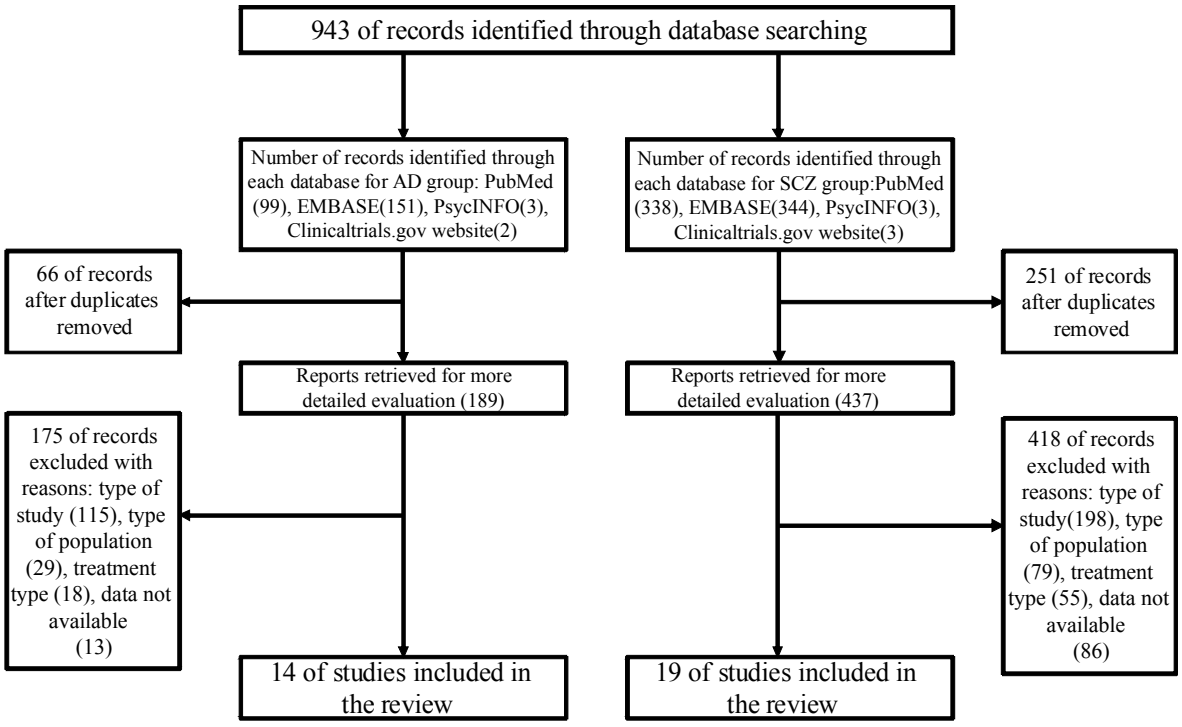

Figure 1

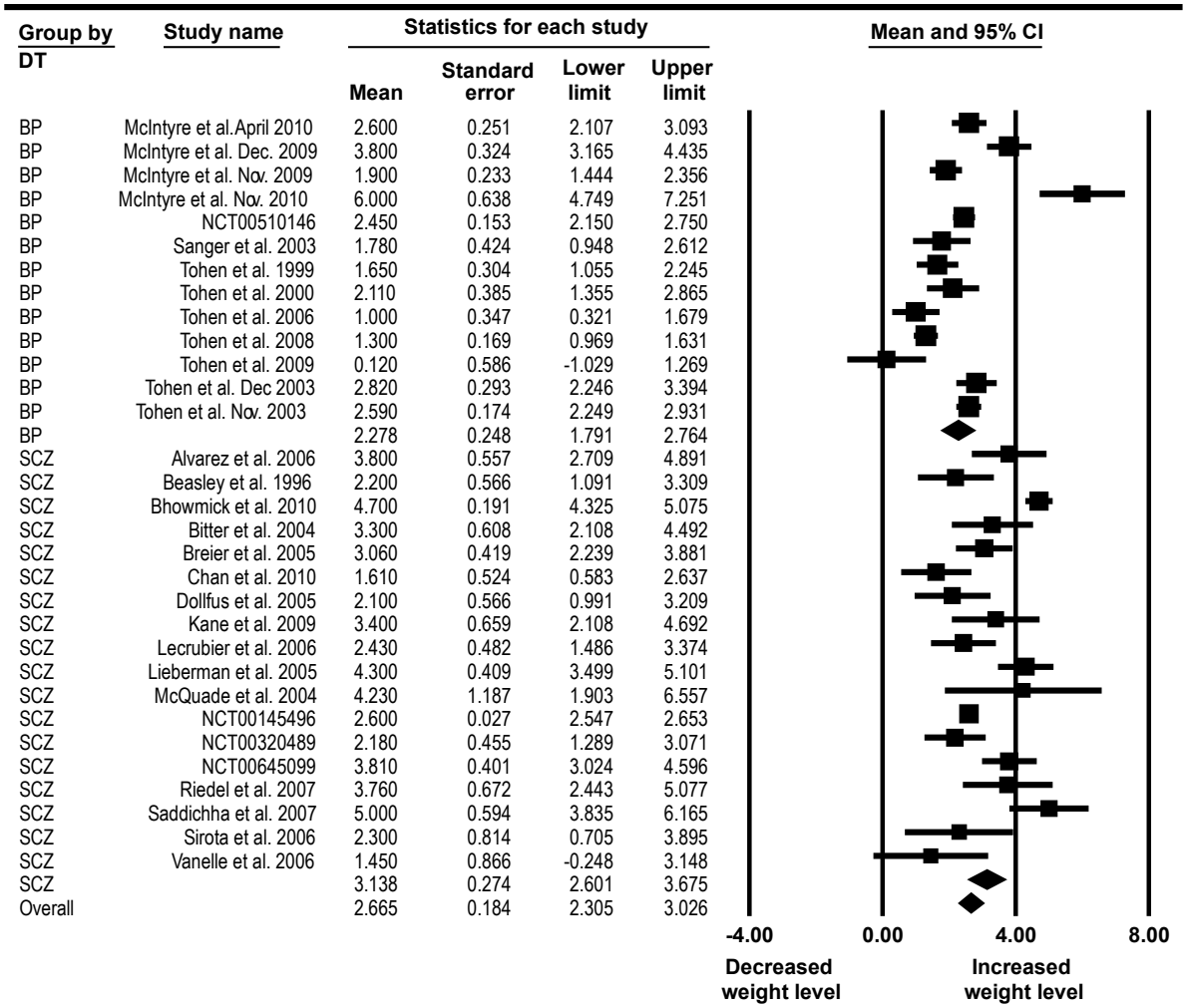
Group by DT
Study name
Statistics for each study
Mean
Standard error
Lower limit
Upper limit
Mean and 95% CI
BP McIntyre et al.April 2010 2.600 0.251 2.107 3.093
BP McIntyre et al. Dec. 2009 3.800 0.324 3.165 4.435
BP McIntyre et al. Nov. 2009 1.900 0.233 1.444 2.356
BP McIntyre et al. Nov. 2010 6.000 0.638 4.749 7.251
BP NCT00510146 2.450 0.153 2.150 2.750
BP Sanger et al. 2003 1.780 0.424 0.948 2.612
BP Tohen et al. 1999 1.650 0.304 1.055 2.245
BP Tohen et al. 2000 2.110 0.385 1.355 2.865
BP Tohen et al. 2006 1.000 0.347 0.321 1.679
BP Tohen et al. 2008 1.300 0.169 0.969 1.631
BP Tohen et al. 2009 0.120 0.586 -1.029 1.269
BP Tohen et al. Dec 2003 2.820 0.293 2.246 3.394
BP Tohen et al. Nov. 2003 2.590 0.174 2.249 2.931
BP 2.278 0.248 1.791 2.764
SCZ Alvarez et al. 2006 3.800 0.557 2.709 4.891
SCZ Beasley et al. 1996 2.200 0.566 1.091 3.309
SCZ Bhowmick et al. 2010 4.700 0.191 4.325 5.075
SCZ Bitter et al. 2004 3.300 0.608 2.108 4.492
SCZ Breier et al. 2005 3.060 0.419 2.239 3.881
SCZ Chan et al. 2010 1.610 0.524 0.583 2.637
SCZ Dollfus et al. 2005 2.100 0.566 0.991 3.209
SCZ Kane et al. 2009 3.400 0.659 2.108 4.692
SCZ Lecrubier et al. 2006 2.430 0.482 1.486 3.374
SCZ Lieberman et al. 2005 4.300 0.409 3.499 5.101
SCZ McQuade et al. 2004 4.230 1.187 1.903 6.557
SCZ NCT00145496 2.600 0.027 2.547 2.653
SCZ NCT00320489 2.180 0.455 1.289 3.071
SCZ NCT00645099 3.810 0.401 3.024 4.596
SCZ Riedel et al. 2007 3.760 0.672 2.443 5.077
SCZ Saddichha et al. 2007 5.000 0.594 3.835 6.165
SCZ Sirota et al. 2006 2.300 0.814 0.705 3.895
SCZ Vanelle et al. 2006 1.450 0.866 -0.248 3.148
SCZ 3.138 0.274 2.601 3.675
Overall 2.665 0.184 2.305 3.026
-4.00
0.00
4.00
8.00
Decreased weight level
Increased weight level

Figure 2

Group by DT	Study name	Mean	Standard error	Lower limit	Upper limit
BP	McIntyre et al.April 2010	13.900	2.403	9.191	18.609
BP	McIntyre et al. Dec 2009	12.400	2.273	7.945	16.855
BP	McIntyre et al. Nov 2009	11.400	2.364	6.767	16.033
BP	NCT00510146	9.360	1.634	6.157	12.563
BP	Tohen et al. 2008	3.900	1.950	0.078	7.722
BP	Tohen et al. Dec 2003	14.000	2.141	9.804	18.196
BP	Tohen et al. Nov 2003	6.000	1.664	2.738	9.262
BP		9.944	1.487	7.028	12.859
SCZ	Breier et al. 2005	3.120	2.527	-1.832	8.072
SCZ	Kane et al. 2009	4.100	2.955	-1.692	9.892
SCZ	Lieberman 2005	9.700	2.100	5.583	13.817
SCZ	McQuade et al. 2004	16.300	3.473	9.494	23.106
SCZ	Vanelle et al. 2006	6.187	7.458	-8.431	20.805
SCZ	Wu et al. 2006	29.250	1.115	27.066	31.434
SCZ		11.695	5.822	0.284	23.107
Overall		10.051	1.441	7.226	12.876

