**Network Meta-analyses in Child and Adolescent Psychiatry: A Meta-review**

Running title: NMAs in Child Psychiatry

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**ABSTRACT**

**Objectives:** Network meta-analyses (NMAs) are gaining traction as the preferred method for evidence synthesis of intervention studies. We aimed to 1) summarize the basics of NMAs; 2) conduct a meta-review of available NMAs on the treatment of child/adolescent psychiatric disorders, appraising their quality. **Methods of the meta-review:** Wesystematically searched Pubmed (Medline), PsycInfo, Embase, Ovid Medline, and Web of Knowledge (last update: 9 January 2018). We appraised the quality of each included NMA using the AMSTAR-2 tool and the PRISMA-NMA checklist, which include specific items for NMAs. **Results:** We retrieved 18 NMAs(ADHD: 6; psychotic disorders: 4; depression: 2; anxiety disorders: 2; OCD: 1; disruptive behavior disorder: 1, bipolar disorder: 1, plus one NMA on antipsychotics across disorders). Results from the AMSTAR-2 assessment showed that only 27% of the appraised NMAs were rated as *moderate*; the majority were rated as either *low* (33%) or *critically low* quality (40%). Only three of the appraised NMAs reported *all* of the PRISMA-NMA items specific for NMAs; the network structure was graphically presented in the majority of NMAs (80%), and inconsistency was only described in 47%. **Conclusions:** Given the paucity of head-to-head trials in child and adolescent psychiatry, NMAs have the potential to contribute to the field, as they provide evidence-based hierarchies for treatment decision-making, even in the absence of trials directly comparing two or more treatments. However, due to important limitations in the included NMAs, additional methodologically-sound NMAs are needed to inform future guidelines and clinical practice in child and adolescent psychiatry.

**INTRODUCTION**

The number of trials aiming to assessing efficacy, effectiveness and safety of available interventions in child and adolescent psychiatry has progressively increased over the past decades.1 Consequently, it may be challenging for busy practitioners to keep up-to-date with research findings on the management of mental health conditions in children and adolescents. In this regard, meta-analyses provide a quantitative evidence synthesis that can be consulted in a time-effective manner by clinicians.2 In addition to standard, pairwise meta-analyses (i.e., pooling data on interventions compared in head-to-head trials), network meta-analyses (NMAs) are gaining traction as the preferred method to synthesize empirical evidence on treatments in medicine.3, 4 NMA, previously referred to also as *mixed-treatment comparisons* or *multiple treatments meta-analysis*, is an innovative statistical approach that allows for the estimation of the comparative efficacy and tolerability of two or more interventions, even when they have not directly been investigated in head-to-head randomized controlled trials.5 NMAs are nowadays common in adult psychiatry and in general medicine, (e.g.,6-11), but their use in child and adolescent psychiatry has been more limited. However, the number of NMAs in child and adolescent psychiatry is now progressively increasing.12

The aims of the present review are twofold: 1) To present and critically discuss the basics of the methodology of NMAs, with a focus on the assumptions that underlie their validity, in order to help clinicians and researchers understand the methodology and appraise the quality of an NMA; 2) To conduct a systematic search of the available NMAs (i.e., a *meta-review*) on the pharmacological and non-pharmacological treatments of the most common child and adolescent psychiatric disorders, appraising their quality.

**METHODOLOGY OF NMAs**

Consider a hypothetical example: we want to compare the efficacy of pharmacological treatments for ADHD in reducing ADHD symptoms. After carrying out a systematic review of all available randomized controlled trials (RCTs), let us assume that only studies comparing treatment X versus treatment Y (Group 1 of RCTs) and treatment X versus treatment Z (Group 2 of RCTs), are available. So, for these two head-to-head comparisons (namely, *X versus Y*, and *X versus Z*) evidence is provided by studies that compare these two pairs of treatments directly and can be grouped in two pair-wise meta-analyses (Figure 1). However, it is not possible to assess the comparative efficacy between Y and Z, because there are no studies, which directly compare treatment *Y versus Z*. In other words, the direct estimate between these two treatments (namely, Y and Z) is missing. If we used a standard (pairwise) meta-analytical approach, there would be no way to determine the comparative efficacy between Y and Z. However, using an NMA approach, *indirect evidence* can be provided “to fill the gap”, because studies that compared *X versus Y* and *X versus Z* can be jointly analyzed, as follows. Treatment X is present in both the groups of RCTs (Figure 1) and so it is possible to establish how much better (or worse) are treatments Y and Z relative to the ‘common’ comparator X, by calculating the indirect estimate between treatment Y and treatment Z via X. For example, if treatment Y is better than X by reducing on average the symptoms by 8 units on a rating scale and Z is better than X reducing the symptoms by 5 units, we can conclude that Y is better than Z by a mean difference of 3 units. In this way it possible to have the relative efficacy of all three comparisons, notwithstanding the lack of direct comparison between Y and Z. In a slightly different scenario, if direct evidence was available for all comparisons (i.e., we found trials comparing *X versus Y*, *X versus Z*, and also *Y versus Z*, respectively), there would be no “gaps” but the NMA would combine direct and indirect estimates and calculate a *mixed estimate* (the weighted effect size derived from the direct evidence - Y *versus* Z directly - and the indirect evidence - Y *versus* Z indirectly via X). Mixed estimates can increase the precision of treatment estimate of already existing direct comparisons, reducing confidence (or credibility) intervals and strengthening inferences concerning the relative efficacy of two treatments.

