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PHARMACOLOGICAL ADD-ON TREATMENTS IN MANAGING ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

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ABSTRACT

Introduction: One of the most common antipsychotic (AP) related adverse drug reactions is weight gain, with a large proportion of patients started on AP even from the onset of schizophrenia, ending up gaining considerable weight.

Aim: The study was designed to research current evidence for reducing weight gain through pharmacological supplementation or other practical interventions, in patients treated with APs.

Method: A review of the published works found on MEDLINE and PubMed from 2015 to 2019 was done, concentrating mostly on research that specifically examined changes in body weight in individuals taking AP medications along with various pharmaceutical supplements. There were 14 major eligible articles found and examined. We have concentrated on many meta-analyses that evaluated various pharmacological classes, including appetite suppressants, anti-obesity medications, anti-diabetics, gastrointestinal medicines, and anticonvulsants, in avoiding or lowering weight gain in patients receiving AP.

Conclusions: Maintaining a balanced weight has a major impact on the patient's quality of life. In addition to having a detrimental effect on the patient's physical and mental health, weight increase makes it more challenging for them to adhere to their treatment schedule. Antipsychotics can cause weight gain, however, there are numerous effective treatments for this condition. Given that they are both well tolerated in the short term, we found topiramate and metformin to be the most effective among them when compared to a placebo. To advance this topic, larger and more comprehensive investigations are required.

Keywords: Weight gain, antipsychotics, add-on treatments.

INTRODUCTION

Patients with Schizophrenia and other related disorders have a much shorter life expectancy. When suicide is excluded as a cause of early death, schizophrenia has a 150% increase in mortality compared to the average person. This can be explained by impairments of the cardio-vascular system associated with the main medical condition (Tek et al., 2016). Smoking, obesity, metabolic syndrome, and diabetes are the primary risk factors (Ciubara et al. 2018; Rajan et al., 2017).

As a severe and chronic illness, schizophrenia alters a person's behavior and ability to think and feel

(Ciobotea et al. 2016; Valcea et al., 2016). Even though antipsychotics (AP) are the first-line therapy for schizophrenia spectrum disorders, only 50% of patients respond and remit to AP monotherapy. Apart from an increased side effect spectrum, adjunctive strategies are often needed to increase efficacy. Several side effects are associated with AP, such as weight gain and metabolic syndrome (Zhang et al., 2016). Studies with AP naive patients are the most revealing on the capacity of a specific AP to produce weight gain (Bak et al. 2014). More than 75% of debut episode schizophrenia patients experience significant weight gain, which often reduces treatment adherence drastically (Zheng et al., 2019).

One of the initial comprehensive meta-analyses to study weight gain in patients treated with AP was by Allison et al. in 1999. The results of this study caused a systematic shift in how trials regarding AP treatments were conducted, and attention to weight gain became the norm (Zhang et al., 2016). Effects on weight and Body Mass Index (BMI) progress over time with the duration of AP use, was an important risk factor (Chirita et al. 2012; Untu et al., 2015). The main explanation at that time was based on changes in appetite and food intake, caused by interactions with the serotoninergic, histaminergic and dopaminergic pathways (Tek et al., 2016). Other factors have been brought into light such as genetics, with polymorphisms of the 5-HT2c receptor (Rc) and H1, H3 histamine Rc affinity, environment, and lifestyle choices of Schizophrenic patients (Zheng et al., 2019).

This study's major goal was to provide information on some of the contemporary possibilities and overall effectiveness of add-on pharmaceutical treatment in avoiding and lowering weight gain in schizophrenic patients using AP.

METHODS AND RESULTS

The primary author completed a literature review of relevant articles from databases such as PubMed and MEDLINE from 2015 to 2019. The primary research direction was on meta-analyses that compared weight changes of patients that are on AP medication while supplementing with different pharmacological agents or non-pharmacological interventions.

The search terms included (“meta-analysis”) AND (“antipsychotics” OR “AP”) AND (“schizophrenia”) AND [(“weight gain” OR “obesity”) OR (“BMI change” OR “Body Mass Index)]. The research also extended to the reference list of the main articles.

