Interventions to Manage Weight Gain for Pediatric Population on Antipsychotics: A Systematic Review

An EBP Capstone Project submitted to the St. David's School of Nursing at Texas State University in partial fulfillment of the requirements for the degree of Doctor of Science in Nursing

Claudia Gaytan, RN, BSN

St. David's School of Nursing, Texas State University

NURS 5391: Translational Science for Evidence-Based Practice and Innovation (Capstone)

Capstone Faculty: Dr. Theresa Garcia

November 24, 2022

Abstract

This article systemically reviews studies that present interventions related to pharmacological and non-pharmacological treatment for the weight management and reduction of pediatric patients prescribed antipsychotics. Using PRISMA guidelines, various databases such as PubMed, CINAHL, PubMed Central and Medline were searched using key words of "weight gain," "BMI," antipsychotics," "pediatrics," "children," "pharmacological," "non-pharmacological," "interventions," and "bipolar disorder." The initial search yielded 1,800 results, 315 were excluded due to duplicates, and 1,451 excluded due to age of the population. There were seven articles including randomized controlled trials, a quasi-experiment and a retrospective chart review. Metformin was found to be the most studied and effective adjunctive medication for weight management, with promising results of melatonin, zonisamide, and topiramate. Four studies showed a decrease or stabilization of weight with an adjunct dose of metformin with the patient's antipsychotic. Also found to be effective was switching to a different antipsychotic. Non-pharmacologic methods was found to be unhelpful. More studies are needed on other treatment options to guide clinicians in their treatment practices.

Keywords: Weight gain, pediatric, antipsychotic, pharmacologic, body mass index

Interventions to Manage Weight Gain for Pediatric Population on Antipsychotics: A Systematic Review

Although there are several antipsychotics approved for children for treatment of bipolar disorder, schizophrenia and other psychiatric disorders, up to 60% of patients suffer from negative cardiometabolic effects, including weight gain (Libowitz & Nurmi, 2021). This increased weight gain may be a cause of poor adherence to medication and therefore, possible relapse of the specific mental illness the medication is to be treating. This is concerning for future patients and clinicians as this creates a two -fold problem; increased risk for hospital readmittance or suicidality due to amplified depression and additional metabolic related issues due to rapid weight gain. While some studies have targeted reducing or slowing down weight gain in children on antipsychotics, there are no clear, updated guidelines for clinicians to follow regarding adding specific medications or non-pharmacological methods to treatment. Treatment recommendations at this time include counseling patients on lifestyle interventions, decreasing doses, stopping medication, switching medication to a different antipsychotic and examining other medications patients may be on that causes weight gain (Ho et al., 2011). The purpose of this systematic review is to determine the best intervention to manage weight gain in the pediatric population that are prescribed antipsychotics.

Background and Significance

The need to monitor and treat weight gain in children on antipsychotic therapy is not new but is also not consistently done by providers. By 18 years of age, 1-6% of children are diagnosed with bipolar disorder (Clacey et al., 2015), one of the psychiatric conditions requiring antipsychotic prescriptions. Clinicians, families, and patients should be aware of the potential side effects and treatment options to reduce these side effects, including weight gain. Obese

children are more likely to have externalizing problems, grade repetition and school problems and there is an association between obesity and ADHD, depression and learning disabilities (Rice & Ramtekkar, 2020). Researchers studied over 300 children who were prescribed antipsychotic medication, found that only 72% percent of them had their BMI calculated at start of treatment and even less had their BMI recorded at 12-week follows and annual follow ups (Sorabh et al., 2022). This lack of assessment and monitoring is alarming because information has been disseminated for years that antipsychotics cause rapid weight gain in children. In a retrospective cohort study of over 6,000 children and adolescents, the long-term use of atypical antipsychotics, in children with a diagnosis of bipolar disorder, was associated with a cumulative increase in BMI (Patel et al., 2017). When antipsychotics cause rapid weight gain in children, this in turn may lead to more serious issues such as diabetes or cardiovascular disease (Schneider et al., 2020). Youth who are prescribed second generation antipsychotics are tw0 to three times more likely to develop diabetes than youth in the general population (Correll et al., 2009). As trends for both type 1 and type 2 diabetes continue to increase in the pediatric population, clinicians prescribing antipsychotics should monitor and intervene in order to avoid adding to the diabetic epidemic in this vulnerable population (Lawrence et al., 2021).

Review of Literature

The existing literature includes much evidence in support of various pharmacologic and non-pharmacologic interventions to monitor and minimize weight gain in this population, yet many providers are not addressing this problem. Psychiatrists reported numerous obstacles to providing continuous metabolic monitoring including lack of training in regard to physical health, lack of patient engagement, severity of the mental health diagnosis, and fear of losing rapport with their young patient (Aouira et al., 2022).

