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Brief Report

# ONDANSETRON IN THE TREATMENT OF PANIC DISORDER

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## INTRODUCTION

Medications with efficacy in treatment of panic disorder each have drawbacks, including discontinuation difficulties for benzodiazepines (Fyer et al., 1987), weight gain during maintenance treatment with tricyclic antidepressants (Noyes et al., 1989), and early activation symptoms with serotonin reuptake inhibitors and tricyclic antidepressants (Gorman et al., 1987; Noyes et al., 1989). Ondansetron is a highly potent and selective competitive antagonist at serotonin receptors of the $5HT_3$ type (Butler et al., 1988). Although marketed in the United State for the treatment of nausea, ondansetron also has been shown to reduce symptoms of anxiety in animal models (Stefanski et al., 1992). It does not impair psychomotor performance (Hall and Ceuppens, 1991) and appears to have low potential for abuse. Ondansetron's different mechanism of action suggests it could be a useful addition to existing panic disorder medication options, if proven effective and well-tolerated. The purpose of this study was to pilot test the safety and efficacy of oral ondansetron in the treatment of panic disorder.

## METHODS

This study was conducted at two anxiety disorders clinics. All patients entering the trial met DSM-III-R criteria for panic disorder with or without agoraphobia by the Structured Clinical Interview for DSM-III-R-Patient Version (SCID-P; Spiter et al., 1989) and had experienced at least one panic attack in each of the 4 prior weeks. Patients were age 18 years or older and were free of major medical illnesses. Women were postmenopausal or had been surgically sterilized. Patients with current DSM-III-R major depressive disorder, obsessive-compulsive disorder, or eating disorders, any history of psychosis, organic mental disorders, mental retardation, bipolar disorder, or severe personality disorders, or history of drug or alcohol abuse in the prior 6 months were excluded. Regular use of psychoactive medication except chloral hydrate was prohibited within 2 weeks of the study entry, and use of fluoxetine was prohibited within 4 weeks of the study entry. Subjects consented to participate after study procedures and possible benefits and adverse effects were explained.

Patients were instructed to enter phobic situations as tolerated, but no systematic exposure instructions were given. Because anti-panic dosage for ondansetron had not been previously established, dose was increased at 4-week intervals to allow some assessment of response at the lower doses. Dosage could be decreased as clinically necessary to reduce adverse effects. For the first 26 patients entered, treatment was initiated with ondansetron 0.25 mg BID for 4 weeks, then increased for nonresponders to 0.5 mg BID for 4 weeks and 1.0 mg BID for the final 4 weeks. Because the lower doses appeared well-tolerated but ineffective for many patients, for the final 5 patients entered, dosage was escalated every 2 weeks instead of every 4 weeks. Patients who were not very much improved after 12 weeks of treatment, or who had received less than 4 weeks treatment at the maximum dose, were permitted to continue ondansetron for up to 4 additional weeks to effect an adequate trial at the maximum dose. Responders were defined by a score of 1 or 2 (much improved to very much improved) on the Clinical Global Impression (CGI) scale (Guy, 1976) at last observation. Other primary outcome measures, in accord

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with panic disorder standards (Shear and Maser, 1994), assessed panic attack frequency and severity, anticipatory anxiety, agoraphobia, overall illness severity, and functional impairment.

For the primary analysis, on the intent-to-treat sample, paired t-tests were used to compare baseline and last observation scores, with last observations carried forward for patients who left the study early. Repeated measures analysis of variance (ANOVA) could not be used due to many missing data points for drop-outs. For a secondary analysis of completers only, ANOVA was used to assess change over time (weeks 0, 4, 8 and 12) with t-tests to assess change between pairs of weeks. All t-tests were two-tailed. Because of the possibility of type I error when multiple comparisons are made, findings significant at the $p < .05$ level here require confirmation and should be interpreted as hypothesis-generating.

## RESULTS

Thirty-one patients entered the study, including 21 (68%) with panic disorder with agoraphobia. Twelve patients (39%) were women. Sites 1 and 2 entered 19 and 12 patients, respectively, and sites did not differ significantly in regard to patients' demographic characteristics. Twenty-five patients were Caucasian, 3 were African-American, and 3 were Hispanic. Mean age was 41.3 ± 12.4 years (range 26–64). Sixteen patients completed the full 12 weeks of treatment, and for 10 patients who had dosage increase delayed due to adverse effects, the protocol was extended up to 4 additional weeks. Among the 15 patients who did not complete the protocol, 10 dropped out during the first 4 weeks. Five dropped out due to adverse effects, 2 due to lack of efficacy, 5 were withdrawn administratively (due to missed visits, patient's fear of drug interaction with antibiotics, moving out of state, refusal to take pills twice a day, withdrawal of consent after the first visit), and reason was unknown for 3.

Fifteen patients (48%) were responders: 9 (29%) were very much improved and 6 (19%) were much improved on the CGI. Sixteen were panic-free during their last week of treatment. Among the 16 patients who completed at least 12 weeks of treatment, 13 (81%) were responders: 7 (44%) were very much improved and 6 (38%) were much improved. Eleven (69%) of the completers were panic-free.

