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Effect of Serotonin Modulating Pharmacotherapies on Body Mass Index and Dysglycaemia Among Children and Adolescents: Systematic Review and Network Meta Analysis Protocol

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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 synthesize all the available evidence on serotonin-modulating medications and their effects on BMI, weight, and glycemic control.

Methods and analysis:

We will conduct a systematic review of all randomized controlled trials evaluating the use of serotonin-modulating medications in the treatment of children 2-17 years with mental health disease. 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 texts trials, extract information from eligible trials and assess the risk of bias and quality of the evidence. Results of this review will be summarized 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 is 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 glycemic control. We anticipate 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.
- Strengths of this review are the wide search strategy, broad inclusion criteria, and use of GRADE to evaluate certainty of the evidence.

Background:

Pediatric obesity is one of the most pressing public health issues in children and adolescents today. The prevalence of childhood obesity is high in both developed and developing countries. The observed prevalence in the United States (US) is 16.9% [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, dyslipidemia, obstructive sleep apnea, 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) are the most common mental health disorders amongst 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 UK [16] and Brazil [17]. Moreover, the worldwide prevalence rate of ADHD is 5.3% [18] while rates of autism have been increasing worldwide [19 20].

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, serotonin selective reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRI). Given the increasing prevalence of diagnosed mental health disorders in children and youth [21 22], prescriptions of second generation antipsychotics doubled from 2001 to 2005 [2 21 23 24]. Of the pharmacotherapies available, antipsychotics and antidepressants, which modulate the serotonin system, are increasing in use [25-27]. Moreover, drugs that are not approved for the use in children or adolescents are being prescribed for a number of off-label uses [27].

Serotonin-modulating drugs have been implicated in an increased risk of developing obesity and TD2M in adults [24 28-30]. Recent systematic review and meta-analysis in paediatrics, evaluated the use of atypical antipsychotic use and found that olanzapine, risperidone and aripiprazole were associated with drug induced weight gain when compared to placebo [31]. 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 [32-34]. Recent findings utilizing rodent models have highlighted the importance of central [35] and peripheral [36] serotonin on adipose tissue and metabolism – but with opposing influences.

In this study we aim to systematically review and synthesize the existing evidence on serotonin modulating pharmacotherapies amongst 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. 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. A network meta-analysis (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 2 treatment approaches at a time [37]. We hypothesize 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 network meta-analysis protocol is registered on PROSPERO International prospective register of systematic reviews (CRD42015024367). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance [38]. We will report the paper according to the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions [39].

Eligibility criteria:

Types of participants

Participants will include children age 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 regards to weight gain or weight loss throughout the study. In addition, studies that included both adolescent and adult participants, sub-studies 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 based on 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, weight (kg), weight z-score, height (cm), height z-score, and prevalence of dysglycaemia measured as the number of participants

with diagnosis of T2DM, impaired glucose tolerance, and/or impaired fasting glucose assessed by oral glucose tolerance test and/or fasting blood glucose, and/or HBA1c.

Types of studies
Parallel, double or multi-arm Randomized Clinical Trials (RCT).

Search Strategy:
We performed the literature search through the major medical interventions 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 medications names (Appendix). We used the randomized controlled trial filter created from McMaster University for Ovid Embase platform, and the Cochrane library filter for Ovid Medline platform. These filters provide good balance between sensitivity and specificity[40 41]. The search was limited to English language and published studies. Additionally, we performed manual hand search of bibliographies of identified randomized 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 [42]. 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 standardized data extraction forms using Google forms [43]. 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 confidence intervals, 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 [41]. 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 categorize 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 [44]. 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 1-2 score for high risk of bias, and 'high risk' if the study met more than 2 scores for high risk of bias [45].

Statistical analysis:

Standard direct comparisons

We will perform all pairwise comparison meta-analysis using R software [46]. Effect estimates and their 95th confidence interval (CI) will be calculated using risk ratio (RR) 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 Chi-square test and quantify it using the I^2 test statistic. We will interpret the I^2 using the Cochrane Collaboration thresholds [41]. 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 multi-arm trials [47]. 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 Gelman and Rubin diagnostic test (gemtc) [48]. We will use the node-splitting method to detect consistency between direct and indirect evidence within a closed loop as well as identify loops with large inconsistency [49 50]. We will measure the model fit using the deviance information criterion (DIC) [49].

We will present the network geometry, and the results in probability statements as well as forest plots to guide the interpretation of the NMA [51]. 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, 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, because 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 binds 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.

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

Additionally, we will examine the robustness of our analysis through sensitivity analyses. The analyses will be performed based on the studies risk of bias arising from loss of follow up, poor compliance, and over all risk of bias (high risk of bias versus low risk of bias). Additionally, we will perform sensitivity analyses based on the length of treatment (≥3 months versus <3 months), and based on the characteristics of the study population, specifically whether or not they included treatment "responders" only.

