Introduction

Depression: The Relevance of the Time Factor

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Depressive disorders are common, serious and sometimes life threatening. Their effects are persistent, debilitating, and costly. Depression causes significant suffering, disability, and social dysfunction, frequently leading to disruption of normal daily activities for both the patient and the immediate family. Depressed patients struggle to recover, often over several months or even years, and many follow a chronic, recurrent, and remorseless course. As well as a high morbidity, depression carries substantial mortality not only in terms of suicide but also from other causes. The economic burden of depression on society is considerable and is comparable to that of other major illnesses like coronary heart disease; U.S. estimates for 1990 were approximately U.S. $44 billion.[1] However, because depression is often not properly recognized—almost half of all patients who contact primary care health services are believed to have a current depressive disorder—and generally begins to affect people at a relatively young age, it exacts costs over a long period of time and places a particularly heavy burden on employment productivity. Depressive disorders are now recognized as a major public health problem, not least by the World Health Organization (WHO).

Few psychiatrists can now recall what life was like for the depressed patient before the age of psychopharmacology. Drug treatments for most of the mood disorders have been available for more than 4 decades. These treatments include lithium and other mood stabilizers for bipolar patients and antidepressants for those with major depressive disorders or dysthymia. Electroconvulsive therapy (ECT), originally applied in schizophrenia, is also an effective treatment for depression, and certain psychotherapies have established their place in the treatment armamentarium. Nevertheless, there is no cure for depressive disorders. Antidepressants, mood stabilizers, ECT, and psychotherapies are symptomatic treatments that may have to be administered for sustained periods to prevent relapse and recurrence. All, with the possible exception of ECT, are slow to take effect, and many patients do not respond. Antidepressant drugs, for example, have long been assumed to take up to 2 to 4 weeks to initiate response, which is seen in only about 70% of patients, less than half of whom will experience full remission of symptoms.

Individual depressed patients vary widely in their response to different antidepressant drugs, and it continues to be necessary to have at hand a range of medications offering multiple mechanisms of action. While second generation agents like the selective serotonin reuptake inhibitors (SSRIs), the serotonin-norepinephrine reuptake inhibitors, the norepinephrine and specific serotonin

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antagonists, and the selective norepinephrine reuptake inhibitors lack many of the side effects and much of the overdosage toxicity of first generation tricyclic antidepressants and monoamine oxidase inhibitors, they have in general not improved substantially on the efficacy of the older drugs. There are many innovative approaches to third generation candidates under investigation, including, for example, such novelties as selective antagonists of central glucocorticoid or substance P receptors,[2,3] but antidepressant therapy still largely relies on the current second generation agents. Nevertheless, not all second generation agents are alike in efficacy, and substantial evidence is emerging that some of them, particularly new dual-action drugs like venlafaxine and mirtazapine, which affect both norepinephrine and serotonin neuronal systems, may offer advantages over SSRIs in terms of faster onset of action and greater rates of response and remission.[4,5] Much of the evidence has been gathered from retrospective analyses of clinical trials not specifically designed to address these issues, but appropriately designed and adequately powered studies are now under way.

In this supplement, some of these points are addressed in greater detail. Norman Sartorius, M.D., Ph.D., long associated with the WHO, discusses the economic and social burden of depression and emphasizes the public health aspects of a disease that has grown to almost epidemic proportions. Despite the availability of effective and acceptable treatments that can be applied even in situations where specialized mental health workers are scarce, very few patients actually receive these treatments, and better training in the use of the new treatment methods is needed. Sartorius emphasizes that the wide application of treatments of proven value is a public health priority and an ethical obligation.

The value of faster onset of antidepressant action is undoubted; getting patients better more quickly not only is beneficial to the individual and the family but also has a potentially important effect on the societal and economic burden of depressive disorders. Nevertheless, there has been a great degree of skepticism about the whole idea that some antidepressants may work faster than others, given our long-held belief that the delayed onset of action may be directly related to the time span needed for brain receptor systems to adapt their sensitivity to changed circumstances. This belief has persisted despite the evidence that rapid changes in mood can be elicited in depressed patients by sleep deprivation, ECT, certain augmentation strategies, and tryptophan depletion. Pierre Blier, M.D., Ph.D., offers further evidence to debunk this philosophy and demonstrates several ways in which the necessary changes in receptors can be short-circuited. Mirtazapine seems to be a particularly good candidate both as monotherapy and in combination with SSRIs for accelerating the onset of antidepressant response.

Appropriate methodology is available to test the concept in a prospective manner, and Michael E. Thase, M.D., evaluates the various methodologies that have been tried. Survival analyses seem to offer the most sensitive measure of early changes in symptomatology and are easily adapted to take account of that most important criterion of many of the methods: the sustained response. Early response is all very well, but if it is not sustained, then it may represent only a nonspecific reaction to placebo or other conditions of the particular clinical trial. Finally, Andrew A. Nierenberg, M.D., reviews the available evidence for faster onset of action and concludes that substantive evidence exists only for venlafaxine and mirtazapine with respect to the SSRIs. Such action seems also to depend on intrinsic effects on symptoms other than sleep and anxiety, areas of depressive psychopathology for which mirtazapine is particularly and rapidly effective. Thus, in the only head-to-head comparison between venlafaxine and mirtazapine, all improvements in depression ratings, be they mean changes in total depression scores or the percentage of responders and remitters, were numerically in favor of mirtazapine even though none of the differences achieved statistical significance.

In conclusion, we should be treating depressive disorders better, even with the current, somewhat inadequate therapies. We are facing a major public health problem. It is highly likely that some of our current dual-acting antidepressants may exert action faster than the more widely used SSRIs, i.e., we may be able to get more patients into response and remission faster than we are currently achieving. Until new third generation therapies emerge that will satisfy the goals of faster action and greater response, we will have to rely on trying to prove definitively that some antidepressants are indeed better than others in efficacy and then translating the results of clinical trials into everyday therapeutic practice.

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