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The Relative Efficacy of Buspirone, Imipramine and Placebo in Panic Disorder: A Preliminary Report

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SHEEHAN, D. V., A. B. RAJ, K. H. SHEEHAN AND S. SOTO. *The relative efficacy of buspirone, imipramine and placebo in panic disorder: A preliminary report.* PHARMACOL BIOCHEM BEHAV **29**(4) 815–817, 1988.—There is a need for safe effective alternatives to benzodiazepines in the treatment of panic disorder. Buspirone, a new nonbenzodiazepine anxiolytic, is compared to imipramine and placebo in the treatment of panic disorder in an 8 week double-blind controlled study of 52 randomly assigned patients. Weekly assessments were made using the Hamilton Anxiety Scale, the Sheehan Clinician Rated Anxiety Scale, the Sheehan Patient Rated Anxiety Scale, the Phobia Scale, the Disability Scale, the Hamilton Depression Scale, the Montgomery Asberg Depression Scale, the Investigator Rated Global Improvement Scale and the Patient Rated Global Improvement Scale. Preliminary results of repeated measures Anovas are reported. Imipramine was superior to placebo on many of the outcome measures. Imipramine was superior to buspirone on the Patient Rated Global Improvement Scale and on the Investigator Rated Global Improvement Scale, but not on other measures. Although buspirone appeared to be more effective than placebo, differences were not statistically significant. Some buspirone patients did very well compared to others, suggesting a possible bimodal distribution of response. Patients on buspirone had fewer and less disruptive side effects than those on imipramine.

Panic disorder Anxiety Buspirone Imipramine Placebo Benzodiazepine

RECENT observations that alprazolam and clonazepam are effective in the treatment of panic disorder has stimulated considerable research interest in the use of benzodiazepines and other mild anxiolytic drugs for the treatment on this disorder. Although it is possible that other benzodiazepines are effective in panic disorder if given in adequate doses, the disadvantages of these drugs in producing sedation, ataxia, significant withdrawal effects and potentiation with alcohol are well known. There is a need for new antipanic drugs that will deliver the same antipanic effect without these disadvantages. This prompted us to study buspirone, a new nonbenzodiazepine anxiolytic in the treatment of panic disorder.

Buspirone belongs to a new class of psychotropic drugs—the azaspirodecanediones [25]. Its pharmacologic profile differs in several ways from that of the benzodiazepines [19]. It does not interact with benzodiazepine or gamma-aminobutyric acid receptors, like benzodiazepines [19]. It shows little activity at alpha adrenergic, cholinergic, histaminergic, picrotoxic, calcium channel, amine uptake, or opiate receptor sites [7,22]. Unlike the benzodiazepines, buspirone is active primarily at the serotonergic and presynaptic dopaminergic receptor sites [7,22]. Like the benzodiazepines, it reduces serotonergic activity in the dorsal raphe [22]. Buspirone enhances nonadrenergic activity on the locus coeruleus and dopaminergic activity in the substantia nigra-c, whereas benzodiazepines depress both [22]. Its mechanism of anxiolytic activity remains uncertain [6,22].

Like the benzodiazepines, buspirone has anticonflict [7, 12, 19, 24] antiaggressive [7, 19, 23] and anti-conditioned avoidance response activity in animals [7]. Unlike benzodiazepines, it has no significant anticonvulsant properties [7,19], does not produce muscle relaxation [19], sedative hypnotic effects [18], nor does it show potential for physical dependence, or abuse in animals [1,19] or humans [5,11]. It does not interact significantly with CNS depressants such as alcohol [14,15]. In contrast to benzodiazepines, it shows no significant impairment of psychomotor or cognitive skills [2, 14, 15, 21] in normal subjects. Abrupt discontinuation of buspirone is not associated with typical anxiolytic withdrawal effects in animals [19] or humans [13]. It shows no euphoriant or stimulating properties compared to placebo in humans [5].

