Initiation of Pharmacotherapy Following CBT in Anxious Youth: Results From the Child/Adolescent Anxiety Multimodal Study (CAMS)

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ABSTRACT

Objective: To describe youth with anxiety disorders who initiate pharmacotherapy following cognitive-behavioral therapy (CBT) in a prospective, randomized trial and to identify predictors of the decision to use pharmacotherapy.

Methods: Data from CBT-treated youth (aged 7–17 years, N = 139) in the Child/Adolescent Anxiety Multimodal Study (CAMS), a multisite, randomized controlled trial that examined the efficacy of CBT, sertraline, their combination, and placebo for pediatric anxiety disorders (*DSM-IV* criteria), were evaluated. Initiation of pharmacotherapy following acute CBT treatment was examined over a 24-week period; the study was conducted from December 2002 through May 2007. Logistic regression models identified features associated with initiating pharmacotherapy, including symptom severity (scores on the Pediatric Anxiety Rating Scale [PARS] and the Screen for Child/Adolescent Anxiety Related Disorders [SCARED]), parent and child treatment expectations, Clinical Global Impressions–Improvement/Severity of Illness (CGI-I/S) scores, and clinical and demographic characteristics.

Results: CBT non-remitters (CGI-S score > 2) who began pharmacotherapy (n = 10) and those who did not (n = 80) were similar in age ($P = .445$), sex ($P = .324$), race ($P = .242$), and symptom severity based on CGI-S ($P = .753$), PARS ($P = .845$), or SCARED ($P = .678$) scores. Mean ± SD improvement (CGI-I score) at week 12 did not differ between patients who initiated pharmacotherapy (3.00 ± 0.82) and those who did not (2.69 ± 0.89, $P = .798$). However, in the logistic regression, age ($P = .003$), race ($P = .021$), and parents' treatment expectation ($P = .037$) were significantly associated with the likelihood of initiating pharmacotherapy. Beginning pharmacotherapy in CBT non-remitters was associated with a significant improvement in CGI-S score (mean ± SD decline: −0.99 ± 0.46; 95% credible interval [CrI], −0.088 to −1.89; $P = .035$) from week 12 to week 36 compared to patients who did not begin pharmacotherapy.

Discussion: Very few CBT non-remitters initiated pharmacotherapy, although beginning medication produced significant improvement. Younger and racial and ethnic minoritized patients as well as those with lower expectations for CBT were less likely to begin medication.

Trial Registration: ClinicalTrials.gov identifier: NCT00052078

J Clin Psychiatry 2023;84(1):22m14524

To cite: Strawn JR, Mills JA, Rothenberg R, et al. Initiation of pharmacotherapy following CBT in anxious youth: results from the Child/Adolescent Anxiety Multimodal Study (CAMS). *J Clin Psychiatry.* 2023;84(1):22m14524.

To share: https://doi.org/10.4088/JCP.22m14524

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Treatment for children and adolescents with anxiety disorders frequently involves cognitive-behavioral therapy (CBT), selective serotonin reuptake inhibitors (SSRIs), or the combination of an SSRI and CBT.[1] Combining CBT and SSRIs produces superior outcomes[2]; however most youth with anxiety disorders receive monotherapy (either psychotherapy or an SSRI),[3] and half of patients fail to remit.[4] For youth who do not remit, the next steps are unclear. In fact, only two studies have systematically examined this population. In the first, a placebo-controlled trial of children and adolescents with generalized, separation and/or social anxiety disorders,[5] most fluvoxamine non-responders improved when they were switched to fluoxetine. In the second study, the Child/Adolescent Anxiety Adolescent Multimodal Study (CAMS),[6] few CBT non-remitters began medication. CAMS provides a window into the uptake of pharmacotherapy following CBT non-response and allows an examination of predictors of initiating pharmacotherapy in CBT non-remitters, including how patient and caregiver expectations of treatment efficacy influence this uptake.

