**Metformin for weight gain associated with second generation antipsychotics in children and adolescents:**

**a systematic review and meta-analysis**

**Running title:** Metformin for weight gain associated with antipsychotics in children and adolescents

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**ABSTRACT**

**BACKGROUND:** Weight gain is a potentially concerning side effect of second generation antipsychotics (SGAs). Metformin, a biguanide with antihyperglycemic effects, is used to manage weight gain in adults treated with SGAs.

**OBJECTIVE:** To perform the first systematic review and meta-analysis of randomized controlled trials (RCTs) assessing the effects of metformin on weight gain in children and adolescents treated with SGAs.

**METHODS:** Based on a pre-registered protocol (PROSPERO-CRD42017074839), we searched PubMed, Embase, PsychoINFO, BIOSIS, Science Direct, Cochrane CENTRAL, and Clinicaltrials.gov through March 2018, with no language/date/type of publication restrictions for RCTs that assessed the effect of metformin or placebo on body weight in children or adolescents (< 18 years of age) treated with selected SGAs (risperidone, aripiprazole, olanzapine and clozapine) for any psychiatric disorder. We also contacted relevant drug manufacturers for possible additional pertinent studies/data. Random-effects model was used and the quality of the included RCTs was assessed with the Cochrane Risk of Bias (RoB) tool.

**RESULTS:** Five RCTs (205 participants in total) were included in the meta-analysis. We found a significant weight decrease in the metformin group compared to placebo after 4, 12 and 16 weeks of treatment [mean difference: -0.98 Kg (95% Confidence Interval (CI): -1.26, -0.69); -1.83 Kg (95% CI:-2.47, -1.18) and -3.23 Kg (95% CI :-5.59,-0.86), respectively]. Weight decrease at weeks 2 and 8 did not reach statistical significance. The decrease in body mass index (BMI) paralleled that of the weight, with a significant effect at weeks 4, 12 and 16. Four studies were rated at overall *unclear*, and one at overall *high* RoB.

**CONCLUSION:** Meta-analytical evidence shows that metformin might decrease weight in children/adolescents treated with SGAs, but additional high quality evidence is needed.

**Key points:**

* This is the first systematic review and meta-analysis exploring the efficacy of metformin to manage weight gain and body mass index increase related to second generation antipsychotics administration in the pediatric population.
* From 12 weeks of treatment, metformin was significantly more efficacious than placebo in reducing body mass index in children and adolescent treated with second generation antipsychotics.

**1-Introduction**

In children and adolescents, second-generation antipsychotics (SGAs) have FDA-approved indication in a number of mental health conditions, including autism spectrum disorder, schizophrenia, bipolar disorder, Tourette’s syndrome and disruptive behavior associated with externalizing disorders [1–4]. Over the past decades, there has been a remarkable increase in the prescription of SGAs across several countries [5–8]. Indeed, SGAs are among the most commonly prescribed medications in children and adolescents in North America [4]. Unfortunately, these drugs are associated with important adverse effects, including weight gain and metabolic disturbances [9,10]. In the Second-generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY), a large naturalistic cohort study conducted from 2001 to 2007, a weight gain of more than 7% was observed during the first 3 months for 85% of patients with olanzapine, 65% of patients with risperidone, and 60% of patients with aripiprazole [11]. These results are confirmed by recent meta-analytic evidence [12]. Obesity in children and adolescents is associated with a dramatic increase of morbidity. Around 25% of youth with obesity present with metabolic syndrome and increased risk for atherosclerosis, heart diseases, and type 2 diabetes mellitus [13–15]. The risk of heart diseases is tenfold higher in youth with obesity compared with normal weight peers [16]. Children and adolescents with obesity may also experience psychological distress related to being bullied, leading to poor self-image and, possibly, depression [17]. Thus, careful screening and early interventions to prevent weight gain and metabolic syndrome are recommended in youth treated with SGAs [18]. Unfortunately, in clinical practice, careful metabolic parameter monitoring is often overlooked in youth treated with SGA [19]. Non-pharmacological strategies for weight gain such as educational or family-based interventions are recommended but they showed limited efficacy and supporting evidence on their effects are extrapolated from studies of children with obesity or type 2 diabetes mellitus [20]. In 1999, metformin was proposed as a promising pharmacological option to manage weight gain associated with the use of SGAs [21]. Metformin is currently approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating type 2 diabetes mellitus in children older than 10 years [22,23]. This drug is also effective in reducing the body mass index (BMI) of children with obesity [24]. Meta-analytic evidences showed that metformin combined with lifestyle interventions was efficacious (albeit with moderate effect size) and well tolerated in decreasing weight in children with obesity aged 10-16 years [25,26]. Additionally, in adults, metformin has been found efficacious in improving glycemic control, as well as weight gain related to SGAs, especially in patients already obese [27–30]. There is also preliminary but increasing evidence on the use of metformin in childhood to counteract the metabolic disturbances, including weigh gain, induced by SGAs [31,32]. To our knowledge, no systematic review and meta-analysis have been conducted to estimate the efficacy of metformin in counteracting the effects on weight of SGAs in children and adolescents. Our study aimed to fill this gap. Given the exploratory nature of this meta-analysis, no *a priory* hypothesis was formulated.