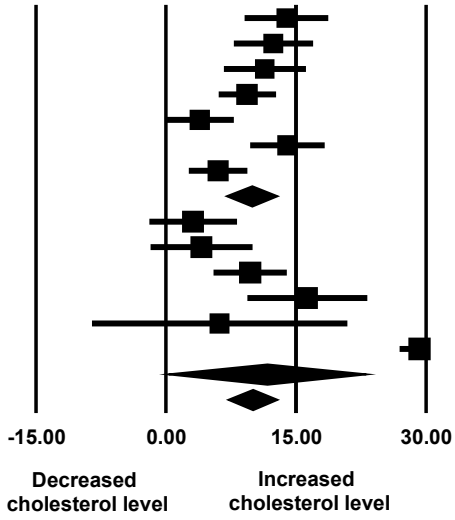

Figure 3

Group by DT	Study name	Mean	Standard error	Lower limit	Upper limit
BP	McIntyre et al. April 2010	2.300	1.048	0.247	4.353
BP	McIntyre et al. Dec 2009	3.100	1.216	0.717	5.483
BP	McIntyre et al. Nov 2009	-0.400	2.080	-4.477	3.677
BP	NCT00510146	1.800	0.614	0.597	3.003
BP	Sanger et al 2003	-1.440	7.970	-17.061	14.181
BP	Tohen et al. 2008	1.800	1.286	-0.720	4.320
BP	Tohen et al. Dec 2003	-0.190	2.376	-4.847	4.467
BP	Tohen et al. Nov 2003	4.000	1.610	0.844	7.156
BP		2.025	0.420	1.201	2.849
SCZ	Breier et al. 2005	5.040	2.003	1.115	8.965
SCZ	Kane et al. 2009	4.900	1.413	2.131	7.669
SCZ	Lieberman et al. 2005	15.000	2.800	9.513	20.487
SCZ	McQuade et al. 2004	7.000	3.037	1.048	12.952
SCZ	Saddichha et al. 2007	6.600	2.147	2.393	10.807
SCZ	Vanelle et al. 2006	2.340	5.803	-9.033	13.713
SCZ	Wu et al. 2006	-0.900	0.037	-0.972	-0.828
SCZ		5.629	2.254	1.212	10.046
Overall		2.146	0.413	1.336	2.956

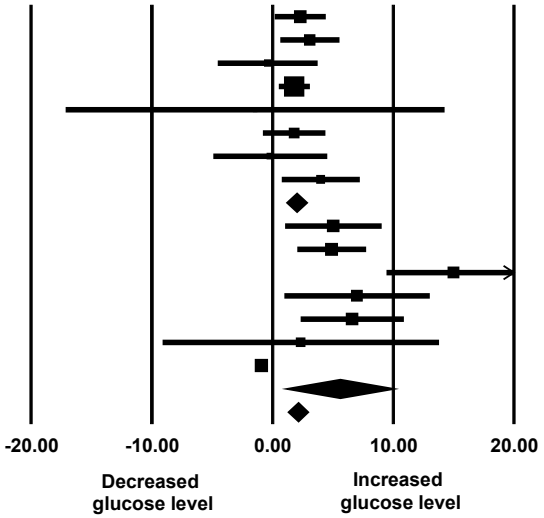

Figure 4

Group by DT	Study name	Mean	Standard error	Lower limit	Upper limit
BP	McIntyre et al. Dec 2009	30.100	7.659	15.089	45.111
BP	McIntyre et al. Nov 2009	35.400	7.019	21.642	49.158
BP	NCT00510146	23.140	4.760	13.811	32.469
BP	Tohen et al. 2008	17.800	7.629	2.848	32.752
BP		26.116	3.558	19.143	33.089
SCZ	Breier et al. 2005	34.710	7.223	20.553	48.867
SCZ	Lieberman et al. 2005	42.900	8.400	26.437	59.363
SCZ		38.192	5.477	27.458	48.926
Overall		29.700	2.983	23.852	35.547

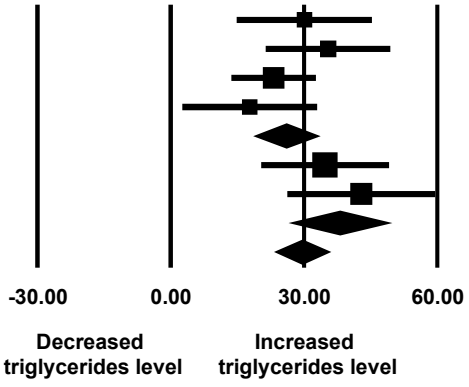

Figure 5

Group by DT	Study name	Statistics for each study		
		Event rate	Lower limit	Upper limit
BP	McIntyre et al. Nov 2010	0.103	0.058	0.176
BP	McIntyre et al. April 2010	0.049	0.026	0.088
BP	McIntyre et al. Dec 2009	0.087	0.057	0.131
BP	McIntyre et al. Nov 2009	0.058	0.033	0.102
BP	NCT00129220	0.029	0.009	0.085
BP	NCT00510146	0.041	0.024	0.068
BP	Tohen et al. 2006	0.046	0.024	0.087
BP	Tohen et al. Dec 2003	0.099	0.064	0.148
BP		0.063	0.047	0.085
SCZ	Alvarez et al. 2006	0.072	0.038	0.133
SCZ	Beasley et al. 1996	0.072	0.030	0.163
SCZ	Bhowmick et al. 2010	0.012	0.001	0.167
SCZ	Kane et al. 2009	0.146	0.109	0.192
SCZ	Lecrubier et al. 2006	0.200	0.142	0.274
SCZ	Lieberman et al. 2005	0.052	0.031	0.084
SCZ	McQuade et al 2004	0.040	0.006	0.235
SCZ	NCT00145496	0.058	0.034	0.097
SCZ	NCT00645099	0.009	0.002	0.036
SCZ	Sirota et al. 2006	0.143	0.047	0.361
SCZ	Vanelle et al. 2006	0.125	0.053	0.267
SCZ		0.078	0.049	0.121
Overall		0.067	0.052	0.086

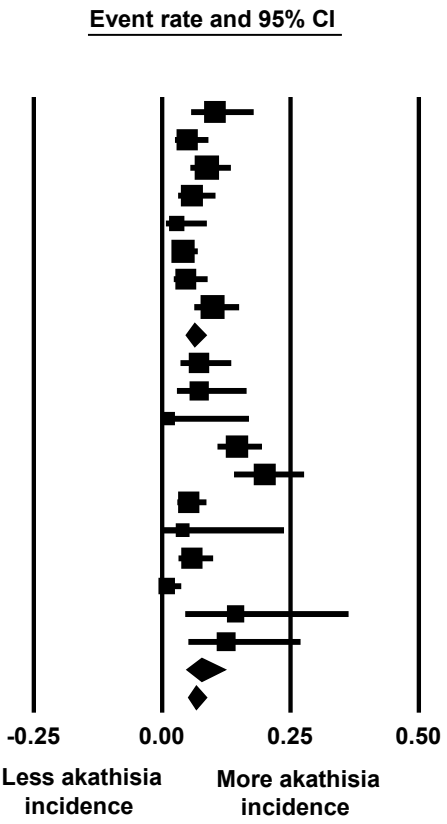

Figure 6

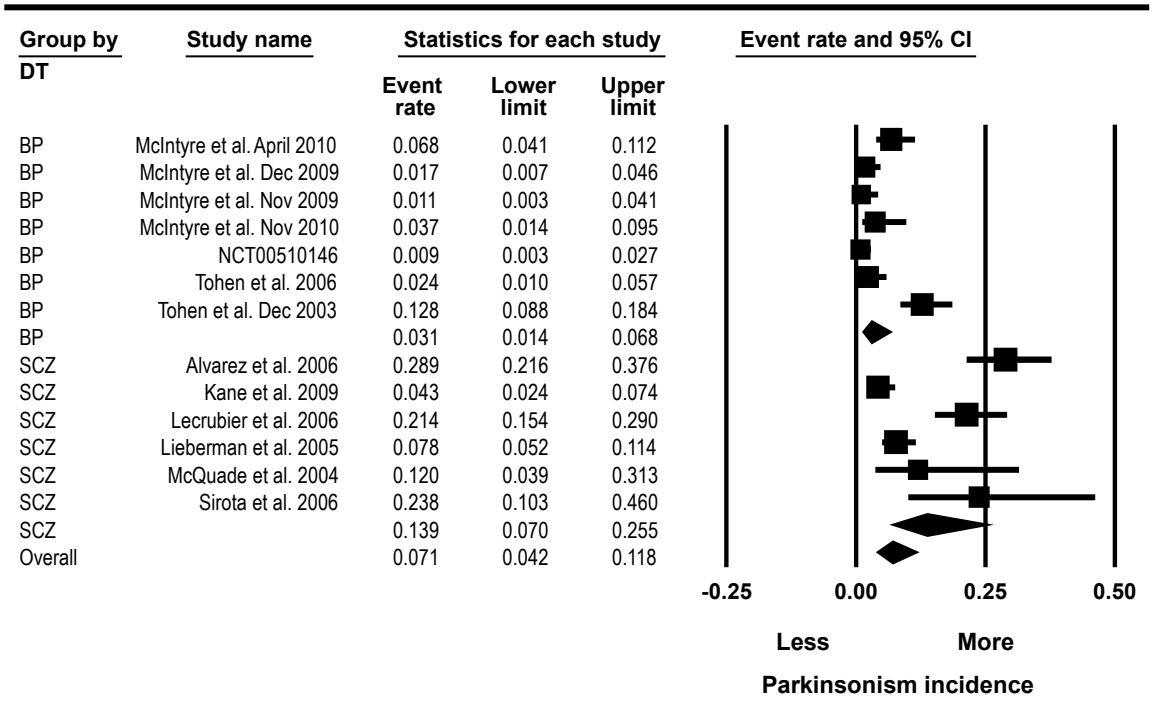
Group by DT
Study name
Statistics for each study
Event rate
Lower limit
Upper limit
Event rate and 95% CI
BP McIntyre et al. April 2010 0.068 0.041 0.112
BP McIntyre et al. Dec 2009 0.017 0.007 0.046
BP McIntyre et al. Nov 2009 0.011 0.003 0.041
BP McIntyre et al. Nov 2010 0.037 0.014 0.095
BP NCT00510146 0.009 0.003 0.027
BP Tohen et al. 2006 0.024 0.010 0.057
BP Tohen et al. Dec 2003 0.128 0.088 0.184
BP 0.031 0.014 0.068
SCZ Alvarez et al. 2006 0.289 0.216 0.376
SCZ Kane et al. 2009 0.043 0.024 0.074
SCZ Lecrubier et al. 2006 0.214 0.154 0.290
SCZ Lieberman et al. 2005 0.078 0.052 0.114
SCZ McQuade et al. 2004 0.120 0.039 0.313
SCZ Sirota et al. 2006 0.238 0.103 0.460
SCZ 0.139 0.070 0.255
Overall 0.071 0.042 0.118
-0.25
0.00
0.25
0.50
Less
More
Parkinsonism incidence