Given that more than 50% of children and adolescents with anxiety disorders do not remit with CBT,[4] understanding pharmacotherapy uptake following CBT non-response is critical, particularly given the superiority of combined treatment.[2,4,7] Understanding child and parent perspectives related to pharmacotherapy in pediatric anxiety disorders and how these perspectives influence the likelihood of initiating pharmacotherapy after CBT nonresponse is also clinically important. Many parents prefer that their children begin treatment with CBT prior to pharmacotherapy[8,9] despite their similar efficacy in prospective trials. In one sample, parents of youth with anxiety disorders (N = 71) rated CBT as more acceptable than pharmacotherapy; however, parents of youth who had previously been treated with pharmacotherapy saw pharmacotherapy as more acceptable.[8] Hesitation about medication may make parents reluctant to try new treatment options, even when an initial course of treatment produces suboptimal results.

With these considerations in mind, we examined children and adolescents who were randomized to CBT in CAMS, a multisite, randomized controlled

Clinical Points

- For anxious youth who do not remit with cognitive-behavioral therapy (CBT), the next steps are unclear.
- Few CBT non-remitters initiate pharmacotherapy, although beginning medication produced significant improvement. Younger and racial and ethnic minoritized patients as well as those with lower expectations for CBT are less likely to begin medication.
- Clinicians may consider adding pharmacotherapy and discussing this in CBT non-remitters.

trial that examined the efficacy of CBT, sertraline, their combination, and pill placebo for the treatment of separation, generalized, and social anxiety disorders.[2] We sought to (1) describe CBT non-remitters who initiated pharmacotherapy compared to those who did not and (2) examine how patient and parent expectations related to the potential efficacy of medication, CBT, and combination treatment regarding the decision to begin pharmacotherapy. We hypothesized that higher expectations for medication efficacy, older patient age, and greater symptom burden would be associated with a higher likelihood of initiating pharmacotherapy.

METHODS

Patients

The CAMS methods have been extensively described,[10] as have baseline characteristics of the patients[11] and acute[2] and long-term outcomes.[6] In short, patients aged 7–17 years (mean age: 10.7 years) who met *DSM-IV* criteria for at least 1 pediatric anxiety triad disorder (generalized anxiety disorder, separation anxiety disorder, and/or social anxiety disorder) were randomized (2:2:2:1) to the following: CBT (n = 139), sertraline (n = 133), sertraline plus CBT (n = 140), or placebo (n = 76). The study protocol was approved and monitored by institutional review boards at each site. Parents/guardians and patients provided informed consent and assent, respectively, prior to any study-related procedures. The original data set for this study is available from the National Institute of Mental Health Data Archive (https://nda.nih.gov), and the study is registered at ClinicalTrials.gov (identifier: NCT00052078). The study was conducted from December 2002 through May 2007.

For these analyses, CBT-treated youths who continued to experience clinically significant symptoms (defined in the next paragraph) following 12 weeks of CBT (n = 90) were examined, as were predictors of beginning anxiety-specific pharmacotherapy during the subsequent 24 weeks of follow-up.[6]

Assessment of Anxiety Symptoms and Remission

As described in the initial efficacy study,[2] categorical remission was defined by a score of 1 or 2 on the Clinical Global Impressions–Severity of Illness scale (CGI-S),[12] which ranges from 1 to 7 (lower scores reflect fewer symptoms and less impairment). Similarly, at week 12, response was defined by a score of 1 or 2 on the Clinical Global Impressions–Improvement scale (CGI-I).[12] The Pediatric Anxiety Rating Scale (PARS) score was the primary dimensional outcome measure for anxiety severity. This instrument includes a 50-item symptom checklist, as well as a second section consisting of specific severity/impairment items that are rated on a 6-point Likert scale, and is administered by an independent rater.[13]

Assessment of Treatment Expectation

At baseline, youth and parents responded to 3 statements related to CBT, medication, or combined treatment: (1) "How much do you expect that doing cognitive-behavioral therapy will affect your child's anxiety problems?" "If treated with cognitive behavioral therapy only, I expect my child's anxiety problems will be…"; (2) "How much do you expect that medication will affect your child's anxiety problems?" "If treated with medication only, I expect my child's anxiety problems will be…"; and (3) "How much do you expect that cognitive-behavioral therapy plus taking medication will affect your child's anxiety problems?" "If treated with the combination medication, I expect my child's anxiety problems will be...." Responses were measured on a 7-point Likert scale with the anchors being 1 = "very much improved" and 7 = "very much worse" and a score of 4 being "no change."