Rating the confidence in estimates of the effect in NMA

For each reported outcome, independently, two of the authors will assess the confidence in the estimates (quality of the evidence), using the recent approach recommended by the GRADE working group [52]. We will present treatment estimates, if present, for direct, indirect, and NMA. Further, we will assess the quality of the evidence for each reported outcome using the GRADE criteria independently by 2 reviewers [45 53-55]. 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 [52]. For rating confidence in the indirect comparisons, we will focus our assessments on first-order loops (that is, loops that are connected to the interventions of interest through only one other intervention with the lowest variances, and thus contribute the most to the estimates of effect [56]. This is because estimates of loops (interventions) can be obtained via any common comparator. For instance, if there are 4 interventions in a network A, B, C, and D, we could indirectly estimate the effects of A versus D via deduction from B (first common comparator), or through C (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 amongst 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 [52].

Discussion:

This systematic review aims to synthesize 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 potential contributor to weight gain and dysglycaemia. The network meta-analysis 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.

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 generalizability 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 2 classifications are being assessed for the first time in meta-analysis; therefore, this approach may need future refinement and validation.

List of abbreviations:

BMI: body mass index; RCT: randomized controlled trials; NMA: network meta-analysis; RCT: randomized control trial; DIC: deviance information criterion; NIH: National Institutes of Health; T2DM: type 2 diabetes mellitus; GRADE: Grading of Recommendations Assessment, Development and Evaluation; FDA: Food and Drug Administration; DSM: Diagnostic and Statistical Manual of Mental Disorders.

Conflict of Interest:
The authors have nothing to disclose

Author contributions:

RA: conceptualized and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. **ND:** conceptualized and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. **IF:** conceptualized and designed the study, and critically reviewed the manuscript, and approved the final manuscript as submitted. **NF:** conceptualized and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. **LM:** conceptualized the study, designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted. **KM:** conceptualized the study and designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted.

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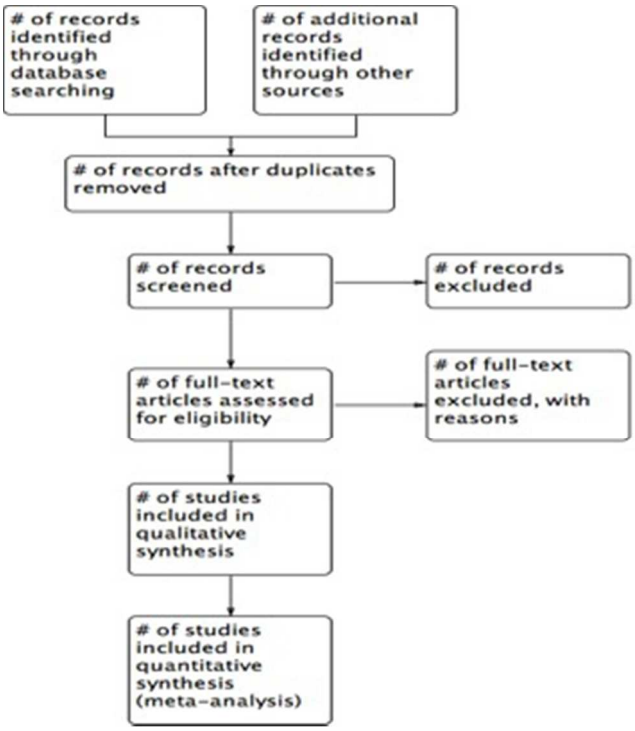

The primary selection process
111x127mm (72 x 72 DPI)

Search strategy:

Ovid Medline

1. exp Child/
2. exp Adolescent/
3. child*.mp.
4. adolescen*.mp.
5. youth.mp.
6. exp Pediatrics/
7. pediatric.mp.
8. teenage*.mp.
9. juvenile.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Amitriptyline/
12. Amphetamine/
13. Aripiprazole.mp.
14. atomoxetine.mp.
15. Buspirone/
16. Citalopram/
17. Clomipramine/
18. Clozapine/
19. Desipramine/
20. Desvenlafaxine.mp.
21. duloxetine.mp.
22. escitalopram.mp.
23. Fluoxetine/
24. Haloperidol/
25. Imipramine/
26. Methylphenidate/
27. mirtazapine.mp.
28. Molindone/
29. Nortriptyline/
30. olanzapine.mp.
31. paliperidone.mp.
32. Paroxetine/
33. quetiapine.mp.
34. Risperidone/
35. Sertraline/
36. Thioridazine/
37. Trazodone/
38. Thiothixene/
39. Venlafaxine.mp.
40. ziprasidone.mp.
41. Fluvoxamine/
42. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. weight.mp.
44. body weight.mp.

