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Therapeutic Inertia: Let's Get After It

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The report by Mojtabai and colleagues¹ in this issue suggests several deficiencies in our care of depressed patients that clinicians and care system administrators should recognize and address to enhance the real-world effectiveness of our treatments for depression. They found higher-than-expected rates of symptomatic non-remission in a group of depressed patients (all having received antidepressant medications for at least 3 months). Using the more conservative 9-item Patient Health Questionnaire (PHQ-9)² threshold for non-remission (a score of ≥ 5), 56% were not in remission. Even the less stringent PHQ-9 threshold (a score of ≥ 10 for non-remission) revealed 28% to not be in remission. Furthermore, less than one-third of non-remitted patients (based on either threshold) had been on any augmentation medication in the prior month.

Study limitations include the use of the PHQ-9 as the outcome. There are many reasons for rather modest levels of depressive symptoms (eg, PHQ-9 scores of 5–10) unrelated to mood disorders (eg, situational adjustment reactions, various general medical conditions, substance use disorders, medications). Second, we know only what medications the participants reported taking in the prior month. Thus, the number, types, and durations of prior trials are unknown. Third, the study did not report the likely large number of persons who initiated but never completed an initial 3 months of medication treatment for their depression. Other studies³ have shown that 10%–40% of those initiating antidepressant medication treatment do not complete a 12-week acute-phase treatment trial.⁴

Nevertheless, this report highlights 3 important challenges in bringing clinical research evidence to clinical practice. The major problem raised by their results is therapeutic inertia, a widely recognized problem in the management of many general medical and neurologic conditions such as hypertension, diabetes, hypercholesterolemia, multiple sclerosis,⁵ and other disorders as well as the management of risk factors linked to longer-term health problems.^{6,7} The second problem entails the underuse of evidence-based

augmentation treatment options along with the overuse of options that are supported by little or no evidence. The third issue is the failure to recognize the limits of our psychopharmacologic treatment armamentarium.

Therapeutic inertia entails two major elements: (1) failure to aggressively yet diligently establish the optimal dose for each patient to achieve the desired outcome (in this case remission) for each treatment implemented, and (2) the failure to change the treatment (or move down a treatment sequence) when the initial treatment(s) do not produce remission. This second component is made more challenging intellectually by the lack of empirically defined treatment sequences for depression and practically by the fractured structure of our mental health “care system.”

The causes of therapeutic inertia are wide-ranging, including clinician or patient failure to recognize that residual symptoms are present, the clinician's prematurely assuming that not much more can be achieved, restricted access to more expensive but potentially more effective treatments like transcranial magnetic stimulation (TMS), and difficulties in scheduling appointments soon enough after medication treatment changes to check on patients in a safe and timely fashion. Therapeutic inertia may be due to the need to accept “better” as “good enough” due to time limitations—particularly in busy clinical practices—despite the clinical value of symptom remission as opposed to response being well-recognized given the association of remission with better daily function⁸ and better prognosis^{9–11} compared to response without remission.

The pursuit of remission requires that clinicians be willing to elevate medication doses while monitoring side effects, follow evidence-based augmentation strategies, make timely changes to failed augmentations, and even change treatment modalities. For example, after several augmentation failures with an initial selective serotonin reuptake inhibitor (SSRI), a switch to TMS may be indicated, which may entail transferring the patient to another clinician.

Measurement-based care (MBC) combats therapeutic inertia by promoting higher medication doses. MBC enhances the chances of achieving remission compared to routine care in which clinical impressions alone inform clinical dosing decisions.^{12–15} By personalizing the dose, dose escalation, and duration of each treatment, MBC helps to bridge the gap between research data (based on group averages) and the application of these data to individual patients.

Implementing MBC in mental health or general medical practices, however, has several challenges,¹⁶ including the

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need to revise workflow processes, select among measures, revise the electronic health record (EHR), and engage and train clinicians and staff. Care systems should provide incentives for the implementation of MBC, including training, EHR revisions, clinical champions, feedback on outcomes to clinicians and staff, and the aforementioned scheduling flexibility.