Other results on major outcome variables for the intent-to-treat analysis are shown in Table 1. There was also significant change on all subscales of the Fear Questionnaire, and the Hopkins Symptoms Checklist-90R (Derogatis, 1977). The secondary analysis of completers by repeated measures ANOVA showed significant improvement on all measures except for frequency of anticipatory anxiety (data available from author). Among completers, significant improvement occurred on most outcome measures between treatment weeks 0 and 4 at the 0.5 mg per day dose. There was further improvement, however, throughout the study.

Among the 5 patients treated with the more rapid dose escalation, 2 were very much improved, 2 were much improved, and 1 was minimally improved at last observation. Three were panic-free. One was consistently rated a responder after 1 week and 3 others were rated responders after 6 weeks.

Among the 10 patients whose treatment was extended 1–4 weeks beyond week 12, only 3 had changes in the CGI change scores from week 12 to endpoint: one went from much to very much improved, one from very much to much improved, and one from much to minimally improved. Treatment outcome did not differ significantly between sites on any measures.

Adverse events spontaneously reported by more than 10% of patients were: indigestion (26%), dizziness (23%), fatigue (23%), headache (19%), constipation (13%), dry mouth (13%), and nausea (13%). Five patients dropped out of the study due to adverse events, including 2 due to lightheadedness, one due to depression, one due to twitching, tremor and diarrhea, and one due to hyperacusis, agitation, lightheadedness, derealization and nausea. Four of the drop-outs due to adverse events occurred during the first 3 weeks, at a dose of 0.25 mg BID, and one occurred after 6 weeks, at a dose of 0.5 mg BID. Adverse events were mild for most patients, and they were most common during the first few weeks of treatment.

## DISCUSSION

The findings suggest that oral ondansetron in doses of 0.5–2.0 mg per day is well-tolerated and may have efficacy in the treatment of panic disorder. The 48% response rate is greater than most published placebo group intent-to-treat response rates in panic disorder, but not beyond the upper limit of placebo response rates. In the absence of a placebo control group it is not possible to attribute the observed improvement to effects of ondansetron, but a recent placebo-controlled study does appear to support ondansetron efficacy in panic disorder (Metz et al., unpublished data).

It is not possible in this trial to distinguish the effects of higher dosage from those of longer duration of treatment in assessing the increasing response over 12 weeks. However, combined with the finding that 4 of the 5 patients with the quicker dose escalation schedule were responders by 6 weeks, it suggests that the higher doses deserve further study. The greater response rate among completers may reflect the attrition of nonresponders which is characteristic of panic disorder studies.

Three measures of panic attack severity improved significantly, although one measure of panic attack frequency did not. Three of 4 measures of anticipatory anxiety improved, as did anxiety sensitivity. In contrast, most measures of agoraphobia and functional impairment/disability did not show significant change. This discrepancy may reflect either a slow rate of im-

**TABLE 1. Mean scores at baseline and post-treatment for all patients[a]**

| Clinician Rating Scales (range of scale) | Baseline | Endpoint | t | df | *p* |
|---|---|---|---|---|---|
| Clinical global impression—Severity (1–7) | 4.3 ± 0.5 | 3.2 ± 1.5 | 4.0 | 29 | <.001 |
| Clinician Panic and Phobic Disorders Scale—Severity (Zitrin et al., 1983) | | | | | |
| Overall (1–7) | 4.4 ± 0.5 | 3.6 ± 1.5 | 2.6 | 25 | <.05 |
| Spontaneous Panic Attacks (1–7) | 4.3 ± 0.9 | 3.2 ± 1.8 | 3.2 | 25 | <.005 |
| Functional Impairment (1–7) | 4.0 ± 0.7 | 3.4 ± 1.4 | 1.8 | 25 | NS[b] |
| Phobic Avoidance (1–7) | 3.7 ± 1.3 | 3.0 ± 1.8 | 2.0 | 25 | NS |
| Anticipatory Anxiety (1–7) | 4.2 ± 1.0 | 3.3 ± 1.6 | 2.1 | 25 | <.05 |
| Panic attack inventory | | | | | |
| Total no. of panic attacks/wk | 3.6 ± 3.0 | 3.0 ± 4.4 | 0.7 | 30 | NS |
| Intensity of panic attacks (0–10) | 3.8 ± 1.9 | 1.7 ± 2.1 | 4.7 | 29 | <.001 |
| Anticipatory anxiety (percent of time present) | 33.9 ± 28.4 | 27.4 ± 27.6 | 1.5 | 29 | NS |
| Intensity of anticipatory anxiety (0–10) | 4.7 ± 2.4 | 3.3 ± 2.5 | 2.8 | 29 | <.05 |
| Hamilton Anxiety Scale (Hamilton, 1959; 0–56) | 18.7 ± 6.8 | 13.5 ± 9.6 | 2.8 | 22 | <.05 |
| **Patient self-rating scales** | **Baseline** | **Endpoint** | **t** | **df** | ***p*** |
| Anxiety Sensitivity Index (Reiss et al., 1986; 0–64) | 28.2 ± 12.4 | 20.2 ± 14.7 | 3.7 | 31 | <.005 |
| Patient Panic and Phobic Disorders Scale—Severity (Zitrin et al., 1983): | | | | | |
| Overall (1–7) | 4.0 ± 1.5 | 3.5 ± 1.5 | 1.5 | 23 | NS |
| Spontaneous panic attacks (1–7) | 4.2 ± 1.5 | 3.2 ± 1.6 | 2.4 | 23 | <.05 |
| Functional impairment (1–7) | 4.2 ± 1.3 | 3.3 ± 1.5 | 2.9 | 23 | <.01 |
| Phobic avoidance (1–7) | 3.9 ± 1.6 | 3.3 ± 1.7 | 1.7 | 23 | NS |
| Anticipatory anxiety (1–7) | 4.3 ± 1.6 | 3.3 ± 1.6 | 3.0 | 23 | <.01 |
| Fear Questionnaire (Marks and Mathews, 1979) | | | | | |
| Agoraphobia (0–40) | 11.1 ± 10.8 | 7.5 ± 10.5 | 2.6 | 30 | <.05 |
| Sheehan Disability Scale (Sheehan, 1983): | | | | | |
| Work (0–10) | 3.8 ± 2.8 | 3.4 ± 3.1 | 0.8 | 23 | NS |
| Social life/leisure (0–10) | 4.3 ± 2.8 | 3.5 ± 3.1 | 1.1 | 23 | NS |
| Family life/home (0–10) | 3.0 ± 2.8 | 2.6 ± 2.7 | 0.6 | 23 | NS |
| Work and social (1–5) | 3.4 ± 1.0 | 3.3 ± 1.3 | 0.3 | 20 | NS |

