The Role of the Serotonergic and Noradrenergic Neurotransmitter Systems in the Treatment of Psychological and Physical Symptoms of Depression

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Major depressive disorder is a medical condition that includes abnormalities of affect and mood, cognition, and physical functioning. In particular, as many as 76% of patients suffering from depression are found to report somatic symptoms, including various types of pain such as headaches, stomach pain, back pain, and vague, poorly localized pain. Although the pathophysiology of depression is still unknown, there is significant evidence for abnormalities of the norepinephrine (NE) and serotonin (5-HT) neurotransmitter systems in depressive disorders. Interestingly, both 5-HT and NE also appear to exert analgesic effects via descending pain pathways and therefore play a modulating role in pain. There are many effective antidepressant treatments available. However, residual symptoms are relatively common, among both partial responders and responders without remission. A recent study from our group has shown that responders who have not achieved remission have significantly more somatic symptoms than remitters following 8 weeks of treatment with fluoxetine. These data may suggest that antidepressants that are particularly effective in the treatment of pain and painful physical symptoms may yield higher remission rates in major depressive disorder.

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Major depressive disorder (MDD) is a medical condition that includes abnormalities of affect and mood, cognition (such as inappropriate guilt and feelings of worthlessness), and physical functioning (such as fatigue, appetite and sleep disturbances, and painful physical symptoms). In particular, as many as 76% of patients suffering from depression report somatic symptoms, including various types of pain such as headaches, stomach pain, back pain, and vague, poorly localized pain.[1,2] Although the biological basis of MDD is still uncertain, monoamines, such as serotonin (5-HT) and norepinephrine (NE), have been the primary focus of many etiological theories of MDD.

NEUROTRANSMITTER SYSTEMS

In particular, the putative role of 5-HT in MDD has been extensively studied, partly because of the broad therapeutic effects in depression of drugs such as the selective serotonin reuptake inhibitors (SSRIs). While some, but not all, studies show reduced endocrine responses to indirect or direct 5-HT agonists in MDD,[3] neuroendocrine studies in depression generally show evidence of impaired 5-HT function in the brain, but it is disputed whether or not this impairment resolves with clinical recovery.[4] A recent study used the endocrine response to the SSRI citalopram to study brain 5-HT function in acute and recovered depressed subjects relative to healthy controls. Prolactin responses to citalopram were blunted similarly in both acutely depressed and recovered subjects, while cortisol responses were blunted in acutely depressed patients but not in recovered subjects.[4] These data support the view that some aspects of impaired 5-HT neurotransmission may be trait markers of vulnerability to depression, with the normalization of the cortisol response to citalopram perhaps indicating resolution of hypothalamic-pituitary-adrenal axis dysfunction. Postmortem studies have also shown both an increase in the density of serotonin 5-HT_2 receptor binding sites and a decreased number of serotonin 5-HT transporter binding sites in brain tissue of depressed patients and suicide victims,[5] as well as an increase in the serotonin 5-HT_{1A} autoreceptors in the midbrain dorsal raphe of suicide victims with major depression.[6] This postmortem evidence for decreased serotonergic activity in MDD is further supported by the results of recent imaging studies that have shown widespread reductions in serotonin 5-HT_{1A} autoreceptor binding with positron emission

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tomography[7] and a reduction in the density of brain serotonin transporter binding sites among depressed patients with single photon emission computed tomography.[8]

Similarly, NE neurotransmission dysregulations have been identified in patients with MDD. Postmortem studies have shown a selective increase in the high-affinity conformation of the brain α_{2A}-adrenoceptors as well as decreased binding to NE transporters in the locus ceruleus of depressed patients.[9] The latter finding was interpreted as suggesting a compensatory down-regulation of this transporter protein in response to an insufficient availability of NE at the synaptic level.[9] Using catheters placed in an internal jugular vein, Lambert et al.[10] estimated the release of NE neurotransmitters at rest and following intravenous desipramine hydrochloride in 19 healthy volunteers and in 9 patients with nonbipolar depressive illness refractory to medication. The brains of these patients exhibited reduced venoarterial NE, with a normalization in NE turnover following pharmacologic blockade of the NE transporter with desipramine. A recent review by Blier[11] underlines that many overlaps exist in the effects of NE and 5-HT and that the complex behavioral patterns of depression may reflect interactions between these 2 neurotransmitter systems, with the projections of 5-HT neurons having an inhibitory effect on NE neurons. Another review by Ressler and Nemeroff[12] concludes that there is abundant evidence for abnormalities of the NE and 5-HT neurotransmitter systems in depressive disorders, with the perturbation of these systems modulating and being modulated by other neurobiological systems that, in turn, are likely to mediate symptoms of depression.

As discussed by Fava and Kendler[3] in their recent review of the literature, available data on the neurobiology of depression seem to suggest that a single neurobiological explanation for depression may not be realistic and that multiple neurotransmitter systems (i.e., 5-HT, NE) and intracellular signaling pathways are most likely affected in MDD.