A total number of 1229 search results were obtained from which 14 eligible articles were identified and reviewed. The primary author had the responsibility of selecting the studies, extracting the data, and writing the main draft of this paper, and the bias potential had been tasked to the co-authors. Out of the 14 meta-analyses, 3 reviewed the effects of Topiramate in preventing AP-induced weight gain, 2 of Metformin, 1 the effects of Glucagon-like peptide-1Rc agonists, 2 reviewed non-pharmacological interventions, 1 reviewed the effects of Metformin with non-pharmacological interventions and 2 reviewed multiple other agents and non-pharmacological interventions; also 2 meta-analyses that reviewed the risk to the experience weight gain associated with a certain AP and 1 meta-analysis that reviewed pharmacogenetics.

RISK ASSESSMENT AND PHARMACOGENETICS

Patients with schizophrenia have a considerably higher risk than the general population of cardiometabolic morbidity. Atypical antipsychotic medications cause weight gain, which increases this risk. Jacob Spertus et al. published a meta-analysis in 2018 of 14 randomized clinical trials with 5923 patients, evaluating the impact of several second-generation antipsychotics on weight gain in comparison to a placebo. In this case, weight gain is defined as an increase in body weight of at least 7%. According to the study, taking olanzapine, risperidone, or paliperidone significantly raised the risk of gaining too much weight by an average of 12.6%, 6%, and 4.6%, respectively (Spertus et al., 2018).

Cenk Tek et al., 2016 meta-analysis reviewed 28 eligible studies with 52 appropriate treatment arms with a total number of patients equal to 4139 (2594 male, 1545 female). Comparing risks of weight gain with different AP in correlation with treatment duration for first-episode psychosis patients. The analysis of the chosen studies revealed an overall mean weight increase difference between AP and placebo of 3.22 kg for the short-term findings (12 weeks). Ziprasidone stood out among the second-age AP in that it did not cause a large short-term weight increase (Tek et al., 2016).

The results for long-term (>12 weeks) treatment observed a significant increase in overall mean weight difference with 5.30 kg between AP and placebo. The highest weight gain compared to placebo was observed for Olanzapine with 9.34 kg and Clozapine with 7.19 kg. Asian populations seem to be less affected than western populations by weight gain from AP medications. Most APs were linked to a significant increase in body weight even for early psychosis patients, with a short duration of treatment (Tek et al., 2016).

Genetic variables are crucial in determining which individual will be less affected by the metabolic adverse effect of AP treatment. Multiple genes have been studied that have shown a direct association with obesity,

but an inclusive pharmacogenetics study of AP-related weight gain is missing (Zhang et al., 2016).

Jian-Ping Zhang et al. investigated 2016, 38 single-nucleotide polymorphisms (SNPs) in 20 genes or genetic regions from 6770 patients. These SNPs were distributed in 15 chromosomes that have been documented to have associations with antipsychotic-related weight gain. The 13 SNPs most significantly associated with AP-related weight gain came from nine genes. HTR2C was the gene among these that were most frequently linked to weight increase brought on by antipsychotics. There was also some evidence linking the ADRA2A gene, DRD2 gene, GNB3 gene, MC4R gene, and INSIG2 gene to AP-related weight gain. The clear result was that AP-induced weight gain has a polygenic determination and has a wide range of distinct genetic variations, particularly in genes encoding AP pharmacological targets (Zhang et al. 2016).

TOPIRAMATE

Topiramate is an anticonvulsant that blocks AMPA-kainate-gated Na+ channels and is a positive modulator of GABA Rcs (Zhuo et al., 2018). The potential mechanisms of action include the presynaptic release of glutamate with excessive glutamate neurotransmission through kainate Rcs lowering the level of excess dopamine and prolonging stimulation of AMPA/KA Rcs with inhibitory action of the glutamate system, blunting the effects of the ionic calcium and sodium channels on modulating GABA-A Rcs. The following are some of the mechanisms for losing weight and enhancing metabolic parameters: reducing hunger by insulin-sensitizing actions that directly positively modulate insulin activity, lowering blood sugar levels and insulin levels, and enhancing the action of lipoprotein lipase in the muscle tissue and the adipose tissue while inhibiting the action of carbonic anhydrase enzymes who are involved in the process mitochondrial and cell lipogenesis (Zheng et al., 2016).

