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Effect of serotonin modulating pharmacotherapies on body mass index and dysglycaemia among children and adolescents: a systematic review and network meta-analysis protocol

Reem A Al Khalifah,[1,2,3] Nicole E De Long,[4] Ivan D Florez,[1,5] Lawrence Mbuagbaw,[1,6,7] Katherine M Morrison[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Lawrence Mbuagbaw;
mbuagbawl@yahoo.com

ABSTRACT

Introduction: Serotonin-modulating medications are commonly prescribed for mental health issues. Currently, there is limited consensus on weight gain and dysglycaemia development among children using these medications. The objective of this study is to review and synthesise all the available evidence on serotonin-modulating medications and their effects on body mass index (BMI), weight and glycaemic control.

Methods and analysis: We will conduct a systematic review of all randomised controlled trials evaluating the use of serotonin-modulating medications in the treatment of children 2–17 years with mental health conditions. The outcome measures are BMI, weight and dysglycaemia. We will perform literature searches through Ovid Medline, Ovid Embase, PsycINFO and grey literature resources. Two reviewers from the team will independently screen titles and abstracts, assess the eligibility of full-text trials, extract information from eligible trials and assess the risk of bias and quality of the evidence. Results of this review will be summarised narratively and quantitatively as appropriate. We will perform a multiple treatment comparison using network meta-analysis to estimate the pooled direct, indirect and network estimate for all serotonin-modulating medications on outcomes if adequate data are available.

Ethics and dissemination: Serotonin-modulating medications are widely prescribed for children with mental health diseases and are also used off-label. This network meta-analysis will be the first to assess serotonin modulating antidepressants and their effects on weight and glycaemic control. We anticipate that our results will help physicians and patients make more informed choices while considering the side effect profile. We will disseminate the results of the systematic review and network meta-analysis through peer-reviewed journals.

PROSPERO registration number: CRD42015024367.

Strengths and limitations of this study

- This systematic review and network meta-analysis will investigate the metabolic effects relating to the use of serotonin modulating medications in children: weight, body mass index and dysglycaemia.
- The strengths of this review are the wide search strategy, broad inclusion criteria and use of GRADE to evaluate certainty of the evidence.

BACKGROUND

Paediatric obesity is one of the most pressing public health issues in children and adolescents today. The prevalence of childhood obesity is high in developed and developing countries. The observed prevalence is 16.9% in the USA,[1] 11.7% in Canada,[2] 5–6% in Australia[3] and 6.1% in developing countries.[4] Childhood obesity leads to several complications, including the development of type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, obstructive sleep apnoea, poor quality of life and depression.[5–8] These complications predispose children to adult-type cardiovascular and metabolic morbidities.[8] The rapid rise in obesity prevalence in children is attributed to a complex interaction of multiple factors including consumption of high energy-dense food, sugar-sweetened beverages, decreased fruit and vegetable intake and decreased physical activity.[9] Furthermore, many common medications can influence weight changes and the development of obesity.[10]

Approximately 4–7% of youth meet the criteria for a mental health disorder.[11 12] Anxiety or major depressive disorder (MDD), along with attention deficit hyperactivity disorder (ADHD), is the most common mental health disorder among children and adolescents.[13 14] Estimates of childhood and adolescent MDD are approximately 2% in Canada,[15] but rates up to 10%

have been reported in the UK[16] and Brazil.[17] Moreover, the worldwide prevalence rate of ADHD is 5.3%[18] while rates of autism have increased by 23%.[19–21]

Treatments for mental illness in children include psychotherapy, education for the patient and family and/or pharmacotherapy. Current Food and Drug Administration (FDA) guidelines include a number of drugs approved for use in children including antipsychotics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors. Given the increasing prevalence of diagnosed mental health disorders in children and youth,[22 23] prescriptions of second generation antipsychotics doubled from 2001 to 2005.[2 22 24 25] Of the pharmacotherapies available, antipsychotics and antidepressants, which modulate the serotonin system, are increasing in use.[26–28] Moreover, drugs that are not approved for use in children or adolescents are being prescribed for a number of off-label uses.[28]