In more complex networks (with four or more competing treatments), indirect estimates can be derived through several loops with many different intermediate comparators. Originally, NMA was the extension of this idea of merging direct and indirect evidence together in a full network of comparisons.13, 14 The synthesis of studies making a direct comparison of two treatments makes sense, only when the studies are sufficiently similar in important clinical and methodological characteristics (the so-called effect modifiers). A valid indirect comparison (such as *Y versus Z*) requires that the sets of X *versus* Y and X *versus* Z studies are similar in the distributions of their characteristics (for example, severity of illness at baseline, treatment dose, sample size, and study quality). Only when this is the case, can we assume that the intervention effects are *transitive* (that is, the above mentioned subtraction holds – i.e., 8 minus 5 equals 3). Transitivity can be viewed as the extension of clinical and methodological homogeneity to comparisons across groups of studies that compare different interventions. In complex network structures, the transitivity assumption should hold for all cases where indirect or mixed estimates are derived. *Consistency* (or coherence) is the statistical manifestation of transitivity and it can be evaluated only when there is direct and indirect evidence for a particular comparison of interventions.3 The distinction between transitivity and consistency is analogous to the distinction between *clinical (or methodological) heterogeneity* and *statistical heterogeneity* seen in standard meta-analyses. Heterogeneity refers to the degree of disagreement between study-specific treatment effects, while inconsistency is measured by differences between direct and indirect estimates beyond what chance can explain.3

An important step in an NMA is to understand the geometry of the network, i.e. which treatments have been directly compared in the included RCTs, how information flows indirectly across the network, and the contribution of each intervention or treatment comparisons.3 A graphical tool to achieve these goals is a network plot (See figure 2 for an example), which depicts the competing interventions by nodes, and uses lines to connect those interventions that have been compared directly in a RCT. The size of the node represents extra information such as the number of studies involving this intervention or the number of participants who have been randomized to this intervention. The width of the lines denotes the number of studies for each comparison, or the number of participants observed in each comparison. The network plot can also be used to reveal information about characteristics that pertain to treatment comparisons, for instance different colours can represent the different quality (i.e. risk of bias) of trials included in each comparison.15

Another fruitful role of the NMA technique is to facilitate simultaneous inference regarding all treatments in order to rank them according to any outcome of interest, for instance; efficacy and acceptability.7, 16 Using NMAs it is possible to calculate the probability of each treatment to be the most effective (first-best) regimen, the second-best, the third-best and so on, and thus to rank treatments according to this hierarchical order. 17This is a very easy to understand and straightforward way to present NMA results, most of all for clinicians who want to know which is the best treatment to be prescribed or used by patients on average.18

Recently, with the increased complexity of analyses that underpin clinical guidelines and health technology appraisals, NMAs have become more widely employed and demanded.19 The issue of choosing among direct, indirect, and mixed evidence (i.e. between pairwise and network meta-analyses) may arise, particularly when important inconsistency is identified. 20Arguments exist for giving priority to direct evidence because it does not rely on the transitivity assumption. 3 In some situations, indirect evidence may be more reliable than direct or mixed evidence. This may be the case if all of the direct evidence (for example, novel treatments compared with placebo), is subject to similar types of bias (for example, in favour of the novel treatment), such that these can theoretically be cancelled out when indirect comparisons are made. 21 More importantly, if there are inconsistencies between direct and indirect evidence, one should not choose between sources of evidence, but should instead investigate the sources of inconsistency to explain the differences.

 Although randomized evidence is used, and NMA techniques preserve the randomization, indirect evidence is not randomized evidence, as the treatments have originally been compared within, but not across studies.3 Therefore, indirect evidence may suffer the biases of observational studies (i.e., confounding or selection bias). In this respect, direct evidence remains more robust and in situations when both direct and indirect comparisons are available in a review, any use of NMAs should be to supplement, rather than replace, the direct comparisons.