Liang et al. (2016) in their study, proposed a comparison test between Topiramate and placebo constructing a meta-analysis from a total of 10 studies, consisting of 453 subjects treated with AP. The results showed Topiramate to be moderately effective in reducing AP-related weight gain (WMD = -1.82 kg), BMI change (WMD = - 1.31 kg/m^2), and fasting glucose increase (SMD = -1.15). It did not find significant evidence of Topiramate having a regulatory effect on lipid metabolism and no improvements in clinical symptoms using PANSS were observed (Liang et al. 2016).

Zheng et al. (2016) demonstrate in a meta-analysis of 16 RCTs with 934 patients, that topiramate added to the AP treatment scheme either as an augmentation therapy or co-initiated is far superior that AP monotherapy. Benefits were seen in lowering body weight, BMI, serum triglycerides, fasting insulin, and in general psychopathology symptoms. The medium dose of Topiramate was between 164.9mg/day and 70.4 mg/day (median 139.0 mg/day) with a range between 50mg/day and 300 mg/day. This study showed an advantage in concomitant initiation of topiramate, and AP versus adding topiramate after the patient had already gained weight (3.5kg loss vs 1.5 kg loss) (Zheng et al., 2016).

Kah Kheng Goh et al. 2019 meta-analysis reviewed if Topiramate can mitigate weight gain in AP-treated patients. It consisted of 10 double-blinded randomized placebo-controlled studies and seven of them open-label randomized controlled trials which in total had 905 patients. Topiramate adjunctive therapy led to significant weight reduction (-3.76 kg) in patients with schizophrenia and a significant BMI reduction (1.62 kg/m^2) in these patients. The effect of treatment differed with patient race and ethnicity, but topiramate seemed to significantly improve psychopathology when compared to the control group. The only adverse effect that occurred more frequently was paresthesia. (Goh et al. 2019).

METFORMIN

Metformin is an antihyperglycemic biguanide used in the first-line treatment of type 2 diabetes mellitus. By blocking hepatic gluconeogenesis, it helps in keeping blood glucose levels constant and raises peripheral insulin sensitivity. It has a well-tolerated profile, and it is rarely associated with hypoglycemia because it does not increase insulin production. People with type 2 diabetes and prediabetes who take metformin lose weight. Appetite suppression and elevation of glucagon-like peptide-1 secretion, which slows stomach emptying, are thought to be the mechanisms that cause weight reduction. Metformin also enhances the action of insulin in the liver which causes a reduction in the rate of hepatic glucose production. AP-induced hyperprolactinemia and prolactin-related symptoms in schizophrenia have been demonstrated to be ameliorated by metformin. (Zheng et al., 2019). Although several studies had shown it to be effective in managing AP weight gain, there are still no clear clinical guidelines in use. (8) Metformin may be associated with lowered levels of folate and serum vitamin B12 which needs constant monitoring in long-term use (Jarskog et al., 2013; Zheng et al., 2019).

Varuni Asanka de Silva et al. (2016) published a meta-analysis of 12 studies, that compared the use of metformin to placebo in patients treated with AP, two of the studies were for children, with a total of 743 patients. It reveals that anthropometric and metabolic parameters improve noticeably when metformin is used concurrently with other treatments. Weight loss was significantly higher (-3.27 kg) and BMI was