Initiation of Pharmacotherapy

Patients were categorized as having initiated pharmacotherapy if they began an SSRI, serotonin-norepinephrine reuptake inhibitor (SNRI), benzodiazepine, 5-HT_{1A} partial agonist, or other medication that was coded as having been initiated for anxiety between week 12 and week 36.

Statistical Methods

Demographic and clinical variables (eg, age, sex, race, socioeconomic status [SES], selected diagnoses) were compared for CBT non-remitters who began pharmacotherapy and those who did not using Bayesian posterior means and proportions comparison tests, as appropriate.[14,15] Logistic regression models were then estimated using the Hamiltonian Monte Carlo (HMC) No U-Turn sampler in Turing.jl.[16] Resulting posterior coefficient estimates are expressed as mean ± SD. The mean and 95% credible interval (CrI) for each odds ratio of effect were computed by transformation of the posterior parameter HMC chains.[17]

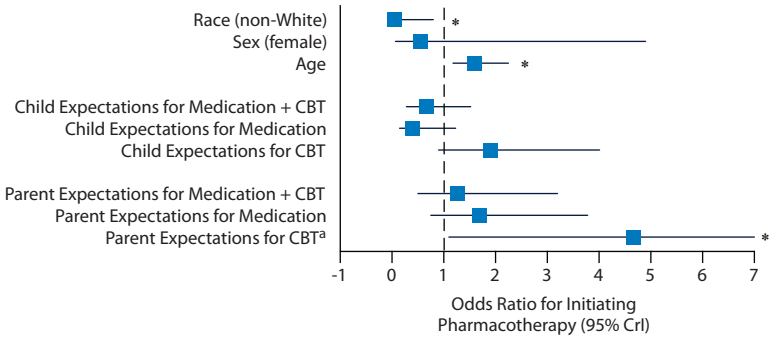
Parent and child expectations related to the efficacy of combined treatment (CBT + SSRI) and medication monotherapy were examined as predictors of initiating pharmacotherapy in CBT non-remitters in the logistic regression. Analyses were performed in *R* (version 4.1.3) and Julia (version 1.7), and posterior 2-tailed probabilities (Bayesian *P* values) < .05 were considered statistically significant.

Table 1. Clinical and Demographic Characteristics of Cognitive-Behavioral Therapy (CBT) Non-Remitters Who Began Versus Those Who Did Not Begin Pharmacotherapy[a]

Characteristic	Initiated Pharmacotherapy (n = 10)	Did Not Initiate Pharmacotherapy (n = 80)	*P* Value
Sex, female (%)	7 (70.0)	42 (52.5)	.324
Age, mean ± SD, y	13.3 ± 2.4	10.5 ± 2.7	.445
White, n (%)	9 (90.0)	56 (70.0)	.242
Education, mean ± SD, y	4.9 ± 0.88	5.7 ± 1.36	.640
SES score, mean ± SD	41.5 ± 7.8	48.0 ± 10.9	.627
ADHD, n (%)	0 (0.0)	15 (18.8)	.214
Baseline severity, mean ± SD score			
PARS	22.0 ± 2.1	19.6 ± 4.3	.613
CGI-S	5.50 ± 0.53	5.15 ± 0.75	.704
Total SCARED	31.7 ± 12.4	23.8 ± 14.6	.681
SCARED, panic/somatic	5.30 ± 4.22	4.53 ± 4.61	.901
SCARED, general anxiety	9.50 ± 3.21	6.01 ± 4.66	.537
SCARED, separation anxiety	4.00 ± 3.50	4.56 ± 4.08	.917
SCARED, social anxiety	9.50 ± 4.70	6.53 ± 4.16	.636
Week 12 severity, mean ± SD score			
PARS	15.2 ± 4.6	13.9 ± 5.0	.845
CGI-S	4.40 ± 0.84	4.03 ± 0.86	.753
Week 12 improvement, mean ± SD score			
CGI-I	3.00 ± 0.82	2.69 ± 0.89	.798
Treatment expectancy for CBT, mean ± SD score			
Child	3.10 ± 1.10	2.45 ± 1.13	.689
Parent	2.80 ± 0.42	2.19 ± 0.73	.466