Serotonin-modulating drugs have been implicated in an increased risk of developing obesity and TD2M in adults.[25 29–31] Recent systematic review and meta-analysis in paediatrics evaluated atypical antipsychotic use and found that olanzapine, risperidone and aripiprazole were associated with drug induced weight gain when compared to placebo.[32] However, this systematic review did not provide effect estimates for many identified medications because of lack of enough data from placebo-controlled trials. Therefore, it is unclear whether all serotonin modulating medications induce weight gain in children and which serotonin modulating drugs have the greatest influence on weight gain.[33–35] Recent findings utilising rodent models have highlighted the importance of central[36] and peripheral[37] serotonin on adipose tissue and metabolism, but with opposing influences.

In this study, we aim to systematically review and synthesise the existing evidence on serotonin modulating pharmacotherapies among children and adolescents (up to 17 years of age) and their effects on body mass index (BMI), weight and dysglycaemia using a network meta-analysis (NMA). Many of the medications used to treat mental health issues were evaluated in trials with a placebo comparator or standard of care to gain drug regulatory agencies approval. This approach allows for head-to-head (pairwise) comparisons, but provides limited evidence of comparative efficacy between medications. An NMA allows estimation of treatment effects among direct and indirect treatment comparisons, whereas a traditional meta-analysis can only evaluate the direct treatment efficacy of two treatment approaches at a time.[38] We hypothesise that serotonin modulating drug use in children and adolescents will result in elevated BMI and weight and could negatively influence glucose metabolism.

METHODS/DESIGN

This systematic review and NMA protocol is registered on the PROSPERO International prospective register of systematic reviews (CRD42015024367). This protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidance.[39] We will report the paper according to the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[40]

Eligibility criteria

Types of participants

Participants will include children aged 2–17 years with mental health illness. The diagnosis of mental health illness will be based on the widely accepted Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria 4 and 5. We will include the following mental health issues: depression, mania, bipolar disorder, anxiety disorders, psychosis (schizophrenia), autism and ADHD. Studies will be excluded if they included participants with eating disorders because of the independent interaction with regard to weight gain or weight loss throughout the study. In addition, studies that included adolescent and adult participants, substudies and secondary analysis of reported eligible studies, or studies in which the author was not able to provide at least one of our outcome measures will be excluded.

Type of interventions

Studies will need to assess the effect of any of the following serotonin modulating medications used in the context of mental health illness compared to placebo or another of the included medications: amitriptyline, amphetamine, aripiprazole, atomoxetine, buspirone, citalopram, clomipramine, clozapine, desipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, haloperidol, imipramine, methylphenidate, mirtazapine, nortriptyline, olanzapine, paliperidone, paroxetine, quetiapine, risperidone, sertraline, thioridazine, thiothixene, trazodone, venlafaxine, ziprasidone. These medications were selected from the National Institute of Health (NIH) drug list for mental health disorders and cross-referenced for their serotonin modulating capabilities. Drugs were not excluded on the basis of the FDA approved age limit or due to their indicated uses due to frequent off-label practices.

Outcomes

The outcomes of interest are BMI (kg/m^2), BMI z-score, BMI categorical changes (% overweight and obese, % normal, % with thinness), weight (kg), weight z-score, height (cm), height z-score, and prevalence of dysglycaemia measured as the number of participants with a diagnosis of T2DM, impaired glucose tolerance, and/or impaired fasting glucose assessed by oral glucose tolerance test and/or fasting blood glucose, and/or glycated haemoglobin. Given that BMI scores vary with gender and age as part of normal growth, we will use the WHO recommended BMI Z-score cut-offs for age and gender

to define overweight and obesity (>+1 SD), normal (>−2 SD and <+1 SD) and thinness (<−2 SD).[41 42]

Types of studies

Parallel, double or multiarm randomised clinical trials.