**METHODS OF THE SYSTEMATIC REVIEW**

In relation to the second aim of the present review, we performed a systematic search in the following electronic databases, with no restrictions in terms of date, language, and type of document (e.g., full text paper, conference proceeding, or dissertation, among others): Pubmed (Medline), Ovid databases (PsycInfo, Embase+Embase classic, OVID Medline), and Web of Knowledge Databases (Web of science (science citation index expanded), Biological abstracts, Biosis, Food science and technology abstracts). We limited the search to children, adolescents and, when appropriate (e.g., for “at risk psychosis”) to young adults. Details on the search strategy and syntax for each database are reported in Supplement 1. The last search was carried out on 9 January 2018. We also hand-searched the reference lists of relevant retrieved papers to find any additional pertinent NMAs.

We rated the quality of the retrieved NMAs using the AMSTAR-222 and the PRISMA-NMA checklist.23 The AMSTAR-222 (Supplement 2) is a 16-item tool used to appraise systematic reviews of randomized and/or non-randomized studies of healthcare interventions but it is not specific to NMAs. Items of the AMSTAR-2 include, among others, presence of a protocol, comprehensiveness of the literature search, and assessment of the risk of bias of individual studies included in the systematic review. The AMSTAR-2 tool generates an overall quality rating (high, moderate, low and critically low) based on strengths/weaknesses in critical domains. Two authors (AT, SC) independently assessed each full-text NMA included in the meta-review, and discussed any disagreements to reach the final rating. Additionally, a statistician with expertise in meta-analyses and NMAs was consulted for any issues with the assessment of items related to the statistical analysis.

The PRISMA-NMA extension statement23 is a reporting guideline developed to improve the completeness of the reporting of systematic reviews and meta-analyses, which has been recently modified to include specific items for NMAs. The PRISMA-NMA statement (see Supplement 3) includes the standard 27 items of the standard PRISMA statement.24 However, 9 of the 27 items have been updated to include points relating to NMAs, and 5 additional items (S1-S5) specifically for NMAs have been added. One author (AT) assessed each of the full-text NMAs using the PRISMA-NMA extension statement. A second author (SC) checked any points that were unclear.

**RESULTS OF THE META-REVIEW**

The screening process is summarized in Figure 3, reporting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for study selection. From an initial number of 80 potentially eligible articles, we included a total of 18 NMAs, focusing on the treatment of the following disorders: ADHD: n= 6 25-33; psychotic disorders: n= 5 34-40; depression: n= 2 41-44; anxiety: n= 2 45, 46; OCD: n= 1 47; disruptive behavior disorders: n= 1 48; bipolar disorder: 149, plus one NMA50 on antipsychotics for a number of conditions (including schizophrenia and related psychosis, ADHD, and disruptive disorders). The inclusion criteria, number and type of included trials, and study outcomes for each of the retained NMAs are reported in Table 1. The findings from each retained NMA are detailed in the Supplementary Table 1 and summarized in the following sections.

*Attention-deficit/hyperactivity disorder (ADHD)*

Five29-33 of the retrieved NMAs focused on pharmacological treatments only, whereas one26 pooled studies on the pharmacological treatment with those on non-pharmacological interventions. With regards to pharmacological options, available NMAs indicate that psychostimulants are the most efficacious class, although they are somehow discordant as to whether methylphenidate (MPH) and amphetamines (AMPH) are equivalent26, 31 or AMPH, and more specifically, lisdexamfetamine (LDX), are superior to MPH.29, 30, 32, 33 However, they all consistently point to better tolerability of MPH in relation to AMPH. The only NMA26 that included both pharmacological and non-pharmacological interventions found that behavioral therapy in combination with stimulants was superior to stimulants or non-stimulants alone. Additionally, stimulants were superior to behavioral therapy, cognitive training and non-stimulants, and MPH and AMPH were found to be more efficacious than atomoxetine (ATX) and guanfacine (GUA).