Recent literature described the used of several medications including metformin in decreasing weight in children treated with second generation antipsychotics (Ellul et al., 2018). A 2018 meta-analysis of placebo versus metformin on body weight of children, concluded that although metformin may decrease weight in children being treated with second-generation antipsychotics, additional high-quality evidence is needed (Pierre et al., 2018). There is a gap in literature comparing the various studies of pharmacological and non-pharmacological treatments found to be effective to assist in providers in treatment decisions.

Purpose and Clinical Question

Various studies support patients on pharmacologic therapy or non-pharmacologic therapy do lose weight or maintain weight while receiving treatment. This systemic review of the literature aimed to summarize and categorize therapies that have been shown to be safe and effective treatment options for reduction of weight or maintenance of weight for pediatric patients on antipsychotic medication regimens. What are the most effective pharmacologic and non-pharmacologic interventions in managing or reducing weight gain in children aged 6-20 on antipsychotic therapy?

Conceptual Framework

A nursing theory that helped guide this project is the Theory of Comfort written by Katherine Kolcaba in 1993. This theory is guided by the assumptions that humans have holistic responses to complex stimuli, comfort is a desirable holistic outcome, and human beings strive to meet their basic comfort needs (Kolcaba, 1993). She goes on to state that an increase in comfort indicates that negative tensions are reduced, positive tensions are engaged, and positive tensions lead to a unitary tend of constructive behaviors. As the clinician builds rapport with their patient, the hope is that the patient becomes more comfortable, confident and trusting with their

physician. This framework fits perfectly for this project because if the prescribed medication decreases comfort in another area of the patient's life, it may decrease the trust and comfort the patient feels with the clinician. A 2018 study including patients diagnosed with bipolar disorder found that clinicians' ability to listen to, understand and value their views on medication-taking along with flexibility regarding treatment options, to be the most important attributes of a clinician (Chakrabarti, 2018).

Methods

Project Design

A systematic review of the literature guided by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used (Stewart et al., 2015). This review is needed due to various claims of evidence found throughout the search process.

Search Strategy

Published literature was searched through Medline, CINAHL, PubMed, PubMed Central and clinicaltrial.gov. Search terms included were "weight gain," "BMI," antipsychotics," "pediatrics," "children," "pharmacological," "non-pharmacological," "interventions," and "bipolar disorder." Ancestry search was utilized by reviewing citations in the text of articles found. Multiple useful studies were found to aid in determining body weight changes for the population of interest.

Inclusion criteria for articles included those of clinical trials, randomized controlled trials, double-blind studies, meta-analyses, systematic reviews, and primary research. Date ranges included were from 2012-2022 with the population of interest being children from ages 6-20 years. Exclusion criteria were any editorials, studies including subjects over 20 years and trials including non-humans. Quality appraisal tools used were Rapid Critical Appraisal Questions for

authored by Melnyk and Overholt. Studies were only included in the review if their Quality Appraisal score was at least 7 out of 11.

Selection Process

The author (CG) completed the literature review and screening of articles. Articles were first reviewed by title and abstract, then by full-text screening for inclusion criteria. Articles were saved to Zotero management software. A Flow Diagram, Figure 1, was provided to help the reader identify the articles included and excluded.

Risk of bias was determined by using Rapid Critical Appraisal Questions (Melnyk & Overholt, 2015). Each tool has a series of questions that ask direct questions about the studies, Appendix A1.

Synthesis Method

The Evidence Synthesis Table, see Table 1, was a resource used to extract data (such as author, publication date, purpose, methods, results) and organize the articles for analysis and synthesis. Themes were concluded by studying the table and determining the type of interventions used in the literature. Themes were sorted into pharmacological interventions, non-pharmacological interventions, and a mixture of each.

Results

Search Results

Using various databases, including Pubmed, Pubmed Central, Medline, and CINAH, a total of 1,784 articles were screen for published literature. Due to publication date prior to 2012, 1,329 articles were excluded.

Characteristics of the Studies

The sample of articles reviewed included 5 randomized controlled trials (Anagostou et al., 2016; Arman & Haghshenas, 2022; Correll et al., 2020; Detke et al., 2016; Mostafavi et al., 2017), 1 quasi-experimental study (Handen et al., 2017), and 1 retrospective studies (Shapiro et al., 2016). These articles assessed the weight gain observed while patients were prescribed antipsychotics as well as pharmacological and non-pharmacological ways to manage weight gain (Anagostou et al., 2016; Arman & Haghshenas, 2022; Detke et al., 2016; Mostafavi et al., 2017; Shapiro et al., 2016). Sample sizes ranged from 24 (Mostafavi et al., 2017) to over 200 participants (Detke et al., 2016). All studies included in literature review had participants that were involved in an outpatient setting. While three studies were completed in other countries (Arman & Haghshenas, 2022; Detke et al., 2016; Mostafavi et al., 2017), four of the studies were accomplished in the United States (Anagostou et al., 2016; Correll et al., 2020; Detke et al., 2016; Handen et al., 2017). Interventions of non-pharmacological means included counseling sessions and programs that consisted of handouts on healthy eating and exercise (Detke et al., 2016). Pharmacological efforts used included addition of metformin (Anagnostou et al., 2016, Handen et al, 2017; Correll et al., 2020), melatonin (Mostafavi et al, 2020), zonisamide or topiramate (Arman & Haghshenas, 2022; Shapiro et al., 2016). One study in the literature review also attempted to measure BMI after switching patients to a different antipsychotic other than the

one they were already on (Correll et al., 2020). Each study used waist circumference, body weight, and BMI as outcome variables measuring weight changes.