45. Body Weight/
46. bmi.mp.
47. Body Mass Index/
48. body mass index.mp.
49. zBMI.mp.
50. 43 or 44 or 45 or 46 or 47 or 48 or 49
51. Mental Health/
52. exp Autistic Disorder/
53. exp Attention Deficit Disorder with Hyperactivity/
54. exp Schizophrenia/
55. exp Depression/
56. exp Anxiety Disorders/
57. exp Bipolar Disorder/
58. 51 or 52 or 53 or 54 or 55 or 56 or 57
59. random.tw.
60. placebo.mp.
61. Double blind.tw.
62. single blind.tw.
63. 59 or 60 or 61 or 62
64. 10 and 42 and 50 and 58 and 63
65. limit 64 to (human and english language)

Embase :

1. exp Child/
2. Adolescent/
3. child*.mp.
4. adolescen*.mp.
5. youth.mp.
6. Pediatrics/
7. pediatric.mp.
8. teenage*.mp.
9. juvenile.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Amitriptyline/
12. Amphetamine/
13. aripiprazole.mp.
14. atomoxetine.mp.
15. Buspirone/
16. Citalopram/
17. Clomipramine/
18. Clozapine/
19. Desipramine/
20. desvenlafaxine.mp.
21. duloxetine.mp.
22. escitalopram.mp.
23. Fluoxetine/
24. Fluvoxamine/
25. Haloperidol/
26. Imipramine/
27. Methylphenidate/
28. mirtazapine.mp.
29. Molindone/
30. Nortriptyline/
31. olanzapine.mp.
32. paliperidone.mp.
33. Paroxetine/
34. quetiapine.mp.
35. Risperidone/
36. Sertraline/
37. Thioridazine/
38. Thiothixene/
39. Trazodone/
40. venlafaxine.mp.
41. ziprasidone.mp.
42. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. weight.mp.
44. body weight.mp.
45. exp "Body Weights and Measures"/

46. bmi.mp.
47. body mass index.mp.
48. zBMI.mp.
49. 43 or 44 or 45 or 46 or 47 or 48
50. mental health/
51. exp autism/
52. exp attention deficit disorder/
53. exp schizophrenia/
54. exp depression/
55. exp anxiety disorder/
56. exp bipolar disorder/
57. 50 or 51 or 52 or 53 or 54 or 55 or 56
58. random.tw.
59. placebo.mp.
60. Double blind.tw.
61. Single blind.tw.
62. 58 or 59 or 60 or 61
63. 10 and 42 and 49 and 57 and 62
64. limit 63 to (human and english language)

PsycInfo:

1. Child.mp.
2. adolescen*.mp.
3. youth.mp.
4. pediatrics/
5. juvenile.mp.
6. pediatric.mp.
7. teenage*.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp serotonin reuptake inhibitors/
10. exp Antidepressant Drugs/
11. antidepressant*.mp.
12. ssri.mp.
13. selective serotonin reuptake inhibitor*.mp.
14. serotonin.mp.
15. exp serotonin/
16. 5HT*.mp.
17. serotonin receptor.mp.
18. serotonin transporter*.mp.
19. serotonin norepinephrine reuptake inhibitors/
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp body weight/
22. exp obesity/
23. exp Body Mass Index/
24. weight.mp.
25. body weight.mp.
26. BMI.mp.
27. zbmi.mp.
28. z-score.mp.
29. body mass index.mp.
30. overweight.mp.
31. obes*.mp.
32. waist circumference.mp.
33. overweight/
34. body fat/
35. exp anthropometry/
36. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 8 and 20 and 36

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	X
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	X
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	X
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	X
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	X
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	X
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	X
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	X
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	X
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	X
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	X
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	X
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	X
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	X

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Effect of Serotonin Modulating Pharmacotherapies on Body Mass Index and Dysglycaemia Among Children and Adolescents: Systematic Review and Network Meta Analysis Protocol

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Diabetes and endocrinology, Paediatrics
Keywords:	Paediatric endocrinology < PAEDIATRICS, MENTAL HEALTH, EPIDEMIOLOGY

Effect of Serotonin Modulating Pharmacotherapies on Body Mass Index and Dysglycaemia Among Children and Adolescents: Systematic Review and Network Meta Analysis Protocol

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Children, body mass index, dysglycaemia, mental health, serotonin-modulating medications.

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Word count: 2628

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 synthesize 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 randomized 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 gray literature resources. Two reviewers from the team will independently screen titles and abstracts, assess the eligibility of full texts trials, extract information from eligible trials and assess the risk of bias and quality of the evidence. Results of this review will be summarized 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 is 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 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.
- Strengths of this review are the wide search strategy, broad inclusion criteria, and use of GRADE to evaluate certainty of the evidence.