Search strategy

We performed the literature search through the major medical intervention databases Ovid Medline, Ovid Embase, PsycINFO and clinical trials.gov from the database inception date to March 2015. The search terms included a combination of subject heading and keywords with various synonyms for mental health diagnoses, children, adolescent, body mass index, weight and specific serotonin modulation medication names (see online supplementary appendix). We used the randomised controlled trial filter created from the McMaster University for Ovid Embase platform and the Cochrane library filter for Ovid Medline platform. These filters provide a good balance between sensitivity and specificity.[43 44] The search was limited to the English language and published studies. Additionally, we performed a manual hand search of bibliographies of identified randomised controlled trials. Search alerts are set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new literature.

Study selection

Two reviewers will assess independently all identified titles and abstracts, and full text eligibility using Covidence web-based software.[45] A third reviewer will resolve any disagreement in eligibility in case consensus is not reached. Records of ineligible articles will be saved in a separate document for future reference. We will include the PRISMA flow diagram demonstrating the search and screening process (figure 1).

Data extraction

The study data will be collected in standardised data extraction forms using Google forms (Google, 2015). The data extraction form will include information pertaining to the study background, eligibility, participant's diagnosis, age, number of interventions, the intervention details, outcomes definition, unit of measurement, baseline outcome measures, estimate of effect with CIs, compliance and numbers lost to follow up. For studies with more than one follow-up period, we will select the longest. Two reviewers will extract the data independently.

Risk of bias assessment

Using the Cochrane risk of bias tool, each included study will be assessed independently for risk of bias.[44] The tool will assess the sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow-up, selective outcome reporting and presence of other biases. Each domain will be assigned a score 'low risk', 'high risk' or 'unclear risk'. We will further categorise the 'unclear risk' category into ' probably low risk' or 'probably high risk' in order to give a better understanding of the risk of bias score.[46] We will rate the overall risk of bias score for each study according to the GRADE risk of bias recommendations; 'low risk of bias' if the study did not meet any high risk of bias criteria, 'moderate risk of bias' if the study met a 1–2 score for high risk of bias, and 'high risk' if the study met 3 scores for high risk of bias.[47]

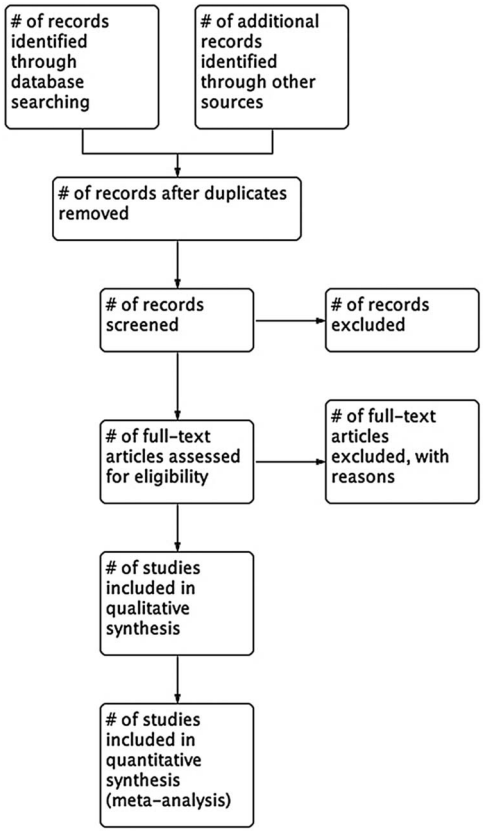

Figure 1 The primary selection process.