Figure 7

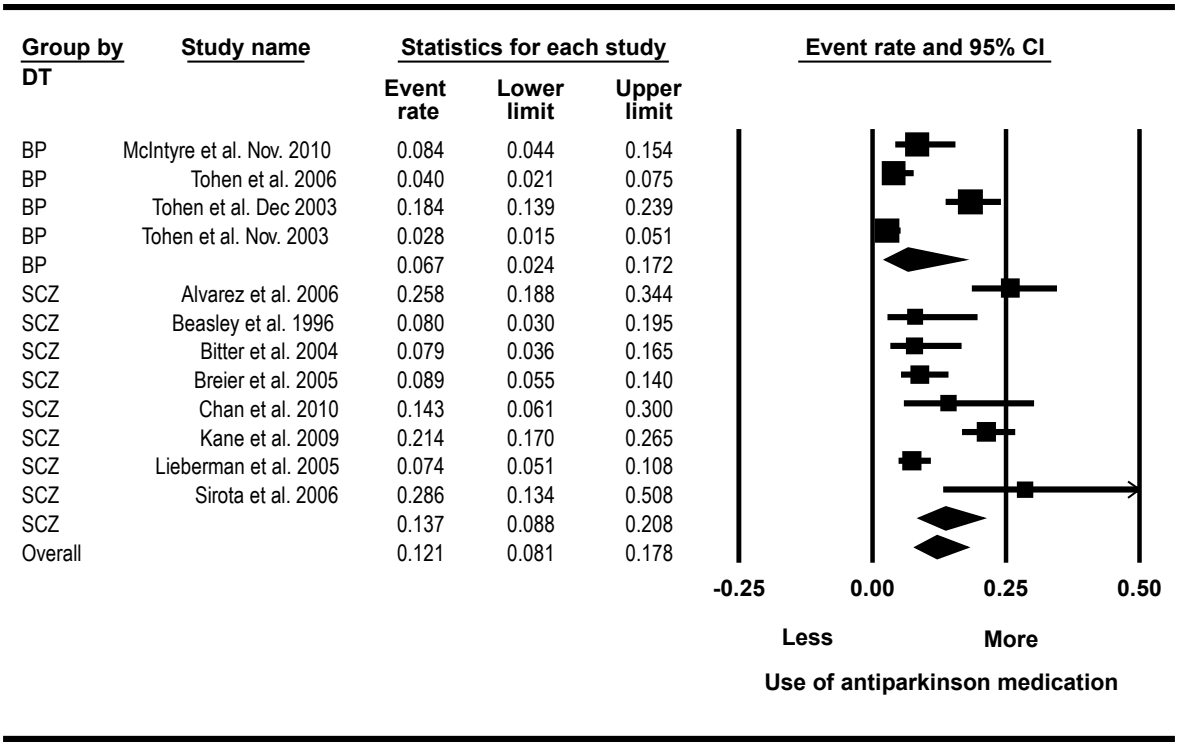
Group by DT
Study name
Statistics for each study
Event rate
Lower limit
Upper limit
Event rate and 95% CI
BP McIntyre et al. Nov. 2010 0.084 0.044 0.154
BP Tohen et al. 2006 0.040 0.021 0.075
BP Tohen et al. Dec 2003 0.184 0.139 0.239
BP Tohen et al. Nov. 2003 0.028 0.015 0.051
BP 0.067 0.024 0.172
SCZ Alvarez et al. 2006 0.258 0.188 0.344
SCZ Beasley et al. 1996 0.080 0.030 0.195
SCZ Bitter et al. 2004 0.079 0.036 0.165
SCZ Breier et al. 2005 0.089 0.055 0.140
SCZ Chan et al. 2010 0.143 0.061 0.300
SCZ Kane et al. 2009 0.214 0.170 0.265
SCZ Lieberman et al. 2005 0.074 0.051 0.108
SCZ Sirota et al. 2006 0.286 0.134 0.508
SCZ 0.137 0.088 0.208
Overall 0.121 0.081 0.178
-0.25
0.00
0.25
0.50
Less
More
Use of antiparkinson medication

Figure 8

3. COMPARING TOLERABILITY PROFILE OF QUETIAPINE, ZIPRASIDONE, ARIPIPRAZOLE AND RISPERIDONE IN SCHIZOPHRENIA AND AFFECTIVE DISORDERS: A META-ANALYSIS

3.1. Introduction

Second generation antipsychotics (SGAs) have become a first-line medication in the treatment of psychotic disorders, such as schizophrenia and schizoaffective disorders (Lublin et al., 2009, Rummel-Kluge et al., 2010b) and a serious consideration in the treatment of several affective disorders (Bowden et al., 2005, Tohen and Vieta, 2009). Several studies have proposed SGA monotherapy or combination therapy in controlled trials, comparing them to placebo or to first-generation antipsychotics (FGAs) (Chen et al., 2011, Correll et al., 2010, Komossa et al., 2010, Leucht et al., 2009b). However, the treatment with SGAs has been associated with concerns about metabolic side effects, which can induce long-term consequences such as metabolic syndrome, diabetes mellitus and cardiovascular diseases (CVD). Patients with severe mental diseases are 2-3 times more at risk for obesity, metabolic syndrome, and related morbidity and mortality compared to general population (Correll et al., 2010, Holt et al., 2010).

Factors that affect patients with severe mental illnesses and contribute to metabolic syndrome and diabetes mellitus include genetic predisposition to certain pathologies such as weight gain, diabetes mellitus and lipid abnormalities (Bellivier, 2005, Gough and O'Donovan, 2005, Hasnain et al., 2009); sedentary life style and poor diet (Meyer and Stahl, 2009, Phelan et al., 2001); high levels of smoking, alcohol intake and drug abuse (Green et al., 2007, Regier et al., 1990); limited access to regular health care services (Chacon et al., 2011); and potential metabolic adverse events which occur during

antipsychotic treatment (Haddad and Sharma, 2007, Meyer and Stahl, 2009, Stahl et al., 2009).

An increased number of evidences have suggested that certain SGAs are associated with increased risk of metabolic complications such as obesity, glucose intolerance and dyslipidemia, which are risk factors for developing diabetes mellitus, metabolic syndrome, CVD and premature death. Thus, the physical health of mental disorder patients is further influenced by SGAs treatment. The SGAs side effects on physical health have become an important issue in mental illnesses' treatment (De Hert et al., 2011b). These side effects are especially important in vulnerable population, such as drug-naïve first-episode patients, children and adolescents (De Hert et al., 2011c). Literature findings revealed that individual SGAs differ in their liability to induce metabolic disturbances (Haddad, 2005, Newcomer, 2005, Allison et al., 1999). Generally, clozapine and olanzapine are known to be associated with the highest risk of clinically significant weight gain, followed by quetiapine, risperidone and sertindole (Allison et al., 1999, Haddad, 2005, Newcomer, 2005). Amisulpride, ziprasidone and aripiprazole have the lowest risk for clinically significant weight gain (Allison et al., 1999, Haddad, 2005, Newcomer, 2005).

Furthermore, based on the published data olanzapine and clozapine also increase the risk of diabetes and dyslipidemia. The findings about quetiapine and risperidone are controversial and need more investigations, while amisulpride, ziprasidone and aripiprazole do not seem to significantly change blood glucose levels or lipid profiles (De Hert et al.,

2011c, Haddad, 2005, Newcomer, 2005, Rummel-Kluge et al., 2010b, De Hert et al., 2011a, Newcomer and Haupt, 2006).

Extrapyramidal symptoms (EPS) including dystonia, parkinsonism and akathisia, are other common side effects associated with antipsychotic treatment (Cavazzoni et al., 2006). The incidence of movement disorders related to the use of antipsychotics is thought to occur due to D_2 receptors blockade in the striatum. The drugs with higher affinity for D_2 receptors cause higher rate of EPS (Balestrieri et al., 2000). Although, SGAs have a more favourable EPS profile than FGAs (Leucht et al., 2009a, Miller et al., 1998), studies have shown that EPS, including akathisia (Kane et al., 2009a) and tardive dyskinesia (Kane, 2004), are also observed with SGAs. Acute development of EPS in several studies has been identified as an important risk factor for later development of tardive dyskinesia in schizophrenia patients (Muscettola et al., 1999, Tenback et al., 2006).

While some studies have shown the similar risk of SGAs-induced EPS in bipolar patients (BP) and schizophrenia, other studies have reported more vulnerability to movement disorders in bipolar patients (Cavazzoni et al., 2006, Gao et al., 2008, Nasrallah et al., 1988).

Schizophrenia and affective disorders both are polygenic and multi-factorial complex disorders in which a myriad of different genes are potentially involved. Even though BP and SCZ differ in neurobiology and phenomenology (McDonald et al., 2004, Muir et al., 2001, Murray et al., 2004), these disorders share some genetic features (Huang et al., 2010, Park et al., 2004, Peerbooms et al., 2010, Purcell et al., 2009). Although the

pathophysiology of both disorders remains unclear, in recent years, the investigation of the factors which contribute to the SGA's tolerability profiles in AD and SCZ has just emerged (Stahl et al., 2009, van Winkel et al., 2008).