Synthesis Across Studies

Findings across the studies provided strong evidence that metabolic disturbances, including decreasing and maintaining BMI, can be managed in patients on prescribed antipsychotics. The three major themes across study findings were: Adjunct Pharmacological interventions, non-Pharmacological interventions, and one study applying both methods as well as switching to a different antipsychotic (Correll et al., 2020).

Theme 1: Adjunct Pharmacological Interventions Most Successful

There were five studies that focused on pharmacological means to decrease or maintain BMI and weight while the patients were taking antipsychotics (Anagnostou et al., 2016; Arman & Hagshenas, 2022; Handen et al, 2017; Mostafavi et al., 2017; Shapiro et al, 2016). Two studies (Anagnostou et al, 2016; Handen et al, 2017) provided metformin to participants as the pharmacological intervention. Anagnostou et al. (2016) gave increasing doses of metformin to children and adolescents and concluded that metformin was superior to placebo in reducing weight gain associated with atypical antipsychotics. Handen et al. (2017) continued this study but offered all participants, including the placebo trial group, the metformin medication regimen. They found the metformin-to-metformin group's BMI remained stable throughout the additional 16-weeks, while the placebo-to-metformin group showed a significant decrease in mean BMI.

In two additional studies, topiramate was the pharmacological intervention of choice. Arman & Haghshenas. (2022) added topiramate to children already receiving aripiprazole. Although no significant decrease in BMI was seen in the group that received topiramate, the placebo group had significant weight gain and BMI increases. Shapiro et al. (2016) conducted a

retrospective chart review comparing patients who had been placed on both topiramate and zonisamide for weight management to those who did not. They found statistically significant weight reduction for all dosing levels of topiramate and zonisamide, with the exception of dosing above 200mg daily.

A final study provided melatonin to patients receiving olanzapine and lithium carbonate as a treatment regimen for bipolar disorder and compared outcomes to a control group receiving no melatonin. Although there was weight gain and BMI increases in both groups, the control group had a marginally significant increase in both.

Theme 2: Adjunct Pharmacological Interventions, Switching, and non-Pharmacological Methods

The Correll et al. (2020) study focused on 127 youth participants, randomizing them into three different groups of increasing adjunct metformin medication, switching their current antipsychotic of aripiprazole to perphenazine and the control group. All participants received the same healthy lifestyle education of strategies to enhance nutrition and physical activity. They concluded that the BMI *z*-score of the metformin and the switch groups both decreased significantly. In the control group, the BMI *z*-score increased, but was not statistically significant when compared to the other two groups.

Theme 3: Non-Pharmacological Interventions Not Helpful

There was one study included in the literature review that described non-pharmacological means as an intervention to reduce increased BMI for patients taking olanzapine (Detke et al., 2016). Patients were divided into two groups, a standard behavioral weight counseling group and an intense behavioral weight counseling group. The standard group received one counseling session at start of the study which included basic information on healthy eating and exercise

habits. The intense group received counseling at every study visit, including dietary training, education on regular exercise, and a pedometer, and review of their exercise habits since the previous session. They found no significant differences in BMI between the standard and the intense group.

The conceptual framework of Theory of Comfort speculates patient's benefits of specific comfort measures. As patient's pursue healing in their journey of a mental illness diagnosis, they often weigh the toll the medication itself has on their body. Second generation related weight gain impairs medication adherence in young patients (Klein et al., 2020). Finding that balance of relief, ease and transcendence described in the Theory of Comfort will help lead future researchers to determine a clear guideline on adjunctive treatments.

Discussion

There were seven different studies found that addressed the research question of, *what are the most effective pharmacological and non-pharmacological interventions in managing or reducing weight gain in children aged 6-20 on antipsychotic therapy*? Non-pharmacologic means of weight gain reduction, although only represented by one study, did not yield any significant decreased in weight gain, while all six pharmacologic interventions yielded a favorable decrease in BMI. The results in the pharmacologic interventions conclude that overall, there are statistically significant decrease or maintenance of body-mass-index with the adjunct medications. The findings in this literature review, provide a resource of evidence to help clinicians promote medication adherence by managing patient side effects of weight gain while taking antipsychotics.