Statistical analysis

Standard direct comparisons

We will perform all pairwise comparison meta-analysis using the R software (R: A language and environment for statistical computing. R Foundation for Statistical Computing[program]. Vienna, Austria, 2015). Effect estimates and their 95th CI will be calculated using the risk ratio for dysglycaemia prevalence, and mean difference for BMI. We will pool all direct evidence using random-effect meta-analysis with the maximal likelihood (ML) estimator. We will assess for heterogeneity by estimating the variance between studies using the χ^2 test and quantifying it using the I^2 test statistic. We will interpret the I^2 using the Cochrane Collaboration thresholds.[44] The I^2 will be used as a criterion for pooling the results, performing subgroup analysis and meta-regression (see below), and rating the indirectness criterion when assessing the confidence in the estimates with GRADE (see below).

The network meta-analysis

We will perform a multiple treatment comparison to estimate the pooled direct, indirect and the network estimates for serotonin modulating medications on our outcome measures. These estimates will be provided if assumptions of homogeneity and similarity are not violated. Effect estimates will be presented along with their corresponding 95% credibility intervals (CrIs), the Bayesian analogue of 95% CIs. However, mixed evidence will only be used if the consistency assumption is met.

We will fit a Bayesian random hierarchical model with non-informative priors using vague normal distribution and adjusting for correlation of multiarm trials.[48] We will obtain the NMA pooled estimates using the Markov Chains Monte Carlo method using the R software. The final output will be produced after model convergence using 100 000 burn-in and 20 000 simulations. We will assess model convergence on the basis of the Gelman and Rubin diagnostic test (gemtc).[49] We will use the node-splitting method to detect consistency between direct and indirect evidence within a closed loop as well as to identify loops with large inconsistency.[50 51] We will measure the model fit using the deviance information criterion.[50]

We will present the network geometry, and the results in probability statements as well as forest plots to guide the interpretation of the NMA.[52] We will rank the probabilities and disseminate each intervention's hierarchical chance percentage of ranking first with 95% CrIs as well as the Surface Under the Cumulative RAnking curve (SUCRA) values, given that the probability ranking is in agreement with the quality of the evidence.

Meta-regression

In case there is significant heterogeneity and inconsistency, we will use meta-regression to explain the heterogeneity, provided we have sufficient data to do so; otherwise, we will perform subgroup analyses. We will use the study level covariates to perform meta-regression: participant's mean age, sex, length of treatment received and reported clinical response to treatment. We will use the effects estimates for clinical response to treatments reported by the authors for each disease, because different scales are used to measure clinical response for each mental health diagnosis.

Furthermore, we will perform a meta-regression to explain differences in the observed point estimates based on the pharmacological properties of the medications. However, since there is no definite classification for these medications based on their metabolic effects, we will evaluate the performance of a model based on the pharmacological classifications compared to a model that will classify each medication based on the clinical indication in the respective trials. The pharmacological classification is based on the primary receptor target (table 1). Serotonin modulating medications can act on varying serotonin/5 hydroxytryptophan (5HT) receptor subtypes and can be either an agonist or antagonist. In addition, many of the serotonin modulating medications bind to other receptors/transporters that may influence weight changes such as dopamine receptors and the norepinephrine transporter. Therefore, accounting for these additional effects can explain observed differences beyond serotonin modulation.

Sensitivity analysis

Additionally, we will examine the robustness of our analysis through sensitivity analyses. We will explore the effects of risk of bias on our outcomes by excluding studies at high risk of bias under the assumption that they may be less accurate or precise. We will also explore differences between studies that included 'responders' only, compared to all who received treatment. Finally, we will explore the impact of using different approaches to measure weight gain.