[a]Remission was based on a week 12 Clinical Global Impressions–Severity of Illness scale (CGI-S) score ≤ 2.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, PARS = Pediatric Anxiety Rating Scale, SCARED = Screen for Child Anxiety Related Disorder, SES = socioeconomic status.

Figure 1. Forest Plot of the Impact of Expectation for Efficacy of Specific Interventions on Initiation of Pharmacotherapy Following 12 Weeks of Cognitive-Behavioral Therapy (CBT)



[a]The 95% credible interval (CrI) for Parental Expectations for CBT is truncated but extends from 1.208 to 23.37.
*$P < .05$.

RESULTS

Characteristics of CBT Non-Remitters Who Began Pharmacotherapy

Based on a categorical definition of remission (CGI-S score ≤ 2), 90 patients who received CBT-only during the acute study phase were identified as non-remitters at week 12. Of these, 10 initiated pharmacotherapy. CBT non-remitters who began medication were similar in age, sex, race, and other demographic characteristics to those who did not begin medication (Table 1). Additionally, symptom severity based on CGI-S score, PARS score, and Screen for Child/Adolescent Anxiety Related Disorders (SCARED)[18] score (and subscores) was similar between the two groups (Table 1). Mean ± SD improvement, reflected by the CGI-I scores following 12 weeks of CBT, was similar between non-responders who began pharmacotherapy (3.00 ± 0.82) and those who did not (2.69 ± 0.89, $P = .798$). Finally, with regard to the study sites (Duke University Medical Center; New York State Psychiatric Institute–Columbia University Medical Center–New York University; Johns Hopkins Medical Institutions; Temple University; University of California, Los Angeles; and Western Psychiatric Institute and Clinic–University of Pittsburgh Medical Center),

more CBT non-remitters from one site (50%, n = 5) began pharmacotherapy compared to other sites, and, at this site, the proportion of non-remitters who began pharmacotherapy was greater than those who did not begin pharmacotherapy ($P = .040$).

Associations Between Initiating Pharmacotherapy and Demographic and Clinical Features

Multivariate logistic models revealed that, among CBT non-remitters, initiating pharmacotherapy was predicted by age ($\beta = 0.47 \pm 0.18$, $P = .003$), but not sex (-0.60 ± 1.13, $P = .604$), education level ($\beta = -0.70 \pm 0.39$, $P = .061$), or symptom severity based on CGI-S score ($\beta = 0.19 \pm 0.59$, $P = .752$). Being non-White was associated with a lower likelihood of beginning pharmacotherapy ($\beta = -2.98 \pm 1.54$, $P = .021$). Additionally, odds ratios for initiating pharmacotherapy are shown in Figure 1.

Patient and Parent Expectations and the Likelihood of Beginning Pharmacotherapy

Parental expectations for the efficacy of CBT predicted the likelihood of initiating pharmacotherapy in non-remitters ($\beta = 1.54 \pm 0.80$, $P = .037$), while the patient's expectations for CBT trended toward an association with initiating pharmacotherapy ($\beta = -0.65 \pm 0.37$, $P = .071$). By contrast, neither parental expectations ($\beta = 0.53 \pm 0.37$, $P = .158$) nor the child's expectations for medication efficacy ($\beta = -0.69 \pm 0.50$, $P = .166$) predicted the likelihood of initiating pharmacotherapy in CBT non-remitters. Finally, neither parental expectation ($\beta = 0.30 \pm 0.39$, $P = .438$) nor child's expectation for the efficacy of combined treatment ($\beta = -0.30 \pm 0.39$, $P = .446$) was associated with the likelihood of initiating pharmacotherapy (Figure 1).

