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Psychoactive drugs and metabolic disorders

Psicofármacos e alterações metabólicas

Fármacos psicoactivos y cambios metabólicos

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Abstract

Objective: the objective of this article is to promote a literature revision and an overview of evidence of the metabolic impacts of the use of psychotropic drugs on metabolic alterations. **Methods:** a descriptive review, including articles in English and Portuguese, was conducted in the Google Scholar and PubMed databases, using the following keywords: body weight, dyslipidemia, metabolic syndrome and antipsychotics, mood stabilizers and antidepressants on PubMed, and dyslipidemia, body weight , metabolic syndrome associated with antipsychotics, mood stabilizers and antidepressants on Google Scholar. **Results:** 46 articles were analyzed, and 46 articles were included. The review revealed a large amount of evidence concerning body weight changes under psychotropic drugs use and the impact of antipsychotics on the main metabolic variables. However, controversies and scanty evidence regarding mood stabilizers in glycemic and dyslipidemic alterations, and especially about antidepressants in metabolic alterations, were noticed. **Conclusions:** it is concluded that the impact of psychotropic drugs on metabolic changes has great clinical relevance and is characterized as a challenge for modern psychopharmacology. Such alterations, seen as possible side effects of these drugs, directly affect the quality and life expectancy of the patient, therefore, deserving attention to obtain success in psychiatric treatment and and in the holistic health context.

Keywords: psychotropic drugs, drug-related side effects and adverse reactions, metabolic side effects of drugs and substances

Resumo
Objetivo: o objetivo deste artigo é promover uma revisão da literatura e uma visão geral das evidências dos impactos metabólicos do uso de drogas psicotrópicas sobre as alterações metabólicas. **Métodos:** uma revisão descritiva, incluindo artigos em inglês e português, foi realizada nas bases de dados do Google Scholar e PubMed, usando as seguintes palavras-chaves: peso corporal, dislipidemia, síndrome metabólica e antipsicóticos, estabilizadores do humor e antidepressivos no PubMed, e dislipidemia, peso corporal, síndrome metabólica associada a antipsicóticos, estabilizadores do humor e antidepressivos no Google Scholar. **Resultados:** Foram analisados 46 artigos, e 46 artigos foram incluídos. A revisão revelou uma grande quantidade de evidências relativas às mudanças de peso corporal sob uso de drogas psicotrópicas e o impacto dos antipsicóticos sobre as principais variáveis metabólicas. Entretanto, foram notadas controvérsias e escassas evidências sobre estabilizadores de humor em alterações glicêmicas e dislipidêmicas, e especialmente sobre antidepressivos em alterações metabólicas. **Conclusões:** conclui-se que o impacto das drogas psicotrópicas nas alterações metabólicas tem grande relevância clínica e é caracterizado como um desafio para a psicofarmacologia moderna. Tais alterações, vistas como possíveis efeitos colaterais dessas drogas, afetam diretamente a qualidade e a expectativa de vida do paciente, portanto, merecendo atenção para obter sucesso no tratamento psiquiátrico e no contexto holístico de saúde.

Palavras-chave: drogas psicotrópicas, efeitos colaterais e reações adversas relacionadas a drogas, efeitos colaterais metabólicos de drogas e substâncias

RESUMEN:
Objetivo: El objetivo de este artículo es promover una revisión de la literatura y una visión general de la evidencia sobre los impactos metabólicos del uso de drogas psicotrópicas en las alteraciones metabólicas. **Métodos:** Se realizó una revisión descriptiva, incluyendo artículos en inglés y portugués, en las bases de datos Google Scholar y PubMed, utilizando los siguientes contraseñas: peso corporal, dislipidemia, síndrome metabólico y antipsicóticos, estabilizadores del estado de ánimo y antidepresivos en PubMed, y dislipidemia, peso corporal, síndrome

