The Gordian Knot of Clinical Research in Anxiety Disorders: Some Answers, More Questions

Published concurrently with this editorial are two high-quality, thought-provoking studies from different research domains, each of which advances yet complicates our understanding of clinical anxiety disorders. One is a multisite randomized controlled trial of psychotherapies for social anxiety disorder (1), the other a meta-analysis of the separation anxiety hypothesis of panic disorder (2). Each study answers key questions that have plagued every clinician and researcher who treats anxiety disorders, yet each raises further issues.

Leichsenring et al. (1) conducted a five-site randomized controlled trial of cognitive-behavioral therapy (CBT), psychodynamic therapy (supportive-expressive therapy), and a waiting list condition for social anxiety disorder. In a brave, ambitious, and rigorous study, the authors balanced researcher allegiance, therapist attention, and supervision between modalities. Psychotropic medications were excluded, somewhat limiting generalizability. Carefully blinded independent evaluators employed standard research instruments. Both CBT and psychodynamic therapy outperformed the waiting list condition (no surprise). Surprisingly, however, the dropout rate for the waiting list group matched those of the active treatment groups (24%–28%). CBT statistically outperformed psychodynamic therapy in remission rate, which was generally fairly low across treatments (36% for CBT, 26% for psychodynamic therapy), but not in response rate, defined a priori as an improvement >30% on the Liebowitz Social Anxiety Scale (the rates were 60% for CBT and 52% for psychodynamic therapy).

What distinguishes separation anxiety from other anxiety disorders is that patients perceive a central dyadic relationship as crucial to their sense of safety.

As in all randomized controlled trials, the nitty-gritty choices in study design help shape the findings. Which form of CBT to test in such an important study was self-evident: Clark and Wells's cognitive therapy (3), a commonly practiced model that had been previously studied in clinical trials. No such simple solution attended the dynamic therapy condition, as no form of manualized psychodynamic therapy had been developed or tested for patients with social phobia. The investigators chose to use supportive-expressive therapy, newly modified for social phobia, an understandable choice with both strengths and limitations. An enormous strength is that supportive-expressive therapy has been successfully transported around the globe and used to treat multiple psychiatric conditions. The original development of supportive-expressive therapy in the 1970s was a groundbreaking achievement in psychodynamic psychotherapy research, establishing the first successfully manualized supportive dynamic treatment (4), enabling testing of this previously

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recalcitrant modality in randomized controlled trials. Supportive-expressive therapy focuses on articulating a core conflictual relationship theme, which relates to, yet lacks equivalence to, the transference relationship that forms a key interventional focus in many forms of psychoanalysis and psychoanalytic psychotherapy. Supportive-expressive therapy lacks the full psychodynamic focus on developmental relationships and events, formative attachments, and unraveling underlying fantasy structure. Elements of this therapy, as described in this study, appear alien to psychodynamic practitioners—for example, the inclusion of an exposure component.

Partly because of the limitations of the highly circumscribed psychodynamic research base (5), this large comparative study constituted the very first test of supportive-expressive therapy for social phobia. The decision to test a newly manualized psychotherapy in a large-scale randomized controlled trial against a standard reference treatment involved a leap of faith; there was no chance to calibrate and adapt supportive-expressive therapy to social phobia, which is ordinarily accomplished in smaller open clinical trials. Even a basic matter like determining the timing of sessions (initially weekly, then twice weekly from sessions 7 through 16, and weekly through session 25) is described as an attempt to match CBT, rather than tuning choices to best capture the music of this new treatment. Termination in dynamic therapy for patients with anxiety disorders is often fraught with ambivalence and rage, re-evoking underlying separation and autonomy conflicts, which loom large in this patient group. Dynamic therapists can use this intensification of affect as therapy draws to a close to deepen understanding and relief from anxiety. Hence the decision to lower the "dose" of this therapy toward its end might have decreased its effect at a crucial juncture (6). Even the rating system to measure the therapists' adherence to the manual, central to defining any manualized psychotherapy, was much less precise for supportive-expressive therapy than for CBT in this study.

Despite these problems, studies such as this one, common in psychopharmacology, are crucially needed to advance a similar evidence base for clinical treatment with psychotherapies. What can we learn from this heroic endeavor? Supportive-expressive therapy clearly seems an active treatment for social phobia, but it fared less well than CBT in this study. The more important, clinically pressing task, to use clinical trial data to personalize which treatment works best for whom (7), will await moderator and possibly mediator findings from this and other studies. Much important information that can improve the lives of patients with anxiety disorders remains unresolved at this juncture, and it is to be hoped that even in the age of clinical diagnosis-free Research Domain Criteria research, the crucial work of delineating what works for patients with particular syndromes continues through major clinical trials like this one (8).

The second anxiety study, Kossowsky and colleagues' meta-analysis of the separation anxiety hypothesis of panic disorder (2), enormously increases our evolving understanding of how anxiety disorders develop. This study at last provides us with a comprehensive evaluation of the breadth of the research literature, including case-control, prospective, and retrospective studies, and definitively links childhood separation anxiety disorder with development of panic disorder (with or without agoraphobia) and other anxiety disorders in adulthood. Ever since 1964, when Klein (9) hypothesized a developmental psychopathological link between separation anxiety disorder and panic disorder, the question of whether childhood separation anxiety constitutes a developmental risk factor for

panic, and its potential clinical and prognostic importance, has danced in and out of our models of anxiety (10). Kossowsky et al. conclude, as many astute clinicians and researchers have believed, that these entities are indeed related, articulating one crucial step on the developmental trajectory of adult anxiety disorders.

What are the implications of this relationship, and how does this knowledge advance our understanding of anxiety? Is childhood separation anxiety always a precursor to adult anxiety disorders, or does it link to a subgroup of those with anxiety? This meta-analysis and the wide range of studies the authors evaluated are silent on this interesting and provocative question, which may or may not carry important clues to treatment response. Kossowsky et al. note that only one study (11) has addressed the key question of whether treating childhood separation anxiety disorder prevents later panic disorder; and in that sole report, early treatment did not prevent later panic. As Kossowsky et al. remark, however, one study of 85 patients is too small to definitively answer this question; more studies are needed that follow patients with anxiety disorders from childhood into adulthood.

Future studies need to unravel whether or not childhood separation anxiety disorder constitutes a key psychopathological entity in itself, engendering the range of adult anxiety disorders, or rather marks a more fundamental disturbance of the quality of formative attachment relationships, which later in development produces clinical manifestations of both childhood separation anxiety disorder and adult anxiety disorders (12). Central attachment relationships form the core of human emotional development. Clinical research in anxiety disorders has underappreciated the importance of vulnerabilities to separation anxiety, as well as its association with nonresponse to psychiatric interventions across modalities (13, 14). Indeed, in that regard, the failure to consider the impact of termination with the therapist in the Leichsenring et al. study may have diminished the apparent effectiveness of the psychodynamic arm, and perhaps of the CBT arm as well.

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