significantly more diminished (−1.13 kg/m^2) when administering metformin compared to placebo in patients treated with antipsychotics. In nine investigations, it was discovered that metformin medication significantly reduced the insulin resistance index IRI (by 1.49 points) compared to placebo. Additionally, it appears that metformin works better in first-episode patients treated with AP to avoid weight gain than in chronic patients who have already put on weight. The data analysis of subgroups reveals that these 5 trials which included first-episode patients, had a mean difference in weight of −5.94 kg, which compared to the trials of chronic patients of −2.06 kg, was much larger. Pointing towards metabolic changes that occur with continued use of AP. In the first few weeks, patients who are naive to AP treatments gain weight quickly and steadily. The mean weight gain in this subset of patients at 12 weeks is 3.8 kg, with a one-point increase in BMI; this weight gain persists throughout the course of AP treatment. Ten of the studies in the meta-analysis did not find any significant evidence of metformin's effect in reducing fasting blood glucose in these patients (de Silva et al., 2016).

In 2015 Wei Zheng et al. published a meta-analysis of 21 studies about weight gain and metabolic abnormalities in patients treated with AP. Out of the 21 studies, 11 were published in English and 10 in Chinese, with a total of 15 hundred patients half on metformin and half on placebo. In anthropometric variables, concomitant treatment with metformin was significantly superior to placebo in weight gain, BMI, and waist circumference. Fasting glucose, fasting insulin, the homeostasis model evaluation insulin resistance score, and glycosylated hemoglobin A1c all showed that metformin had a much better impact on glucose metabolism when compared to placebo. Metformin was also significantly superior to placebo in its effects on serum lipids such as total cholesterol, TG, and HDL but not in LDL. The metformin group was also shown to have significantly lower levels of leptin. The recommended dose of add-on metformin from this study is 750 mg/day and even lower for Chinese patients. Ethnic differences between east Asians and Caucasians influence fat distribution. In the metformin group, side effects such as nausea and/or vomiting were around 14% of patients and diarrhea was 7%, resulting that monitoring for these side effects being mandatory (Zheng et al., 2015).

GLP-1RA (GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST) USED IN WEIGHT CONTROL

As an endogenous peptide, GLP-1 increases the secretion of insulin and decreases the secretion of glucagon, a process that is strictly controlled by blood glucose levels. Synthesized in the intestinal mucosa, GLP-1s also affect lowering food intake, by promoting satiety, through their capacity to delay gastric emptying. GLP-1RAs are well established in their properties of lowering glucose and weight in both patients that have and do not have diabetes (Dragan et al., 2017; Lupu et al., 2019). One of the considerable benefits of GLP-1RA treatment is a lowering of major adverse cardiovascular risks for the following: mortality from cardiovascular events, myocardial infarction (non-fatal subtype), and non-fatal stroke. Seeing as 35% of excess deaths in patients with schizophrenia are attributable to cardiovascular disease and diabetes, there has been increasing interest in using GLP-1RAs in treating these patients, to counteract the weight gain brought on by AP therapy as well as for the effects on the cardiovascular system and metabolism. Additionally, several GLP-1RAs are now accessible as weekly injections, easing their administration and increasing adherence to treatment among schizophrenia patients (Siskind et al., 2018).

Siskind et al. (2018) published a meta-analysis of 168 patients from three studies, to demonstrate if GLP-1RA is effective and tolerable in managing weight gain for patients treated with generic AP and those treated with Clozapine or Olanzapine. Two of the studies used exenatide 2 mg s.c. once per week and the other used liraglutide 1.8 mg once per day administered subcutaneously, at doses that match the standard maximum for use in diabetes. The studies ranged from 12 to 24 weeks with a mean of 16.2 weeks. Patients with add-on treatment of GLP-1RAs lost an extra 3.7 kg more than the control subjects, approximately at the point of 5% body weight for the whole group. Greater decreases in BMI, visceral fat, fasting glucose, and HbA1c were also observed to be associated with GLP-1RA medication (Siskind et al., 2018).

These findings suggest that cotreatment with GLP-1Ras induces a significant weight decrease in overweight or obese schizophrenic patients who are actively on AP treatment. Patients on Clozapine and/or Olanzapine had better outcomes, which is consistent with the recent discovery that these two AP block the GLP-1 pathway. The study did not find any evidence that these benefits were modified by age, sex, psychosis severity, or nausea as a side effect (Siskind et al., 2018).