*Psychotic disorders*

We found three NMAs35-39 focusing on the pharmacological treatment of schizophrenia spectrum disorders, and one34 on pharmacological, as well as non-pharmacological interventions for youth at clinical high risk (CHR) of psychosis. The three NMAs35-39 on schizophrenia spectrum disorders provided mixed results, with one highlighting no significant difference in terms of efficacy among included antipsychotics,39 another one37 showing superiority of clozapine over other compounds (except olanzapine), and yet, another one36 pointing to olanzapine and risperidone as the only compounds statistically superior to placebo for both total and positive scores of the Positive and Negative Syndrome Scale (PANSS). As for the adverse effects profile, whereas no differences in overall discontinuation for adverse effects have been found across antipsychotics, available NMAs quite consistently show that olanzapine is associated with the highest amount of weight gain. Additionally, one NMA37 reported that molindone and ziprasidone were superior to placebo for weight gain prevention. Prolactin was found to be significantly increased following treatment with risperidone, paliperidone, and olanzapine in another NMA.39

The NMA34 focusing on youth at CHR of psychosis concluded that N-methyl-D-aspartate receptor (NMDAR) modulators were significantly better than family therapy, need-based interventions, risperidone, amisulpride, cognitive behavioral therapy, omega-3, olanzapine, supportive therapy, and integrated psychological interventions, but not placebo, in reducing negative symptoms.

*Depressive disorders*

We retrieved two NMAs, focusing on pharmacological41, 44 and psychotherapeutic42, 43 interventions, respectively. The former41, 44, concluded that among all the included antidepressants (amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine), only fluoxetine was statistically better than placebo [albeit the upper value of the credible interval (- 0.03) was close to non-significance]. As for tolerability, fluoxetine was better than duloxetine. Furthermore, imipramine, venlafaxine, and duloxetine were associated with significantly higher discontinuation rates due to adverse events than placebo.

As for psychotherapeutic interventions42, 43, at post-treatment, interpersonal therapy (IPT) and cognitive behavioral therapy (CBT) were found to be significantly more efficacious than play therapy, whilst psychodynamic therapy and play therapy were not significantly superior to waitlist. At follow-up (combining short, i.e., 1-6 months, and long-term, i.e., 6-12 months, follow-up), there was evidence that IPT and CBT were significantly more beneficial than problem-solving therapy. However, when focusing on long-term follow-up only, CBT was not superior to any control condition.

*Anxiety disorders*

We retained two NMAs, one including both pharmacological and psychotherapeutic interventions,46 and another one selectively focusing on pharmacological treatment.45 The former46 concluded that CBT was superior to fluoxetine and sertraline for primary anxiety symptoms and rates of remission, respectively. However, the combination of sertraline and CBT was found to significantly reduce clinician-reported primary anxiety symptoms and response more than either treatment alone. The second NMA45 showed that fluoxetine, fluvoxamine, paroxetine, and sertraline were more efficacious and better tolerated than placebo; additionally, venlafaxine was found to be less well tolerated than fluvoxamine, paroxetine, and sertraline.

*Obsessive compulsive disorder (OCD)*

The only NMA47 that we found, pooled both pharmacological and psychotherapeutic interventions, showing: 1) significant differences between CBT or behavioral therapy and drug placebo, but not psychological placebo; 2) marginally better efficacy of sertraline, compared to placebo; 3) superiority of CBT plus sertraline vs. sertraline alone; 4) good tolerability for all interventions.

*Disruptive behavior disorders*

The only NMA48 that we retrieved, focused on psychological interventions and concluded that the probability of being the best treatment was the same for multicomponent interventions and for interventions with only a parent component, followed by interventions with only a child component.

*Bipolar disorder*

We found the summary of results of an NMA on the comparative efficacy and safety of aripiprazole conducted by its manufacturers, and revised by an independent Evidence Review Group.49 No differences were reported in terms of efficacy among the included compounds (aripiprazole, olanzapine, quetiapine, and risperidone). With regards to safety, aripiprazole was associated with less weight gain than olanzapine and quetiapine, and less prolactin increases than olanzapine, quetiapine, and risperidone.

*Effects of antipsychotics on weight across several disorders*

An NMA50 set out to assess the evidence for the comparative safety of antipsychotics in terms of weight and BMI changes for a broad range of disorders. As for weight changes, results showed that molindone and ziprasidone were associated with the lowest weight gain, whereas clozapine, lurasidone, and olanzapine were associated with the highest weight gain. Of note, not all of the second-generation antipsychotics contributed to more weight gain than the first-generation antipsychotics. In fact, ziprasidone, pimozide, and aripiprazole led to less average weight gain than haloperidol. Results for BMI changes were similar.