The conceptual framework of Theory of Comfort discusses a patients desire to have a holistic approach of their needs. With these studies in mind, increasing comfort in a patient's life related to their prescribed medication regiment, may help increase the trust and comfort a patient feels with their respective clinician. Managing side effects, such as increased BMI discussed in this literature review, is an additional way to increase patient comfort, decrease anxiety related to negative emotions of weight gain and increase medication adherence (Usher et al., 2013).

Recommendations from Findings

Although practice guidelines indicate that lifestyle modification may help with antipsychotic weight gain, the inconsistent ability for patients with severe psychiatric diseases may make this impractical and this review of studies did not support the use of non-pharmacological methods to manage weight gain. With more than 80% of children showing significant weight gain while taking antipsychotics, the time for clinicians to enact change in

their prescribing is now (Dayabandara et al., 2017). Furthermore, patients who are obese are up to 13 times more likely to discontinue their prescribed antipsychotic (Weiden et al., 2006). In clinical practice, it may be worth taking a closer look at medications to add to a patient's regimen to manage the increase in body mass index that seems inevitable. Adding metformin to a patient's regimen has shown promising effectiveness in weight management. Other medications to consider, with side effect profile in mind, would be metformin, zonisamide and topiramate.

Limitations

Limitations in this review include limited studies in children and adolescents addressing pharmacological means to manage increased BMI, the small amount of time each study took place in, and the long-term safety of the adjunctive medications considered. The search results yielded minimal studies in pharmacological and non-pharmacological means of reducing BMI in children and adolescents. Many primary studies and systematic reviews found, used evidence from a study that began in 2016 and concluded with data gathering 2021. This was the Improving Metabolic Parameters in Antipsychotic Child Treatment (IMPACT) study conducted by the United States FDA (Correll et al., 2020). Although final data was collected at the end of 2021 for primary outcome measures, data continues to be collected from the participants in this trial.

Although weight gain is rapid in adolescents, many of the studies in Table 1, were conducted in very short time frames. Studies lasted from 12-weeks (Mostafavi et al., 2016), to 52-weeks (Detke et al., 2016). This is not an adequate amount of time to determine if body mass index and weight gain will be maintained throughout the patient's use of the prescribed antipsychotic. Another item to consider, is the knowledge of being in a study, may have affected the patient's efforts to maintain or lose weight.

While side effect profile were relatively minor during the reviewed studies, this continues to be a concern for patients and their families. In addition, among patients with schizophrenia and other mental health disorders, medication side effects are significantly associated with medication non-adherence (Dibonaverntura, 2012). More thorough, longer, and additional studies will help determine if these medications are safe, effective, and manageable for patients in this population.

Conclusions and Implications

Practitioners are taught to be careful and detailed in their prescribing practices. This literature review acknowledged a lack of follow-up and unclear guidelines on management of metabolic side effects with children and adolescents prescribed antipsychotics. While there still needs to be further clinical studies to determine the best intervention to manage weight gain and BMI, having practitioners more informed on this growing problem is the first step.

Further studies with larger sample sizes for longer periods of time will be the preliminary course of action to begin formulating guidelines to decrease the incidences of pediatric metabolic disturbances related to antipsychotics. These studies will optimistically give more clear answers of options clinicians can use for their patients. For current practice, practitioners should set guidelines in their clinic based on the Center for Disease Control and Prevention's recommended metabolic parameter, their patients baseline measurements, percentage of weight gained on the current antipsychotic, family history, and illness severity. This will assist practitioners in trialing a medication from one of the reviewed studies to decreased or maintain BMI for their patients.

To continue addressing the problem of weight gain while taking antipsychotics, researchers should focus on alternative adjunctive medications that clinicians can use. Although metformin was studied as an adjunct in half of the pharmacological intervention studies,

melatonin, zonisamide, and topiramate had promising findings. Future studies should focus more on these medications, specifically focusing on the children and adolescent population. Additionally, researchers should also focus on more in-depth understanding of other factors in play such as environment, severity of illness, and family history of metabolic disturbances.

Resources

Anagnostou, E., Aman, M., Handen, B., Sanders, K., Shui, A., Hollway, J., Brian, J., Arnold, L., Capano, L. Hellings, J., Butter, E., Mankad, D., Tumuluru, R., Kettel, J., Newsom, C., Hadjiyannakis, S., Peleg, N., Odrobina, D., McAuliffe-Bellin, S., Zakroysky, P…..& Veenstra-VanderWeele, J. (2016). Metformin for treatment of overweight induced by atypical antipsychotic medication in young people with autism spectrum disorder: A randomized clinical trial. *JAMA Psychiatry, 73(*9), 928-937. https://doi.org/10.1001/jamapsychiatry.2016.1232.