metabólico asociado a antipsicóticos, estabilizadores del estado de ánimo y antidepresivos en Google Scholar. **Resultados:** Se revisaron 46 artículos y se incluyeron 46 artículos. La revisión reveló una gran cantidad de pruebas sobre los cambios en el peso corporal bajo el uso de fármacos psicotrópicos y el impacto de los antipsicóticos en las variables metabólicas clave. Sin embargo, se observaron controversias y escasas pruebas sobre los estabilizadores del estado de ánimo en los cambios glucémicos y dislipidêmicos, y especialmente sobre los antidepresivos en los cambios metabólicos. **Conclusiones:** Se concluye que el impacto de los psicofármacos en las alteraciones metabólicas tiene gran relevancia clínica y se caracteriza por ser un reto para la psicofarmacología moderna. Dichas alteraciones, vistas como posibles efectos secundarios de estos fármacos, afectan directamente a la calidad y esperanza de vida del paciente, por lo que merecen atención para lograr el éxito en el tratamiento psiquiátrico y en el contexto de la salud holística.

Palabras clave: fármacos psicotrópicos, efectos secundarios y reacciones adversas relacionados con los fármacos, efectos secundarios metabólicos de los fármacos y sustâncias

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Introdução

The advent of modern psychopharmacology began in the mid-1940s with the introduction of drugs for psychiatric treatment purposes. Until the late 1950s, five major groups of drugs were known to be able to promote positive and significant clinical effects in psychiatric disorders: Antipsychotics, Tricyclic Antidepressants, MAO-inhibitors Antidepressants, Anxiolytics and Mood Stabilizers [1]. Initially, in the 1960s, reports of

adverse effects with glycemic alterations in patients using antipsychotics began to emerge, promoting treatment adherence difficulties and clinical challenges in drug management [2]. Antipsychotics such as Clozapine, Olanzapine, and Risperidone have high impact evidence on metabolic variables [3] and, in a corroborating way, studies show alterations in metabolic variables, more precisely in body weight, due to the use of mood stabilizers for the disorder bipolar mood treatment, for example [4].

Therefore, it is evident the growing lines of research that demonstrate side effects on relevant variables in metabolism under the use of psychotropic drugs in general. In addition, multiple metabolic alterations that influence weight gain, including: alterations in lipid and glycemic metabolism under the use of tricyclic class antidepressants, MAO-inhibitors antidepressants, atypical antidepressants, as well as mood stabilizers, such as lithium carbonate, started to have growing amount of evidence over the years [5–7].

In the face of pharmacological advances, there was the development of new classes of psychotropic drugs with reduced side effects, with emphasis on the group of antidepressants, such as the Selective Serotonin Reuptake Inhibitors (IRSS). Headed in the 1980s by the advent of fluoxetine through of its commercialization, this group was more recognized as Prozac, and promoted a revolution in psychopharmacology for its mechanisms of action with low metabolic impacts and side effects. This way, it created an alternative for partial reduction in the context of psycho-drug influences on increasingly metabolic alterations evidenced [6] in the context of depressive treatment. However, the impact of other psychotropic drugs, such as mood stabilizers and antipsychotics, on metabolic variables is still a current context and a clinical challenge to be elucidated.

Given the above, the objective of the present study focuses on promoting a review of the literature on the metabolic impacts and body weight impacts, with emphasis on glycemic and lipid metabolism issues, associated with the use of psychotropic drugs.

Methods

A search, considering articles published in English and Portuguese and without date limitation criteria, was conducted in bibliographic references, in the Google Scholar and PubMed databases. For research on PubMed and Google Scholar, the following titles were used: diabetes, dyslipidemia,

metabolic syndrome and antipsychotics, mood stabilizer and antidepressants. For Google Scholar, the titles were: dyslipidemia, diabetes, metabolic syndrome in association with antipsychotics, mood stabilizers and antidepressants.

Results

Weight gain induced by psychotropic drugs

The use of drugs for the treatment of mental illnesses can result in weight gain as a considerable side effect. Several studies analyze the significant impact of weight gain associated with the use of antipsychotics [8] and the use of mood stabilizers [9]. The incidence of overweight and obesity in the population that uses psychotropic drugs has clinical relevance in terms of reductions in quality of life and negative influences on the physical and mental spheres of patients with diagnosed psychiatric disorders [10], reflecting the importance of weight monitoring and clinical management of according to the reported clinical repercussions.