***Appraisal of the quality of the included NMAs***

***AMSTAR-2***

We applied the AMSTAR-2 tool to 15 out of the 18 retrieved NMAs, since two31, 37 were reported as conference proceedings and one as a summary only, which prevented us from conducting a full assessment of the quality of these three NMAs.49 The initial agreement between the two authors who independently scored each NMA using was 97% (total scored items: 240; disagreement: 8 items). This initial disagreement was resolved after discussion between the two authors. The ratings of the overall confidence in the results of the NMAs are shown in Table 1. The minority, 27%, of NMAs were rated as moderate (4/15), and the majority rated as either low 33% (5/15) or critically low 40% (6/15). As detailed in Supplement 4, the majority of the retrieved NMAs presented with methodological concerns. For instance, only 40% of the assessed NMAs (6/15) had a publicly accessible, comprehensive protocol. The search was deemed comprehensive in around 45% of the NMAs (7/15). None of the retained NMAs fully assessed the potential impact of the risk of bias of individual studies on the results of the meta-analysis. Heterogeneity was assessed and discussed in around 45% of the NMAs (7/15). Importantly, only two NMAs 34, 39 discussed the issue of the transitivity assumption. Additional details of the AMSTAR-2 assessment including the overall rating, for each NMAs are reported in Supplement 2.

***PRISMA-NMA***

We found that 2 out of the 15 NMAs included the self-completed PRISMA-NMA statement, and 10 out of the 15 (67%) included a PRISMA flow diagram. The additional items included specifically for NMAs (S1-S5) were reported to varying extents in the NMAs (see Table 1 for summary). The geometry of the network (item S1), (methods used to explore the geometry and biases relating to it, including how the network would be graphically presented), was described in 40% of the NMAs (6/15). The latter point (graphical presentation) was often not stated. The network structure was presented (item S3) as a network graph (including all of the included studies) in the majority of NMAs (80%), and a summary of the characteristics of the treatment network (item S4) was described in 13 of the 15 NMAs. The methods used to assess inconsistency (item S2) were only described in 7/15 (47%) NMAs, and the results of any investigation of inconsistency (item S5) was reported in 9/15 (60%) NMAs. The full PRISMA-NMA checklists of individual NMAs are reported in Supplement 5.

**DISCUSSION**

This paper provides an introduction to the basics of NMAs, highlighting important methodological assumptions underpinning their validity, and, presents the results of a systematic overview of published NMAs in child and adolescent psychiatry, analysing their methodological strengths and weaknesses. Our overarching goal was to understand how, and to what extent, meta-analyses based on this relatively novel approach, can inform clinical practice in child and adolescent psychiatry beyond the evidence available from standard (pairwise) meta-analyses. 51We found a total of 18 NMAs focusing on the pharmacological and/or non-pharmacological treatment of a number of common disorders encountered by clinicians in their daily practice, including ADHD, anxiety, OCD, depressive, and psychotic disorders.

NMAs have the potential to contribute to the field of child and adolescent psychiatry, as they provide evidence-based hierarchies for the treatment choice, even in the absence of trials directly comparing two or more treatments. Indeed, given the limited number of trials with of head-to-head comparisons between two or more treatment options in child and adolescent psychiatry,1 and, consequently, the low number of studies included in comparative pairwise meta-analyses, there is uncertainty on how to rank treatment choice for a number of child and adolescent psychiatric disorders.

Available guidelines for the pharmacological treatment of ADHD differ in their recommendations, some guidelines rank methylphenidate over amphetamines(e.g.52 , in children), others recommend *psychostimulants* as first-line treatment without further specification.53 Additionally, atomoxetine is recommended as third 52, second53 or potentially first-line treatment54 across the available guidelines. As for depressive disorders, the extent to which individual pharmacological agents differ, in terms of efficacy/tolerability is topic of discussion.55 Likewise, current guidelines do not provide a ranking in terms of the choice for the pharmacological treatment of anxiety, 56OCD,57 and psychotic disorders.58-60

Do published NMAs provide the evidence to fill these gaps? We assert, for a number of reasons, that caution should be exercised before translating the conclusions of the available NMAs into clinical recommendations. Firstly, the quality of the majority of the NMAs retained in this meta-review was rated as *low* or *critically low* quality using the AMSTAR-2 tool, which assesses the quality of a meta-analysis in general (i.e., not specifically an NMA). Many failed to rigorously address crucial methodological aspects specifically related to NMAs, such as the inconsistency and transitivity. Notable exceptions included an NMA on ADHD pharmacological and non-pharmacological treatments, 25-26 another on antidepressants 41-42 and another on the treatment of OCD.47 These three NMAs were rated at *moderate* quality and reported all the five specific items for NMAs from the PRISMA-NMA statement. The AMSTAR-2 and the PRISMA-NMA statement are easily accessible; and we would encourage researchers aiming to perform an NMA to carefully consider such guidance when planning, conducting, and reporting the findings of their NMA. Particular attention should be paid to issues that were critical in the majority of the NMAs included in this meta-review, i.e., pre-defined protocol, comprehensive search including unpublished data, assessment of the impact of study bias and heterogeneity. In relation to aspects specifically related to NMAs, it is crucial to take into account the issues of consistency and transitivity when establishing the inclusion/exclusion criteria, e.g., type of comorbidities or treatment characteristics (such as oral *vs* transdermal formulations) that may influence the transitivity assumption. A multidisciplinary team of researchers, including clinicians and methodologists, seem best suited to rigorously address these issues. Additionally, considering that the issue may lie in the reporting, rather than a factual methodological flaw, we suggest that editors systematically request authors to upload specific checklists such as the PRISMA-NMA statement, and to allow for longer abstracts and extensive supplemental materials.