Aouira, N., Khan, S., Heussler, H., Haywood, A., Karaksha, A., & Bor, W. (2022). Practitioners' perspective on metabolic monitoring of second-generation antipsychotics: Existing gaps in knowledge, barriers to monitoring and strategies. *Journal of Child and Adolescent Psychopharmacology, 32*(5), 296-303. https://doi.org/10.1089/cap.2022.0021

Arman, S., & Haghshenas, M. (2022). Metabolic effects of adding topiramate and aripiprazole in bipolar patients aged between 6-18 years, a randomized, double-blind, placebo-controlled trial. *Journal of Research in Medical Sciences, 27,* 23. https://doi/org/10.4103/jrms.jrms_672_21

Bussell, K., Reeves, G., Hager, E., Zhu, S., Correll, C., Riddle, M., & Sikich, L. (2018). Dietary consumption with antipsychotic-induced weight gain and changes following healthy lifestyle education. *Journal of Child and Adolescent Psychopharmacology, 31*(5), 364-375. https://doi.org/10.1089/cap.2020.0173

Clacey, J., Goldacre, M., & James, A. (2015). Paediatric bipolar disorder: international comparisons of hospital discharge rates 2000-2010. *The British Journal of Psychiatry, 1*(2), 166-271. https://doi.org/10.1192/bjpo.bp.115.001933

Correll, C., Manu, P., Olshanskiy, V., Napolitano, B., Kane, J., & Malhotra, A. (2009). Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA Psychiatry, 302*(16), 1765-1763. https://doi.org/10.1001/jama.2009.1549

Correll, C., Sikich, L., Reeves, G., Johnson, J., Keeton, C., Spanos, M., Kapoor, S., Bussell, K., Miller, L., Chandrasekhar, T., Sheridan, E., Piromohamed, S., Reinblatt, S., Alderman, C., Scheer, A., Borner, I., Bethea, T., Edwards, S., Hamer, R., & Riddle., M. (2020). Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial. *World Psychiatry, 19*(1), 69-80. https://doi.org/10.1102/wps.20714

Dayanbandara, M., Hanwella, R., Ratnatunga, S., Seneviratne, S., Suraweera, C., & de Silva, V. (2017). Antipsychotic-associated weight gain: Management strategies and impact on treatment adherence. *Neuropsychiatric Disease and Treatment, 13*, 2231-2241. https://doi.org/10.2147/NDT.S113099

Detke, H., DelBello, M., Landry, J., Hoffmann, V., Heinloth, A., & Dittmann, R. (2016). A 52-week study of olanzapine with a randomized behavioral weight counseling intervention in adolescents with schizophrenia or bipolar I disorder. *Journal of Child and Adolescent Psychopharmacology, 26*(10), 922-934. https://doi.org/10.1089/cap.2016.0010

Dibonaventura, M., Gabriel, S., Dupclay, L., Gupta, S., & Kim, E. (2012). A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. *BMC Psychiatry, 12(*20). https://doi.org/10.1186/1471-244X-12-20

Ellul, P., Delorme, R., & Cortese, S. (2018). Metformin for weight gain associated with second-generation antipsychotics in children and adolescents: A systematic review and meta-analysis. *Central Nervous System Drugs, 32*(12), 1103-1112. https://doi.org/10/1007/s40263-018-0571-z

Handen, B., Anagnostou, E., Aman, M., Sanders, K., Chan, J., Hollway, J., Brian, J., Arnold, E., Capano, L., Williams, C., Hellings, J., Butter, E., Mankad, D., Tumuluru, R., Kettel, J., Newsom, C., Peleg, N., Odrobina, D., McAuliffe-Bellin, S., & Marlar, S. (2017). A randomized, placebo-controlled trial of metformin for the treatment of overweight induced by antipsychotic medication in young people with autism spectrum disorder: Open-label extension. *Journal of the American Academy of Child & Adolescent Psychiatry, 56*(10), 849-856. https://doi.org/10.1016/j.jaac.2017.07.790

Ho, J., Panagiotopoulos, C., McCrindle, B., Grisaru, S., Pringsheim, T. (2011). Management recommendations for metabolic complications associated with second generation antipsychotic use in children and youth. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 20*(3), 234-241.

Klein, C., Topalian, A., Starr, B., Welge, J., Blom, T., Starr, C., Deetz, I., Turner, H., Sage, J., Utecht, J., Fornari, V., Patino, L., Higdon, C., Sutton, J., Sorter, M., Correll, C., & DelBello, M. (2020). The importance of second-generation antipsychotic-related weight gain and adherence barriers in youth with bipolar disorders: Patient, parent and provider perspectives. *Journal of Child and Adolescent Psychopharmacology, 30*(6), 376-380. https://doi.org/10.1089/cap.2019.0184

Lawrence, J., Divers, J., Isom, S., Saydah, S., Giuseppina, I., Pihoker, C., Marcovina, S., Mayer, E., Hamman, R., Dolan, L., Dabelea, D., Pettitt, D., & Liese, A. (2021). Trends in

prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001-2017. *JAMA 326*(8), 717-727. https://doi.org/10.1001/jama.2021.11165

Libowitz, M. & Nurmi, E. (2021). The burden of antipsychotic-induced weight gain and metabolic syndrome in children. *Frontiers in Psychiatry, 12.* https://doi.org/10.3389/fpsyt.2021.623681

Melnyk, B., & Fineout-Overholt, E. (2015). *Evidence-based practice in nursing & healthcare: A guide to best practice* (3rd ed.). Wolters Kluwer.