NON-PHARMACOLOGICAL INTERVENTIONS

Weight management through non-pharmacological interventions must be a priority in the initial stages of AP treatment. Incorporating dietary and physical activity has shown promise in terms of avoiding weight gain in patients with schizophrenia (Faulkner et al., 2007).

Guy Faulkner et al. meta-analysis reviewed 23 studies, 5 of which assessed a cognitive/behavioral intervention and 18 assessed a pharmacological add-on in patients with schizophrenia. Two cognitive-

behavioral trials with a combined 104 patients, achieved significant treatment effect, with a mean weight change after therapy of −3.38 kg. The other 3 cognitive/behavioral trials, comprising 129 patients, also showed a significant treatment effect at end of therapy with a mean weight change of −1.69 kg (Faulkner et al., 2007).

Mario Álvarez-Jiménez et al. (2008) researched if non-pharmacological interventions could be used to manage AP-induced weight gain, in a meta-analysis of 10 trials with 482 patients. Six of the studies investigated strategies using cognitive-behavioral interventions, 3 nutritional counseling, and one a combination of exercise and nutritional interventions. Six of the trials had the objective to reduce body weight in those that had already gained weight and four studies tried to prevent AP weight gain. Non-pharmacological interventions obtained a statistically significant reduction in mean body weight (-2.56 kg) compared to usual treatment. Effects on BMI also had significant results with a mean change in body mass index of -0.91kg/m^2. These positive effects are the result of a combination of techniques that in a flexible manner address individual needs with a focus on promoting therapeutic alliances (Álvarez-Jiménez et al. 2008).

NON-PHARMACOLOGICAL AND METFORMIN INTERVENTIONS

Wei Zheng et al. published in January 2019 the first meta-analysis that explored the effectiveness and acceptability of adding metformin to a lifestyle intervention (MLC) to treat schizophrenic patients' AP-induced weight gain. The study was divided into three parts: „MLC versus metformin alone", „MLC versus lifestyle intervention" and „MLC versus placebo". The MLC group surpassed the metformin-alone group in mean body weight changes WMD: −1.50 kg and mean BMI change WMD: −1.08 kg/m^2. The MLC group also surpassed the lifestyle group in mean body weight changes, WMD: −3.30 kg, mean BMI changes WMD: −1.45 kg/m^2, and waist circumference WMD: −2.10 cm. The MLC group showed improvements when compared to control in both body weight reduction WMD: −5.05 kg and mean BMI changes WMD: −2.85 kg/m^2 with MLC showing significantly less weight gain of more than 7% body mass. These results show that the MLC is a safe and effective method for controlling weight gain when compared to lifestyle modification, placebo, or metformin treatment alone (Zheng et al., 2019).

LARGE-SCALE COMPARATIVE META-ANALYSIS

One of the largest meta-analyses on the results of pharmaceutical and non-pharmacological therapies on physical health in adults with schizophrenia spectrum disorders was published in February 2019 by Davy Vancampfort et al., 27 meta-analyses encompassing 128 trials and 47 thousand study participants were compiled and analyzed in the study. A total of 17 different pharmacological interventions were documented: aripiprazole augmentation, fluoxetine, metformin, nizatidine, dextroamphetamine, famotidine, fluvoxamine, metformin with sibutramine, NMDA receptor antagonists including amantadine and memantine, d-fenfluramine, ranitidine, orlistat, topiramate, rosiglitazone, GLP-1 RAs (glucagon-like peptide-1 receptor agonists) and using quetiapine or aripiprazole instead of olanzapine (Vancampfort et al., 2019).

A total of 78 trials from 6 meta-analyses, involving 3,944 patients investigated non-pharmacological interventions for reducing body weight in schizophrenic patients. The most effective intervention was individual lifestyle counseling followed by exercise interventions alone. Dietary interventions alone and psychoeducation that focused on promoting a healthy lifestyle had a medium effect. Cognitive behavioral therapy focused on promoting a healthy and group lifestyle counseling has only a small effect on preventing weight gain (Vancampfort et al., 2019).

