See article by van der Voort et al

Distinguishing Functional From Syndromal Recovery: Implications for Clinical Care and Research

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The report by van der Voort and colleagues[1] provides persuasive evidence that both major depressive and bipolar disorders are associated with substantial functional impairment not only during but also following the end of syndromal episodes. Some reports[2] have suggested that most depressed patients have full functional recovery once they achieve symptomatic remission; others[3] are less certain. The present report is based on a sample of patients larger and far more representative than samples of subjects selected for clinical trials. This more definitive and generalizable study clearly shows that syndrome resolution is associated with improvement in but not full normalization of function. In short, functional recovery is neither rapid nor complete even a year after patients no longer meet criteria for being in the syndromal state.

This study also found that longer episode durations and more mood episodes were each associated with both worse and slower functional recovery. This finding is consistent with the notion that these mood episodes create environmental or life circumstances, or brain function changes, from which functional recovery takes time. For example, disrupted work or marital relationships may require much effort, time, and realignment of expectations before these critical relationships are back on track and again running smoothly. This finding also makes the case for earlier intervention in order to avoid an accumulation of ever more tragic circumstances or central nervous system effects created by prolonged and recurrent illness episodes.

A third critical finding was that depressive symptoms were found to be a major contributor to prolonged poor function and delayed functional recovery, *even after recovery from the syndrome*. This important finding highlights that the aim of treatment must be full and complete symptom resolution (symptom remission) rather than response or removal of most of the symptoms, not only to reduce the risk of relapse[4] but also to enhance recovery. This finding also aligns with other studies that have shown remission to be associated with a far better prognosis than is response without remission.[5,6]

Three Types of Recovery

Overall, the report makes a strong evidence-based case for distinguishing among 3 types of recovery: syndromal, symptomatic, and functional. Syndromal recovery occurs when the patient is no longer in the predefined syndromal episode such as major depression. It is not surprising, however, that as patients no longer meet the diagnostic criteria that define the syndromal episode, their function is better than it was during the syndromal episode.

Symptomatic recovery focuses on the complete absence of mood symptoms (symptom remission) for a prolonged time period (weeks to months). However, this concept was not meant to imply that function would necessarily become normal either during or at the end of this period. Rather, the notion of full symptomatic recovery from an episode was meant to provide sufficient certainty that, in the event of a subsequent syndromal episode, that episode was very likely a new episode (a recurrence) as opposed to a return of the most recent episode (a relapse).[7]

Functional recovery implies that the patient will return to his or her most functional period prior to the onset of the disorder. This type of recovery, on the basis of the report by van der Voort et al,[1] is slower than expected and, I would add, may require different interventions than those used to achieve and sustain syndromal and symptomatic remission—at least in a meaningful subset of patients.

Clinical Implications

What are the clinical implications of the apparent fact that for many patients, functional recovery cannot be expected to co-occur with the achievement of either syndromal or symptomatic recovery? It would seem that the overall treatment plan for managing depressed patients should address each treatment goal in sequence. First, *end the syndromal state* by medication, therapy, the combination thereof, or somatic treatments. Second, for those who still have some symptoms after the syndrome criteria are no longer met, adjust or augment treatments and manage comorbid conditions (eg, substance abuse, anxiety, insomnia) and concurrent medications to *achieve a period of full and prolonged complete symptom remission.* After this second step, some but not all of these patients will have functionally recovered. Those at greater risk for not achieving functional recovery seem to be those with more severe, recurrent, and prolonged episodes, and perhaps those with more general medical or psychiatric comorbidities. For those patients without full functional recovery, the third step must be to identify and *treat effectively the relevant causes of incomplete functional recovery to normalize day-to-day function*. It is remarkable that some[8,9] but not all[10] clinical practice guidelines do not emphasize the need to reappraise, reevaluate, or treat those depressed patients who have well-controlled symptoms but subpar function.

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What might cause functional recovery to be so slow or incomplete in so many patients, even in the context of good-to-excellent symptom control? Potential causes might be grouped into domains that, in turn, could become treatment targets. Illustrative domains might include (1) residual symptoms of the mood disorder itself (eg, cognitive impairment, anxiety, insomnia, fatigue, mood lability, hypomania, low self-esteem, fatigue; even remitted depressed patients can have some residual symptoms[11]); (2) symptoms or effects on daily function from other current comorbid psychiatric conditions (eg, panic attacks, agoraphobia, substance abuse); (3) symptoms from poorly controlled concomitant general medical conditions, or the medications used to treat them or the psychiatric conditions; (4) perceived or actual excessive environmental demands or stressors; (5) disrupted interpersonal relations (eg, with family members, workplace/school colleagues, or friends) or situational residua from prior mood episodes, such as withdrawal from friends or previously rewarding daily activities. It is likely that several of these causes will not be adequately addressed by medication alone.[12,13]

It remains to be defined how to disentangle these potential causes of incomplete recovery in a given patient, as well as how to understand how each cause actually contributes to poor recovery. For example, how do comorbid anxiety symptoms contribute to impaired function, and what are the best methods for treating them? Do agents that enhance cognition meaningfully improve the degree of or chances for functional recovery in depressed patients? If multiple domains are pertinent to a specific patient, which domains should be treatment priorities? When are specific actions, advice, or interventions needed?

Research Opportunities

Research has not focused at the clinical level on function and quality of life, though most patients and clinicians readily recognize their importance in practice. Is failure to achieve functional recovery an important risk factor for syndromal relapse? For whom? How can we develop a reliable, valid differential diagnostic process to identify the myriad potential causes of incomplete functional recovery? Selecting among and evaluating various treatment options is an existing research opportunity and challenge. How might we reliably differentiate those patients whose function will normalize without additional treatments from those patients who require treatment? Currently, we cannot distinguish these two important groups of patients.

This report also highlights the value of clinical registries, given our need for generalizable information in large representative samples with overall time frames of 1 year plus, as well as the heterogeneity of the mood disorders. Samples from clinical trials have very limited generalizability,[14] small sizes, and limited durations of follow-up. Well-designed registries can address issues such as course of illness, variations in outcomes, longer time frames, identification of risk factors, and other issues for which trial samples are not suited.

In addition, the report underscores the need for brief, practice- and patient-friendly measures of function, since symptoms and function are distinct and both are valid and essential treatment targets. While there are several available scales, it would be very useful to be able to crosswalk between measures and to establish conversion tables so results from diverse studies could be compared. In addition, a consensus on what is a clinically meaningful change in each scale would be extremely valuable to clinicians who will have to decide whether or not a treatment is succeeding.

Conclusion

Syndromal, symptomatic, and functional recovery are 3 valid targets in the acute treatment of depressed patients. To these, one must add prevention of relapse or recurrence as the valid postacute treatment-phase target. Total symptom remission, not just syndromal recovery, is critical for longer-term functional recovery and reduction of the risk of relapse. In cases in which functional recovery is not achieved even in the context of maximal symptom control (complete symptom remission whenever possible), a broad net should be cast to identify and ultimately treat those factors that prevent complete recovery of function and that will likely increase the risk of future syndromal relapses. Day-to-day function and quality of life deserve far greater emphasis and attention in clinical practice, practice guidelines, and clinical research.

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