Mostafavia, S., Solhi, M., Mohammadi, M., & Akhondzadeh, S. (2017). Melatonin for reducing weight gain following administration of atypical antipyshcotic olanzapine for adolescents with bipolar disorder: A randomized, double-blind, placebo controlled trial. *Journal of Child and Adolescent Psychopharmacology, 27*(5), 440-444. https://doi.org/10.1089/cap.2016.0046

Nicol, G., Kolko, R., Mills, M., Gunnarsdottir, T., Yingling, M., Schweiger, J., Lenze, E., Newcomer, J., & Wilfley, D. (2016). Behavioral weight loss treatment in antipsychotic treated youth. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology, 4*(2), 96-104. https://doi.org10.21307/sjcapp-2016-014

Patel, A., Chan, W., Aparasu, R., Ochoa-Perez, M., Sherer, J., Medhekar, R., & Chen, H. (2017). Effect of psychopharmacotherapy on body mass index among children and adolescents with bipolar disorders. *Journal of Child and Adolescent Psychopharmacology, 27(*4), 349-358. https://doi.org/10.1089/cap.2016.0133

Pierre, E., Richard, D., & Samuele, C. (2018). Metformin for weight gain associated with second-generation antipsychotics in children and adolescents: A systematic review and

meta-analysis. *CNS Drugs, 32*(12), 1103-1112. https://doi.org/10.1007/s40263-018-0571-z

Shapiro, M., Reid, A., Olsen, B., Taasan, M., McNamara, J., Nguyen, M. (2016). Topiramate, zonisamide and weight loss in children and adolescents prescribed psychiatric medications: A medical record review. *The Journal of Psychiatry in Medicine, 51*(1), 56-68. https://doi.org/10.1177/0091217415621266

Sorabh, S., Joseph, B., Casey, K., Teresa, B., & Neelkamal, S. (2022). Low rates of clinician monitoring for second generation antipsychotic medications in community pediatric practice. *Community Mental Health Journal, 58*(3), 541-546. https://doi.org/10.1007/s10597-021-00852-3

Stewart, L., Clarke, M., Rovers, M., Riley, R., Simmonds, M., Stewart, G., & Tierney, J. (2015). Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *Journal of the American Medical Association, 313*(16), 1657-1665. https://doi.org/10.1001/jama.2015.3656

Usher, K., Park, T., & Foster, K. (2013). The experience of weight gain as a result of taking second-generation antipsychotic medications: The mental health consumer perspective. *Journal of Psychiatric and Mental Health Nursing, 20*(9), 801-806. https://doi.org/10.1111/jpm.12019

Weiden, P., Mackell, J., & McDonnell, D. (2006). Obesity as a risk factor for antipsychotic noncompliance. *Schizophrenia Research, 66*(1), 51-57. https://doi.org/10.1016/s0920-9964(02)00498-x

Table 1 *Evidence Synthesis Table*

Author	Purpose	Frame - work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
Anagnostou, 2016	Evaluate efficacy of metformin weight gain associated with SGA's	No frame work discussed	RCT; Double blind-placebo controlled	61 children and adolescents; Ontario, Ohio, Pennsylvania, and Tennessee;	16-week of treatment on metformin compared to placebo; measured were BMI, height, weight, fasting glucose and insulin	BMI scores were statistically significant in reducing BMI compared to placebo group	Participants had been taking their SGA for various amounts of time prior to study; lifestyle modifications could have been occurring; GI discomfort was corrected for in study; metformin gastrointestinal discomfort adverse event significantly higher than placebo group	BMI scores were statistically significant in reducing BMI compared to placebo group; this shows that metformin given BID 500mg and greater may be effective in decreasing weight gain associated with SGA
Arman, 2022	Evaluate efficacy of the addition of topiramate to aripiprazole on weight gain	No frame work discussed	RCT; Double blind-placebo controlled	40 children ages 6-18; child psychiatric units of Iranian hospitals	12-weeks of treatment on topiramate compared to placebo; measured were BMI, height, weight, waist circumference,	During 3-month follow up measures of weight, BMI and HDL were significantly increased in those who did	Large amount of participation dropouts, smalls sample size	Topiramate can be used as adjuvant treatment to control both mania and metabolic adverse effects of aripiprazole