**2-Method**

*2.1-Search strategy*

The protocol for the present systematic review/meta-analysis was registered on the international Prospective Register of Systematic Reviews PROSPERO (<https://www.crd.york.ac.uk/PROSPERO>, protocol number: CRD42017074839). The systematic review and meta-analysis were conducted and reported following the PRISMA recommendations (Preferred Reporting Items for Systematic review and Meta-Analysis [33]). The following electronic databases were searched with no restriction in terms of language, type of document, or date: PubMed (MEDLINE), Embase, PsychoINFO, BIOSIS, Science Direct, and Cochrane CENTRAL. The following search terms/syntax were used for Pubmed: metformin AND (antipsychotic\* OR Risperidone OR Aripiprazole OR Olanzapine OR Clozapine) AND (child OR children OR adolesc\* OR youth\* OR pediatr\* OR paediatr\* OR early onset). The search terms/syntax were adapted accordingly for the other databases. Reference lists of the retained articles and relevant review articles were hand-searched to retrieve any additional pertinent reports not detected via the electronic database search. Furthermore, we searched *Clincialtrials.gov* to retrieve any pertinent study not yet published as full text article at the time of the search. The last search was completed on 30 March,2018. Additionally, we contacted relevant drug manufacturers to inquire about any relevant published or unpublished study not identified in our search.

*2.2-Selection of the relevant articles*

Studies were included in our systematic review if they met the following criteria: 1) randomized controlled trials (RCTs), regardless of the level of blinding and follow-up time; 2) participants under the age of 18 years old; 3) participants treated with any SGAs and randomized to metformin or placebo, whatever the psychiatric disorders for which they received the antipsychotic; 4) weight and/or BMI values at baseline and study endpoint as study outcomes. Any non-randomized studies were excluded. No restriction in terms of ethnical origins of the participants were applied.

*2.3-Selection of studies and data extraction*

The eligibility process was conducted in two separate stages: 1) two researchers (PE and RD) independently screened all non-duplicated references initially retrieved as potentially pertinent and excluded those clearly not pertinent based on title or abstract. A final list was agreed with discrepancies resolved by consensus between the two authors. When consensus was not reached, a third, senior researcher (SC) acted as arbitrator; 2) the full-text version of the articles passing stage 1 screening was downloaded and assessed for eligibility by the two researchers, independently. Discrepancies were resolved by consensus between the two researchers and, if needed, the third senior researcher also acted as arbitrator. When required, corresponding authors were contacted to clarify study eligibility.

*2.4-Risk of bias of included studies*

Risk of bias for each study included in the meta-analysis was assessed using the Cochrane Risk of Bias (RoB) Tool [34][33][32][31]. RoB domains included: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. As in Cortese *et al.*[35], the overall rating of risk of bias for each study was the lowest rating for any of the criteria (e.g., if any item was scored high risk of bias, the study was scored at high risk of bias; if all the items were scored at low risk, the study was rated at overall low risk).

*2.5-Statistical Analyses*

Mean difference (MD) for each study was first calculated as mean pre- to post- treatment change in the intervention group minus the mean pre- to post- treatment change in the control group, divided by the pooled pre-test standard deviation with a bias adjustment [36]. Analyses were conducted on as per protocol data, with the exception of one study [37] that presented only data for intention to treat analyses only. The MD for each trial were then combined using the inverse variance method. Given the inherent heterogeneity of studies, random-effects model was used. The statistic I² was calculated to estimate between-trial MD heterogeneity. I2 represents the percentage of variance due to between-studies heterogeneity rather than sampling error [38]. Analyses were performed with RevManager 5 (http://community.cochrane.org/help/tools-and-software/revman-5).

