**Novel Treatment Insights from Meta-analyses: The Scientific Silver Lining of Covid-19**

Due to the impact of the Covid-19 pandemic and the measures to contain it, many investigators, including those in the field of child and adolescent mental health, have turned to evidence synthesis and meta-research as a way, at least in part, to maintain their academic productivity. Rather than as a forced choice, we prefer to consider this as a unique opportunity to look back and synthesize/appraise the existing evidence to inform clinical practice and future research. Indeed, over the past year the Journal has published a number of highly valuable meta-analyses. Among these, we have selected three focused on psychotherapeutic interventions and two related to the pharmacological treatment of mental health conditions in children and youth that, in our opinion, are particularly informative. They utilize advanced meta-analytic techniques, including individual participant data meta-analysis (IPDMA),1 which allows for highly powered moderation analyses by assessing individual, rather than aggregate-level patient data, network meta-analysis (NMA),2 which, under certain methodological assumptions, allows one to compare two or more interventions even when they have not been compared head-to head in individual trials included in the meta-analysis, and spatial meta-analysis,3 which permits evaluation of contextual moderators based on geographic dimensions.

First, we would like to highlight two complimentary meta-analytic studies focused on behavioral treatments for ADHD conducted by collaborative research groups from Belgium and the Netherlands and Belgium.4,5 In the first of these projects, Groenman and colleagues4 stress the need to establish moderators of treatment response, given the diversity among youth with ADHD and the subsequent need to tailor interventions to fit the individual youth/family. To overcome limits of prior efforts to identify treatment response moderators, they utilized IPDMA, allowing examination of treatment response over 21 studies and 2233 participants. Treatment was associated with small to medium improvement on symptoms of ADHD, inattention, ODD, CD and overall impairment. Moreover, the data revealed that higher CD or ADHD symptoms, a CD diagnosis, and single parenthood was associated with poorer outcomes overall and with notable increases in symptoms among untreated youth, leading the team to emphasize the need to prioritize care for these high-risk youth.

In a complementary project, Dekkers and colleagues5 initiated a meta-regression analysis study designed to identify which behavioral techniques included in parent training programs for youth with ADHD account for improvement in parenting sense of competence, parent–child relationship quality, and parental mental health. The team scored the manuals used in each trial to establish the dosage of specific techniques taught, then used this metric to explore outcomes, as well as to evaluate effects of factors such as delivery method, format, and medication use. Twenty-nine studies and 35 behavioral techniques were included. A higher dosage of stimulus control training, such as “preparing a plan before entering a problematic situation”, was associated with increases in parental sense of competence and positive mental health. A higher dosage of reinforcing desired behavior strategies related to larger decreases in negative parenting, while a higher dosage of psychoeducation was negatively related to parental outcomes. The latter finding may reflect the lower proportion of time subsequently available for other active parent training components.

Finally, we would like to call attention to an innovative study exploring the effects of cultural racism on psychotherapy outcomes. Using public survey data (e.g., the American National Election Survey), Price and colleagues6 calculated an “anti-Black cultural racism” score for each state in the US. Using spatial meta-analysis, they assessed if levels of racism were associated with treatment outcomes. They examined 194 studies from Weisz and colleagues’7 comprehensive 2017 meta-analysis of 50 years of psychotherapy outcomes, based on sample make-up (≥50% Black participants, n=36; ≥50% White participants, n=158). A higher rating of anti-Black cultural racism was associated with lower treatment ESs, but only in studies where the majority of participants were Black.

Each of these studies identifies key factors affecting treatment response and can be used to increase the effectiveness and efficiency of our interventions by underscoring the need to increase focus on high-risk youth, to focus on intervention techniques associated with greatest positive change, and to attend more carefully to broader cultural factors that undermine the impact and promise of our work.

In regard to pharmacological treatment, DelBello et al.8 conducted the first meta-analytic work comparing the efficacy and tolerability of second-generation antipsychotics for major depressive episodes in youths with bipolar disorder. Using NMA, they pooled data from 4 randomized controlled trials (RCTs) and demonstrated that lurasidone had the highest probability of being the most efficacious treatment, considering both reduced depression symptom severity and response rate. Olanzapine/fluoxetine combination (OFC) was associated with the highest chance of remission. All cause discontinuation was lowest for quetiapine and lurasidone. OFC had the lowest rate of discontinuation due to efficacy, while quetiapine had the lowest rate of discontinuation due to side effects. Even though these findings certainly need to be replicated in larger NMAs, the study by DelBello et al. provides a first indication to prescribers in the process of initial decision making regarding the best second-generation antipsychotics for major depressive episodes in youth.

