Rational Treatment of Panic Disorder with Antidepressants

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Rational treatment of panic disorders with antidepressants rests on decisions of drug choice, dosage, and duration of treatment. In this paper, we selectively review the author's research with the standard antidepressant, imipramine, in the treatment of panic disorder with agoraphobia as it relates to practical issues. We develop general guidelines for treatment, suggest researchable ways of increasing the net effectiveness of treatment with this class of drugs, and discuss limited generalizations to the extant literature on selective serotonin reuptake inhibitors in panic disorders.

\textbf{KEY WORDS:} Imipramine; selective serotonin reuptake inhibitors; panic disorder; agoraphobia; maintenance therapy.

\textbf{INTRODUCTION}

Despite clinical and phenomenological differences among the discrete types of anxiety disorders classified in the Diagnostic and Statistical Manual (DSM-IV) (1), these disorders may represent different levels of complexity, severity, and duration of the same basic process of the anticipation of threat. Supporting this is the observation that there is considerable overlap in the symptoms of panic disorder, agoraphobia, generalized anxiety disorder, phobias, and obsessive-compulsive disorder. Panic disorder with agoraphobia, for example, may be a prototypical anxiety disorder that encompasses chronic/generalized anxiety, panic attacks, and phobic avoidance. This article will focus first on the empirical basis for the short- and long-term treatment of panic disorder with agoraphobia based on the standard antidepressant, imipramine. Subsequently, we will consider the extent to which these findings may generalize to other antidepressants and to panic disorder without agoraphobia.

\textbf{LONGITUDINAL TREATMENT ISSUES}

It is important to raise some conceptual issues regarding long-term treatment before presenting the empirical findings. The first such issue is that frequently published naturalistic follow-up studies do not shed light on treatment issues because of many methodological shortcomings. Naturalistic follow-up studies, may, however, reflect on the course of illness, and/or current practice conditions, which seem to be characterized by frequent interruptions and resumptions (2). In the case of practice conditions, the state of affairs seems very dismal. A study by Goisman et al. (3) shows that the probability of remission within 1 year for panic disorder with agoraphobia is between 15 and 24%, and that of these, 37% relapse subsequently, despite the fact that the vast majority of patients were receiving drug treatment and that three out of four of them were receiving psychological interventions. An example of misleading conclusions from naturalistic follow up studies is that despite ongoing pharmacotherapy, nearly 80% of patients who entered remission with combined treat-
ment and who continued their pharmacological treatment relapsed within a 2-year period (4).

There are two long-term treatment issues that relate specifically to clinical practice. The first is that of the long-term or enduring effects of acute treatment which are tested experimentally using discontinuation studies that assess the risk of relapse after discontinuation of acute treatment. The second is that of the long-term treatment, or maintenance treatment, effects which are experimentally studied with maintenance studies to assess the prophylactic or protective effects of long-term treatment. These are in fact, two sides of the same coin and are best-studied in controlled discontinuation/maintenance studies.

Unlike disorders such as major depression, panic disorders are chronic and fluctuating rather than episodic (5). Definitions that apply to episodic disorders (e.g., recovery, recurrence) are not as readily applicable to panic disorder. What constitutes a full syndromal expression of panic disorder is not delineated, which is further confounded by the current tendency in treatment outcome studies to group patients having panic disorder with agoraphobia together with patients who have panic disorder without agoraphobia.

Despite difficulties in applying to panic disorder the familiar definitions and qualifiers from other disorders, we can have an operationalized definition of what is response in panic disorder. Response can be defined as an improvement of significant magnitude and/or minimal or absent symptoms. What is required of individual researchers is a clear characterization of the sample and of the relevant symptom domains. Such an operationalized definition of response was validated and consistently utilized in a series of studies by the author using imipramine in treating panic disorder with agoraphobia and it is to those studies we now turn.

**ACUTE TREATMENT**

The results of a placebo-controlled, randomized, multidose study of imipramine in patients with panic disorder with agoraphobia but without significant dysphoria or depression and without concurrent exposure instructions were reported by Mavissakalian and Perel (6). The dose-response findings are summarized in Figs. 1 and 2 using the composite index of end-state functioning (ESF) that was also used to identify responders. Responders were operationally defined as those patients who had achieved response simultaneously on six of seven key outcome measures (ESF score ≥ 6) as evidenced either by reductions of 50% or more from pretreatment or by scores that signified minimal or absent symptoms on clinician and patient ratings of panic and phobic anxiety and avoidance [see Mavissakalian and Perel (7) for detailed descriptions of the seven outcome measures]. Analysis of variances followed by pairwise comparisons of week 8 ESF scores revealed significant over-