Secondly, when it comes to clinical decision-making, an important initial question is around the choice of pharmacological *vs.* non-pharmacological options. We found only one NMA encompassing both pharmacological and non-pharmacological treatments in the same network, 25-26 and suggest that the extent to which this is in line with the transitivity assumption cannot be taken for granted and should be addressed specifically in any NMA.

Thirdly, in general, the retained NMAs focused on the *statistical* significance and one should bear in mind that statistical significance does not automatically translate into clinical significance.

Fourthly, another critical consideration concerns the quality of the evidence upon which NMA's are based.  Although NMAs provide a ranking of interventions with respect to effect size, the quality of the evidence in support of each comparison can be substantially different.61 This was generally not highlighted in the retained NMAs and we suggest it should be part of the discussion of each NMA reporting.

Finally, available NMAs are based on aggregated data, and as such provide evidence that can inform decision-making at the group, rather than individual level. Including the individual-patient data in NMAs will allow for a more reliable estimation of predictors of individual responses.62

It goes without saying that empirical evidence on efficacy/tolerability synthesized in meta-analyses is just one of the elements that should inform clinical guidelines, along with clinical judgment, consumers’ preferences, financial considerations, and other practical issues.

***Conclusion***

Recently, there has been a welcome interest in conducting NMAs on the pharmacological/non-pharmacological treatments in child and adolescent psychiatry. However, due to a number of important limitations in the majority of the NMAs retained in this meta-review, additional methodologically-sound NMAs are needed to inform future guidelines and clinical practice in child and adolescent psychiatry.

