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Medication and Cognitive Behavioral Therapy for Pediatric Anxiety Disorders:

No Need for Anxiety in Treating Anxiety

Joan Rosenbaum Asarnow, PhD, ABBP, Michelle S. Rozenman, PhD, and Gabrielle A. Carlson, MD

David Geffen School of Medicine, Semel Institute of Neuroscience & Behavior, Department of Psychiatry & Biobehavioral Sciences, University of California, Los Angeles (Asarnow, Rozenman); Stony Brook University School of Medicine, Department of Psychiatry & Pediatrics, State University of New York at Stony Brook (Carlson)

Anxiety disorders are among the most prevalent pediatric behavioral health conditions, affecting roughly 32% of youths prior to adulthood, and associated with impaired functioning that can continue into adulthood and increase in severity.^{1,2} In this issue of *JAMA Pediatrics*, Wang et al³ report an updated meta-analysis evaluating the comparative efficacy of cognitive behavioral therapy (CBT) and pharmacotherapy for pediatric anxiety disorders. Results supported the efficacy of CBT, selective serotonin reuptake inhibitors (SSRIs), and their combination; limited support was provided for serotonin-norepinephrine reuptake inhibitors (SNRIs). We briefly review the evidence followed by implementation issues.

Results of the meta-analysis indicate that CBT and SSRIs were each more likely to result in diagnostic remission/treatment response compared with wait list/no treatment and pill placebo, respectively. Combined CBT and medication led to greater improvements in anxiety symptoms compared with CBT alone (2 studies) or medication alone (1 study). Comparison of CBT and SSRIs (2 studies) indicated greater declines in anxiety (symptoms and diagnostic remission) among CBT-treated vs SSRI-treated children.^{4,5} Some, but less, support was found for SNRIs on a few outcomes in some trials; there was no support for tricyclic medications, benzodiazepines, or buspirone. Adverse events and treatment dropout were more common during pharmacotherapy compared with CBT, although SSRIs and pill placebo did not statistically differ in dropout rates, dropout due to adverse events, or any specific adverse events. With regard to psychiatric adverse events, no suicide deaths or attempts were reported in any study and suicidal behavior appeared to be less than in

Corresponding Author: Joan Rosenbaum Asarnow, PhD, ABBP, David Geffen School of Medicine, Semel Institute of Neuroscience & Behavior, Department of Psychiatry & Biobehavioral Sciences, University of California, Los Angeles, 300 Medical Plaza, Los Angeles, CA 90095-6968 (jasarnow@mednet.ucla.edu).

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depression studies. Behavioral activation, which is sometimes confused with mania, is a psychiatric adverse event especially noteworthy in children younger than 12 years.⁶

From a clinical perspective, the key issues are how many children will recover, how much recovery is expected, and how rapidly will recovery occur. Findings from the Child/Adolescent Anxiety Multimodal Study,⁵ the largest and most rigorous randomized clinical trial included in the meta-analysis, provide a relatively clear answer to these questions. Focusing on children ages 7 to 17 years with primary diagnoses of separation anxiety, generalized anxiety, or social phobia, roughly 81% of youths receiving combined SSRI (sertraline) and CBT had shown “much or very much” clinical improvement compared with 55% for SSRI only, 60% for CBT only, and 24% for pill placebo following 12 weeks of treatment. Remission, defined by the loss of all targeted anxiety diagnoses, was observed in 68%, 46%, 46%, and 24% of youths receiving combined SSRI plus CBT, SSRI only, CBT only, and placebo treatment, respectively, at 12 weeks.⁷ Children receiving combined SSRI plus CBT and those receiving SSRI only began to improve earlier, separating from placebo by 4 weeks. At 12 weeks, the CBT-only and SSRI-only groups showed similar improvements with each group improving more relative to pill placebo. Therefore, current evidence indicates that treatments with demonstrated efficacy in the reviewed trials can yield substantial improvements in anxiety symptoms within a relatively brief period.

