**Commentary: For Adolescents with Subthreshold Depression, Is an Ounce of Prevention Worth a Pound of Cure?**

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**Perspective on the Meta-Analysis.**

Globally, depression is among the leading neuropsychiatric disorders of adolescence.

“Conventional wisdom” indicates that an “ounce of prevention is worth a pound of cure,” a

perspective bolstered by some studies demonstrating that psychological interventions for subthreshold depression reduce acute symptoms and prevent the onset of MDD over

short-term follow-up.

 However, the meta-analysis by XXX and colleagues, the first to pool results from all available relevant studies in the field, provides evidence that would seem to challenge this “conventional wisdom.”1 The meta-analysis included twelve randomized controlled trials of children and adolescents. This editorial focuses on the ten studies with adolescents (13.5 to 17.4 years) who were recruited from schools (n = 6), medical settings (n = 3), and mass mailings (n=1). The youth received short–term psychotherapies ranging from 6 to 16 sessions, primarily Cognitive Behavioral Therapy (CBT) or Interpersonal Therapy (IPT), or inactive control/care as usual. Results showed significant short-term benefits in reducing acute depression symptoms, even though effect size was small to medium (number needed to treat = 8.4). At 6 to 18 months follow-up, however, the likelihood of meeting full criteria for MDD was not significantly different between the intervention and control conditions. We, child and adolescent psychiatrists, have difficulty yielding our commitment to “conventional wisdom” and look for evidence that this meta-analysis is not the last word on the value of early interventions for subthreshold depression to prevent MDD in adolescents.

**Defending our “Conventional Wisdom.”**

Most salient, the authors state that they may not have had an adequate sample size to

detect differences between groups at follow-up. The meta-analysis reported a pooled effect size of 0.42 and a relative risk of 0.52. That means that the youth who received psychotherapy had, on average, a 48% lower chance of developing MDD than those who did not ---- a large difference; but due to the imprecision of the estimates, the confidence interval for the relative risk was wide enough to cross zero, indicating no statistical significance. The range includes the worst-case scenario that adolescents who receive therapy have a 25% higher incidence of MDD to the best-case scenario that those who receive therapy have a 108% lower incidence of MDD.2 Thus, it is not possible to state, with 95% confidence, that there is a prevention effect, likely due to imprecision related to low numbers of included studies. Furthermore, there was a moderate degree of heterogeneity across studies, possibly related to differences in recruitment methods, the intervention and control conditions, the modality used to administer the interventions, the number of intervention sessions, and the measures used to assess outcomes. Importantly, analyses did not rule out the possibility of significant publication bias. In addition to limitations of the meta-analysis per se, characteristics of individual studies should be considered. Perhaps longer follow-up periods would have demonstrated a prevention effect across the studies. Shankman and colleagues conducted a 15-year longitudinal study that examined the naturalistic trajectories of high school students with subthreshold depression. They found that within the first year after study recruitment, 24.5% developed MDD.3 Thus, it is unclear whether the meta-analysis’ length of follow-up was sufficient to detect subsequent MDD episodes.

Finally, we wonder whether mitigation of the risk for MDD is the only meaningful

outcome. The Shankman group showed that in addition to increased risk for MDD, youth with subthreshold depression had an increased risk for anxiety and alcohol-use disorders.3 If we broadened the lens to ask whether psychotherapy for subthreshold depression would prevent the incidence of a broader range of outcomes, we might see a more convincing difference between conditions. While these outcomes could not be included in the meta-analysis, we believe that additional research should address them prior to concluding that treatment for sub-threshold depression does not confer a protective effect. As such, the results of the meta-analysis showing a failure of treatment for subthreshold depression to prevent subsequent MDD episodes and/or related conditions should not be considered definitive.

 **“New Wisdom” from the Meta-Analysis.**

When based on solid evidence, meta-analyses can be highly informative for clinical practice. In other cases, the main value of meta-analyses is to emphasize gaps in the field. We believe the latter is the case of the current meta-analysis. The findings of small to medium effects at post-test are consistent with prior studies demonstrating only modest improvements following short-term treatment for diagnosed MDD. Notably, the Treatment of Adolescent Depression Study (TADS) showed that only 40.3% of the CBT group showed a ”sustained response” by six weeks that was maintained at 12-weeks of treatment.4 Such modest short-term outcomes have not improved over four decades despite the wide dissemination of evidence-based psychotherapies.5 Alongside this previous evidence, the current meta-analysis suggests that alternative treatment approaches for depression (including subthreshold depression) are needed. For example, Behavioral Activation Therapy links the brain’s dopaminergic system with behavioral reinforcers that may be more developmentally relevant to adolescents’ reward-focused activity.6 However, such new approaches continue to target diagnosed MDD and under-emphasize the consensus that early-onset MDD is a more severe disorder than adult-onset MDD.7 An evidence-base is needed that shifts to the earliest identification of at-risk youth with consideration of heritable liabilities, early adverse experiences, and evolving neuroaffective control of social stressors that interact to adversely affect the central nervous system.8

Luby and colleagues’ work demonstrates that these risks may be evident as early as

preschool,9 suggesting the need for a developmental approach to early-onset depression

symptoms. Such an approach obviates the phenomenology-based DSM that under-emphasizes the effects of development on the expression of psychopathology and categorizes depressive disorders into distinct entities. However, the boundaries between depressive disorders, as well as between disorders and subsyndromal symptoms, are not as strict as the DSM paradigm suggests.10 A developmental perspective considers that subsyndromal depression represents early evidence of an evolving depressogenic cascade. “Subsyndromal” marks the point in this cascade that the process, and the patient, is observed. We need a reconceptualization of early onset depression and interventional approaches that serve the developmental needs of young people.

**Implications for the Way Forward.**

What does this meta-analysis suggest regarding our efforts to help youth experiencing

subsyndromal depression? Child and adolescent psychiatrists work to resolve symptoms, relieve

suffering, and improve functioning for adolescents with depression symptoms and disorders,

even in the face of persistent symptoms. The meta-analysis by XXX et al. shows that, based on available evidence, the effects of treating subthreshold depression are small to moderate and that there is no solid evidence to assess its prevention of MDD episodes. However, these results should challenge our “conventional wisdom” and compel us to develop treatments that are more effective in the short term, as well as enduring and protective for the longer term,11 and, thereby, allow a definitive meta-analysis. The meta-analysis results further compel us to shift the research paradigm away from the DSM to a developmental conceptualization and treatment of early onset depression. Clinically, our goal should be to understand the developing brain and support the maturing youth. With a team of parents, peers, educators, therapists, and pediatricians we may leverage an ounce of prevention in search of a pound of cure. There is no room for complacency in the early identification, prevention, and treatment of youth with evolving MDD.

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