**Meta-analyses in Child and Adolescent Psychiatry: Getting Closer to Clinical Practice**

Samuele Cortese, MD., Ph.D.

Samuele Cortese is with the Center for Innovation in Mental Health, Academic Unit of Psychology and Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, UK; theSolent NHS Trust, Southampton, UK; the New York University Child Study Center, New York, NY, USA; and the Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK

**Address correspondence to:**

Dr. Samuele Cortese

Academic Unit of Psychology and Clinical and Experimental Sciences (CNS and Psychiatry) University of Southampton, Highfield Campus, Building 44, Southampton, SO17 1BJ, UK

Phone: +44 (0) 2380599645

E-mail: samuele.cortese@soton.ac.uk

**Acknowledgements**:N/A

Rigorously conducted meta-analyses provide evidence synthesis which has the potential to inform daily clinical decision making and development of clinical guidelines. In the past decade, there has been an increasing amount of studies on pharmacological and non-pharmacological treatments for childhood and adolescent psychiatric disorders. Given this large body of research, busy clinicians may tend to rely on meta-analyses, rather than individual trials, to keep abreast of the evidence base supporting intervention strategies in child and adolescent psychiatry. A number of meta-analyses focused on treatments for child and adolescent mental health problems have primarily addressed the question: “Is treatment X more efficacious/effective (or safer) than the control condition?”. This is clearly an important starting point for clinicians when discussing the benefits and risks and of treatment X with their patients/families. But clinicians need to know more. For instance, they may look for the evidence base to answer the following questions: “Is treatment X the most efficacious/effective (or safest) option for my patient?”; “When will treatment X likely start working?”; “If the dose/intensity of the treatment does not seem to be effective, is it worthy to increase it? And if so, how?”

The meta-analysis by Strawn and colleagues1 in this issue of the *Journal* is a nice example of how meta-analytic methods may be used to generate evidence base to address clinical relevant questions beyond whether a particular treatment is more efficacious/effective than placebo. The authors extracted weekly severity data from nine randomized placebo-controlled trials (RCTs) of SSRIs (five RCTs) and SSNRIs (four RCTS), including a total of 1673 participants (< 18 years) with anxiety disorders. Using an advanced statistical method (Bayesian inferential approach), they aimed to answer the following questions: “What is the temporal course of SSRIs and SSNRIs treatment response?; “Do the trajectory and magnitude of SSRIs and SSNRIs treatment response differ?”; and “Are high doses of SSRIs more effective than low doses for the treatment of anxiety?”. Strawn and colleagues found that statistically significant improvement in terms of reduction of anxiety severity ratings occurred early (at week 2) for both SSRIs and SSRNIs, and became clinically significant (Cohen’s d > 0.4) at week 6. SSRIs emerged as statistically more efficacious than SSNRIs starting from week 2, and their superiority was maintained over the remaining weeks of treatment. Antidepressant-related improvement was greatest during the first weeks of treatment (approximately 50% of the treatment-related improvement occurred by the fourth week) and then decreased over the following weeks. Of note, study sponsorship (industry *vs.* non industry funded) did not significantly affect these results. Finally, although SSRIs dose did not impact the magnitude of the response, improvement occurred earlier with high doses of SSRIs (sertraline: > 120 mg/day; fluvoxamine: > 100 mg; paroxetine: > 20 mg; fluoxetine > 33 mg). These results are particularly intriguing in the light of current recommendations to increase the dose when clinical improvement is not achieved by the fourth week of treatment, which is not supported by the results of this meta-analysis. Additionally, the superiority of SSRIs *vs.* SSNRIs is puzzling, considering that the only FDA-approved antidepressant for children and adolescents with anxiety (generalized anxiety disorder, ages 7-17) is the SSNRI duloxetine.