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**Table 1. Characteristics of the network meta-analyses included in the meta-review.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **First author (year)** | **N****trials** | **Type of included trials** | **Participants** | **Eligible****treatments** | **Outcomes** |
| Roskell 33 (2014) | 32 | Parallel RCTs | Children and/or adolescents with ADHD, with or without comorbid ODD | MPH, LDXATX, DEX | Efficacy: changes in ADHD-RS, CGI-ISafety: all-cause and AE discontinuations |
| Locatelli 31 (2016) (conference proceeding only) | 34 | Parallel double blind RCTs > 2 weeks | Children and/or adolescents with ADHD; no further information | MPH (MPH-I and MPH-MR), LDXATX, BUP | Efficacy: clinical improvement (decline in ADHD-RS questionnaire score by at least 25% or improved CGI-I) |
| Catala-Lopez 25,26 (2017) | 190 | Parallel RCTs ≥ 3 weeks(cross-over included if they reported pre cross-over results) | Children and/or adolescents with ADHD (<18 y), as per DSM or ICD | Pharmacological: stimulants, non-stimulants, antipsychotics, other unlicensed drugsNon- pharmacological:BT, CT, neurofeedback,complementary and alternative medicine interventions | Primary: treatment response (ADHD symptoms or global functioning) and all-cause treatment dis- continuation rates.Secondary outcomes: tolerability, serious AEs and specific AEs |
| Joseph (2017) 27,28,29 | 36 | Parallel RCTs (cross-over included if they reported pre cross-over results) | Children and/or adolescents aged 6-17 | d-AMPH, ATX, CIR, GIR, GXR,LDX, MPH-IR, or MPH-ER/OROS | Efficacy: change in ADHD-RS, CGI-S, CPRSs, or SNAP-IV; achievement of response at the CGISafety: all cause discontinuation and discontinuation due to AEs |
| Li (2017). 30 | 62 | RCTs, regardless of level of blinding | Children and adolescents with ADHD aged 4-17 | ATX, BUP, CLON, GXR, LDX, MPH | Efficacy: changes on validated ADHD scalesSafety: Withdrawals due to all-cause, or AEs and lack of efficacy |
| Luan (2017) 32 | 73 | RCTs, regardless of level of blinding, > 3 weeks | Children and adolescents with ADHD as per DSM-I, aged 6-18 | ATX, CLON, GXR, BUP, LDX, MPH | Efficacy: changes on ADHD-RSSafety: all cause withdrawals, withdraw due to AEs, withdrawal due to lack of efficacy |
| Harvey 35,36 (2016) | 11 | RCTs and non RCTs | Patients ≤18with schizophrenia, schizoaffective disorder or schizophreniform disorder | Not specified a priori | Primary: efficacy outcome change in PANSS score.Secondary: efficacy and tolerability outcomes: mean change in subscale PANSS scores, weight, odds of all-cause treatment discontinuation and odds of discontinuation due to AEs |
| Krause (2017)(conference proceeding only) 37 | 27 | RCTs | Children and adolescents with schizophrenia  | Not specified | Primary outcome: change in severity symptoms. Secondary outcomes: change in positive and negative symptoms, categorical response to treatment, dropouts for any reason and for inefficacy, quality of life and social functioning, weight gain, sedation, prolactin increase, EPS, use of antiparkinsonian medication |
| Pagsberg 38,39 (2017) | 12 | RCTs | Children and adolescents (<19 y) with schizophrenia spectrum disorders as per DSM- 5 or ICD-10 or previous editions revisions from DSM-III and ICD-9 | Any antipsychotic identified from the World Health Organization Anatomical Therapeutic Chemical classification system (code N05A) | Major outcomes: change on PANSS total and positive symptoms or BPRS), body weight, plasma triglyceride, frequency of all-cause discontinuation, EPS and treatment with antiparkinsonian drugs, and akathisiaMinor outcomes: study-defined response rates, change on PANSS negative symptoms, depressive symptoms, CGI-Severity and Improvement, frequency of discontinuations due to lack of efficacy or to AEs, sedation, insomnia, weight gain of at least 7%, prolactin change, AEs, and serious AEs |
| Devoe 34 (2017) | 32 | RCTs or observational interventions | Youth at clinical high risk (CHR) for psychosis (APS, ARMS, ultra-high-risk UHR, or schizotypy) | All interventions for youth at CHR | Primary outcome:Conversion to psychosis in individuals with negative symptomsSecondary outcome:Prevalence of negative symptoms in youth at clinical high risk of psychosis |
| Zhou 43,44 (2015) | 52 | Prospective RCTs | Children or adolescents (aged 6-18) with major depression, minor depression, intermittent depression, or dysthymia or with depressive symptoms above cut-off | BT, cognitive therapy, CBT, family therapy, IPT, play therapy, problem-solving therapy, psychodynamic therapy, and supportive therapy | Primary outcome: efficacy (change scores in depressive symptoms) at post –treatmentSecondary outcome: efficacy at follow-up (change scores in depressive symptoms from baseline to the end of follow-up)Acceptability: all cause-discontinuation |
| Cipriani 41,42 (2016) | 34 | Double-blind RCTs | Children and adolescents (aged 9–18), with a primary diagnosis of major depressive disorder according to standardized diagnostic criteria. | Amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine | Primary outcomes: mean overall change in depressive symptoms and proportion of patients who discontinued treatment due to any AEsSecondary outcomes: response rate, all-cause discontinuation, and suicidal behavior/ideation. |
| Uthman 45 (2009) | 16 | RCTs | Children and/or adolescents diagnosed with anxiety disorders according to DSM-III, DSM-III-R and DSM-IV | Any pharmacotherapy agent retrieved | Efficacy: CGI-I to 1 or 2Acceptability: withdrawn for AEs |
| Wang 46 (2017) | 115 | RCTs and non-randomized comparative studies. Singe-cohort observational studies, case reports, and case series included if they re- ported any AEs | Children and adolescents aged 3-18 with panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, or separation anxiety | CBTAny medication for anxiety | Changes in primary anxiety symptoms severity, treatment response (loss of principle anxiety diagnosis or CGI-S= 1 or 2), remission (loss of principle anxiety diagnosis or CGI-S= 1 or 2), drop outs due to AEs and AEs |
| Skapinakis 47 (2016) | 17 | RCTs (cross-over trials included if data available from pre-cross-over phase) | Patients <74 y (including a subgroup analysis on children) with OCD based on ICD, DSM, Feighner or research diagnostic criteria | Pharmacological: amitriptyline, imipramine, clomipramine, all SSRIs, all SNRIs, mirtazapineNon pharmacological: BT, CBT, CT | Efficacy:Reduction in the total scores of the Yale–Brown Obsessive–Compulsive Scale, children’s versionAcceptability: total drop-outs |
| Epstein 48 (2015) | 84 | RCTs and non RCTs | Children/adolescents <18 y with conduct disorder, oppositional defiant disorder, or intermittent explosive disorder | Pharmacological: alpha-agonists, anticonvulsants, first and second-generation antipsychotics, beta-adrenergic blocking agents, stimulants, SSRIs, mood stabilizers, and antihistaminesNon pharmacological:BT; functional behavioral interventions; parent training; dialectical behavior training; psychotherapy; and contingency management methods | Behavioral and functional outcomes |
| Uttley 49 (2013) | 7 | RCTs | NS | Aripiprazole, olanzapine, quetiapine, risperidone | NS |
| Pillay 50 (2017) | 71 | RCTs and non RCTs, controlled cohort studies, controlled before-after studies | Children and young adults (≤24 y) with schizophrenia/psychoses, bipolar disorder, autism spectrum disorder, ADHD, conduct disorder/disruptive disorder, tic disorders, OCD, depression, eating disorders, or behavioral issues  | Aripripazoleasenapine,chlorpromazineclozapinehaloperidollurasidonemolindoneolanzapinepaliperidonepimozidequetiapinerisperidonethioridazineziprasidone | Weight change |