Background:

Pediatric obesity is one of the most pressing public health issues in children and adolescents today. The prevalence of childhood obesity is high in both developed and developing countries. The observed prevalence in the United States (US) is 16.9% [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, dyslipidemia, obstructive sleep apnea, 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) are the most common mental health disorders amongst 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 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, serotonin selective reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRI). 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 the 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 the use of 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 utilizing 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 synthesize the existing evidence on serotonin modulating pharmacotherapies amongst 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. 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. A network meta-analysis (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 2 treatment approaches at a time [38]. We hypothesize 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 network meta-analysis protocol is registered on PROSPERO International prospective register of systematic reviews (CRD42015024367). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis 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 age 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 regards to weight gain or weight loss throughout the study. In addition, studies that included both adolescent and adult participants, sub-studies 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 based on 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, % underweight), weight (kg), weight z-score, height (cm), height z-score, and prevalence of dysglycaemia measured as the number of participants with diagnosis of T2DM, impaired glucose tolerance, and/or impaired fasting glucose assessed by oral glucose tolerance test and/or fasting blood glucose, and/or HBA1c.

Types of studies
Parallel, double or multi-arm Randomized Clinical Trials (RCT).

Search Strategy:
We performed the literature search through the major medical interventions 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 medications names (Appendix). We used the randomized controlled trial filter created from McMaster University for Ovid Embase platform, and the Cochrane library filter for Ovid Medline platform. These filters provide good balance between sensitivity and specificity[41 42]. The search was limited to English language and published studies. Additionally, we performed manual hand search of bibliographies of identified randomized 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 [43]. 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 standardized data extraction forms using Google forms [44]. 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 confidence intervals, 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 [42]. 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 categorize 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 [45]. 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 1-2 score for high risk of bias, and 'high risk' if the study met more than 2 scores for high risk of bias [46].

Statistical analysis:

Standard direct comparisons

We will perform all pairwise comparison meta-analysis using R software [47]. Effect estimates and their 95th confidence interval (CI) will be calculated using risk ratio (RR) 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 Chi-square test and quantify it using the I^2 test statistic. We will interpret the I^2 using the Cochrane Collaboration thresholds [42]. 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 multi-arm 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 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 identify loops with large inconsistency [50 51]. We will measure the model fit using the deviance information criterion (DIC) [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, because 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 binds 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.

Table 1.
Pharmacological interventions related to the serotonergic system

SSRIs	**Serotonin-NRIs**	**Serotonin modulators**	**Dopamine D_2 receptor antagonists**	**Dopamine $D_{2/D3}$ and 5HT2 $_{A/C}$ receptor antagonists**	**Selective-NRIs**	**5HT $_{1A/2}$ partial agonist and Dopamine D_2 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

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 the 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, compare 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, independently, two of the authors will 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, if present, for direct, indirect, and NMA. Further, we will assess the quality of the evidence for each reported outcome using the GRADE criteria independently by 2 reviewers [46 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 (that is, loops that are connected to the interventions of interest through only one other intervention with the lowest variances, and thus contribute the most to the estimates of effect [57]. This is because estimates of loops (interventions) can be obtained via any common comparator. For instance, if there are 4 interventions in a network A, B, C, and D, we could indirectly estimate the effects of A versus D via deduction from B (first common comparator), or through C (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 amongst 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 synthesize 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 potential contributor to weight gain and dysglycaemia. The network meta-analysis 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 generalizability 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 2 classifications are being assessed for the first time in meta-analysis; therefore, this approach may need future refinement and validation.

List of abbreviations:

BMI: body mass index; RCT: randomized controlled trials; NMA: network meta-analysis; RCT: randomized control trial; DIC: deviance information criterion; NIH: National Institutes of Health; T2DM: type 2 diabetes mellitus; GRADE: Grading of Recommendations Assessment, Development and Evaluation; FDA: Food and Drug Administration; DSM: Diagnostic and Statistical Manual of Mental Disorders.

Conflict of Interest:
The authors have nothing to disclose

Author contributions:

RA: conceptualized and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. **ND:** conceptualized and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. **IF:** conceptualized and designed the study, and critically reviewed the manuscript, and approved the final manuscript as submitted. **LM:** conceptualized the study, designed the study, critically reviewed and edited the manuscript, and approved the final manuscript as submitted. **KM:** conceptualized the study and designed the study, critically reviewed and edited the manuscript, and approved the final manuscript as submitted.