Psychotropic drug-induced weight gain has a multifactorial trigger, but it is strongly associated with changes in satiety mechanisms. In antidepressants, significant weight gains are reported for amitriptyline (1.52kg), mirtazapine (1.74kg) and nortriptyline (2.00kg), in addition to not having seen substantial gains with the use of different tricyclic antidepressants [11]. Evidence have evaluated the impact of changes in neurotransmitter systems on weight gain, with dopaminergic and histaminergic receptors being linked to satiety mechanisms and adrenergic receptors with stimulation of increased appetite [12].

Influences of psychotropic drugs on hypothalamic mechanisms of satiety/appetite also have strong evidence. Changes in the secretion of orexigenic and anorexigenic neuropeptides associated with the use of antipsychotics and their mechanisms of action in the dopaminergic blockade reflect a higher proportion of orexigenic as an evidenced adverse effect [13]. In addition, blockades of serotonergic receptors are also related to increased appetite and, consequently, induced weight gain, suggesting that patients with mutations in the coding genes of such receptors are more susceptible to body weight gain when using such psychotropic drugs [14].

According to Abosi et al. [11], several psychotropic drugs antagonize histamine (H1), serotonin (5-HT2a, 5-HT2c) and alpha-1 adrenergic receptors, therefore, the affinity of psychotropic drugs for many of these

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receptors is related to weight gain. In addition, the blockade of H1 receptors can culminate in an increase in carbohydrate intake and, consequently, collateral weight gain [11].

Regarding mood stabilizers, it is suggested that thyrotoxicity and the incidence of subclinical hypothyroidism associated with its use are related to weight gain as an adverse effect [5]. However, other hypotheses point to the side effect of psychotropic drugs in the modulation of leptin and adiponectin. As leptin is a hormone responsible for controlling food intake and maintaining body weight through the protein kinase B (PKB) phosphorylation mechanism, when it is in the presence of psychotropic drugs such as lithium, there is a blockage in the ability of leptin to reduce food intake and, consequently, a weight gain promotion, suggesting a reduction in leptin sensitivity in the face of the concomitant use of some psychotropic drugs [14-15]

Glycemic alterations induced by psychotropic drugs

The emergence of psychopharmacotherapy was revolutionary, however, such advances did not come without burden. The report of an increase in the number of cases of diabetes mellitus (DM) around the 1960s, along with the increasing consumption of psychotropic drugs, led to investigations that culminated in evidence of an association between increased blood glucose levels, or the emergence of DM, and a secondary side effect of the use of psychiatric drugs in several studies, mainly associated with atypical antipsychotics such as clozapine and olanzapine [16].

Arranz et al. [17] demonstrated in a controlled study that the previous use of antipsychotics in patients with schizophrenia causes a decrease in insulin sensitivity and hyperinsulinemia, common comorbidities in this diagnosis [17]. Furthermore, within the most common antipsychotic groups, the ones most associated with DM are chlorpromazine and thioridazine, while haloperidol is the one that provides the lowest risk [16]. There is evidence that the use of aripiprazole can improve glucose metabolism disorders caused by other antipsychotics as observed in the clinical trial by Littrell et al. [18].

The main mood stabilizers, lithium and valproic acid (VPA), have been highlighted to cause disturbances in glycemic metabolism, however, in a secondary way to weight gain, but holistic understandings of such changes

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and their significant impacts have not been fully elucidated yet [16]. In a six-year clinical trial, in which the fasting blood glucose of patients undergoing treatment with lithium was evaluated, no changes were observed in the mean values of serum glucose among the participants. Only one patient developed a condition of DM, although there was a relative increase in body weight among patients during the treatment period [16, 19].

Dyslipidemias induced by psychotropic drugs

Dyslipidemias caused by psychotropic drugs are mostly secondary effects of weight gain. The exact mechanisms for the change in the lipid profile have not been fully clarified yet, however, such alterations may arise with considerable weight gain due to previously prescribed drugs and/or increases in lipid biosynthesis through gene expressions of enzymes essential for lipid metabolism [20].