Author	Purpose	Frame - work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
					FBG, A1C, LDL, HDL	not receive topiramate		
Correll, 2020	Compare weight change, BMI, for each pharmacologic intervention with the control group	No frame work discussed	RCT	117 youth aged 8-17 years prescribed SGA's; United States	Subjects randomized to placebo, metformin or switch to another SGA group while receiving HLE; Height, weight, BMI, 24-hour dietary recall	Subjects that were in switch group had significant reduction in BMI *z*-score and percent overweight; metformin group non-significant weight loss and BMI *z*-score	Participants had their own personalized lifestyle plan included; participants had been on their respective SGA prior to study for different amounts of time	Both the dosing of metformin or switching to aripiprazole proved decrease in BMI, while the control group did not produce these same results
Detke, 2016	Compare effectiveness of standard versus intense weight interventions for adolescents taking SGA olanzapine	No frame work discussed	RCT	203 adolescents diagnosed with bipolar or schizophrenia on SGA olanzapine; 29 health centers in the United States, Russia, Poland and Germany	BMI, weight and waist circumference were primary measures	No statistical significance in weight gain between the two groups	Over half of patients discontinued treatment; all patients given washout period of SGA prior to start of study	Both groups gained a substantial amount of weight on the SGA with a majority gaining greater than 7%> of their baseline weight; counseling towards weight

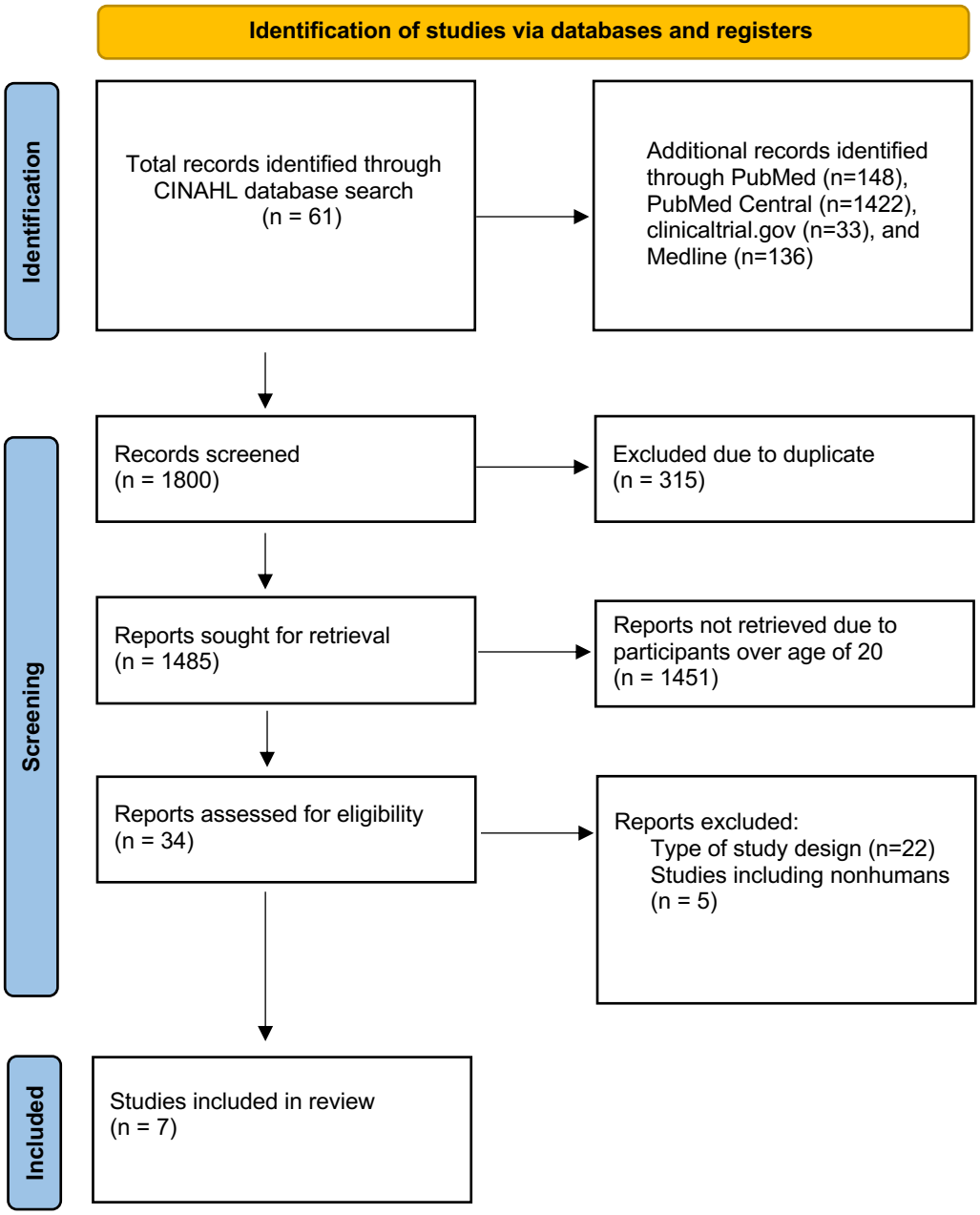
Author	Purpose	Frame - work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
								loss or exercise may not be helpful when actual programs are not implemented for this population
Handen, 2017	If the BMI of children taking metformin was sustained and if there were any adverse effects of placebo individuals switching to metformin	No frame work discussed	Quasi-Experimental	52 children from the phase 1 trial, aged 6-17 years, all were given metformin; Canada, Vanderbilt University, Boston, Ohio State University and University of Pittsburgh	different dosages of metformin for different age groups; vital signs, height, weight, physical exam, abdominal and hip circumference	Children already on metformin in phase 1 trial had maintenance of BMI in phase 2 but no additional weight loss	patients were on different antipsychotics at different dosages; some had antipsychotic increased or switched	This article may show that there is a limit to how much one could decrease BMI on a metformin, antipsychotic combination; metformin can be effective for weight loss and maintenance in children taking antipsychotics