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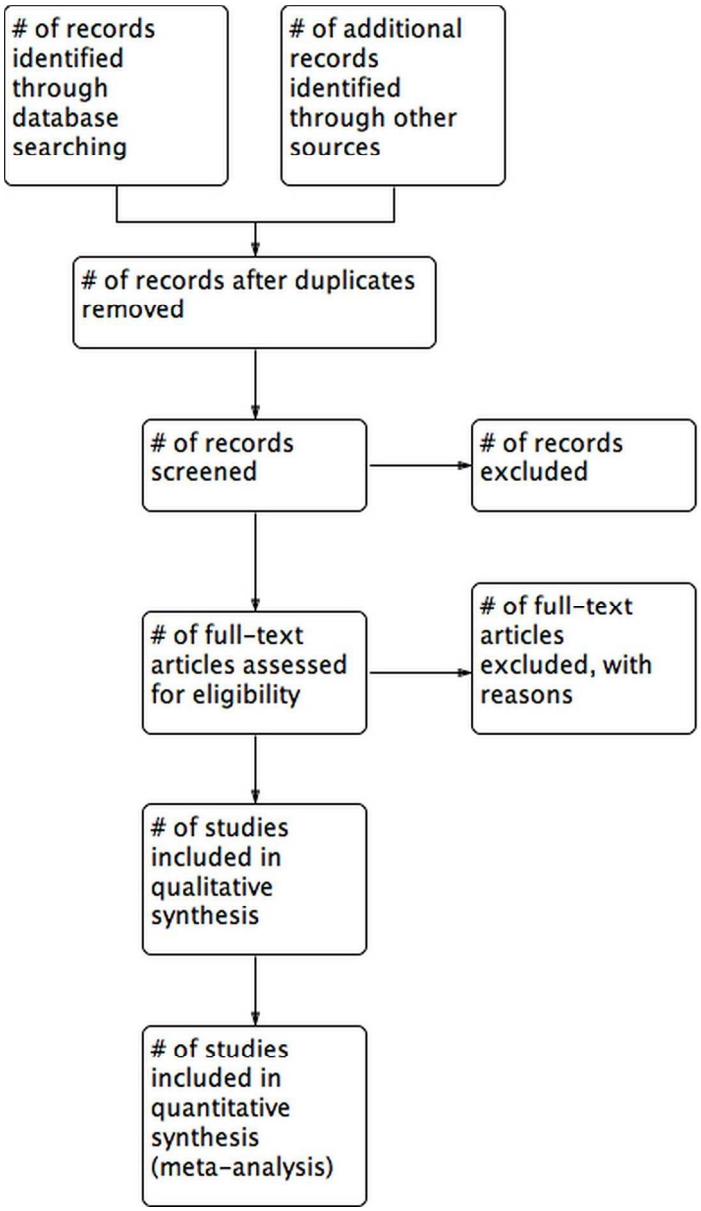

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Search strategy:

Ovid Medline

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4. adolescen*.mp.
5. youth.mp.
6. exp Pediatrics/
7. pediatric.mp.
8. teenage*.mp.
9. juvenile.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Amitriptyline/
12. Amphetamine/
13. Aripiprazole.mp.
14. atomoxetine.mp.
15. Buspirone/
16. Citalopram/
17. Clomipramine/
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19. Desipramine/
20. Desvenlafaxine.mp.
21. duloxetine.mp.
22. escitalopram.mp.
23. Fluoxetine/
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26. Methylphenidate/
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40. ziprasidone.mp.
41. Fluvoxamine/
42. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
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44. body weight.mp.

45. Body Weight/
46. bmi.mp.
47. Body Mass Index/
48. body mass index.mp.
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53. exp Attention Deficit Disorder with Hyperactivity/
54. exp Schizophrenia/
55. exp Depression/
56. exp Anxiety Disorders/
57. exp Bipolar Disorder/
58. 51 or 52 or 53 or 54 or 55 or 56 or 57
59. random.tw.
60. placebo.mp.
61. Double blind.tw.
62. single blind.tw.
63. 59 or 60 or 61 or 62
64. 10 and 42 and 50 and 58 and 63
65. limit 64 to (human and english language)

Embase :

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5. youth.mp.
6. Pediatrics/
7. pediatric.mp.
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10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
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12. Amphetamine/
13. aripiprazole.mp.
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40. venlafaxine.mp.
41. ziprasidone.mp.
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43. weight.mp.
44. body weight.mp.
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46. bmi.mp.
47. body mass index.mp.
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50. mental health/
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56. exp bipolar disorder/
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58. random.tw.
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61. Single blind.tw.
62. 58 or 59 or 60 or 61
63. 10 and 42 and 49 and 57 and 62
64. limit 63 to (human and english language)

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17. serotonin receptor.mp.
18. serotonin transporter*.mp.
19. serotonin norepinephrine reuptake inhibitors/
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29. body mass index.mp.
30. overweight.mp.
31. obes*.mp.
32. waist circumference.mp.
33. overweight/
34. body fat/
35. exp anthropometry/
36. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 8 and 20 and 36

