Personalizing the Care of Geriatric Depression

As a common disorder with devastating outcomes (1), geriatric depression is a major health hazard. The various antidepressants have similar efficacy, but each agent helps a rather small number of depressed elderly patients (2). Identification of predictors of treatment response and personalization of treatment (that is, matching treatment with patient) have long been contemplated as a strategy to increase efficacy, to prevent relapses, and to preempt disability, worsening of medical morbidity, and cognitive decline.

Clinical and psychosocial predictors of response to single antidepressants or comprehensive interventions have been identified. These include anxiety, hopelessness, executive dysfunction, limitations in physical and emotional functions, chronicity of the current episode, and low income (3). Such predictors can help in personalizing the first step of treatment for a given patient. Accordingly, a patient with one or more predictors of poor outcome may receive interventions targeting each modifiable predictor as well as more vigilant follow-up. For example, a low-income depressed elderly patient whose symptoms did not respond to an adequate trial of an antidepressant and who is experiencing hopelessness may benefit from a trial of a different antidepressant, therapy focusing on hopelessness, and case management connecting him or her with social services.

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While personalization of treatment is promising in the management of geriatric depression, its actual impact in clinical practice has yet to be tested. Important clinical questions include how long to maintain a given treatment and which patients are candidates for making a treatment change before much time is lost and the patient is exposed to the accumulation of many noxious effects of depression. An article by Andreescu et al. in this issue (4) addresses these questions. Unlike most earlier studies, this one focuses on predictors of full response identified both at baseline and on change in depressive symptoms after treatment is under way. The authors used signal detection theory on pooled data from three acute treatment trials of either nortriptyline or paroxetine. They found that response by the fourth week of treatment was a critical factor in determining the probability of response by 12 weeks. Of course, a strong treatment response by the fourth week suggests that the treatment should continue. However, if only a moderate response has occurred by that time, the clinician has to choose whether to continue the same treatment or do something different—switch to another treatment, for example, or augment the first treatment with another drug or a nonbiological intervention. The study provides valuable information for making these decisions. For example, moderate response by week 4 predicted full response by week 12 in 43% of all patients. However, patients who had low levels of anxiety at baseline had a 61% chance of full response, whereas those with moderate or severe anxiety at baseline had a 39% chance of response. The probability of full response was even lower (33%) in patients who had experienced depressive episodes from early life. Using the probability of full response in treatment decisions can

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spare patients from long exposure to treatments that have a low likelihood of success as well as from premature discontinuation of treatments that would likely be helpful.

Another important step in personalizing treatment is to develop an understanding of the type and nature of brain abnormalities occurring in patients with late-life depression. This knowledge can be informative in two ways. First, identifying persisting abnormalities during remission may indicate a high risk for relapse or persistent cognitive impairment. Second, finding brain abnormalities predictive of poor outcomes of depression may initiate a search for their clinical correlates, which then can be used to personalize treatment.

In another article in this issue, Wang et al. (5) use functional MRI to compare activation and deactivation of brain regions in currently depressed elderly patients, elderly patients in remission from depression, and healthy elderly comparison subjects. The stimulus was an emotional oddball task, which activates or deactivates distributed brain networks and structures relevant to depression. The study documented activation changes that were limited to the depressive state as well as persistent changes occurring in both depressed patients and patients in remission from depression. Depressed patients showed attenuated activation of the right middle frontal gyrus and greater deactivation of the posterior part of the posterior cingulate relative to remitted patients and comparison subjects. The middle frontal gyrus exerts inhibitory control on emotional structures, and the posterior cingulate is connected to the hippocampus and the posterior cortex and participates in memory retrieval and self-consciousness (6). Notably, patients with Alzheimer's disease and those with mild memory impairment exhibit just the opposite deactivation effects on the posterior cingulate (7, 8). Thus, the observations of Wang et al. may explain why mild cognitive impairment in depressed elderly patients often subsides after remission of depression and does not progress to dementia. Reduced activation of structures that participate in executive function (the supramarginal gyrus bilaterally, the left anterior cingulate, and the anterior part of the posterior cingulate) occurred both in depressed and remitted patients relative to comparison subjects. The persistence of reduced activation in these structures is consistent with the clinical observation that executive dysfunction in depressed elderly patients remains after remission of depression (9, 10). Executive dysfunction (11) and microstructural abnormalities in white matter connecting structures that subserve executive functions (12) have been associated with poor or slow response of geriatric depression to antidepressant treatment. Taken together, these findings suggest that functional and structural abnormalities of networks relevant to executive dysfunction characterize a subgroup of depressed elderly patients who experience poor outcomes. Bedside tests of these abnormalities are a possible next step toward a more biologically informed personalization of treatment.

So far, the empirical basis for personalizing treatment principally consists of post hoc analyses of unitary treatments (e.g., a course of an antidepressant or psychotherapy). While this knowledge is necessary, it is insufficient for two reasons. First, depressed elderly persons face a bewildering constellation of health threats and social constraints and thus have many different contributors to poor treatment outcomes. Second, the skills available in various treatment settings and sectors can promote or inhibit treatment success. Therefore, to benefit depressed elderly patients in the community, personalization of care must employ comprehensive care algorithms targeting both modifiable predictors of poor outcomes and organizational barriers to care. Accordingly, the model of geriatric depression needs to integrate the current biological concepts of depression with patients' unique reactions to adverse experiences and with their unmet social and heath care needs. The care algorithms based on this model should 1) target clinical/biological predictors of adverse outcomes of depression; 2) address unmet needs through linkage to appropriate social services; 3) enhance the competencies of elderly persons so that they make use of their resources; 4) attend to patient psychoed-

ucation and preferences and increase treatment engagement; 5) coordinate care and mitigate the interacting medical, psychiatric, and social problems; and 6) provide continuity of care, prevent relapses or recurrences of depression, and preempt medical events and social stressors. An expeditious way of developing an effective approach to personalized care is to work with indigenous community services supported by the reimbursement system and provide targeted training and organizational changes that would facilitate the provision of needed services.

The studies of Andreescu et al. and Wang et al. are examples of progress made in understanding the biology of geriatric depression and in improving the clinical decision-making process. We can expect more growth in both areas. The field of geropsychiatry is also ready to take the next step and incorporate the emerging biological and clinical sophistication in comprehensive treatment models that will reach the great number of elderly persons suffering from depression its consequences.

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