**3-Results**

*3.1- Search*

From an initial pool of 76 potentially relevant references, five studies were included in the meta-analysis [35-39]. Figure 1 reports the PRISMA flowchart detailing the screening process. Supplemental table 1 reports the references discarded after reading the full text, with the specific reasons for exclusion.

*--- Insert Figure 1 here ---*

*3.2- Characteristics of studies included in the meta-analysis*

Three studies were published as full text reports in peer reviewed journals [37,39,40][38–40] and two additional studies were found on *ClinicalTrials.gov* [41,42]. The duration of the studies varied from 16 to 26 weeks. For all the studies, both weight and BMI values (at baseline and endpoint) were available. The age range of participants ranged between 11.25 and 14.2 years.

*3.3 Results of the meta-analysis*

 3.3.1 Effect of metformin on weight

*--- Insert figure 2, 3 and 4 here ---*

Meta-analysis results on weight gain are reported in Figure 2, 3 and 4. The difference between metformin and placebo in weight change from baseline to weeks 2 and 8 did not reach statistical significance [MD: -0.29 (95% Confidence Interval (CI): -1.00, 0.41); -1.54 [95% CI: -3.52, 0.45]. There was evidence of heterogeneity at week 2 (Tau² = 0.16; Chi² = 2.67, degrees of freedom (df) = 1 (P = 0.10); I² = 63%) and at week 8 (Tau² = 1.28; Chi² = 2.55, df = 1 (P = 0.11); I² = 61%). The difference between metformin and placebo in weight change from baseline to week 4, 12 and 16 was significant [-0.98 (95% CI -1.26, -0.69); -1.83 (95% CI: -2.47, -1.18) and -3.23 (95% CI [-5.59, -0.86)], respectively. Heterogeneity values at week 4, 12, and 16 were as follows: Tau² = 0.01; Chi² = 2.10, df = 2 (P = 0.35); I² = 5%, Tau² = 0.00; Chi² = 2.16, df = 3 (P = 0.54); I² = 0%, Tau² = 1.20; Chi² = 1.41, df = 1 (P = 0.24); I² = 29%, respectively .

 3.3.2 Effect of metformin on BMI

*--- Insert figure 5 and 6 here ---*

The results of the meta-analysis on BMI are reported in Figure 5 and 6. Results paralleled those for weight with no statistical significance at week 4 [-0.29 (95% CI: -0.59, 0.01) but significant values at weeks 12 and 16 [-0.63 (95% CI: -0.86, -0.40) and -1.00 (95% CI: -1.54, -0.46), respectively] between weight changes in the metformin and placebo groups. Heterogeneity values at week 4,12, and 16 were as follows: Tau² = 0.04; Chi² = 4.20, df = 1 (P = 0.04); I² = 76%, Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%, Tau² = 0.03; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%, respectively.

*3.4 Risk of bias*

As shown in Table 1, one study [42] was deemed at overall high risk of bias, whereas the other were rated at overall unclear risk of bias [36–39].

*--- Insert Table 1 here ---*

*3.5 Changes in relation to the original protocol*

Given the paucity of available data, we were unable to conduct the planned analysis on the effect of metformin on glucose and cholesterol parameters or on the tolerability of metformin.

**4-Discussion**

To our knowledge, this is the first systematic review and meta-analysis exploring the efficacy of metformin in counteracting weight gain and BMI increase related to SGAs administration in the juvenile population. Our meta-analysis showed that from 12 weeks of treatment, metformin was significantly more efficacious than placebo in reducing BMI in children and adolescent treated with SGA. Our results are in agreement with those in adults where the efficacy of metformin in reducing weight gain was demonstrated by several meta-analyses [27,43–45]. Although our meta-analysis could not provide additional information beyond week 16, preliminary evidence from an open-label study suggested that the effects was maintained after 16 weeks of treatment [46]. It is also fundamental to note that metformin is used off-label in this indication in psychiatry. In addition, a 10 years follow-up study of the Diabetes Prevention Program Research Group has shown that lifestyle intervention program is more efficacious than metformin for weight loss [47]. Even if the efficacy of metformin in the adult populations exposed to SGA if more robust, it is recommended to never used it before healthy lifestyle interventions [48,49].