\*Similar results for BMI

*AEs: adverse events; APS: Attenuated Psychosis Syndrome; ARMS: at risk mental state; ATX: atomoxetine; BPRS: Brief Psychiatric Rating Scale; BUP: bupropion; BT: Behavioral Therapy; CBT: Cognitive Behavioral Therapy; CGI: Clinical Global Impression; CIR: clonidine immediate release; GIR: Guanfacine immediate release, CLON: clonidine; CT: cognitive training; CTRS-S: Conner’s Teaching Rating Scale; DEX: dexamphetamine; EPS: extrapyramidal side effects; GXR: guanfacine extended release; IPT: interpersonal therapy;, LDX: lisdexamfetamine;, MPH: methylphenidate; MPH-IR: methylphenidate immediate release; MPH-MR: methylphenidate modified release; MPH-ER: methylphenidate extended release; NS: not stated, SMD: standardized mean difference; OR: odds ratio; PANSS: positive and negative syndrome scale; RR: relative risk; SNRI: selective noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor*

**Table 2. Summary of PRISMA-NMA Statement results and AMSTAR-2 ratings**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **NMA** **Author (Year)** | **AMSTAR-2 Rating**  | **PRISMA NMA Statement (Key NMA Questions\*)** | **Included PRISMA flow diagram** | **Included PRISMA statement (self-reported)** |
| ***S1*** | ***S2*** | ***S3*** | ***S4*** | ***S5*** |
| ADHD |
| Roskell (2014) | Low |  |  |  | ✓ | ✓ | ✓ |  |
| Catala-Lopez (2017) | Moderate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Joseph (2017) | Critically Low |  |  | ✓ | ✓ |  | ✓ |  |
| Li (2017) | Critically Low |  |  | ✓ |  |  |  |  |
| Luan (2017) | Critically Low | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |
| PSYCHOTIC DISORDERS |
| Harvey (2016) | Critically Low | ✓ | ✓ | ✓ | ✓ |  |  |  |
| Pagsberg (2017)  | Low |  | ✓ | ✓ | ✓ | ✓ | ✓ |  |
| Devoe (2017)  | Low | ✓ |  | ✓ | ✓ | ✓ | ✓ | ✓ |
| ANXIETY DISORDERS |
| Uthman (2009) | Critically Low |  |  | ✓ |  |  |  |  |
| Wang (2017) | Low |  |  |  | ✓ | ✓ | ✓ |  |
| DEPRESSIVE DISORDERS |
| Zhou (2015) | Moderate |  | ✓ | ✓ | ✓ |  |  |  |
| Cipriani (2016) | Moderate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |
| OCD |
| Skapinakis (2016) | Moderate | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |  |
| DBD |
| Epstein (2015) | Critically Low  |  |  |  | ✓ |  | ✓ |  |
| ANTIPSYCHOTICS AND WEIGHT |
| Pillay (2107) | Low | ✓ |  | ✓ | ✓ | ✓ |  |  |

\* S1 - Geometry of the network; S2 - Assessment of Inconsistency; S3 - Presentation of network structure; S4 - Summary of network geometry; S5 - Exploration for inconsistency

*Abbreviations: PRISMA Preferred Reporting Items for Systematic Reviews and meta-analyses; AMSTAR A MeaSurement Tool to Assess systematic Reviews; NMA network meta-analysis; ADHD attention deficit hyperactivity disorder; OCD obsessive compulsive disorder; DBD disruptive behavior disorder*

**Figures captions**

Figure 1. Direct and indirect comparisons

Figure 2. Example of network plot (from 9)

Figure 2. PRISMA flow diagram