Relationship Between Beginning Pharmacotherapy and Improvement in CBT Non-Remitters

A post hoc examination of the impact of beginning pharmacotherapy in CBT non-remitters revealed that beginning pharmacotherapy was associated with a significant improvement in CGI-S score from week 12 to week 36 (mean ± SD decline: -0.99 ± 0.46; 95% CrI, -0.088 to -1.89; $P = .035$) compared to not begining pharmacotherapy.

DISCUSSION

Youth who do not remit following 12 weeks of CBT rarely initiate pharmacotherapy, although CBT non-remitters who began pharmacotherapy had a decrease in CGI-S score of approximately 1 point (mean ± SD decline: -0.99 ± 0.46; 95% CrI, -0.088 to -1.89; $P = .035$) compared to patients who did not begin pharmacotherapy. Practice guidelines and expert consensus statements that prioritize CBT as an initial treatment for anxiety presuppose that, if CBT is ineffective, parents and youth will begin or augment with pharmacotherapy. However, these data do not support that presupposition. The failure to initiate pharmacotherapy may relate to many factors, including (1) lack of stepped care guidelines from well-powered sequencing trials, (2) the possibility that symptom reduction (but not remission) obviated the need for additional treatment (from the parents' perspective), (3) demoralization, (4) concerns about medication, (5) treatment inertia, and (5) potential lack of collaboration between CBT therapists and pharmacotherapists.

The trajectory of improvement may affect the likelihood of beginning pharmacotherapy in patients who failed to respond to psychotherapy. For example, patients who, despite persistent symptoms, experienced some improvement may have been more willing to continue CBT in the hopes of continued improvement. However, it is also possible that there is inertia regarding beginning a new treatment (eg, pharmacotherapy) even when treatment gains have been modest and patients continue to experience significant symptoms. That said, there was no significant difference in CGI response scores for CBT non-responders who initiated pharmacotherapy and those who did not.

These data illustrate the stepped care irony: few patients with the option—following lack of remission with CBT—to begin pharmacotherapy did so. While the correct approach for sequencing pharmacotherapy and CBT in pediatric anxiety disorders is unclear, multiple factors influence the decision to begin with one treatment versus another and subsequently the decision to add medication following non-remission with CBT (or CBT after non-remission with medication). Parents may wish to avoid medication or to avoid the stigma associated with medication, and, for some, this decision may be influenced by cultural beliefs related to medication or concerns related to the time commitment for CBT. When to augment or change treatment—either adding CBT to pharmacotherapy or augmenting pharmacotherapy with an SSRI—is a critical question for parents, patients, and clinicians. While a Sequential Multiple Assignment Randomized Trial (SMART)[19] is underway to identify the optimal approach for sequencing medication and CBT in youth with anxiety disorders, an earlier SMART trial[20] examined this sequencing in depressed youth. In that study, patients with major depressive disorder treated with interpersonal therapy for adolescents (IPT-A) without the expected improvement at either 4 or 8 weeks (20% or 40%) were randomized to increase the frequency of IPT-A or fluoxetine augmentation. That study revealed that earlier augmentation produced superior outcomes compared to delayed (week 8) augmentation.[20]

Acceptability of pharmacotherapy represents a significant barrier to beginning treatment.[8,9] In the primary care setting, the lower acceptability may relate to skepticism and fears that medication will be continued indefinitely.[21] Additionally, clinician beliefs may contribute to a lack of willingness to prescribe medications. For example, in one qualitative examination of barriers to treatment,[22] providers who felt that psychotherapy was more effective than medication "rarely prescribed medication." Potentially consistent with that finding, 50% of the patients in the present study who

began medication came from a single site, raising the possibility that site expertise, experience, or background influenced the decision to begin pharmacotherapy. Also, psychotherapists' bias against medication could have influenced the uptake of pharmacotherapy following CBT, although this variable is difficult to assess in the current sample.

Regarding the acceptability of pharmacotherapy relative to the evidence base for psychotherapy, we must evaluate CBT monotherapy interventions as first line. SSRIs produce faster improvement in pediatric anxiety,[14] and the additive benefit of CBT in patients treated with SSRIs takes > 10 weeks to emerge.[7] These converging lines of evidence highlight the need to determine whether in situations where monotherapy is first, should SSRI pharmacotherapy be the first-line monotherapy?