In another study, Farhat and colleagues9 utilized IPDMA to assess the discriminative ability of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) in determining response and remission in child and adolescents with obsessive compulsive disorder and establishing evidence-based cut-offs for response and remission. In doing so, Farhat et al. filled a crucial gap in the field. Prior to this work, no established definitions of response and remission following treatment for OCD in youths were available. The meta-analysis found that the CY-BOCS had acceptable discriminative ability to determine response and remission, as shown by a pooled area under the curve (AUC) = 0.89 and = 0.92, respectively. Moreover, optimal cut-offs for response and remission were a ≥35% reduction from baseline to posttreatment and a raw score of ≤12, respectively. We look forward to these cut-offs being used in clinical practice and being consistently implemented in future research, to allow comparability across studies.

Overall, we think that these two meta-analyses complement nicely each other, contributing to an increasingly rigorous evidence base to guide prescribers in the initial phase and/or monitoring of pharmacological treatment in child and adolescent psychiatry.

 Therefore, despite challenges related to the pandemic, researchers in our field contributed to the science of child and adolescent mental health by turning to meta-analyses and other data synthesis methods, using novel analytic strategies, with the goal of developing more refined clinical assessment and treatment guidelines. We hope this compilation of the Best of 2022 provides our readers with guidance to improve their evidence-based care for the youth they treat.

**References**

1. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ (Clin Res Ed*). 2010;340:c221. https://doi.org/

10.1136/bmj.c221.

1. Cortese S, Tomlinson A, Cipriani A. Meta-Review: Network Meta-Analyses in Child and Adolescent Psychiatry. *J Am Acad Child Adolesc Psychiatry.* 2019;58(2):167-179.
2. Johnson BT, Cromley EK, Marrouch N. Spatiotemporal meta-analysis: Reviewing health psychology phenomena over space and time. *Health Psychol Rev*. 2017;11:280-291. <https://doi.org/10.1080/17437199.2017.1343679>.
3. Groenman AP, Hornstra R, Hoekstra PJ, Steenhuis L, Agebati A, et al., An Individual Participant Data Meta-analysis: Behavioral Treatments for Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry* 2022;61(2):144−158.
4. Dekkers TJ, Hornstra R, MSc van der Oord S, Luman, M, Hoekstra PJ, Groenman AP, van den Hoofdakker BJ. Meta-analysis: Which Components of Parent Training Work for Children With Attention-Deficit/Hyperactivity Disorder? *J Am Acad Child Adolesc Psychiatry* 2022;61(4):478–494.
5. Price MA, Weisz JR, McKetta S, Hollinsaid NL, Lattanner MR, Reid AE, Hatzenbuehler ML. Meta-analysis: Are Psychotherapies Less Effective for Black Youth in Communities With Higher Levels of Anti-Black Racism? Am Acad Child Adolesc Psychiatry 2022;61(6):754–763.
6. Weisz JR, Kuppens S, Ng MY, et al. What five decades of research tells us about the effects of youth psychological therapy: A multilevel meta-analysis and implications for science and practice. Am Psychol. 2017;72:79-117. <https://doi.org/10.1037/a0040360>.
7. DelBello, M.P., Kadakia, A., Heller, V., Singh, R., Hagi, K., Nosaka, T., & Loebel, A. Systematic review and network meta-analysis: Efficacy and safety of second-generation antipsychotics in youths with bipolar depression. *J Amer Acad Child Adol Psychiatr.* 61(2): 243-254.
8. Farhat, L.C., Vattimo, E.F.Q., Ramakrishnan, D., Storch, E.A., et al. Systematic review and meta-analysis: An empirical approach to defining treatment response and remission in pediatric obsessive-compulsive disorder. *J Amer Acad Child Adol Psychiatr.* 61(4): 495-507. <https://doi.org/10.1016/j.jaac.2021.05.027>