Pharmacological interventions were investigated in 14 meta-analyses containing 82 studies with 4,691 patients. A medium effect size for preventing weight gain was observed for aripiprazole augmentation, topiramate, d-fenfluramine, and metformin. Amantadine, GLP-1 Ras, and NMDA receptor antagonists all demonstrated a marginally significant impact. Fluoxetine, dextroamphetamine, famotidine, the combination of metformin and sibutramine, orlistat, and rosiglitazone did not cause any appreciable weight loss as compared to the control group. Additionally, evidence for moving from olanzapine to quetiapine or aripiprazole was insufficient (Vancampfort et al., 2019).

Combined interventions were reviewed in only one meta-analysis with 122 patients that proved they have a small significant effect on body weight. (Vancampfort et al., 2019).

In summary, Davy Vancampfort et al. demonstrate that the most effective interventions for body weight control in patients under AP treatment are individual lifestyle counseling and exercise interventions after which come add-on therapies such as psychoeducation, aripiprazole augmentation, topiramate, di-fenfluramine, and metformin (Vancampfort et al., 2019).

A meta-analysis of 27 research, involving 1,349 patients, was published in 2018 by Chuanjun Zhuo et al. It examined the most effective additional treatments for preventing AP-induced weight gain. Results on the effectiveness of supplementary therapies included Topiramate (4 studies), Metformin (13 studies),

Reboxetine (3 studies), Ranitidine (2 studies), and Sibutramine (4 studies). Topiramate showed the lowest mean difference in body weight at -3.07 kg, followed by Sibutramine at -2.97 kg, Metformin at -2.50 kg, and Reboxetine with MD = -2.25 kg. All showed weight reductions compared to the placebo, except for Ranitidine (Zhuo et al., 2018).

The authors could demonstrate which add-on treatments were consistently significant with a decrease in body weight by excluding studies with fewer than 12 months of follow-up. With more than 12 months of treatment metformin, sibutramine and topiramate maintained their efficiency with -2.54 kg, -2.98 kg and -2.95 kg mean body weight difference. Although helpful for weight management Sibutramine shouldn't be used to manage weight gain brought on by AP. The Sibutramine Cardiovascular Outcomes Trial verified that long-term therapy increased the risk of non-fatal myocardial infarction and non-fatal stroke significantly in participants with preexisting cardiovascular disease (Zhuo et al., 2018).

CONCLUSIONS

While obesity is linked to physical comorbidity, its relation to mental health has been less explored. Knowledge gaps still exist in the association between obesity and various psychiatric conditions like schizophrenia. Additionally, gaining weight is linked to poor quality of life, social shame, subpar treatment compliance, and expensive medical care. The evidence for pharmaceutical and non-pharmacological therapies that can be used to prevent weight gain is currently lacking, even though both conventional and new-generation APs are linked to weight increase. For all patients who are taking AP, particularly those on olanzapine, weight gain should be thoroughly discussed and closely monitored.

Two choices that can be utilized in adjunctive therapy without risk are topiramate and metformin. They are both excellent adjunct treatments for reducing weight gain brought on by antipsychotics and both have short-term well-tolerance profiles.

The focus of research should shift in the future to comprehensive studies of antipsychotic switching and adjuvant treatment regimens, as well as lifestyle and preventative intervention programs. Weight gain and metabolic side effects should always be monitored and managed for every patient started on antipsychotics.