The lack of uptake of pharmacotherapy following non-remission with CBT may relate to the development of hopelessness or demoralization in patients and families. When youth continue to experience significant symptoms, despite weekly psychotherapy for 3 months, they may abandon hope for future treatments, including pharmacotherapy. This possibility speaks to the need for CBT therapists and pharmacotherapists to have ongoing relationships, for pharmacotherapy discussions to be incorporated into the psychotherapy when appropriate, and for psychotherapists to be comfortable referring for pharmacotherapy when patients fail to remit with an adequate trial of CBT.

When parents expect CBT to be very effective, their children are more likely to begin post-CBT pharmacotherapy. The relationship between expectations for CBT and the likelihood of beginning pharmacotherapy following non-remission with CBT may relate to several factors. First, when patients and families with high expectations for CBT failed to remit, they may feel that they failed what they believed is an effective therapy and are, therefore, willing to try an alternate therapy. Second, those with higher expectations may have been more able to reflect on their experience with CBT and to reflect on the fact that they gave it their all, and thus the "next step" was more palatable. Third, those who expected less from CBT efficacy may have "given up" when they did not remit with CBT. This possibility is also consistent with the small number of individuals who initiated pharmacotherapy on failing to remit with CBT.

Pharmacotherapy expectations did not influence pharmacotherapy uptake. Patients and families who received CBT monotherapy had not experienced medication during the acute treatment phase, raising the possibility that this lack of direct experience with pharmacotherapy neither increased or decreased the likelihood of beginning pharmacotherapy. Further, this sample—a treatment-seeking population that chose to participate in a randomized trial—may have had greater expectations or more positive expectations than other children and adolescents with anxiety disorders.

The reasons why younger patients were less likely to begin medication may relate to several factors. First, residual symptoms may be more impairing or more frequently reported in adolescents. Second, adolescents might have more domains (eg, sports, school presentations, social events) that are affected by the anxiety. A third possibility is that parents may perceive medication as more acceptable in older youth secondary to a perception that younger children may be more at risk of side effects.

After failing to remit with CBT, racial and ethnic minoritized youth were more than 3 times less likely (4.1% vs 13.8%) to begin pharmacotherapy compared to White patients. This finding is particularly concerning given that, in some studies, racial and ethnic minoritized youth have less response to SSRI + CBT and are less likely to receive quality, standard-of-care psychotherapy and pharmacotherapy.[23] The finding that racial and ethnic minority participants are less likely to seek additional treatment compared to their White counterparts underscores the need to understand this disparity and whether clinicians' implicit bias might affect the offering or discussion of pharmacotherapy. Additionally, many racial and ethnic minority groups, in particular Black individuals, have suffered institutionalized discrimination within the White-dominated health care system,[24] and this discrimination has enduring consequences in terms of distrust in the health care system,[25,26] and perhaps pharmacotherapy.

While this study is the first to systematically examine the uptake of pharmacotherapy following inadequate response to CBT, there are several important limitations. First, the number of patients who began pharmacotherapy is small. While this represents an important finding, the small number of patients limits our ability to examine predictors of beginning medication. This sample size precluded detection of any statistically significant demographic differences between groups; however, the precision of logistic regression coefficient estimates is influenced more by the total sample size (n = 90) than by the specific number of events (eg, starting or not starting medication). Further, the estimated effect controls for the influence other variables in the model (ie, partial correlation rather than a simple correlation), which is why, despite an absence of group differences, we identified significant predictors of initiating pharmacotherapy. The way in which age and baseline severity influence the decision to begin medication warrants additional investigation. Despite the greater improvement in symptoms among those non-remitters who decided to initiate pharmacotherapy, their higher baseline severity may have influenced their decision to take medication. Second, we did not probe the reasons for treatment decision making. Third, site effects may have influenced the uptake of pharmacotherapy, which cannot be examined secondary to the small number of patients beginning pharmacotherapy. Fourth, given the short duration of the trial, some patients may have initiated treatment following a longer course of CBT (ie, >36 weeks). Fifth, perceptions and concerns related to polypharmacy

