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Can Long-Term Antidepressant Use Be Depressogenic?

Sir: We appreciated the thoughtful review on the loss of antidepressant efficacy by Byrne and Rothschild.[1] We would like to put forward another possible explanation for the observation: long-term antidepressant use may be depressogenic. While this idea seems counterintuitive, there are reasons to seriously consider it. It has become clear that long-term use of antidepressants may destabilize patients with bipolar illness and give rise to dysphoric mixed states or rapid cycling,[2–4] despite the fact that the initial effect of antidepressants in these subjects is therapeutically antidepressant.[4]

It is not uncommon for the chronic effect of a drug to be different from the initial effect. The best psychiatric example is that of the classic antipsychotics. The acute motoric effect of these drugs is bradykinetic (parkinsonism), but the chronic effect is hyperkinetic (tardive dyskinetic choreoathetoid movements).[5] It has been postulated that a neuroleptic-induced increase in the number of synapses or perforated synapses[6,7] may underlie this change. Similarly, neuronal sprouting of serotonergic neurons in the simple nervous system of snails can be modified with long-term alteration of serotonin concentrations,[8,9] raising the possibility that antidepressant agents may cause neuroplastic changes. In other words, it is possible that antidepressant agents modify the hardwiring of neuronal synapses not only to render antidepressants ineffective but also to induce a resident, refractory depressive state. Although this proposal is purely speculative, the possibility needs to be considered.

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Drs. Rothschild and Byrne Reply

Sir: We appreciate the comments of Dr. El-Mallakh and colleagues regarding our article[1] on the loss of antidepressant efficacy during maintenance therapy and their interesting suggestion that long-term antidepressant treatment may itself be depressogenic. In our article, we did offer this as one of several possible explanations for the phenomenon of loss of antidepressant efficacy. A change in the depressive disease due to medication therapy may be secondary to decreased dopaminergic tone owing to direct or indirect antidopaminergic effects of the antidepressant[2] or long-term changes in neurotransmitter systems, analogous to the changes by which antidepressants may destabilize patients with bipolar disorder. In addition, as was discussed in our article, tricyclic antidepressants may shorten the time between recurrences in unipolar depressive illness as well as in bipolar disorder.[3] We also speculated that the long-term use of antidepressants could cause the depletion of one or more effector or precursor substances. For example, serotonin reuptake inhibition, by increasing extrasynaptic serotonin levels, could in theory cause a depletion of tryptophan in the brain by down-regulating the mechanism by which tryptophan is transported across the blood-brain barrier. Another example, as pointed out by Dr. El-Mallakh and colleagues, is that the neuronal sprouting of serotonergic neurons in the central nervous system of snails can be modified with long-term alteration of serotonin concentrations.[4,5]

We agree with Dr. El-Mallakh and colleagues that the hypothesis that antidepressants may be depressogenic is speculative. We have not observed the phenomenon of antidepressant tachyphylaxis ("poop-out") to be a permanent or refractory state. In fact, there are many strategies discussed in our article[1] that are effective for treating a loss of antidepressant efficacy. One of these strategies, raising the dose of the antidepressant, is by far the most popular strategy[6] and has been reported to produce full remission in 67% of patients who experience loss of antidepressant efficacy during fluoxetine treatment.[7] If long-term treatment with antidepressants were depressogenic, one would expect that raising the dose of the antidepressant would make the patient worse, not better. Finally, as we discussed in our article, the clinical presentation of loss of antide-

pressant efficacy often differs from the initial presentation of the depressive syndrome, with depressed mood, apathy, and fatigue returning, but not the vegetative symptoms of depression. Clearly, further studies are needed to ascertain the rate of loss of antidepressant efficacy during maintenance treatment, whether it occurs more often with a particular type of antidepressant, and whether there are particular patients who are more at risk for the occurrence of loss of efficacy.

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Environmental Factors in Panic Disorder

Sir: Recently, mental health professionals in the Anxiety and Depression Clinic at Montefiore Medical Center, New York, noticed that a substantial subgroup of patients with panic disorder described hot weather and humidity as potential triggers of panic attacks. Since these findings raised important questions concerning the role of environmental factors in panic disorder, Montefiore clinicians developed a questionnaire to systematically evaluate the prevalence of hot weather, humidity, and various other conditions as catalysts for panic attacks. The questionnaire asked patients to rate on a scale from 0 to 3 whether panic was triggered or worsened by such conditions (0 = never, 1 = sometimes, 2 = most of the time, and 3 = always). Patients (N = 154) participated by completing the questionnaire and undergoing a semistructured interview to establish a DSM-IV diagnosis of panic disorder.

After review of the data, some patterns became quite evident. Over 53% of patients endorsed that humidity either caused or worsened panic attacks at least some of the time. Moreover, 65% responded that hot weather also had such an effect. While these findings are only preliminary, they clearly reinforce the notion that humidity and hot weather are important environmental factors in panic disorder. Two recent articles[1,2] support such a conclusion, yet no study has ever systematically assessed the prevalence of hot weather and humidity as environmental factors in panic attacks. Furthermore, it is unclear whether such conditions are specific or nonspecific anxiogenic stressors. Regarding the latter, heat stress can induce autonomic arousal, resulting in symptoms such as increased heart rate and sweating,[3] which may precipitate a panic attack in panic disorder patients who tend to be overly sensitive to visceral cues.

In addition to hot weather and humidity, other environmental factors such as organic solvents and gases have been reported to induce panic attacks in patients with multiple chemical sensitivity syndrome, which is a controversial syndrome and may represent a subgroup of panic disorder.[4]

Certainly, our findings may have a number of important clinical implications. First, mental health professionals should be advised as to the potential association that apparently exists between environmental factors and panic attacks. Such an awareness serves to lend credence to patient accounts that incorporate environmental conditions. Second, and more importantly, the findings present a potentially viable treatment strategy in managing panic attacks in environmentally dependent patient subgroups. In many patients who are adversely affected by hot weather and humidity, a cool, climate-controlled area is frequently able to subdue or alleviate attacks. To this end, clinicians could advise patients to properly moderate temperature in their home environment. In extreme cases, relocation to a suitable environment may be advisable. However, regardless of application, the findings suggest a new, optimistic avenue in the continuing fight against panic disorder.

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