Some psychotropic drugs, such as holoperidol, clozapine and rispiridone, are involved in the inhibition of enzymes associated with lipid metabolism, which promotes an increase in the concentrations of intermediates other than cholesterol synthesis and contributes to the increase in lipids such as triglycerides [21].

According to Teixeira and Rocha [16], antipsychotics such as clozapine and olanzapine are the most cited drugs in relation with increases in total cholesterol, LDL-cholesterol and HDL-cholesterol [16]. As for other antipsychotics, the results were questionable or contradictory. The controversy regarding the impact of antipsychotics on dyslipidemic changes is also evidenced in a literature review on systematic reviews evaluating their effect on the triggering of metabolic syndromes (MS), in which the authors point out the still persistent inconclusiveness on the subject and verify the need for further prospective studies to accurately measure the risk of incidence of hyperlipidemia, hypertension and diabetes in patients exposed to treatment with antipsychotics [22].

In addition, another recent study reports that clozapine and olanzapine are responsible for a greater impact on weight gain, but that the evidence for the different effects of antipsychotics on glucose and lipid metabolism is not convincing [23].

However, Galling et al. [24] in their clinical trial, mentions effects of reducing total cholesterol and LDL cholesterol under the use of partial

dopamine D2 agonists, such as aripiprazole (SMD=-0.33, 95% CI=-0 .55, -0.11, p=0.003; SMD=-0.33, 95% CI=-0.54, -0.10, p=0.004) [24]. This evidence supports previous findings [25, 27] and the most recent ones [28]. Concerning mood stabilizers, studies are contradictory about dyslipidemia, demonstrating, in some cases, possible beneficial effects in patients who used valproic acid or carbamazepine [16, 29].

Discussion

Mood Stabilizers

Increased body weight is among the main side effects of using mood stabilizers. According to Malhi et al. [4], the use of valproic acid (VPA) and lithium is associated with weight gain, increased appetite and alterations in the metabolism of lipids and carbohydrates, in addition to endocrine disruptions that may lead to the development of hypothyroidism [4]. Drug intervention based on lithium carbonate and valproic acid has been reported, respectively, to lead to weight gains between 0.2 and 1.1 kilograms in 12 weeks [30], however, weight gain has less impact under the use of the drug carbamazepine.

A study conducted by Carman et al. [31], highlighted a superior and statistically significant weight gain (p = 0.001) in the group using valproic acid compared to the carbamazepine group, demonstrating data with a 47% gain of more than 10% of the body weight and a 24% incidence of weight gain of 5-10% after initiation of VPA therapy in adults [31].

As for the mechanisms associated with weight gain under the use of mood stabilizers, evidence shows that the increases in body weight induced by VPA use are not yet fully understood, however, it appears to be related to hypothalamic alterations in the gene expression of neuropeptides associated with the control of energy metabolism, changes in adipokines, and reduced levels of resistance to ghrelin and leptin that are associated with increases in energy intake and the etiology of obesity [32].

Alterations in glucose metabolism have not been directly associated with the use of the main mood stabilizers (Lithium and valproic acid), with the hypothesis that secondary changes derived from weight gain [5]. In a corroborating way, changes in glucose sensitivity and the triggering of long-term diabetes mellitus (DM) were not reported by Vestergaard in a 6-year study period [19].

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Finally, dyslipidemias associated with the use of mood stabilizers have controversial evidence. Positive effects linked to an increase in circulating HDL in epileptic children taking valproic acid or carbamazepine, compared to the control group, have been reported [29]. On the other hand, other studies do not show significant changes in HDL and triglyceride levels associated with the use of valproic acid or carbamazepine [33, 34]. Verrotti et al. [32] points out that the mechanisms implicated in elevations in insulin concentrations induced by mood stabilizers, such as VPA, are correlated with effects on pancreatic β cells, on sympathetic nervous system and ketacolaminergic responses, and on increases in plasma levels of long-chain fatty acids (LFA) [32].

Antidepressants

Regarding changes in body weight and among the different classes of antidepressants, serotonin reuptake inhibitors (SSRIs) are among the drugs with the lowest relative risk of weight gain. An 8-week study reported that a 7% increase in body weight was found in only 0.5% of patients treated with citalopram compared to 0.9% who were treated with placebo [35].