Based on broad SGAs prescriptions for different diagnoses in psychiatry, it would be interesting to see whether the side effects have a different expression and severity according to phenotype. In a previous article, we examined the potential difference in olanzapine-induced metabolic side effects between SCZ and AD patients, in which we found more vulnerability in SCZ patients regarding these side effects. However, only the weight gain was significantly higher in schizophrenic patients compared to AD patients (Moteshafi et al., 2012). As only olanzapine side effects were considered in our prior work (Moteshafi et al., 2012), the current meta-analysis extends our earlier work to other most frequently prescribed SGAs: quetiapine, risperidone, ziprasidone and aripiprazole. This study aimed to compare the tolerability and safety profiles of these SGAs in different diseases, and in particular to investigate whether the side effects have a different expression and severity according to phenotype between SCZ and AD patients groups.

A difference in severity of side effects could mean that a phenotype *per se* influences a medication's tolerability profile. We hypothesized that phenotype of disease may affect induction and severity of side effects. With the increasing use of SGAs in psychiatry, this investigation is valuable, not only to inform clinicians, but also to provide clues to the pathophysiology of schizophrenia-spectrum and affective disorders.

3.2. Methods

3.2.1. Data sources and search strategy

Systematic reviews of the literature on four antipsychotics (quetiapine, risperidone, ziprasidone and aripiprazole) in the treatment of schizophrenia and affective disorders that reported randomized controlled trials (RCTs) were performed. The keywords used for the search were *quetiapine, risperidone, ziprasidone, or aripiprazole* in conjunction with *schizophrenia or affective disorder, bipolar disorder, major depression, bipolar mania, unipolar depression*. The search engines were PsycINFO (1967-2010), PubMed (MEDLINE), EMBASE (1980-2010) and clinicaltrials.gov website. There were no limitations on language. A hand search of published review articles, as well as cross-referencing, was carried out to gather further data. It is important to mention that at this stage, we could not find any article that reports SGAs side effects for both schizophrenia and affective disorder patients; therefore, we searched for articles that report SGAs side effects in either SCZ or AD groups; the results were then compared together. Authors of the selected studies that met inclusion criteria were contacted to provide unreported or additional data. Two reporters independently checked all reports for inclusion and exclusion criteria.

3.2.1.1. Inclusion criteria

Studies were searched for two diagnostic groups: affective disorders and schizophrenia. Inclusion criteria were studies that contained (1) adults patients (18-65 years old) which

had a diagnostic of schizophrenia or affective disorders such as, major depression, bipolar mania, or bipolar depression; (2) randomized controlled trials (open-label or double-blind); (3) oral monotherapy treatment with quetiapine, risperidone, ziprasidone, or aripiprazole; (4) fixed and flexible-dose studies with a duration of three weeks or longer; and (5) reported data on metabolic or extrapyramidal side effects.

3.2.1.2. Exclusion criteria

Trials in both groups were left out if they contained (1) combination therapy of any agent with another medication such as anti-manic or antidepressant; (2) other psychotic diagnoses such as schizoaffective or schizophreniform disorders; (3) incomplete or unavailable data even after contacting author; (4) study groups of children or adolescents; (5) non-randomized design; or (6) treatment with depot antipsychotics.

3.2.2. Data extractions and outcome parameters

Two reviewers (H.M. and E.S.) independently checked abstracts and chose related articles, then one reviewer (H.M.) extracted data while checking the inclusion criteria. Trial abstracts were screened initially and then in the second step full-texts were reviewed. Data from schizophrenia and affective disorders group were compared. The data extractions were separated along two dimensions: (a) clinically important metabolic side effects such as change of weight, blood glucose and cholesterol levels. Weight change was reported as the change in kilograms from baseline to endpoint; the changes in other metabolic parameters were defined as the change from baseline to endpoint in mg/dl. (b) some EPS

related adverse events (such as akathisia and parkinsonism), as well as the use of antiparkinson medication for treating EPS were checked. The outcome variable was incidence of EPS related side effects, as measured by treatment-emergent adverse event data.

3.2.3. Meta-analytic calculations

Using Comprehensive Meta-Analysis (CMA) software version 2.2.05 (Borenstein et al., 2010), effect size estimates for each side effect was calculated. For each group of subjects, AD and SCZ patients, effect size estimates were calculated from (i) mean and standard deviation of metabolic side effects or (ii) events rates for extrapyramidal side effects. Continuous outcomes (metabolic side effects) were analyzed by estimating means and confidence intervals for each group of subjects: schizophrenia and affective disorders. Also, dichotomous outcomes (extrapyramidal side effects) were analyzed by estimating event rate and confidence intervals for each group of subjects. The effect size estimates for all studies in each patients' group (SCZ or AD) were pooled together to yield an overall effect size estimate for each group. Then, CMA was used to compare the point estimate of each group to see whether the difference between the points was significant or not. The level of significance for the effect size estimates was set at $p=0.05$.

For all analyses, effect size estimates were pooled with the random-effects model, which is more strict than fixed-effects model and permits population-level inferences as well (DerSimonian and Laird, 1986). Meanwhile we assessed the heterogeneity of study

with the I-squared statistic, supposing that I^2 statistics greater than 50% proposed considerable heterogeneity.

3.2.3.1. Sub-analyses and addressing potential confounding factors

Sub-analyses, including between-group differences, were carried out for potential confounding factors in age, sex ratio, and medication daily dose. The effects of treatment duration on the results were examined by performing subgroup analyses including short-term (less than 12 weeks) and longer term studies (more than 12 weeks), separately. We also performed mixed-effects meta-regression to investigate whether percentage of male patients involved in studies were correlated with the differences in effect size and to explain potential heterogeneity.

3.3. Results

3.3.1. Literature searching results

3615 abstracts were identified initially in which 1732 were related to the SCZ group and 1883 to the AD group. Among these, 3535 were discarded on the basis of duplication or evaluating abstract and article, according to the following criteria: (1) type of article/study (e.g., case study, review, letter to the editor and crossover study); (2) type of population (e.g., non randomized, nonschizophrenia patients, age range); (3) treatment type (e.g., combination therapy or depot administration); (4) incomplete or non available data. As a result, 80 studies (n=14319) were accepted for both groups: for SCZ patients N=47,

n=7700[2] and for AD group N=33, n=6619. SCZ group articles contained 15 for quetiapine, 9 for aripiprazole, 8 for ziprasidone and 15 for risperidone. AD group articles contained 16 for quetiapine, 9 for aripiprazole, 4 for ziprasidone and 4 for risperidone.

It should be mentioned that for the AD group we could only find articles related to the bipolar disorder (BP); we could not find related studies on other affective disorders, considering our inclusion criteria. More information on the sorting process in each group is shown in Figures 1 and 2. In addition, Tables 1 and 2 provide details of demographic characteristics among studies included in the meta-analysis.

3.3.2. Outcome results

3.3.2.1. First outcome: metabolic changes

(a)Weight gain

In quetiapine treatment, 10 studies for the SCZ (n=1683) and 12 for the BP group (n=3411) were reviewed for weight changes. Even though the increase from baseline was more in SCZ group, there was no statistically significant difference between the two groups (1.72 kg vs. 1.15 kg; p=0.108).

For aripiprazole treatment, four studies in the SCZ (n=1493) and six in the BP group (n=844) were checked. The analysis revealed a slight decrease from baseline in the SCZ group and an increase in weight from baseline for the BP group; however, there was no

[2] "N" refers to the number of articles whereas "n" is the number of patients.

statistically significant difference between the two groups (-0.4 kg vs. 0.49 kg, respectively; p=0.109).

For risperidone, 13 studies in the SCZ (n=1278) and two in the BP group (n=272) were examined. Even though the analysis revealed an increase from baseline in both groups, there was no statistically significant difference between the two disorders (1.32 kg vs. 1.55 kg, for SCZ and BP, respectively; p=0.486).

Despite checking all articles for ziprasidone, we could not find enough data related to its monotherapy and metabolic side effects. Therefore, we were not able to compare any metabolic parameters for this agent. In addition, for risperidone treatment the data was only available on weight changes. Thus, the rest of metabolic changes will only be reported for quetiapine and aripiprazole treatment.

(b) Cholesterol change

Quetiapine increased blood cholesterol levels to 8.05 mg/dl in SCZ group (N=4, n=1473) and decreased cholesterol level in BP group (N=7, n=2433) to 2.8 mg/dl. The SCZ group showed significantly more cholesterol increase than the BP group (p=0.000). Details are shown in Figure 3.

For aripiprazole, two studies in the SCZ (n=393) and two in the BP group (n=360) were examined for changes in blood cholesterol levels. Aripiprazole decreased the levels of cholesterol in both groups. However, the difference between the two groups was not significant (-5.76 vs. -3.52 mg/dl, for SCZ and BP, respectively; p=0.629).

(c) Glucose change

For quetiapine, five studies (n=1553) in the SCZ group and ten (n= 3214) in the BP group were checked for changes in blood glucose levels. Quetiapine increased blood glucose levels similarly in both groups. (4.01 vs. 3.85 mg/dl, for SCZ and BP, respectively; p=0.927).

Aripiprazole increased blood glucose levels in the SCZ (N=2, n=441) and the BP groups (N=2, n=360). Mean change was 2.02 mg/dl in the SCZ vs. 3.51 mg/dl in the BP groups, with no significant difference between the two groups (p=0.490).

(d) Triglyceride change

For quetiapine, four studies (n=1269) in the SCZ and seven studies (n= 2342) in the BP group were examined for changes in blood triglyceride levels. The analysis revealed an increase in triglyceride levels in both groups; however, the difference between the groups was non-significant (17.57 mg/dl vs. 7.93 mg/dl, for SCZ and AD, respectively; p=0.099).

(e) LDL change

Quetiapine increased mean LDL levels in SCZ group (N=3, n=1001) up to 5.00 mg/dl and decreased LDL level in BP group (N=7, n=2427) to 2.78 mg/dl. This change on LDL levels was significant between the two groups (p =0.000). Details are shown in Figure 4.

(f) HDL change

We could not find enough studies to compare HDL changes among treatment groups.

3.3.2.2. Second outcome measure: extrapyramidal side effects

As known, SGAs extrapyramidal side effects are less than those of conventional antipsychotics. In our study, as well, EPS-related adverse event rates and their intensity were low in both groups; however, there were significant differences in the frequency of some EPS associated with SGAs treatment between the two groups.