may have existed for a subset of patients with ADHD who were already treated with stimulant medications and who wished to avoid an additional medication (eg, SSRI or SNRI). Sixth, with regard to the assessment of expectation, no comprehension test was administered and, therefore, it is possible that families or patients may have differed in their understanding of the questions. Last, additional barriers may have influenced the uptake of pharmacotherapy in CBT non-responders, including cost and access, although patients were provided referrals by study clinicians or, in some cases, received pharmacotherapy within the research clinics proper.

These findings highlight the low likelihood of beginning a potentially effective treatment—pharmacotherapy—in patients who failed to remit with CBT. For clinicians, these data underscore the importance of early improvement and raise the possibility of parents and children not engaging in subsequent treatment secondary to a demoralization associated with a lack of CBT response. Additionally, given the relationship between initiating pharmacotherapy and treatment expectation, these findings speak to our need—as clinicians—to not only frankly discuss the strong evidence-base for interventions, but also to address patients' and parents' ambivalence and to emphasize remission as the goal of treatment.

Submitted: May 7, 2022; accepted August 2, 2022.

Published online: December 5, 2022.

Relevant financial relationships: **Dr Strawn** has received research support from AbbVie, the National Institutes of Health (NIH, [5R01HD098757 and 1R01HD099775]; National Institute of Child Health and Human Development [NICHD], National Institute of Mental Health [NIMH], National Institute of Environmental Health Sciences [NIEHS], and Clinical and Translational Science Award [CTSA] program [UL1TR001425]), and the Yung Family Foundation. He receives royalties from Springer Publishing for three texts and from UpToDate and has received material support from Myriad Genetics and honoraria from the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry (AACAP), Genomind, and Neuroscience Educational Institute. He provides consultation to the US Food and Drug Administration as a Special Government Employee. **Dr Mills** has received financial support from the Yung Family Foundation. **Dr McCracken** has received research support from NIMH, NICHD, and Roche. He has served as a consultant to Roche, Tris Pharma, Teva, Octapharma, GW Biosciences, and Impel. He has received speaker honoraria from AACAP. **Dr Piacentini** has received grant or research support from NIMH, The Nicholas Endowment, and private donors. He serves as a consultant to Spinnaker Health, Inc. He serves on the advisory boards (unpaid) and has received speaking honoraria and travel reimbursement from the International Obsessive-Compulsive Disorder Foundation, Trichotillomania Learning Center, and Tourette Association of America. He has received book royalties from Guilford Press and Oxford University Press. **Dr Walkup** serves on the advisory boards of the Anxiety and Depression Association of America, the Tourette Association of America, and the Trichotillomania Learning Center. He receives royalties from Wolters-Kluwer, Oxford University Press, and Guilford Press. Finally, he has received honoraria from AACAP, American Academy of Pediatrics, and the American Psychiatric Association. **Drs Strawn**, **Piacentini**, **Peris**, and **McCracken** also receive support from the Patient-Centered Outcomes Research Institute (PCORI). **Drs Rothenberg** has no financial relationships relevant to the subject of this report.

Funding/support: The original study (the Child/Adolescent Anxiety Multimodal Study [CAMS]) was supported by the NIMH. The current analyses were supported by the Yung Family Foundation, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD; Grant R01HD098757). These analyses were partially funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (PEDS-2019C1-16328).

Role of the sponsor: None of the study funders had any role in the analysis, writing, or content of this piece and had no role in the decision to submit the manuscript for publication.

Acknowledgements: The Multimodal Study was supported by NIMH grants U01 MH064089, U01 MH64092, U01 MH64003, U01 MH63747, U01 MH64107, and U01 MH64088.

Additional information: Views expressed within this article represent those of the authors and are not intended to represent the position of NIMH, NIH, or the Department of Health and Human Services. The original data set for this study is available from the NIMH Data Archive (https://nda.nih.gov). Dr Mills served as statistical expert for this study.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.