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check	Page
ADMINISTRATIVE INFORMATION				
Title:				1
Identification	1a	Identify the report as a protocol of a systematic review	X	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	X	2 & 4
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	X	9
Sponsor	5b	Provide name for the review funder and/or sponsor	NA	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA	
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	X	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	4
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	X	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	X	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that	X	Supplementary

		it could be repeated		file
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	X	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	X	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	4-5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	X	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	X	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	X	6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		6-7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	X	6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	X	7-8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Effect of Serotonin Modulating Pharmacotherapies on Body Mass Index and Dysglycaemia Among Children and Adolescents: Systematic Review and Network Meta Analysis Protocol

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Effect of Serotonin Modulating Pharmacotherapies on Body Mass Index and Dysglycaemia Among Children and Adolescents: Systematic Review and Network Meta Analysis Protocol

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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 synthesize 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 randomized 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 gray literature resources. Two reviewers from the team will independently screen titles and abstracts, assess the eligibility of full texts trials, extract information from eligible trials and assess the risk of bias and quality of the evidence. Results of this review will be summarized 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 is 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 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.
- Strengths of this review are the wide search strategy, broad inclusion criteria, and use of GRADE to evaluate certainty of the evidence.

Background:

Pediatric obesity is one of the most pressing public health issues in children and adolescents today. The prevalence of childhood obesity is high in both developed and developing countries. The observed prevalence in the United States (US) is 16.9% [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, dyslipidemia, obstructive sleep apnea, 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) are the most common mental health disorders amongst 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 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, serotonin selective reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRI). 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 the 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 the use of 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 utilizing 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 synthesize the existing evidence on serotonin modulating pharmacotherapies amongst 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. 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. A network meta-analysis (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 2 treatment approaches at a time [38]. We hypothesize 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 network meta-analysis protocol is registered on PROSPERO International prospective register of systematic reviews (CRD42015024367). This protocol was developed following the Preferred reporting items for systematic review and meta-analysis 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 age 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 regards to weight gain or weight loss throughout the study. In addition, studies that included both adolescent and adult participants, sub-studies 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 based on 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 diagnosis of T2DM, impaired glucose tolerance, and/or impaired fasting glucose assessed by oral glucose tolerance test and/or fasting blood glucose, and/or HBA1c. Given that BMI scores vary with gender and age as part of normal growth, we will use the World Health Organization (WHO) recommended BMI Z-score cutoffs for age and gender to define overweight and obesity (>+1 SD), normal (>-2 SD and <+1 SD), and thinness (<-2SD)[41 42].

Types of studies
Parallel, double or multi-arm Randomized Clinical Trials (RCT).

Search Strategy:
We performed the literature search through the major medical interventions 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 medications names (Appendix). We used the randomized controlled trial filter created from McMaster University for Ovid Embase platform, and the Cochrane library filter for Ovid Medline platform. These filters provide good balance between sensitivity and specificity[43 44]. The search was limited to English language and published studies. Additionally, we performed manual hand search of bibliographies of identified randomized 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 standardized data extraction forms using Google forms [46]. 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 confidence intervals, 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 categorize 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 [47]. 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 1-2 score for high risk of bias, and 'high risk' if the study met more than 2 scores for high risk of bias [48].

Statistical analysis:

Standard direct comparisons

We will perform all pairwise comparison meta-analysis using R software [49]. Effect estimates and their 95th confidence interval (CI) will be calculated using risk ratio (RR) 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 Chi-square test and quantify 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 multi-arm trials [50]. 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 Gelman and Rubin diagnostic test (gemtc) [51]. We will use the node-splitting method to detect consistency between direct and indirect evidence within a closed loop as well as identify loops with large inconsistency [52 53]. We will measure the model fit using the deviance information criterion (DIC) [52].

We will present the network geometry, and the results in probability statements as well as forest plots to guide the interpretation of the NMA [54]. 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, because 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 binds 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.

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

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 the 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, compare 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, independently, two of the authors will assess the confidence in the estimates (quality of the evidence), using the recent approach recommended by the GRADE working group [55]. We will present treatment estimates, if present, for direct, indirect, and NMA. Further, we will assess the quality of the evidence for each reported outcome using the GRADE criteria independently by 2 reviewers [48 56-58]. 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 [55]. For rating confidence in the indirect comparisons, we will focus our assessments on first-order loops (that is, loops that are connected to the interventions of interest through only one other intervention with the lowest variances, and thus contribute the most to the estimates of effect [59]. This is because estimates of loops (interventions) can be obtained via any common comparator. For instance, if there are 4 interventions in a network A, B, C, and D, we could indirectly estimate the effects of A versus D via deduction from B (first common comparator), or through C (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 amongst 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 [55].