(a) Incidence of akathisia

The akathisia event rate did not differ significantly between the two groups for quetiapine treatment. Based on five articles included in the BP group (n=961), the event rate was 6.4%; according to six articles in the SCZ group (n=1095), the incidence of akathisia was 4.8% (p=0.463).

Patients treated with aripiprazole in the BP group (N=8, n=1307) showed more akathisia incidence compared to SCZ patients (N=8, n=2264), 14.6% vs. 5.4% respectively. This difference was significant (p=0.001). Details are shown in Figure 5.

For ziprasidone treatment 10 studies (n=1459), four studies (n=584) in the BP and six studies (n= 875) in the SCZ group, were checked. Even though akathisia incidence was higher in the BP group compared to the SCZ group, 13.2% vs. 7.7% respectively, this difference was not significant (p=0.065).

For risperidone treatment not enough data was available to conduct any comparison between the two groups, in the incidence of akathisia.

(b) Incidence of parkinsonism

The incidence of parkinsonism did not differ significantly between the two groups for quetiapine treatment. Based on eleven articles included in the BP group (n=3134), the event rate was 7.5%; according to eight articles in the SCZ group (n=1870), the incidence of parkinsonism was 9.6% (p=0.326).

In aripiprazole treatment, there was no significant difference between the SCZ (N=7, n=1979) and the BP groups (N=4, n=701). The event rate was 6.7% vs. 10.4%, for SCZ and BP, respectively (p=0.069).

The incidence of parkinsonism was not significantly different between the two groups of patients with risperidone treatment. Based on two articles included in the BP group (n=300), and seven articles in the SCZ group (n=1194), the event rate was 23.4% vs. 29.3%, respectively (p=0.4).

In ziprasidone treatment, the difference in incidence of parkinsonism was not significant between the SCZ (N=6, n=868) and the BP groups (N=3, n=444). The event rate was 7.5% vs. 14.5%, for SCZ and BP, respectively (p=0.209).

(c) Antiparkinson medication use

Quetiapine treatment was not associated with significant difference in the use of antiparkinson medication between the two groups. According to four articles included in the BP group (n=489), the event rate was 5.1%; in ten articles in the SCZ group (n=2146), the use of such medication was 7.7% (p=0.455).

In aripiprazole treatment, there was no significant difference in the use of antiparkinson medication between the SCZ (N=6, n=1958) and the BP groups (N=4, n=603). The event rate was 16.7% vs. 17.4%, for SCZ and BP, respectively (p=0.905).

Antiparkinson medication use differed between the two groups for risperidone treatment. SCZ patients (N=8, n=1097) used less antiparkinson medication compared to BP patients' group (N=2, n=280), 23.1% vs. 28.3% respectively. However this difference was not significant (p=0.575).

In ziprasidone treatment, there was no significant difference in the use of antiparkinson medication between SCZ (N=7, n=1093) and BP groups (N=2, n=317). The event rate was 21.1% vs. 35.3%, for SCZ and BP, respectively (p=0.227).

3.3.2.3. Heterogeneity

Heterogeneity of all outcomes (metabolic and extrapyramidal) were explored by I^2 statistic; they were all heterogeneous (I^2>50%). Sub-analyses were assessed to determine possible sources of heterogeneity in the results.

3.3.3. Sub-analyses

3.3.3.1. Age

All studies reported mean age and standard deviation (SD) of participants; no difference was observed between the two groups of patients in all four treatment groups. See Tables 1 and 2 for more information on demographic characteristics among studies included in the meta-analysis.

3.3.3.2. Sex ratio

Number of male and female patients was also reported in all studies. Significantly more males participated in the studies of SCZ group studies compared to the BP groups in all treatment groups, except for risperidone treatment group. Considering the significant difference in male percentage between SCZ and BP patients' groups, this variable was included in the statistical analysis as a regressor.

By performing a meta-regression on akathisia incidence in aripiprazole treatment, the percentage of male gender was not a significant moderator to explain the heterogeneity in BP and SCZ patients' groups.

When we performed meta-regression analyses to find the source of heterogeneity in quetiapine treatment, we only found that the male percentage of BP patients' group could be a significant moderator in explaining the heterogeneity of LDL and Cholesterol. In the SCZ group no meaningful regression could be done due to small number of studies; however, because of the significant difference on the sex ratio between BP and SCZ, the sex ratio could be a source of heterogeneity.

3.3.3.3. Dose

Based on studies in BP and SCZ groups which specified mean daily dose, no difference was observed between the two groups in all five treatment types.

3.3.3.4. Treatment duration

We stratified the studies based on treatment duration. The results of short-term studies (between 3 and 12 weeks) for quetiapine treatment remained the same as the main analysis. It means increases in cholesterol and LDL levels stayed significantly higher for SCZ patients compared to AD patient in short-term studies. In addition, akathisia incidence was considerably higher in the BP group compared to the SCZ group. The other parameters continued to display no significant difference, similar to the results of the main analysis.

In aripiprazole treatment, stratification of studies by treatment duration, showed significantly more akathisia and parkinsonism incidence in BP group compared to SCZ. It should be noted that parkinsonism incidence was not significantly different before stratification.

For risperidone and ziprasidone treatment, all parameters displayed no significant difference, as in the main analysis.

For studies more than 12 weeks, we did not find enough data to check in the BP group in all treatment types.

3.4. Discussion

In this chapter we examined the difference in frequency and intensity of metabolic and extrapyramidal side effects of four common atypical antipsychotics in SCZ and AD patients. In our previous article (Moteshafi et al., 2012), we also presented the first meta-analysis comparing the potential difference in olanzapine-induced side effects between SCZ

and AD patients. Based on our hypothesis, there is a difference between SCZ and AD patients for metabolic and extrapyramidal side effects. Recently, atypical antipsychotic agents have been linked to several forms of morbidity, including obesity, hyperlipidemia, and type-2 diabetes mellitus, which predict metabolic syndrome, cardiovascular morbidity and malignancy (De Hert et al., 2011a, Henderson et al., 2005, Newcomer et al., 2002). Metabolic syndrome is a significant public health problem in patients with severe mental illnesses and particularly schizophrenia. The mechanisms responsible for an association between mental disorder, antipsychotic treatment and metabolic syndrome remain elusive (Bond et al., 2010). According to different phenotypes of these mental illnesses and frequent use of SGAs to treat them, studying the degree of sensitivity and tolerability of SGAs in AD and SCZ patients seems essential.

In general, as many studies have indicated, atypical antipsychotics do not form a homogenous group causing similar adverse events; therefore, some SGAs can lead to metabolic disturbances, while the others may not; our findings are consistent with other studies in this regard (Gao et al., 2008, Rummel-Kluge et al., 2010a, Rummel-Kluge et al., 2010b, Simon et al., 2009).

As in our previous article on olanzapine-induced side effects (Moteshafi et al., 2012), we examined the metabolic side effects (weight gain, blood glucose, cholesterol, LDL and triglyceride levels) of the other four most commonly prescribed SGAs—quetiapine, ziprasidone, aripiprazole and risperidone—as our first outcome. We found that, olanzapine (Moteshafi et al., 2012) and quetiapine, as also mentioned in the other studies (Rummel-

Kluge et al., 2010b, Simon et al., 2009), are associated with more changes in metabolic parameters relative to other SGAs. In a meta-analysis comparing all SGAs head-to-head, weight gain was seen significantly more with clozapine and olanzapine treatment than with other antipsychotics (Rummel-Kluge et al., 2010b). Moreover, one study indicated that olanzapine treatment resulted in the most weight gain followed by quetiapine and risperidone (Simon et al., 2009). Aripiprazole and ziprasidone caused the lowest risk for clinical weight gain (De Hert et al., 2009, De Hert et al., 2011c). In our prior meta-analysis (Moteshafi et al., 2012), olanzapine induced significantly more weight gain in SCZ patients compared to the AD group. Based on our present meta-analysis, with quetiapine treatment, SCZ patients gained more weight; however, the difference was not significant.

The mechanism of SGA-induced weight gain is still unexplained. Several hypotheses consider a complex interaction of neurotransmitters, hormones and cytokines in appetite and weight gain controls (Srivastava et al., 2008). Some factors such as a high affinity of these medications to serotonin (5-HT_{2C}, 5-HT_{2A}, 5-HT_6) , dopamine (D_2 and D_3), histamine (H_1), adrenergic (α_1 and α_2) and muscarinic (M_1, M_2, M_3 and M_5) receptors could be responsible for weight gain (Allison et al., 1999, Czobor et al., 2002, Haddad, 2005, McQuade et al., 2004, Reynolds et al., 2005). Higher affinity to H_1, 5-HT_{2A} and 5-HT_{2C} receptors is associated with hunger and may lead to increased food intake (Correll et al., 2011, De Hert et al., 2011c). Furthermore, the blockade of H_1 and α_1 receptors can induce sedation, which may lead to immobility and weight gain (Czobor et al., 2002). Genetic data also propose a role of leptin receptor activity, G-protein signaling, cannabinoid receptor

activity and promelanin-concentrating hormone signaling in the SGAs weight gain (Correll et al., 2011, De Hert et al., 2011c).

We also examined the mean changes in glucose levels for quetiapine and aripiprazole. Even though we found increases of glucose levels from baseline for these two SGAs, the difference between BP and SCZ was not significant. This outcome was similar to olanzapine-induced glucose changes (Moteshafi et al., 2012). The mechanism underlying the effect of some SGAs, especially olanzapine, on glucose levels and insulin resistance remains unclear. However, there is some indication that the long-term use of olanzapine may decrease insulin secretion, which may lead to hyperglycemia (Nakamura and Nagamine, 2010). A proposed mechanism for hyperglycemia is related to the drug's affinity for the H_1, M_3 and 5-HT_{2C} receptors, which is correlated with an increased risk of diabetes (Nasrallah, 2008). Another possible mechanism for the increase of insulin resistance with olanzapine treatment could be impairing the ability of insulin to stimulate glucose uptake into peripheral tissues such as skeletal muscle and adipose tissue.

There is recent evidence indicating that polymorphism in 5-HT_{2A} and 5-HT_{2C} receptor coding genes, HTR2A and HTR2C, seems to be associated with development of metabolic abnormalities such as C-peptide and insulin elevation during olanzapine and clozapine treatment (Bai et al., 2011, Gunes et al., 2009, Melkersson et al., 2010).