Author	Purpose	Frame - work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
Mostafavi, 2017	Effect of melatonin in weight gain reduction for adolescents taking SGA olanzapine	No frame work discussed	Randomized, double blind placebo controlled trial	24 adolescents diagnosed with bipolar; outpatient clinics in Iran	24 patients given olanzapine, lithium carbonate and melatonin; other group received olanzapine, lithium carbonate and placebo; Measured were BMI, weight and height before treatment, at 6 weeks and at 12 weeks	Marginally significant findings for group receiving melatonin and for body weight across time	Trial was 12 weeks; exclusion criteria included patients having any active medical conditions, metabolic abnormalities, BMI >25 or eating disorders; small sample size	The decreased amount of weight gain that 3mg per day of melatonin provides a natural hormone to reduce weight gain in children on SGA's
Shapiro, 2016	Effectiveness on weight reduction of two anticonvulsants, topiramate and zonisamide	No frame work discussed	Retrospective chart review	47 children under the age of 18 prescribed SGA's with an adjunct medication of topiramate or zonisamide ; University of Florida 2011-	Electronic records reviewed for prescription of these 2 anticonvulsants	Statistically significant weight reduction for all dosing levels of topiramate and zonisamide with exception of dosing every 200mg;	No consistent reason for drop out, adherence or adverse events; subjects prescribed topiramate due to better tolerability; potential risks and side effects need to be explored more as	Dosages below 200mg of zonisamide and topiramate appear to have a good safety profile as an adjunctive medication and shows promise in reducing weight for

Author	Purpose	Frame - work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
				2013 chart review;			zonisamide are not FDA approved for any indication in children as of yet	children on SGA's; zonisamide is not currently FDA approved for children

AiWG= antipsychotic-induced weight gain BMI=body mass index; FBG=fasting blood glucose FGA=first generation antipsychotics HDL= High density lipoprotein HLE= Healthy lifestyle education LDL= Low density lipoprotein SGA=second generation antipsychotics; RCT=randomized controlled trial.

Figure 1 Flow Diagram



Appendix

Rapid Critical Appraisal Questions for Randomized Clinical Trials (RCT)

VALIDITY			
1. Are the results of the study valid?			
a. Were the participants randomly assigned to the experimental and control groups?	Yes	No	Unknown
b. Was random assignment concealed from the individuals who were first enrolling participants into the study?	Yes	No	Unknown
c. Were the participants and providers blind to the study group?	Yes	No	Unknown
d. Were reasons given to explain why participants did not complete the study?	Yes	No	Unknown
e. Were the follow-up assessments conducted long enough to fully study the effects of the intervention?	Yes	No	Unknown
f. Were the participants analyzed in the group to which they were randomly assigned?	Yes	No	Unknown
g. Was the control group appropriate?	Yes	No	Unknown
h. Were the instruments used to measure the outcomes valid and reliable?	Yes	No	Unknown
i. Were the participants in each of the groups similar on demographic and baseline clinical variables?	Yes	No	Unknown
RELIABILITY			
2. What are the results?			
a. How large is the intervention or treatment effect (NNT, NNH, effect size, level of significance)?	__	__	__
b. How precise is the intervention or treatment (CI)?	__	__	__
APPLICABILITY			
3. Will the results help me in caring for my patients?			
a. Were all clinically important outcomes measured?	Yes	No	Unknown
b. What are the risks and benefits of the treatment?			
c. Is the treatment feasible in my clinical setting?	Yes	No	Unknown
d. What are my patient's/family's values and expectations for the outcome that is trying to be prevented and the treatment itself?			