Discussion:

This systematic review aims to synthesize 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 potential contributor to weight gain and dysglycaemia. The network meta-analysis 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 generalizability 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 2 classifications are being assessed for the first time in meta-analysis; therefore, this approach may need future refinement and validation.

List of abbreviations:

BMI: body mass index; RCT: randomized controlled trials; NMA: network meta-analysis; RCT: randomized control trial; DIC: deviance information criterion; NIH: National Institutes of Health; T2DM: type 2 diabetes mellitus; GRADE: Grading of Recommendations Assessment, Development and Evaluation; FDA: Food and Drug Administration; DSM: Diagnostic and Statistical Manual of Mental Disorders.

Conflict of Interest:
The authors have nothing to disclose

Author contributions:

RA: conceptualized and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. **ND:** conceptualized and designed the study, drafted and critically reviewed the manuscript, and approved the final manuscript as submitted. **IF:** conceptualized and designed the study, and critically reviewed the manuscript, and approved the final manuscript as submitted. **LM:** conceptualized the study, designed the study, critically reviewed and edited the manuscript, and approved the final manuscript as submitted. **KM:** conceptualized the study and designed the study, critically reviewed and edited the manuscript, and approved the final manuscript as submitted.

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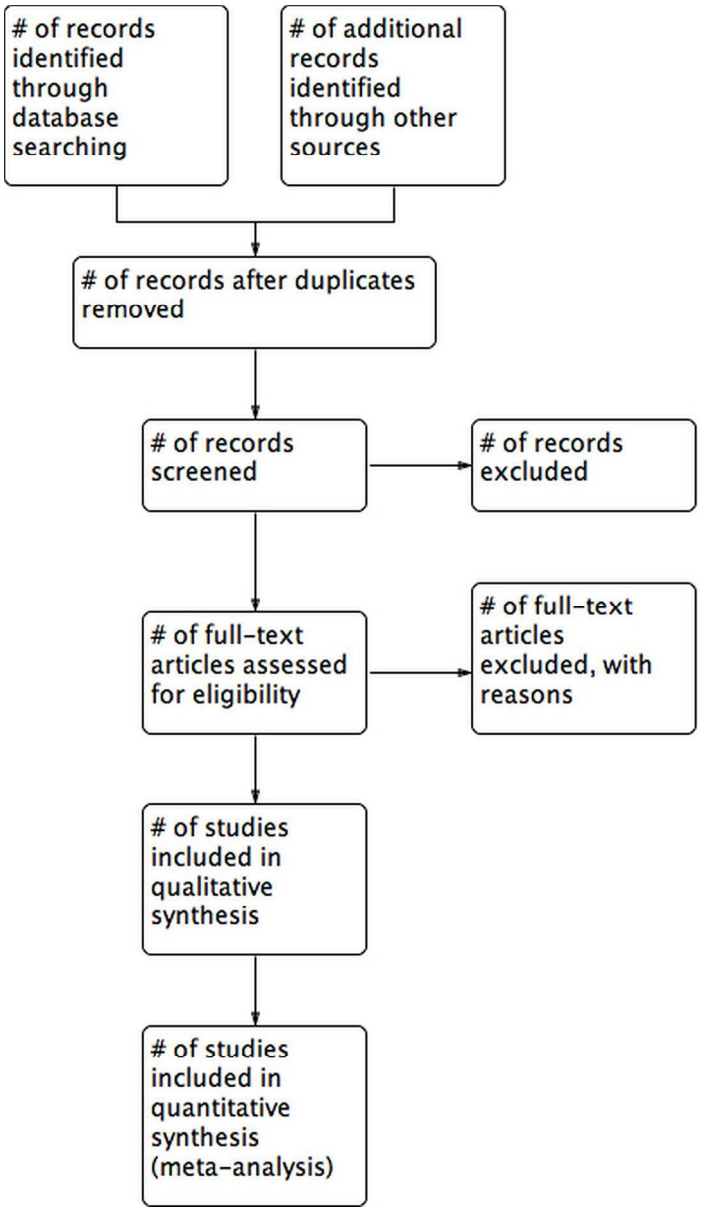

99x172mm (300 x 300 DPI)

Search strategy:

Ovid Medline

1. exp Child/
2. exp Adolescent/
3. child*.mp.
4. adolescen*.mp.
5. youth.mp.
6. exp Pediatrics/
7. pediatric.mp.
8. teenage*.mp.
9. juvenile.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Amitriptyline/
12. Amphetamine/
13. Aripiprazole.mp.
14. atomoxetine.mp.
15. Buspirone/
16. Citalopram/
17. Clomipramine/
18. Clozapine/
19. Desipramine/
20. Desvenlafaxine.mp.
21. duloxetine.mp.
22. escitalopram.mp.
23. Fluoxetine/
24. Haloperidol/
25. Imipramine/
26. Methylphenidate/
27. mirtazapine.mp.
28. Molindone/
29. Nortriptyline/
30. olanzapine.mp.
31. paliperidone.mp.
32. Paroxetine/
33. quetiapine.mp.
34. Risperidone/
35. Sertraline/
36. Thioridazine/
37. Trazodone/
38. Thiothixene/
39. Venlafaxine.mp.
40. ziprasidone.mp.
41. Fluvoxamine/
42. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. weight.mp.
44. body weight.mp.