The last metabolic factor we looked at was mean variations in lipid parameters. Lipid profile in our meta-analysis showed that quetiapine increased significantly the mean level of total cholesterol and LDL in the SCZ group. Quetiapine contributed to more triglyceride

increases for SCZ patients compared to the BP group; however, this difference was not significant. It is noteworthy that based on the results reported by Zhornitsky et al. (2011), quetiapine may associate with more LDL and cholesterol changes in the SCZ group compared to other mental disorders, which is in agreement with our findings. In this systematic review (Zhornitsky et al., 2011), quetiapine efficacy and tolerability profiles across psychotic disorders were evaluated. The findings suggest a possible interaction between schizophrenia genes and quetiapine treatment in increasing metabolic disturbances (Stahl et al., 2009).

Aripiprazole treatment decreased the cholesterol levels in SCZ patients, and was associated with a small increase in cholesterol levels for AD group, a group difference which is also not statistically significant. Due to lack of available data, we could not evaluate triglyceride and LDL levels for aripiprazole treatment.

As mentioned in our prior article (Moteshafi et al., 2012), olanzapine treatment increased blood cholesterol and triglycerides levels in both groups and induced more changes in SCZ patients compared to BP patients. However, the differences between two patients groups were not significant, for both blood cholesterol and triglycerides levels.

Some SGAs are associated with dyslipidemia, including increased levels of LDL, total cholesterol and triglycerides, which can result in CVD (Casey, 2004). At present, the exact mechanism underlying changes in lipids due to certain SGAs treatment is unknown. A plausible mechanism depends on the SGAs role in lipogenesis increase, lipolysis reduction, and enhancement of antilipolytic insulin's effect in adipocytes, which may result in lipid

accumulation (Albaugh et al., 2011, Chaggar et al., 2011). In addition, several hypotheses have been proposed regarding biological factors such as weight gain, dietary changes and the development of glucose intolerance to explain the high frequency of dyslipidemia with specific antipsychotic medications (Meyer, 2001). Moreover, Ferno and his colleagues (Ferno et al., 2005) indicated that some antipsychotics upregulate the genes which are involved in biosynthesis of cholesterol and fatty acids. In their findings, first or second generation antipsychotic agents stimulate cellular lipogenesis via a direct activation of the sterol regulatory element binding protein (SREBP).

Our meta-regressions showed that male percentage was a significant moderator in the BP group and could explain some of the heterogeneity. In studies with a higher proportion of male participants, more cholesterol and LDL changes happened in the BP group. The number of studies for the SCZ group was too small for a meta-regression. In the quetiapine treatment group, we conducted our meta-analysis for the short-term treatment studies. The results of cholesterol and LDL levels stayed the same as our main analysis, which means significantly more changes in the SCZ group compared to BP.

The biological mechanism underlying different metabolic disturbances between SCZ and AD patients in SGAs treatment is not yet clear. Some authors have indicated possible inherent genetic vulnerability to metabolic irregularity in schizophrenia patients (Dasgupta et al., 2010, Spelman et al., 2007, Venkatasubramanian et al., 2007). They believe that schizophrenia may be an independent and important risk factor for both diabetes and impaired glucose tolerance; although, some other studies are not in line with this suggestion

(Arranz et al., 2004, Zhang et al., 2004). Other studies have described that stress, particularly dysfunction of the hypothalamo-pituitary-adrenal (HPA) axis activity and therefore increases in cortisol and DHEA (dehydroepiandrosterone) levels, in both acute phases of chronic schizophrenia and bipolar disorder patients may disturb metabolic parameters (Gallagher et al., 2007, Steen et al., 2011). In some reports, schizophrenic patients showed more sensitivity to daily stress than bipolar patients (Myin-Germeys et al., 2003). In addition, the polymorphism of brain-derived neurotrophic factor (BDNF) gene was recently found to be associated with antipsychotic-induced weight gain in patients with chronic schizophrenia (Zhang et al., 2008).

Furthermore, the duration of treatment or prior antipsychotic medication might influence the metabolic results. BP patients have a better psychosocial functioning profile, and most of them take less antipsychotic medications compared to SCZ patients. Sedentary lifestyle, poor diet, smoking and drug abuse, and finally antipsychotic treatment are all important factors which may affect weight gain and other metabolic parameters in schizophrenic patients.

Putting all these findings together may help to conclude that the patients with schizophrenia might be more prone to obesity and other metabolic disturbances compared to other mental disorders.

As our second outcome, we examined extrapyramidal symptoms related to SGAs treatment for different mental illnesses. Based on our results, akathisia occurred more frequently in the AD group versus SCZ group in relation to quetiapine, ziprasidone and

aripiprazole treatment. However, this difference in akathisia incidence was significant only with aripiprazole treatment.

In our results, incidence of parkinsonism was higher in the AD group compared to the SCZ group for ziprasidone and aripiprazole treatment; however, the differences between the two disorders were not statistically significant.

Antiparkinson medication use was also checked and no significant difference was found between SCZ and AD. However, in the AD group, antiparkinson medication was used more often when the patients were under ziprasidone and aripiprazole treatment.

Some reports in the literature suggest that bipolar disorder patients, especially in the depression phase, are more likely to develop EPS than SCZ patients (Gao et al., 2008, Nasrallah et al., 1988). They mentioned that each atypical antipsychotic has a different liability, and based on their review, haloperidol, aripiprazole, risperidone and ziprasidone treatments were associated with more overall EPS in BP patients compared to the SCZ group.

We performed meta-regression to find the source of heterogeneity in aripiprazole treatment. Akathisia incidence showed no relationship with the male percentage in BP patients. So, male percentage was not a significant moderator to explain the heterogeneity.

Furthermore, as mentioned earlier, when the studies were stratified based on treatment duration, in studies less than 12 weeks, significantly more akathisia incidence was observed in the BP patients compared to the SCZ group in aripiprazole and quetiapine treatments.

Some limitations affect this meta-analysis, which are explained in detail in (Moteshafi et al., 2012). These limitations may confound our results and may explain the heterogeneity detected in the analysis.

The result of this meta-analysis proposes that factors such as life style and disease phenotype may contribute to more susceptibility to some SGAs-induced metabolic side effects in the SCZ group. Genetic polymorphism may be an important factor that contributes to metabolic side effects of SGAs between SCZ and AD patients. In addition to a genetic predisposition for metabolic syndromes among schizophrenic patients, lifestyle risk factors such as stress, poor diet, lack of exercise and smoking are more common in schizophrenic patients (Bai et al., 2011, Liou et al., 2012).

Patients with severe mental illnesses should be monitored regularly, especially for metabolic issues induced by SGAs therapy.

3.5. References

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Table legends

Table 1: Demographic characteristics among schizophrenia studies included in the meta-analysis

Table 2: Demographic characteristics among affective disorders studies included in the meta-analysis

Tables

Table 1

Medication/Study	Age (mean± SD), y	Dose(mean± SD),mg/day	Treatment duration, w	Male/Female, N
Quetiapine				
Riedel et al. 2005	30.6±10.9	589.7	12	15/7,22
Riedel et al. 2007	36.69±11.71	586.8±169.1	8	10/6,16
Arvantis et al.1997	37.4±9.4	75, 150, 300, 600,750	6	191/67,258
Borison er al. 1996	36±9	307	6	48/6,52
Kahn et al. 2007	34.3±10	400, 600,800 XR/400IR	6	277/181,458
Lieberman et al. 2005	40.9±11.2	543.4	72	255/82,337
Lindermayer et al. 2008	39.2±10.3	300,600,800XR/300,600IR	6	310/110,420
Peuskens et al. 2007	37	674	52	49/35,84
Small et al. 1997	36.5±9	250,750	6	139/51,190
Zhong et al. 2006	40.2±10.8	525±231	8	260/78,338
Conley et al. 2005	43.7±5.9	463.6±50.5	12	10/2,12
Atmaca et al. 2003	30.1±8.4	535.7±110.5	6	6/8,14
Buckley et al. 2004	39±11.1	600	8	38/16,54
Cpolov et al. 2000	37±10	455±174	6	158/63,221
Sirota et al. 2006	38.3±12.2	637.2±121.1	12	15/4,19
Aripiprazole				
Kolotkin et al. 2008	38.1±10.8	10-30	26	165/113,278
Cutler et al. 2006	40.5	2, 5, 10	6	216/63,279
Kasper et al. 2003	37.3±11.7	29.01	52	511/350,861
Kerwin et al. 2007	38.1±10.8	18.7	26	169/115,284
Kane et al. 2007	42.6±12.4	28.8	6	114/40,153
McQuade et al. 2004	38.6±10.6	25.1	26	114/42,156
Pigott et al. 2003	42.2	15	26	84/71,155
Kane et al. 2009	37.3±10.4	19.3	28	190/95,285
Chrzanowski et al.2006	41.7±12.2	15-30	52	59/45,104

Ziprasidone				
Breier et al. 2005	38.2±12.1	115.96±39.91	28	172/99,271
Sacchetti et al.2009	41.6±10.2	142±23	18	52/21,73
Lieberman et al. 2005	40.1±11	112.8	78	129/56,185
Kane et al. 2006	35.6±9.5	153.8±17	6	103/49,152
Olié et al. 2006	39.4	118	12	41/19,60
Arato et al. 2002	50	40, 80,160	52	144/63,207
Hirsch et al. 2002	39.2	116.5	28	92/56,148
Cutler et al. 2008	40±9.9	160	4	113/36,149
Risperidone				
Liberman et al. 2005	40.6±11.3	3.9	72	115/46, 161
Yang et al. 2010	35.97±10.15	4.09±1.56	8	194/87, 281
Hwang et al. 2003	34.1±9.9	6.88±1.54	6	25/11, 36
Zhong et al. 2006	39.6±10.8	6±1.8	8	20/18, 38
Riedel et al. 2005	39.3±12.3	4.9	6	94/46, 140
Riedel et al. 2007	39.6±12.4	5.1±1.4	12	16/19, 35
Dollfus et al. 2005	39.6±10	6±2.1	8	11/6, 17
Sechter et al. 2002	38.4±10.7	6.92±2.14	24	14/10, 24
Bondolfi et al. 1998	38.3±12.9	6.4±2.1	8	244/92, 336
Azorin et al. 2001	39.5±11.3	9±4	12	17/4, 21
Atmaca et al. 2003	27.9±7.8	6.7±3.6	6	11/18, 29
Saddichha et al. 2007	26.7±6.3	4.5±1.2	6	46/30, 76
Peuskens et al. 1999	37±12	8	8	180/97, 277
Conley et al. 2005	46.3±8.7	4.31±0.63	12	85/39, 124
Lin et al. 2010	38	4	6	24/18,42