Despite the large number of included studies and novel information presented, the review is constrained by the limitations of the existing evidence base and meta-analytic methods. The meta-analysis and many of the included studies omit analyses of functional outcomes. Anxious children often show school refusal and avoidance behavior that interferes with optimal development. While it is important to know whether anxiety symptoms and global anxiety decline, it is equally and arguably more important to consider treatment effects on school and social functioning. Results varied by informant, with the strongest evidence emerging for clinician reports, compared with parent report, and relatively weak support based solely on child self-report. Only 1 study conducted a head-to-head comparison of CBT, pharmacotherapy, and their combination.⁵ The meta-analysis was not restricted to randomized clinical trials and included less rigorous nonrandomized comparative studies. The results provide minimal data on which drugs are most effective. Ironically, the best-researched medications are off-label for childhood anxiety treatment (excluding obsessive-compulsive disorder) with US Food and Drug Administration approval only for duloxetine. Relatively few studies conducted longer-term follow-ups to assess durability of improvements. This important limitation is underscored by Child/Adolescent Anxiety Multimodal Study findings that approximately half of youth receiving gold-standard CBT, SSRI, or CBT plus SSRI treatments experienced diagnostic recurrence within roughly 6 years of initial treatment.⁸ These data suggest that anxiety disorders may be best viewed as conditions that can be effectively treated in the short term, but characterized by continuing longer-term risk. Future research is needed to evaluate strategies for longer-term monitoring and preventive care after acute treatment.

Meta-analytic methods also have their weaknesses, requiring cautious interpretation. By combining results across trials statistical power is enhanced, improving the ability to detect statistically reliable between-group differences, yet the meta-analysis is only as strong as the

individual studies included in the analysis. When disparate studies are combined, results need to be considered in the context of this cross-study heterogeneity. Results of meta-analyses may differ from those of individual clinical trials, and rigorous replication of large randomized clinical trials provides the strongest evidence for treatment efficacy.

The field has struggled to improve the pace at which research evidence is translated into practice improvements. The meta-analysis by Wang et al³ brings up-to-date information on the scientific evidence. However, translating these findings into practice is challenging owing to multiple factors including limited access to behavioral health clinicians, a shortage of clinicians with training in child and adolescent mental health, and evidence based pediatric anxiety treatments.⁹ There are numerous approaches for overcoming these problems, including integrated medical-behavioral health care, co-located behavioral health and primary care services, and increasing training and rapid consultation on pediatric behavioral health.¹⁰ However, pharmacotherapy may still be the primary available treatment option, particularly in primary care where most youths have access to care.¹⁰ Further, when youths are referred to specialty behavioral health settings where CBT and other psychotherapies are available, many families do not follow up on referrals. A key priority for the future is to identify effective strategies for bringing evidence-based treatments to the children who need them.

Another challenge requiring research attention is that of developing strategies for delivering identified “effective treatments” under routine practice conditions in a manner that yields benefits like those in the reported trials, which included rigorous training/quality control protocols that are difficult to reproduce beyond research settings. These challenges have contributed to interest in technology-enhanced treatment approaches (eg, internet CBT, mobile health). An advantage of these approaches is that they can standardize treatment delivery/quality and be delivered within a stepped-care framework, where less severely ill children receive technology-enhanced treatments, with more intensive in-person treatment reserved for more severely ill children. These approaches can address workforce and quality control issues, while also addressing time, transportation, stigma, and other barriers that can limit rates of accessing care.

In conclusion, the important meta-analysis by Wang et al³ demonstrates that there are acute treatments that work. Still, roughly 40% to 50% of anxious children who receive gold-standard CBT or SSRI remain symptomatic following acute treatment.^{5,11} While is comparable with effects for treatments of pediatric medical conditions, such as asthma,¹² this means that full remission is not expected for many children, even with our best treatments. Additional research and practice advances are needed to clarify how best to address this prevalent and impairing illness. The hope is that at the next review, treatments with stronger, more pervasive, and lasting benefits will be identified, with strategies for integrating these treatments within service delivery systems tested and ready to be implemented to improve behavioral health in our children.

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