In outpatients with generalized anxiety disorder (GAD), double blind studies have found buspirone to be as effective as diazepam [8, 9, 20] and chlorazepate [3,10], lorazepam and alprazolam [4], while being better tolerated and producing significantly less sedation [3, 4, 8–10, 16, 17].

The DSMIII considers panic disorder to be different from and more severe than generalized anxiety disorder. There have been no studies investigating the efficacy of a nonbenzodiazepine anxiolytic in the treatment of panic disorder. We conducted a double blind placebo controlled study of 55 patients comparing buspirone, imipramine and placebo over eight weeks of active drug treatment. The impact of these drugs on the various dimensions of this disorder were studied in detail.

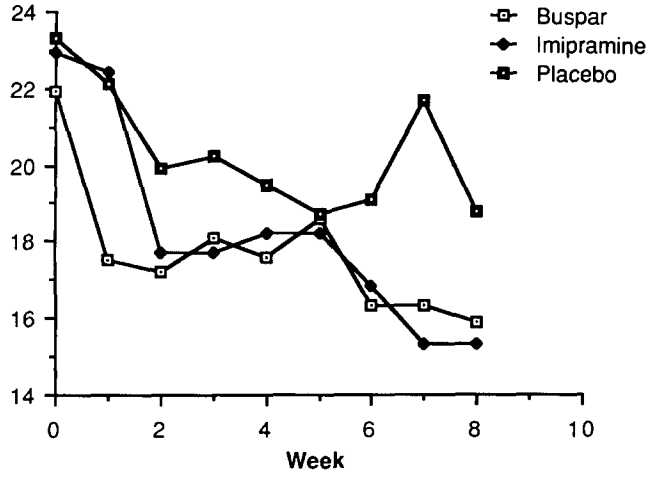

FIG. 1. Hamilton Anxiety Scores. There were two dropouts in the buspirone group and one dropout in the imipramine group.

Of the 52 patients who completed the study 37 were female and 15 were male. The mean age was 35.2 years, mean duration of illness 11 years and mean age of onset 24.9 years. A majority (73%) had had prior drug treatment.

Previous studies suggest that panic disorder required higher doses of anxiolytics for satisfactory efficacy than did generalized anxiety disorder. The highest dose of buspirone used in generalized anxiety studies was 60 mg/day with most patients getting benefit at approximately 30 mg/day. In this study we used a maximum of 60 mg/day of buspirone. The mean doses at the end of the study for buspirone patients was 57.2 mg/day, and for imipramine patients was 291.7 mg/day.

Weekly assessments were made using the Hamilton Anxiety Scale, the Sheehan Clinician Rated Anxiety Scale (SCRAS), the Sheehan Patient Rated Anxiety Scale (SPRAS), the Phobia Scale, Disability Scale, Hamilton Depression Scale, Montgomery Asberg Depression Scale, Investigator Rated Global Improvement Scale and Patient Rated Global Improvement Scale.

Repeated measures analysis of variance was used to examine efficacy. Preliminary results indicate that imipramine (dose range 10–60 mg/day) was superior to buspirone (dose range 10–60 mg/day) and placebo ($p=<0.05$) on the Patient Rated Global Improvement Scale and on the Investigator Rated Global Improvement Scale. Imipramine was superior to placebo, but not buspirone, on the number of unexpected panic attacks, the Hamilton Anxiety Scale, and the SCL-90 (Anxiety factor). Although buspirone appeared to occupy an intermediate position between placebo and imipramine on most of the outcome measures, it was not statistically superior to placebo (Fig. 1). There was some evidence for a bimodal distribution of response in the buspirone group. Patients who responded well to buspirone tended to be female, older, to have a later onset of illness, lower baseline anxiety scores, and were less likely than buspirone non-responders to report a history of use of benzodiazepines in the week prior to placebo washout. Although buspirone did not appear to demonstrate superior antipanic effects, it was considerably less disruptive than imipramine in terms of its side effect profile.

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