Table 2

Medication/Study	Age (mean± SD), y	Dose (mean± SD), mg/day	Treatment duration, w	Male/Female, N
Quetiapine				
McElroy et al. 2010 b	38.4	300,600	8	179/282,461
Bowden et al. 2005	38	584	12	60/47,107
Endicott et al. 2008	37.1±11.1	300,600	8	308/390,698
Altamura et al. 2003	50.6±8	157.7±157.6	52	5/9,14
McElroy et al. 2010 a	34±11.2	232	8	9/10,19
Weisler et al. 2009	40.9±11.6	50, 150,300	8	220/302,522
Cutler et al. 2009	41.25±12.1	150,300XR	6	126/168,294
Young et al. 2010	42.5	300,600	8	192/326,518
Calabrese et al. 2005	36.95±11.3	300,600	8	150/192,342
Suppes et al. 2010	39±11.3	300XR	8	45/88,133
Thase et al. 2006	37.7±10.7	300,600	8	137/169,306
Langosch et al. 2008	45.4±11	465±167	52	6/16,22
Liebowitz et al. 2010	45.4±11.2	176.6±95.5XR	52	132/255,387
McIntyre et al. 2005	42.8	600	12	37/64,101
Vieta et al. 2007	34.7	300,600	8	32/41,73
Bortnick et al. 2010	43.3±10.5	162.2±96 XR	8	52/95,147
Aripiprazole				
Sachs et al. 2006	40.4±10.5	27.7	3	69/68,137
Vieta et al. 2005	42.6±11.9	15-30	12	76/99,175
CN138-096*	39±11	17.6±8.3	8	71/115,186
CN138-146*	41±12	15.5±7.5	8	75/112,187
Keck et al. 2006	39±13.2	24.3	26	30/48,78
Keck et al. 2003	40.5±12.7	27.9	3	59/71,130
Kemp et al. 2010	38.2±12.8	15-30	26	27/51,78
El Mallakh et al. 2010	40.3±11.5	15,30	3	128/139,267
Young et al. 2009	40.5	22	12	72/95,167
Ziprasidone				
Keck et al. 2003	39±10.6	130.1±34.5	3	73/58,131
Keck et al. 2009	38.9±11	125.2±31.9	52	61/66,127
Vieta et al. 2010	38.5±11.6	121.4	9	108/70,178
Potkin et al. 2005	38.9±11.6	112	3	68/71,139
Risperidone				
Muller-Siecheneder et al. 1998	41±12.2	8±1.45	6	25/37,62
Smulevich et al. 2005	41.3±13.1	4.1±1.8	12	83/71,154
Hirschfeld et al. 2004	38.1±11.9	4.1±1.4	3	71/63,134
Khanna et al. 2005	34.7±12	5.6±1.2	3	99/47,146

*Unpublished studies

Figure legends

Figure 1: Flow Diagram Describing the Search Process for schizophrenia group

Figure 2: Flow Diagram Describing the Search Process for affective disorder group

Figure 3: Forest plot of the effect size estimates of cholesterol changes (mg/dl) in schizophrenia compared to bipolar disorder patients (p=0.000) by quetiapine treatment. CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figure 4: Forest plot of the effect size estimates of LDL changes (mg/dl) in schizophrenia compared to bipolar disorder patients (p=0.000) by quetiapine treatment. CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figure 5: Forest plot of the effect size estimates of akathisia incidence in schizophrenia compared to bipolar disorder patients (p=0.001) by aripiprazole treatment. CI: confidence interval, DT: diagnostic type, SCZ: schizophrenia patients, BP: bipolar disorder patients.

Figures

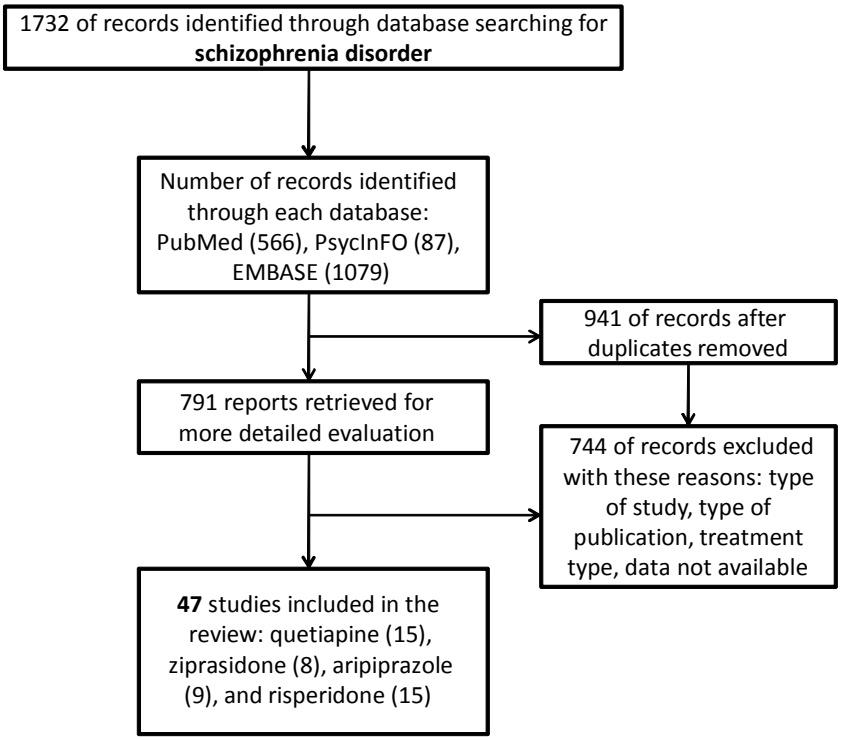

Figure 1

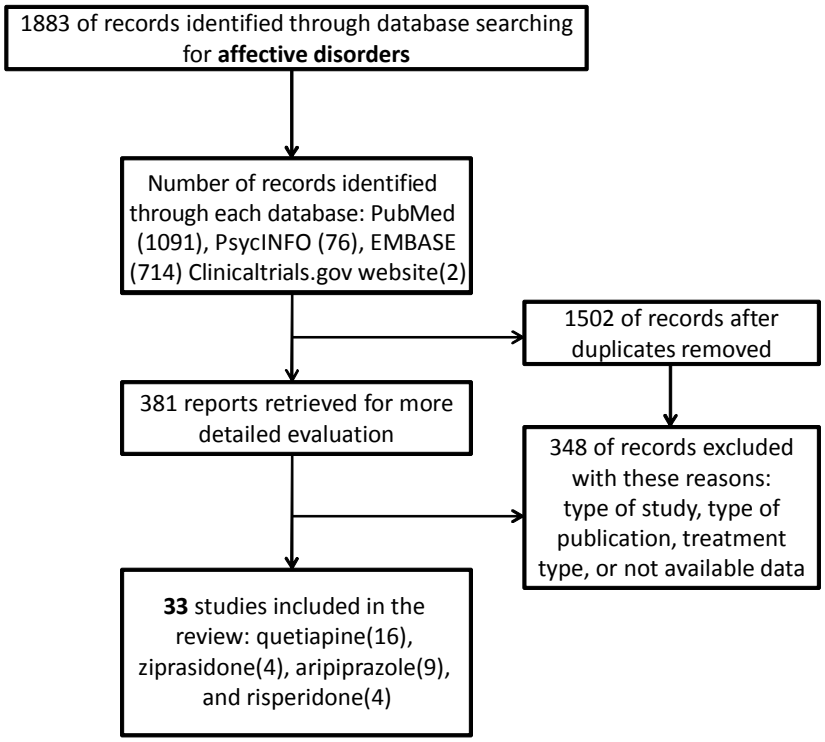
1883 of records identified through database searching for **affective disorders**
Number of records identified through each database: PubMed (1091), PsycINFO (76), EMBASE (714) Clinicaltrials.gov website(2)
1502 of records after duplicates removed
381 reports retrieved for more detailed evaluation
348 of records excluded with these reasons: type of study, type of publication, treatment type, or not available data
33 studies included in the review: quetiapine(16), ziprasidone(4), aripiprazole(9), and risperidone(4)

