Norepinephrine and selective norepinephrine reuptake inhibitors in depression and mood disorders: their pivotal roles

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More than 40 years of research through experimental models and in the clinical setting have clearly indicated the importance of the norepinephrine (NE) system in the pathophysiology of depression and mood disorders. Data amassed from basic research and clinical trials of pharmacologic agents have demystified the workings of this system and, most recently, have shown how this system works in concert with other neuronal systems — in particular, the serotonin (5-HT) system — in patients with these complex disorders.

Three specific monoamine neurotransmitters, NE, 5-HT and dopamine, have been linked to depression and mood disorders. Researchers have theorized that one or another of these neurotransmitters is the key to the pathophysiology of these psychologic disorders. Yet, since the 1980s, the field of psychiatry has focused almost exclusively on the 5-HT system to expand knowledge about the pathophysiology of depression and anxiety. This focus paved the way to the "serotonin age" in psychopharmacologic treatment.

Recent clinical evidence promises to level the playing field for the competing theories as to which neuronal system is responsible for the development of depression and mood disorders. This evidence indicates that psychopharmacologic agents with potent effects on NE neurotransmission are highly effective antidepressants. In fact, preclinical research has clearly shown that the 5-HT, NE and dopamine systems interact extensively, and it would be difficult to investigate how a given pharmacologic agent affects one system without considering its influences on the others. For example, NE receptor antagonists directly affect the 5-HT system,[1–3] and selective serotonin reuptake inhibitors (SSRIs) ultimately influence the NE system.[4,5]

In other words, it appears that previous attempts to find a single hypothesis to explain the complex causes of mood and anxiety disorders and their treatment have been relatively simplistic. For a more complete understanding of how to manage these disorders, we need thorough knowledge of the NE system, how pharmacologic agents act within it and how they influence other neurotransmitter systems, such as the 5-HT system. New treatment paradigms are emerging as our knowledge of the interdependence of monoamine neurotransmitters expands and as new research about the role of other biochemical messengers is undertaken. Our growing knowledge of the interconnections among these systems is also helping us to appreciate the importance of tandem behavioural and psychopharmacologic approaches to the treatment of depression, because both can affect the physiology of these systems.

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To bring clinicians up to date on developments in this area, we have produced this supplement to explore current knowledge of the role of depression and antidepressants within the NE system, interactions between the NE, 5-HT and other neuronal systems (see Blier,[6] page S3 and Leonard,[7] page S11) and NE signal pathways in the pathophysiology of depression and mood disorders (see Young,[8] page S17).

In discussing the management of these complex disorders, we will review a variety of health-related quality-of-life (QOL) questionnaires and their applicability in the clinical setting (see Kennedy et al,[9] page S23). The most valuable of these questionnaires have evolved beyond simple symptom-rating scales to become tools for analyzing treatment progression. They allow clinicians to evaluate the short-term and long-term responses to therapy of patients with depression and mood disorders because they are sensitive enough to detect differences in effectiveness among various antidepressants, including the selective NE reuptake inhibitors (NRIs). QOL measures are meant to supplement, not replace, clinical measures by indicating whether the health care intervention has resulted in a satisfying difference in patients' lives — and only the patients can make that assessment.

We will also review current knowledge of selective NRIs, particularly the first drug of this new, more specific generation of psychopharmacologic drugs, reboxetine. Like other selective agents, a selective NRI targets specific receptors — in this case, within the NE system — while ignoring others that may provoke unwanted side effects. Reboxetine's pharmacologic profile differs from that of the nonselective NRIs and rivals those of the SSRIs in terms of safety and efficacy for patients with depression and mood disorders.[10]

We conclude that the NE system, which has been ignored to a certain extent over the past 20 years, is of fundamental importance in the pathophysiology of depression and mood disorders. It should not be overlooked by clinicians seeking to alleviate symptoms in patients with major depressive and some anxiety disorders. Clinicians should be aware that reboxetine and other novel antidepressants acting on the NE system represent a valid, safe and efficacious therapeutic choice in the treatment of these disorders.

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