Rating the confidence in estimates of the effect in NMA

For each reported outcome, two of the authors will independently assess the confidence in the estimates (quality of the evidence), using the recent approach recommended by the GRADE working group.[53] We will present treatment estimates for direct, indirect and NMA evidence if the assumptions are met. Further, we will assess the quality of the evidence for each reported outcome using the GRADE criteria independently by two reviewers.[47 54–56] GRADE assesses five categories for pairwise comparisons: risk of bias, imprecision, inconsistency, indirectness, publication bias, in addition to intransitivity for indirect comparisons, and incoherence for the NMA estimates.[53] For rating confidence in the indirect comparisons, we will focus our assessments on first-order loops (ie, loops that are connected to the interventions of interest through only one other intervention with the lowest variances), and because of their major contribution to the indirect effect estimates.[57] This is because estimates of loops (interventions) can be obtained via any common comparator. For instance, if there are four interventions in a network A, B, C and D, we could indirectly estimate the effects of A versus D via deduction from B (the first common comparator), or through C (the second common comparator). Within each loop, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. Our overall rate of confidence in the NMA estimate will be the higher of the confidence rating among the contributing direct and indirect comparisons. Nevertheless, we may rate down confidence in the NMA estimate if we find that the direct and indirect estimates are incoherent.[53]

DISCUSSION

This systematic review aims to synthesise the available evidence around adverse metabolic health outcomes with commonly used serotonin modulation medications for the treatment of childhood mental health disorders. We will show the relative ranking of each medication as

Table 1 Pharmacological interventions related to the serotonergic system

SSRIs	Serotonin-NRIs	Serotonin modulators	Dopamine $_{D2}$ receptor antagonists	Dopamine $_{D2/D3}$ and 5HT2 $_{A/C}$ receptor antagonists	Selective NRIs	5HT $_{1A/2}$ partial agonist and Dopamine $_{D2}$ antagonist	Mixed SRIs and NRIs (TCAs)	NSSRIs Or NaSSRIs (TeCAs)	CNS stimulants (Central release of catecholamines)
Fluoxetine Sertraline Paroxetine Fluvoxamine Citalopram Escitalopram	Desvenlafaxine Duloxetine Venlafaxine	Trazodone	Haloperidol Thiothixene Thioridazine Molindone	Aripiprazole Clozapine Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone Lurisidone	Atomoxetine	Buspirone	Clomipramine Desipramine Imipramine Nortriptyline Amitriptyline	Mirtazapine	Amphetamine Methyl-phenidate

CNS, central nervous system; HT, hydroxytryptophan; NaSSRIs, noradrenaline/selective norepinephrine reuptake inhibitors; NRIs, norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; TeCAs, tetracyclic antidepressants.

a potential contributor to weight gain and dysglycaemia. The NMA results will help healthcare providers and patients anticipate weight and metabolic profile changes. This will allow healthcare providers and patients to make better-informed choices while considering the side effect profile. Nonetheless, the effect of long-term metabolic changes on cardiovascular disease will need to be established through long-term studies.

Our study has several strengths. First, we will include all mental health diagnoses for which serotonin modulating medications are being used; this will increase the generalisability of our study findings. Second, we are planning a meta-regression based on the pharmacological differences between medications to explain the observed differences in metabolic effects. This approach will further our understanding of serotonin modulating medications and help advance future research. However, our proposed two classifications are being assessed for the first time in meta-analysis; therefore, this approach may need future refinement and validation.

Author affiliations
[1]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
[2]Department of Pediatrics, Division of Endocrinology and Metabolism, McMaster University, Hamilton, Ontario, Canada
[3]Department of Pediatrics, King Saud University, Riyadh, Saudi Arabia
[4]Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada
[5]Department of Pediatrics, Universidad de Antioquia, Medellín, Colombia
[6]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St. Joseph's Healthcare, Hamilton, Ontario, Canada
[7]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon

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Contributors RAAK and NEDL were involved in the conceptualised and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. IDF was involved in the conceptualised and designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted. LM was involved in the conceptualised and designed the study, critically reviewed and edited the manuscript, and approved the final manuscript as submitted. KMM was involved in the conceptualised and designed the study, critically reviewed and edited the manuscript, and approved the final manuscript as submitted.

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