Figure 2

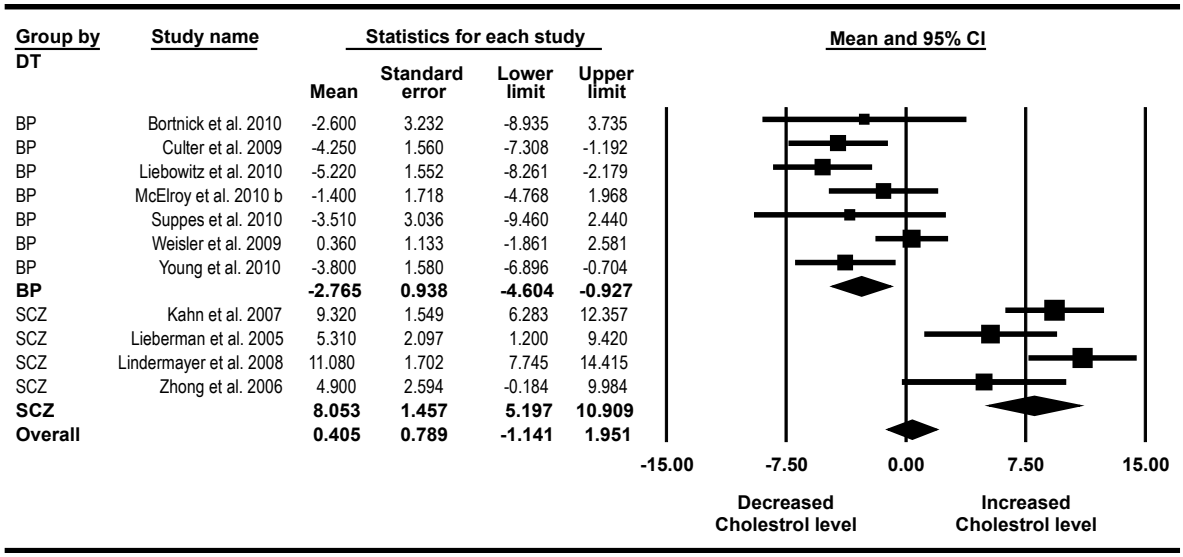

Figure 3

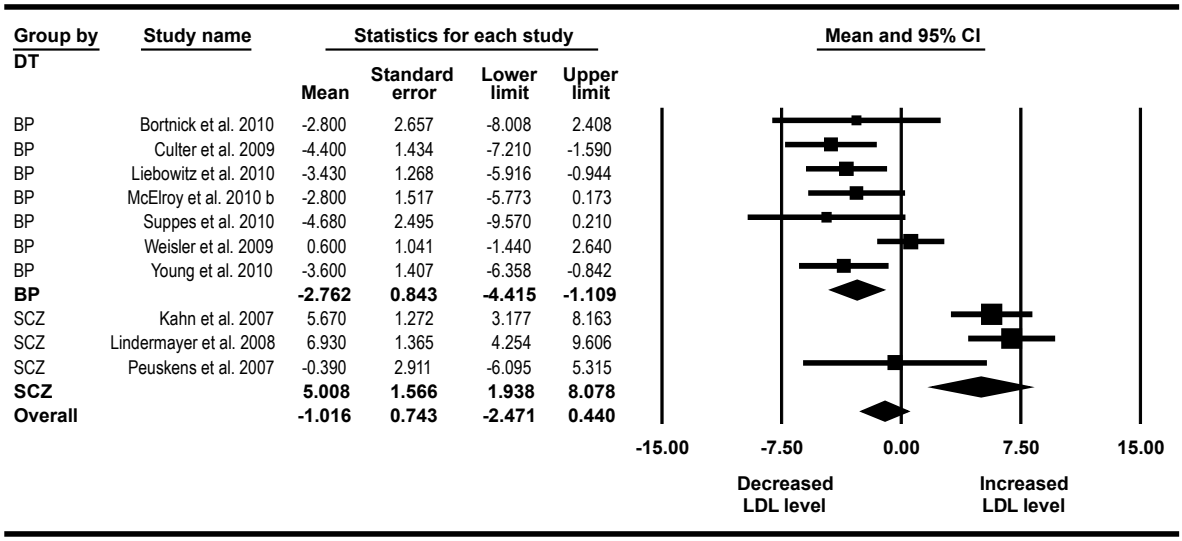

Figure 4

Group by	Study name	Event rate	Lower limit	Upper limit
DT				
BP	CN138-096	0.275	0.215	0.345
BP	CN138-146	0.214	0.161	0.280
BP	El Mallakh et al. 2010	0.124	0.090	0.169
BP	Keck et al. 2003	0.110	0.066	0.178
BP	Keck et al. 2006	0.065	0.027	0.147
BP	Sachs et al. 2006	0.176	0.121	0.250
BP	Vieta et al. 2005	0.114	0.075	0.171
BP	Young et al. 2009	0.114	0.074	0.172
BP		**0.146**	**0.107**	**0.197**
SCZ	Chrzanowski et al.2006	0.050	0.021	0.113
SCZ	Cutler et al 2006	0.022	0.010	0.047
SCZ	Kane et al. 2007	0.039	0.018	0.085
SCZ	Kane et al. 2009	0.091	0.063	0.131
SCZ	Kasper et al. 2003	0.129	0.108	0.153
SCZ	Kerwin et al. 2007	0.014	0.005	0.037
SCZ	McQuade et al. 2004	0.059	0.031	0.109
SCZ	Pigott et al 2003	0.078	0.045	0.133
SCZ		**0.054**	**0.032**	**0.088**
Overall		**0.108**	**0.083**	**0.141**

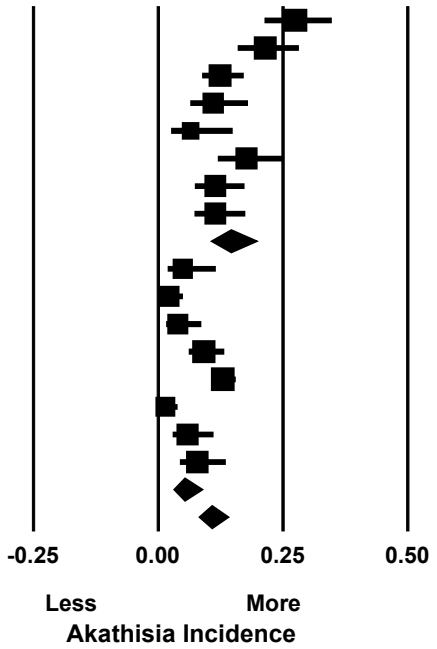

Figure 5

4. CONCLUSION

This meta-analysis illuminates the relative side effect profiles of second-generation antipsychotics when prescribed for schizophrenia and affective disorder patients. The thesis covers the result of the first meta-analysis comparing metabolic and extrapyramidal side effects of second generation antipsychotics in the two groups of patients. It should be noted that in previous studies they have compared side effects of SGAs in patients with a particular disease (e.g., schizophrenia), while this thesis is focused on the difference of SGAs side effects in two psychiatric conditions.

In recent years metabolic syndrome and cardiovascular diseases have become a major concern in the patients with mental disorders who are treated with second-generation antipsychotics (Correll, 2007, De Hert et al., 2011b, Fleischhacker et al., 2008, Mitchell et al., 2012). Patients with schizophrenia have a twofold increased weight gain, diabetes and hypertension (De Hert et al., 2009). The aim in these two meta-analyses was to study the degree of sensitivity and tolerability of SGAs in AD and SCZ patients.

The results of this thesis suggest that schizophrenia patients may be more vulnerable to some SGAs-induced metabolic side effects. Based on the results, olanzapine and quetiapine are associated with more changes in metabolic parameters relative to other SGAs. These findings are consistent with other studies (Rummel-Kluge et al., 2010b, Simon et al., 2009). According to the findings of this thesis, olanzapine induces significantly more weight gain while quetiapine is associated with significantly higher LDL and total cholesterol mean change in schizophrenic patients compared to the AD group.

In these meta-analyses, olanzapine induced significantly more weight gain in SCZ patients compared to the BP group, while with aripiprazole treatment, BP patients gained weight and SCZ patients lost weight. Olanzapine treatment increased blood glucose, cholesterol and triglycerides levels more in schizophrenic patients compared to BP patients. However, these changes were not significant between the two groups. By examining lipid profile of five SGAs between SCZ and BP patients, quetiapine treatment was associated with significant elevation in mean level of total cholesterol and LDL in the SCZ group compared to BP patients. In quetiapine treatment, SCZ patients gained more weight and showed more changes in triglycerides levels; however, these differences were not significant. In addition, for treatment with aripiprazole, risperidone and ziprasidone, no significant difference in metabolic side effects was found between SCZ and AD groups, but the SCZ group showed more elevation in these side effects.

The biological mechanism underlying different metabolic disturbances between SCZ and AD patients in SGAs treatment is not yet clear. Research groups have indicated different aspects of antipsychotic-induced metabolic disturbances in patients with chronic schizophrenia. This meta-analysis proposes that factors such as life style and disease phenotype may contribute to the observed greater susceptibility in the SCZ group. Genetic polymorphism may be an important risk factor influencing SGAs side effects between SCZ and AD patients. In addition to a genetic predisposition for metabolic syndromes among schizophrenic patients, lifestyle risk factors such as stress, poor diet, lack of exercise and smoking are more common in schizophrenic patients (Bai et al., 2011, Liou et al., 2012).

The results on EPS symptoms defined that, in general, affective disorder patients tend to be more susceptible for movement disorders compared to schizophrenia patients with SGAs treatment, except for olanzapine treatment. It has been mentioned in other studies that patients with bipolar disorder are particularly sensitive to the development of EPS. On the one hand, previous studies have shown that treatment of bipolar disorder with first generation antipsychotics is associated with more incidence of EPS compared with treatment of schizophrenia (Nasrallah et al., 1988). On the other hand, results of Cavazzoni et al. (2006) showed that this greater vulnerability in AD groups is only present with first generation antipsychotics treatment and not for olanzapine treatment, which agrees with the findings of our work in regard to olanzapine. In addition, based on the results of the review by Gao et al. (2008) different tolerability in different psychiatric conditions are more likely due to the nature of illness of each individual psychiatric disorder. The exact reasons for different tolerability profiles for SGAs treatments among various psychiatric conditions are unclear. A reduced risk of EPS, especially akathisia, is important and can be expected to improve acceptability of treatment for patients with mental disorders.

In conclusion, side effects are important to consider for prescribers, because the efficacy of treatment may be reduced due to the presence of certain side effects. Therefore, better understanding of SGAs side effects, as far as possible, should be the primary aim of mental disorders treatment. The findings of this thesis, which have primarily focused on SGAs side effects in schizophrenia and bipolar disorder, provide new insight into the prescription of SGAs for different mental disorders and suggest the necessity of respecting

guidelines for screening and regular monitoring, especially for metabolic side effects in patients with severe mental illnesses.

Obviously, these findings need further investigation and the variable confounders are still to be clarified. In the presented meta-analyses the impact of previous exposure to antipsychotic treatments, race/ethnicity, severity of psychiatric illnesses and initial weight in both groups have not been examined, which may impact the generalizability of the findings. Thus, future works may include all these variable confounders in order to improve power and generalizability of this meta-analysis. In addition, it would also be useful to examine other side effects of SGAs such as sedation and somnolence, and compare them among different psychiatric conditions. Studies on safety profile of antipsychotics could help clinicians to better screen and monitor antipsychotic therapy for different mental disorders. Therefore, conducting studies on long-term safety of antipsychotic drugs should be considered a priority in psychopharmacology, as treatment with antipsychotics is often continued for a long period of time or even for the patients' whole life.

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ANNEXE

04 Feb 2012

Dear Dr Stip,

DRS-S-11-01522R2, entitled "Comparing tolerability of olanzapine in schizophrenia and affective disorders: a meta-analysis"

I am pleased to inform you that your manuscript is now acceptable for publication in Drug Safety.

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