The second component of therapeutic inertia—that of starting new treatments, whether switch or augmentation—is not fully addressed by MBC. This issue is addressed by treatment sequences or algorithms.¹⁷ These typically provide a range of evidence-based augmenting or switching treatment options at each treatment step depending on the success of the prior treatment step(s). Controlled trial evidence indicates that when implemented with MBC procedures, these treatment algorithms produce better overall outcomes than usual practice. The Texas Medication Algorithm Project¹⁸ found that, when implemented with MBC, treatment algorithms outperformed treatment as usual (TAU) for persons with major depression, schizophrenia, or bipolar disorder. Similarly, with depressed inpatients, the German Algorithm Project revealed that several different treatment sequences combined with MBC each outperformed TAU¹⁷ and reduced costs.¹⁹

The implementation of treatment sequences for depression is challenging because very few clinical practice settings are designed to provide the full range of psychotherapeutic, psychopharmacologic, and brain stimulation treatments for depression. Secondly, there is no agreement on which sequences are best suited for which patients. For example, is TMS optimally delivered after 2 or 4 failed monoamine reuptake blocking agents? However, prompts provided in the EHRs regarding the outcomes achieved and the time spent in each treatment step might promote greater attention to changing or augmenting the treatment when it is not producing the preferred result. Care systems need to incentivize these efforts and make appointment scheduling flexible enough to support timely follow-up visits in order to vigorously pursue remission, thereby mitigating therapeutic inertia especially when a new augmentation or switch treatment is being started. Real-world data across a large range of depressed patients could identify potentially effective sequences for particular patients that could then be assessed in controlled point-of-care trials.

Mojtabai et al¹ also found that clinicians frequently chose augmenting agents minimally supported by controlled trial evidence. For example, half of the augmenting efforts employed bupropion (with an SSRI, as well as with a serotonin-norepinephrine reuptake inhibitor [SNRI] and a tricyclic) (see Appendix 3 in the article). Yet, two randomized controlled trials have shown no advantage of using bupropion plus an SSRI over an SSRI alone.^{20,21} In 1 in 8 patients, SNRIs were combined with either tricyclics or SSRIs. Furthermore, lithium was not used at all in this cohort despite evidence demonstrating its efficacy as an augmenting agent.²² It would seem logical to use evidence-based treatments before untested combinations.

The deficiency also highlights the need to bridge the gap between research evidence and clinical practice. Clinicians and care system administrators must find ways to promote the use of evidence-based treatments before untested combinations. Medical or EHR chart reviews in outpatient clinic settings might enhance the use of evidence-based treatment.

Finally, the findings of Mojtabai et al¹ indirectly raise the question of the limitations of our current treatments. They found that 28%–33% of the non-remitted patients were on augmentation medications yet still not in remission, which suggests that even when we use evidence-based augmentation agents, non-remission persists in many patients. While disappointing, it is not surprising since even after 4 very diligently delivered medication treatment attempts in the Sequenced Treatment Alternatives to Relieve Depression trial,²³ one-third of the participants had still not reached remission. Furthermore, up to half of those who had previously remitted relapsed over the 12 months of continuation-phase treatment.²³

It seems likely that our current treatments will not be able to produce remission in a substantial number of depressed persons. For example, in a large cohort of patients with chronic kidney disease who were not on dialysis, Hedayati et al²⁴ found sertraline no better than placebo in outpatients with major depressive disorder. Several randomized controlled trials to address post-stroke depression or overall function found SSRIs to be uniformly ineffective.²⁵

In recognition that a substantial proportion of depressed patients may not be able to achieve or sustain remission with our current armamentarium, the concept of “difficult to treat” depressions (DTD)^{26,27} has been proposed as a potentially useful clinical heuristic. At some point during a series of incompletely effective treatments, a thorough workup for the many treatable medical and psychosocial causes of depression is recommended. This workup also forms the basis for proceeding through any untried evidence-based treatments that remain before making a formal shift in treatment goals from symptom remission to symptom control with enhancement of function and quality of life for those with DTD.

A systematic approach to treatment selection (evidence-based first) and its delivery (MBC) in sequences of reasonable treatment options can improve the outcomes we can achieve with our depressed patients.

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