REFERENCES

1. Álvarez-Jiménez, M., Hetrick, S. E., González-Blanch, C., Gleeson, J. F., & McGorry, P. D. (2008). Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. *The British journal of psychiatry: the journal of mental science*, *193*(2), 101–107. https://doi.org/10.1192/bjp.bp.107.042853
2. Bak, M., Fransen, A., Janssen, J., van Os, J., & Drukker, M. (2014). Almost all antipsychotics result in weight gain: a meta-analysis. *PloS one*, *9*(4), e94112. https://doi.org/10.1371/journal.pone.0094112
3. Chirita, R., Sacuiu, I., Burlea, A., & Chirita, V. (2012). The role of nitric oxide inhibitors in treatment on symptom severity and cognitive deficits in schizophrenia. *International Journal of Neuropsychopharmacology, 15*, 113-113.
4. Ciobotea, D., Vlaicu, B., Ciubara, A., Duica, C. L., Cotocel, C., Antohi, V., & Pirlog, M. C. (2016). Visual Impairment in the Elderly and its Influence on the Quality of Life. *Revista de Cercetare si Interventie Sociala*, *54*, 66.
5. Ciubara, A.B., Tudor, R.C., Nechita, L., Tita, O., Ciubara, A., Turliuc, S. & Raftu, G. (2018). The Composition of Bioactive Compounds in Wine and Their Possible Influence on Osteoporosis and on Bone Consolidation. *Revista de Chimie*. *69*(5), 1247-1253. https://doi.org/10.37358/RC.18.5.6300
6. de Silva, V. A., Suraweera, C., Ratnatunga, S. S., Dayabandara, M., Wanniarachchi, N., & Hanwella, R. (2016). Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC psychiatry*, *16*(1), 341. https://doi.org/10.1186/s12888-016-1049-5
7. Dragan, F., Lupu, V. V., Pallag, A., Barz, C., & Fodor, K. (2017, May). Rational consumption of nutrients at school-aged children. In *IOP Conference Series: Materials Science and Engineering*, 200(1), 012063. https://doi.org/10.1088/1757-899X/200/1/012063
8. Faulkner, G., Cohn, T., & Remington, G. (2007). Interventions to reduce weight gain in schizophrenia. *The Cochrane database of systematic reviews*, (1), CD005148. https://doi.org/10.1002/14651858.CD005148.pub2
9. Goh, K. K., Chen, C. H., & Lu, M. L. (2019). Topiramate mitigates weight gain in antipsychotic-treated patients with schizophrenia: meta-analysis of randomised controlled trials. *International journal of psychiatry in clinical practice*, *23*(1), 14-32. https://doi.org/10.1080/13651501.2018.1449864
10. Jarskog, L. F., Hamer, R. M., Catellier, D. J., Stewart, D. D., Lavange, L., Ray, N., Golden, L. H., Lieberman, J. A., Stroup, T. S., & METS Investigators (2013). Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. *The American*

journal of psychiatry. *170*(9), 1032–1040. https://doi.org/10.1176/appi.ajp.2013.12010127