According to Fava [6] studies with SSRI with an acute approach suggest that weight gain associated with its short-term uses are unlikely, however, long-term treatment may be linked to weight gains [6]. In a 1-year long-term evaluation study under antidepressant treatment, weight gain was considerably greater with mirtazapine (29%), tricyclic antidepressants (TCA) (22%), and ultimately serotonin reuptake inhibitors (SSRIs) (19%) [36].

However, a 26-week study of continuous treatment with fluoxetine 20mg/day showed that only 4.8% of patients had weight gain of the order of 7% of body weight, a rate close to the one found in the placebo group with 6.3% [37]. Some researchers point to serotonergic alterations associated with the use of SSRI as a hypothesis for the pathophysiology of weight gain associated with the use of serotoninergic reuptake inhibitor antidepressants [6, 38].

According to Aronne and Segal [38], selective serotonin reuptake inhibitors (SSRIs) have mechanisms of appetite reduction effects via central anorexigenic food control pathways, in contrast, antidepressants from the monoamine oxidase inhibitor (MAOI) and antidepressants tricyclic (TCA)

classes may promote increases in energy intake via increased sensitization of central orexigenic food control pathways [38].

As for glycemic changes associated with the use of antidepressants and their different classes and mechanisms of action, the scientific literature is still scarce; however, changes in glucose metabolism related to insulin sensitivity associated with the use of antidepressants have reports of mediation through hippocampal levels due to neurohormonal effects of metabolism. Futhermore, tricyclic antidepressants are the only ones associated with possible alterations in glycemic metabolism [39].

Eker et al. [40] identified comparisons of glycemic parameters of patients undergoing treatments with antidepressants and from that, reductions in pre- and post-treatment fasting glycemia were identified, but without statistical significance (89.34±6.64 x 87.31±9, 44; p=0.130), differently for the pre- and post-intervention HOMA index patterns (3.29 (1.73) x 2.82 (1.76); p=0.059) [40].

In the case of dyslipidemic alterations, the results are conflicting. Eker et al. [40] identified studies with significant associations detected for the use of SSIR and reduction in circulating HDL, increase in triglycerides and total cholesterol, but , point out in their discussions that they observe in their results levels of total and HDL cholesterol increased in the escitalopram group, while there was no change in the other drug groups and that the heterogeneity of findings in different evidence suggests that different types of serotonin reuptake inhibitors can promote different changes in the lipid profile [40]. The effects of antidepressant use on glycemic and lipid metabolism is still unclear and needs further studies to better understand.

Antipsychotics

Weight gains are among the most evidently reported side effects of antipsychotic use. According to Gramaglia et al. [41] especially second-generation antipsychotics, such as Clozapine, Olanzapine and Risperidone, also seem to influence the triggering of metabolic syndrome (MS), thus, increases in food intake, weight gain, and elevations in hepatic lipid deposits and adipose tissue are correlated [41].

A current systematic review points to Aripiprazole, Risperidone, Olanzapine, Clozapine, and Quetiapine among the class representatives with the greatest impact on the increase (7%) of body weight (32%) [3].

Such evidence corroborates some findings by Allison et al. [42], in a previous systematic review, in which was demonstrated an average weight change followed by 10 weeks of treatment, in which the drug use of Clozapine, Olanzapine and thioridazine are among the three drugs with the greatest impact on body weight change (+ 3.99 kg), (+ 3.51 kg), (+ 3.49 kg), respectively [42].

In a 14-week double-blind trial, the authors report a strong positive association between weight gain and the use of clozapine and olanzapine, but a weak association between haloperidol and risperidone [18]. Among the mechanisms explaining weight gain associated with antipsychotic use, it has been reported that dopaminergic blockade triggered by antipsychotics has orexigenic adverse effects and that antipsychotics involved in blocking histamine H1 receptors have been associated with increased appetite and weight gain [16]. However, other receptor types such as 5-HT2A and 5-HT2C have also been targets of importance in understanding such factors of antipsychotic activity.