 The exact mechanisms underlying the effects of metformin in reducing weight gain related to antipsychotic treatment remain to be elucidated. Metformin is a biguanide which has been found to inhibit hepatic glucose production, lower circulating free fatty acids and ultimately reduce gluconeogenesis and intestinal absorption of glucose [50]. It also improves the uptake of glucose and its use by the muscle instead of adipocytes [51]. The main mechanism of weight loss may result from a reduction of insulin resistance and an increase in the sense of satiety [52]. In the specific context of SGAs use, the efficacy of metformin might be accounted for by these two mechanisms [53]. Of note, a recent study showed that only about half of the weight gain observed in youths taking antipsychotics is fat.) [54]. Metformin attenuation of weight gain might represent some attenuation of fat increase and some attenuation of lean mass (muscle and/or water). Because those mechanisms are mostly speculative, further research is needed to gain insight into the precise mechanisms of action of metformin in patients treated with SGA.

Our results should be considered in the light of the study strengths and limitations. As for the strengths, we performed a systematic search in several databases, without language restrictions, as well as in Clinicaltrials.gov. We also contacted studies' authors and drug companies to gather additional unpublished data. A number of limitations should be taken into account. First, we could only retain a limited number of studies that explored the effects of metformin in the pediatric populations. However, there is no an established minimum number of studies to be included in a meta-analysis and and, given the high clinical relevance of the topic, this first evidence synthesis in the field should hopefully encourage further methodologically sound investigation . Second, none of the included study was rated at overall low risk of bias, with the majority (n=4) of studies rated at overall unclear risk of bias and one study at high risk of bias. However, we note that we used stringent criteria to rate the risk of bias (a study had to present with all items at low risk of bias to be rated at overall risk of bias). Furthermore, may items were rated as unclear due to missing information in the publication, which calls for a better and more complete reporting in the field. Third, due to the paucity of data, we did not perform sub-group analysis based on the type of SGA. For similar reasons, we were unable to perform separate analyses according to the specific mental health conditions for which SGA was used. However, unlike studies in adults, all SGAs have been associated with significant metabolic alterations in children and adolescents [55]. Furthermore, we were not able to meta-analyze the outcome on the tolerability of metformin. However, evidence from non-randomized studies is available to inform prescribers on this relevant issue. For instance, in a long-term follow-up study of 6.5 years on 700 pediatric patients treated with metformin, 40% presented mild gastro-intestinal symptoms (such as abdominal pain, nausea, metallic taste, bloating, and diarrhea), 20% with an anemia and 5.7% showed elevated liver transaminases [56]. Clinician must be aware of the high rate of gastro-intestinal distress which can be a major issue in treatment adherence. Long-term use of metformin was also associated with vitamin B12 decrease [31]. The overall adverse event rate was estimated at 5.6% participant-years of exposure [56]. In adults, a study on 47,597 patients during a follow up of 7.2 ± 3.2 years showed that the long term use of metformin was associated with a significant decrease in colorectal cancer occurrence [57]. These results were replicated in another cohort [58]. More generally, in a cohort including 82,720 adult metformin users, long-term adherence to metformin was associated with decreased risks of all-cause mortality after a 2.4 year follow up [59]. However, caution is required in the pediatric context, especially in relation to the use of metformin for weight gain prevention related to SGA treatment, considering the possible risks of metformin and the fact the non-pharmacological alternatives have been found effective. However, in situations where non-pharmacological approaches are not feasible or unsuccessful, metformin may be considered as a possible intervention, supported by preliminary evidence, as showed in this meta-analysis. Of note, no serious adverse events were reported in any of the studies included in our meta-analysis.

**5- Conclusion**

## Our study provided meta-analytic evidence showing that metformin may be beneficial, in the short term, to counteract weight gain in children and adolescents treated with SGA. However, our findings should be relicate din larger trials before being considered to support clinical recommendation and they should be considered with caution due to the low number of studies (with a low number of participants) included and the overall heterogeneity between them [42,59–64][42,60–65]. If replicated in further large high quality trials, our findings suggest that, since effects took about 4 weeks for the effects to be significant, an early administration of metformin, soon after the patient is started in SGA, would be warranted, reflecting the currently available guidelines for adults [66]. It is important to bear in mind that the American Psychiatric Association recommends to not routinely prescribe antipsychotic medications as a first-line intervention for children and adolescents, which is actually the best way to avoid metabolic side effect [67]. Multimodal treatment strategies encompassing metformin and non-pharmacological strategies (such as diet and educational or family-based interventions) are likely to represent the most efficacious intervention to counteract weight gain associated with SGA in youth and should be a research priority for the field.

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**Compliance with Ethical Standards**

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