11. Liang, H., Li, H., Hu, Y., Li, S., Lü, L., & Song, X. (2016). Effects of topiramate for atypical antipsychotic-induced body weight gain and metabolic adversities: a systematic review and meta-analysis. *Zhonghua yi xue za zhi*, *96*(3), 216-223. https://doi.org/10.3760/cma.j.issn.0376-2491.2016.03.014
12. Lupu, A., Paduraru, G.,Dragan, F., Starcea, M., Lupu, V. V., Moisa, S., Ioniuc, I., Pertea, L.I., Rosu, V.E., Miron, I. (2019). Nutrition and oral health in children. *Romanian Journal of Oral Rehabilitation*, *11*(2), 201-205. https://www.rjor.ro/wp-content/uploads/2019/06/NUTRITION-AND-ORAL-HEALTH-IN-CHILDREN.pdf
13. Rajan, T. M., & Menon, V. (2017). Psychiatric disorders and obesity: A review of association studies. *Journal of postgraduate medicine*, *63*(3), 182–190. https://doi.org/10.4103/jpgm.JPGM_712_16
14. Siskind, D., Hahn, M., Correll, C. U., Fink-Jensen, A., Russell, A. W., Bak, N., Broberg, B. V., Larsen, J., Ishøy, P. L., Vilsbøll, T., Knop, F. K., Kisely, S., & Ebdrup, B. H. (2019). Glucagon-like peptide-1 receptor-agonists for antipsychotic-associated cardio-metabolic risk factors: a systematic review and individual participant data meta-analysis. Diabetes. *Obesity and Metabolism*. *21*(2), 293-302. https://doi.org/10.1111/dom.13522
15. Spertus, J., Horvitz-Lennon, M., Abing, H., & Normand, S. L. (2018). Risk of weight gain for specific antipsychotic drugs: a meta-analysis. *NPJ schizophrenia*, *4*(1), 12. https://doi.org/10.1038/s41537-018-0053-9
16. Tek, C., Kucukgoncu, S., Guloksuz, S., Woods, S. W., Srihari, V. H., & Annamalai, A. (2016). Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. *Early intervention in psychiatry*, *10*(3), 193–202. https://doi.org/10.1111/eip.12251
17. Untu, I., Chirita, R., Bulgaru-Iliescu, D., Chirila, B.D., Ciubara, A., Burlea, S.L. (2015). Ethical Implications of Bio-Psycho-Social Transformations Entailed by the Aging Process. *Revista de Cercetare si Interventie Sociala*, 48, 216-225. https://www.rcis.ro/images/documente/rcis48_16.pdf
18. Valcea, L., Bulgaru-Iliescu, D., Burlea, S. L., & Ciubara, A. (2016). Patient's rights and communication in the hospital accreditation process. *Revista de cercetare si interventie sociala*, *55*, 260-270. https://www.rcis.ro/images/documente/rcis55_17.pdf
19. Vancampfort, D., Firth, J., Correll, C. U., Solmi, M., Siskind, D., De Hert, M., Carney, R., Koyanagi, A., Carvalho, A. F., Gaughran, F., & Stubbs, B. (2021). The Impact of Pharmacological and Non-Pharmacological Interventions to Improve Physical Health Outcomes in People with Schizophrenia: A Meta-Review of Meta-Analyses of Randomized Controlled Trials. *Focus (American Psychiatric Publishing)*, *19*(1), 116–128. https://doi.org/10.1176/appi.focus.19103
20. Zhang, J. P., Lencz, T., Zhang, R. X., Nitta, M., Maayan, L., John, M., Robinson, D. G., Fleischhacker, W. W., Kahn, R. S., Ophoff, R. A., Kane, J. M., Malhotra, A. K., & Correll, C. U. (2016). Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis. *Schizophrenia bulletin*, *42*(6), 1418–1437. https://doi.org/10.1093/schbul/sbw058
21. Zheng, W., Li, X. B., Tang, Y. L., Xiang, Y. Q., Wang, C. Y., & de Leon, J. (2015). Metformin for Weight Gain and Metabolic Abnormalities Associated With Antipsychotic Treatment: Meta-Analysis of Randomized Placebo-Controlled Trials. *Journal of clinical psychopharmacology*, *35*(5), 499–509. https://doi.org/10.1097/JCP.0000000000000392
22. Zheng, W., Xiang, Y. T., Xiang, Y. Q., Li, X. B., Ungvari, G. S., Chiu, H. F., & Correll, C. U. (2016). Efficacy and safety of adjunctive topiramate for schizophrenia: a meta-analysis of randomized controlled trials. *Acta psychiatrica Scandinavica*, *134*(5), 385–398. https://doi.org/10.1111/acps.12631
23. Zheng, W., Zhang, Q., Cai, D., Yang, X., Ungvari, G.S., Ng, C.H., Wu, R., & Xiang, Y. (2019). Combination of Metformin and Lifestyle Intervention for Antipsychotic-Related Weight Gain: A Meta-Analysis of Randomized Controlled Trials**.** *Pharmacopsychiatry, 52 1*, 24-31. https://doi.org/10.1055/s-0044-101466
24. Zhuo, C., Xu, Y., Liu, S., Li, J., Zheng, Q., Gao, X., Li, S., Jing, R., Song, X., Yue, W., Zhou, C., & Upthegrove, R. (2018). Topiramate and Metformin Are Effective Add-On Treatments in Controlling Antipsychotic-Induced Weight Gain: A Systematic Review and Network Meta-Analysis. *Frontiers in pharmacology*, *9*, 1393. https://doi.org/10.3389/fphar.2018.01393

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