According to Cordás and Kachani [43] antipsychotic-induced weight gain would be related to a combination of an increase in caloric intake and a reduction in physical activity and basal metabolism, pointing to evidence that suggests a nutritional monitoring program for patients using atypical antipsychotics [43]. In 2004, the Food and Drug Administration (FDA) warned about monitoring the metabolic parameters of all patients using antipsychotics, especially those with greater impacts and changes in body weight.

In addition, pharmacological strategies to combat antipsychotic-induced weight gain have grown in the field of research. According to Mizuno et al. [25], non-pharmacological strategies in isolation, as well as the pharmacological exchange for neutral agents in weight gain, are insufficient for the purposes of efficient control of antipsychotic-induced weight gain and support the use of metformin as an intervention to counteract such bodily changes.

As for the glycemic and dyslipidemic changes, experimental evidence demonstrates inhibition of glucose transporters (GLUT) in peripheral and brain cells of rats, thus indicating possible mechanisms associated with glycemic alterations induced by psychotropic drugs, especially clozapine and olanzapine [26].

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However, glycemic changes secondary to weight gain and increased adiposity induced by antipsychotics may also be among the etiological mechanisms of glucose alterations due to their use, and given that changes in insulin sensitivity are relevant to the development of alterations in lipid metabolism, these may concomitantly possess explainable mechanisms for the development of dyslipidemic changes.

Changes in plasma concentrations of adrenaline and noradrenaline under clozapine treatment have been identified that may promote new insights into the mechanisms of glycemic and lipid alterations from increased hepatocellular activity in the release of plasma glucose, thereby ruling out isolated influences of weight gain and adiposity [44, 45].

Although, evidence prove that the combined or isolated use of aripiprazole have positive and/or non-significant impact on glycemic and lipid metabolism [28, 46].

Srisurapanont et al. [28], reported a reduction in total and LDL cholesterol levels under therapy with the combined use of aripiprazole and other antipsychotics when compared to clozapine monotherapy (MD-11.06 (95% CI-18)., 25, -387) [28], supporting previous reports that evaluated concomitantly glycemic, circulating total cholesterol and circulating LDL cholesterol changes under the association with aripiprazole, and did not related statistically significant assessments (p=0.41) in blood glucose levels.

However, showed a considerable association in the reduction of average total cholesterol mg/dl (MD -12.81 (95% CI -19.35, -6.27) and LDL mg/dl (MD - 11.69 (95% CI -19) .12, -4.26) compared to clozapine or olanzapine monotherapy [42].

According to Ijaz et al. [22], a hypothesis for a reduction in metabolic and dyslipidemic side effects with the monotherapy or combined use of aripiprazole may be related to its action on the serotonergic and non-dopaminergic system, as it differs from other atypical antipsychotics, such as clozapine and olanzapine, it acts as a partial agonist at dopamine D2 receptors and has a high affinity for serotonin 5-HT2C receptors.

Conclusion

The present review allows the conclusion that the impact of psychotropic drugs, such as mood stabilizers and antipsychotics, on metabolic alterations have considerable clinical repercussions and is a challenge for modern psychopharmacology. Changes in body weight, with significant weight gains, are verifiable in patients treated with medications such as olanzapine, quetiapine, valproic acid and lithium, which can lead to numerous comorbidities and reduced life expectancy.

In addition, glycemic and dyslipidemic alterations and those that influence the incidence of type II diabetes mellitus (DM II) in individuals undergoing treatment with antipsychotics have considerable and growing evidence in the literature, however, with results that are still inconclusive and require further studies, under the impact of mood stabilizers on blood glucose and lipid profile.

Pharmacological strategies to combat the metabolic alterations induced by psychotropic drugs are growing as a field of scientific investigation, nonetheless, there is still a need for larger amounts of consolidated evidence for precision in therapeutic use. There was a reduced density of evidence and research on the metabolic impact of the use of antidepressants and their different classes, a context from which more research is needed on the subject for a better understanding of the side effects of antidepressants on glycemic and lipid metabolism.

Finally, knowledge about the main metabolic changes promoted by different psychotropic drugs and their different relative impacts is important for psychiatric and nutritional assessment, with the aim of providing better guidance to the patient about healthy habits and eating in order to minimize side effects associated with treatment.

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