Should the results of the Strawn et al. meta-analysis be considered as a definitive evidence-based answer to clinically relevant questions for the pharmacological treatment of anxiety disorders in children and adolescents? Should clinicians change their prescribing practice based on this meta-analysis? Our enthusiasm should be balanced against the limitations of this meta-analysis. As acknowledged by the authors themselves, given the small number of included studies, the conclusions of the meta-analysis should be considered with caution. Additionally, although the authors performed a comprehensive search in a number of electronic databases and clinical trial registries to retrieve published studies, they were unable to include unpublished data from drug manufactures. It is possible that the inclusion of unpublished data might have changed the estimates. Furthermore, different types of anxiety disorders were lumped together in the analysis, so that results are not necessarily informative for the management of individual anxiety disorders. However, as highlighted by the authors, different anxiety disorders tend to share the same degree of response to pharmacological treatments. Moreover, the meta-analysis shows that SSRIs, as a class, were superior to SSNRIs, in terms of efficacy, but is not informative on which drug, among SSRIs, should be preferred. Finally, daily decision making in the choice of a pharmacological agent is based not only on its efficacy/effectiveness but also on its tolerability profile. Whereas the Strawn et al. meta-analysis concludes that SSRIs are superior to SSRNIs in terms of efficacy, one should consider that some side effects, such as activation, may be more common with SSRIs compared to SSNRIs. As such, efficacy results should be balanced against tolerability data.

In addition to addressing these specific limitations, how can future meta-analyses in child and adolescent psychiatry provide more clinically friendly evidence-base?

An important issue is around the difference between statistically and clinically significant findings. Often times, meta-analyses results are reported in terms of statistical significance only, which may not be satisfactory for clinical decision making. Strawn and colleagues highlighted when clinically, as opposed to statistically only, significant effects emerged relying on Cohen’d values. Perhaps a more intuitive and clinically informative approach would be to relate the findings to “minimal relevant difference”, i.e., assess how the changes in the scores measuring symptoms severity compare to the smallest change that patients/clinicians would identify as important. Minimal relevant differences have been used in recent meta-analyses in child and adolescent psychopathology (e.g.,2).

Another relevant aspect concerns the comparative efficacy and/or tolerability of available interventions. When several treatment strategies are available, clinicians would need to know which is is the best and how each of the available options ranks in terms of efficacy and safety. Unlike standard, pairwise meta-analyses (i.e., relying on head-to head comparisons from individual studies), network meta-analyses (NMAs) allow the estimation of the comparative efficacy and tolerability of two or more interventions even when they have not directly been investigated head-to-head in RCTs.3 NMAs have become the gold standard to rank treatments based on their efficacy and or tolerability/acceptability. Whereas NMAs are nowadays quite popular in the adult psychiatry literature (as in the rest of medicine), they use in child and adolescent psychiatry research has been more limited, although the number of published NMAs is rapidly increasing. This trend is welcome and we look forward to further methodologically sound NMAs in the field.

Finally, perhaps the most clinically relevant information from meta-analyses is the one which concerns specific types of patients, rather than the whole group of patients with a particular disorder. For instance, a practitioner treating Johnny, 8-year old with ADHD, tics, and IQ = 70, needs to know what is the best treatment for Johnny’s ADHD, rather than for ADHD in general. Subgroup and meta-regression analyses would allow addressing this need, but it is often challenging or impossible to conduct them in standard meta-analyses that rely on summary statistics from individual studies (e.g., pooling effect sizes representing the overall effect at the group level), due to lack of data. By contrast, meta-analyses based on individual patient data (IPD) allow exploring the effects of patient-related variables. However, it is often challenging to gather data related to individual study participants from study authors or drug manufacturers. Indeed, a recent study highlighted high degrees of variability in the commitment and procedures to share individual patient data across several drug companies.4 A change both in mind-set and policies seems needed to implement a culture of data sharing in the field. In this respect, initiatives from regulatory bodies may play a pivotal role. For example, the European Medicine Agency has committed to publish the clinical study reports submitted to the Agency (starting from 2015) and aims to implement a policy supporting the publication of individual patient data. Although this will not address the issue of gathering individual patient data from old studies, it will contribute to a paradigm shift towards data sharing in the field.

In conclusion, the meta-analysis by Strawn et al. is a welcome example of a clinically relevant meta-analysis. *JAACAP* will continue supporting the publication of high level meta-analyses based on advanced analytic approaches aimed at providing clinically informative results. On a related vein, the *Journal* will encourage study authors to provide access to individual patient data. More broadly, *JAACAP* will encourage and advocate for a research culture grounded on data sharing and transparency, aimed at generating the best available evidence supporting the daily clinical management of youth with mental health conditions.

Reference List

 (1) Strawn. *JAACAP* [serial online] 2018.

 (2) Storebo OJ, Ramstad E, Krogh HB et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev* 2015;CD009885.

 (3) Mavridis D, Giannatsi M, Cipriani A, Salanti G. A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health* 2015;18:40-46.

 (4) Goldacre B, Lane S, Mahtani KR et al. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. *BMJ* 2017;358:j3334.