45. Body Weight/
46. bmi.mp.
47. Body Mass Index/
48. body mass index.mp.
49. zBMI.mp.
50. 43 or 44 or 45 or 46 or 47 or 48 or 49
51. Mental Health/
52. exp Autistic Disorder/
53. exp Attention Deficit Disorder with Hyperactivity/
54. exp Schizophrenia/
55. exp Depression/
56. exp Anxiety Disorders/
57. exp Bipolar Disorder/
58. 51 or 52 or 53 or 54 or 55 or 56 or 57
59. random.tw.
60. placebo.mp.
61. Double blind.tw.
62. single blind.tw.
63. 59 or 60 or 61 or 62
64. 10 and 42 and 50 and 58 and 63
65. limit 64 to (human and english language)

Embase :

1. exp Child/
2. Adolescent/
3. child*.mp.
4. adolescen*.mp.
5. youth.mp.
6. Pediatrics/
7. pediatric.mp.
8. teenage*.mp.
9. juvenile.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Amitriptyline/
12. Amphetamine/
13. aripiprazole.mp.
14. atomoxetine.mp.
15. Buspirone/
16. Citalopram/
17. Clomipramine/
18. Clozapine/
19. Desipramine/
20. desvenlafaxine.mp.
21. duloxetine.mp.
22. escitalopram.mp.
23. Fluoxetine/
24. Fluvoxamine/
25. Haloperidol/
26. Imipramine/
27. Methylphenidate/
28. mirtazapine.mp.
29. Molindone/
30. Nortriptyline/
31. olanzapine.mp.
32. paliperidone.mp.
33. Paroxetine/
34. quetiapine.mp.
35. Risperidone/
36. Sertraline/
37. Thioridazine/
38. Thiothixene/
39. Trazodone/
40. venlafaxine.mp.
41. ziprasidone.mp.
42. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. weight.mp.
44. body weight.mp.
45. exp "Body Weights and Measures"/

46. bmi.mp.
47. body mass index.mp.
48. zBMI.mp.
49. 43 or 44 or 45 or 46 or 47 or 48
50. mental health/
51. exp autism/
52. exp attention deficit disorder/
53. exp schizophrenia/
54. exp depression/
55. exp anxiety disorder/
56. exp bipolar disorder/
57. 50 or 51 or 52 or 53 or 54 or 55 or 56
58. random.tw.
59. placebo.mp.
60. Double blind.tw.
61. Single blind.tw.
62. 58 or 59 or 60 or 61
63. 10 and 42 and 49 and 57 and 62
64. limit 63 to (human and english language)

PsycInfo:

1. Child.mp.
2. adolescen*.mp.
3. youth.mp.
4. pediatrics/
5. juvenile.mp.
6. pediatric.mp.
7. teenage*.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp serotonin reuptake inhibitors/
10. exp Antidepressant Drugs/
11. antidepressant*.mp.
12. ssri.mp.
13. selective serotonin reuptake inhibitor*.mp.
14. serotonin.mp.
15. exp serotonin/
16. 5HT*.mp.
17. serotonin receptor.mp.
18. serotonin transporter*.mp.
19. serotonin norepinephrine reuptake inhibitors/
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp body weight/
22. exp obesity/
23. exp Body Mass Index/
24. weight.mp.
25. body weight.mp.
26. BMI.mp.
27. zbmi.mp.
28. z-score.mp.
29. body mass index.mp.
30. overweight.mp.
31. obes*.mp.
32. waist circumference.mp.
33. overweight/
34. body fat/
35. exp anthropometry/
36. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 8 and 20 and 36

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check	Page
ADMINISTRATIVE INFORMATION				
Title:				1
Identification	1a	Identify the report as a protocol of a systematic review	X	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	X	2 & 4
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA	
Support:				
Sources	5a	Indicate sources of financial or other support for the review	X	9
Sponsor	5b	Provide name for the review funder and/or sponsor	NA	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA	
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	X	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	4
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	X	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	X	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that	X	Supplementary

		it could be repeated		file
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	X	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	X	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	4-5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	X	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	X	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	X	6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		6-7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	X	6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	X	7-8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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