TREATMENT OF MAJOR DEPRESSIVE DISORDER

Several treatment approaches to MDD have been found to be effective in randomized clinical trials. These approaches include psychotherapy, antidepressant medications, and electroconvulsive treatment (ECT). The use of ECT typically generates response rates that tend to be higher than any other treatment, but its present use is mostly limited to patients with MDD who are either highly resistant to treatment or psychotic. In the realm of psychotherapy, 2 types of time-limited psychotherapy have been shown to be effective in treating MDD, interpersonal psychotherapy and cognitive therapy.[13] Antidepressant drugs have typically been classified on the basis of their effects on the neuronal synapses, such as the blockade of the reuptake of neurotransmitters, the blockade of certain neurotransmitter receptors, or the inhibition of the monoamine oxidase enzymes. The only exception is the tricyclic antidepressant (TCA) group, which is identified on the basis of its distinctive chemical structure. The first antidepressant drugs marketed in both the United States and Europe were the monoamine oxidase inhibitors (MAOIs) and the TCAs. The latter group of drugs was known to have relatively higher NE reuptake inhibiting activity (such as in the case of the secondary amine TCAs—desipramine and nortriptyline) or to have more of a mixed effect on the uptake of 5-HT and NE, although still predominantly noradrenergic (such as in the case of the tertiary amine TCAs—amitriptyline and imipramine). The only exception to this rule is clomipramine, which is predominantly a serotonergic TCA. TCAs also block several neurotransmitter receptors, raising issues of tolerability because of significant anticholinergic effects and sedation/weight gain (presumably related to histamine H_1 receptor blockade). Among the drugs in which the main pharmacologic effect is the reuptake of neurotransmitters, the relative selectivity for a particular system led to the development of both SSRIs, such as fluoxetine, sertraline, citalopram, and paroxetine, and serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine. Some antidepressants have been classified primarily for blocking serotonin 5-HT_2 receptors (i.e., nefazodone, trazodone), others for blocking α_2 autoreceptors and heteroreceptors as well as serotonin 5-HT_2 and 5-HT_3 receptors (i.e., mirtazapine). Finally, bupropion is considered to affect both dopamine and NE neurotransmission.

Despite the availability of effective treatments, psychiatrists are still faced with the dilemma that MDD is widely undertreated and that only approximately 50% of all MDD outpatients initially exposed to either a time-limited psychotherapy targeted for depression or a single antidepressant medication respond to treatment. The remaining 50% continue to experience symptoms and remain functionally impaired after initial treatment.[14] This large percentage of initial nonresponders and partial responders presents a significant challenge to clinicians, who must seek additional therapeutic measures for many of their patients in order to achieve remission.[15–17] These next-step treatment approaches, employed after the patient does not initially respond adequately to antidepressants, have not been studied in any systematic fashion (although there are controlled clinical trials of certain treatment strategies such as lithium augmentation of antidepressants) and are the focus of an ongoing National Institute of Mental Health (NIMH) multicenter study (Sequenced Treatment Alternatives to Relieve Depression [STAR*D]) that involves the enrollment and 12-month follow-up of over 4000 patients with MDD.[18]

Even among responders, residual symptoms are common,[19] and the term *response without remission* has been used to describe this clinical phenomenon. As shown in

the review by Nierenberg and Wright,[20] many depressed patients improve but fail to achieve full remission with antidepressant treatment and continue to have residual symptoms, which cause distress and dysfunction and confer a greater risk of relapse and recurrence compared with patients who become symptom-free. These investigators conclude that clinical trials of antidepressants have shown that some dual-acting antidepressants (e.g., SNRIs, clomipramine) may have higher remission rates and fewer residual symptoms than SSRIs.

Given that residual symptoms following antidepressant treatment are relatively common, as a result of either partial response or response without remission, it is important that we, as clinicians, assess systematically both psychological and physical symptoms. Many patients with MDD who have improved significantly with treatment may still be suffering from psychological and somatic symptoms. For example, our recent study[21] showed that responders (50% or greater reduction in depressive symptoms) who have not achieved remission have significantly more somatic symptoms than remitters following 8 weeks of treatment with fluoxetine. These data may suggest that antidepressants that are particularly effective in the treatment of painful physical symptoms may yield higher remission rates in patients with MDD. In fact, we have raised the question[22] as to whether, in the event the treatment of somatic symptoms with an antidepressant renders patients pain-free and/or achieves a significant reduction in aches and pains, the physical and somatic symptom improvement will bring about a more rapid and perhaps more robust improvement in depression. Future studies are needed to elucidate this relationship between the treatment of somatic symptoms and remission to determine whether treatments that are particularly effective with respect to somatic symptoms lead to greater rates of remission of MDD. There is a large body of clinical experience using TCAs in the treatment of chronic pain; TCAs appear to have greater analgesic efficacy than SSRIs.[23–26] TCAs inhibit NE and 5-HT reuptake, which may enhance the activity of the neuronal network implicated in the diffuse noxious inhibitory controls.[27]

In a review of the literature of antidepressants in persistent pain, Sindrup and Jensen[26] conclude that TCAs with both NE and 5-HT inhibition (e.g., amitriptyline) are more effective than noradrenergic TCAs (e.g., desipramine) in providing pain relief. Thus, pain control may require a combination of serotonergic and noradrenergic inhibition. This is consistent with data indicating that both 5-HT and NE exert analgesic effects via descending pain pathways.[28–30] This finding may also explain the increased efficacy of TCAs, compared with SSRIs, in providing pain relief, as reported by some studies.[31] It can also explain the recently reported success of the SNRI duloxetine in treating both depression and painful physical symptoms among depressed patients[32] and of venlafaxine, another SNRI, in treating neuropathic pain.[33] Mirtazapine, a histamine H_1 receptor blocker with dual effects on 5-HT and NE, was also reported recently to be efficacious in pain syndromes among cancer patients.[34]

In summary, there is some evidence of a shared neurotransmitter brain/body connection that may account for the relatively greater efficacy of antidepressant drugs affecting both 5-HT and NE in the treatment of psychological and physical symptoms of depression.

Drug names: amitriptyline (Elavil, Endep, and others), bupropion (Wellbutrin and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Aventyl and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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