[a]*Sample size is lower for some scales due to missing data.*
[b]*NS, not significant.*

provement in panic symptoms (due to low starting dosage or delayed effect) with a lag in the secondary improvement of phobia and disability or simply less efficacy for some aspects of the disorder.

Adverse events tended to occur early in treatment, on the lowest dose, and they were usually mild. For the last 5 patients entered, the more rapid biweekly escalation of dose was well-tolerated. It remains unknown whether patients might benefit further from dosage greater than 2 mg/day. Only 2 patients (6.%) dropped out of the study due to symptoms resembling the activation syndrome that has been described in antidepressant treatment of panic. Nevertheless, because of the large number of dropouts for stated reasons other than adverse effects, the tolerability of ondansetron requires further study.

A placebo-controlled trial is necessary to confirm the suggestions of this open label pilot study. Furthermore, because of exclusion of women of childbearing potential due to safety considerations, the generalizability of these findings to more typical clinical samples is uncertain.

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## REFERENCES

Butler A, Hill JM, Ireland SJ, Jordan CC, Tyers MB (1988) Pharmacological properties of GR 38032F, a novel antagonist at 5-$HT_3$ receptors. Br J Pharmacol 94:397–412.

Derogatis LR (1977) SCL-90 Administration, Scoring and Procedures Manual for the Revised Version. Baltimore: Johns Hopkins University School of Medicine.

Fyer AJ, Liebowitz MR, Gorman JM, Campeas R, Levin A, Davies SO, Goetz D, Klein DF (1987) Discontinuation of alprazolam treatment in panic patients. Am J Psychiatry 143:303–308.

Gorman JM, Liebowitz MR, Fyer AJ, Goetz D, Campeas RB, Fyer MR, Davies SO, Klein DF (1987) An open trial of fluoxetine in the treatment of panic attacks. J Clin Psychopharmacol 7:329–332.

Guy W (1976) ECDEU Assessment Manual of Psychopharmacology. Washington, DC: DHEW.

Hall ST, Ceuppens PR (1991) A study to evaluate the effect of ondansetron on psychomotor performance after repeated oral dosing in healthy subjects. Psychopharmacol 104:86–90.

Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50–55.

Marks IM, Mathews AM (1979) Brief standard self-rating scale for phobic patients. Behav Res Ther 14:225–238.

Noyes R Jr, Garvey MJ, Cook BL, Samuelson L (1989) Problems with tricyclic antidepressant use in patients with panic disorder or agoraphobia: Results of a naturalistic follow-up study. J Clin Psychiatry 50:163–169.

Reiss S, Peterson RA, Gursky DM, McNally RJ (1986) Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. Behav Res Ther 24:1–8.

Shear MK, Maser JD (1994) Standardized assessment for panic disorder research. Arch Gen Psychiatry 51:346–354.

Sheehan J (1983) The Anxiety Disease. New York: Harper & Row.

Spitzer RL, Williams JBW, Gibbon M, First MB (1989) Structured Clinical Interview for DSM-III-R—Patient Version (SCID-P). New York: New York State Psychiatric Institute, Biometrics Research.

Stefanski R, Palejko W, Kostowski W, Plaznik A (1992) The comparison of benzodiazepine derivatives and serotonergic agonists and antagonists in two animal models of anxiety. Neuropharmacology 31:1251–1258.

Zitrin CM, Klein DF, Woerner MG, Ross DC (1983) Treatment of phobias. I. Comparison of imipramine and placebo. Arch Gen Psychiatry 40:125–138.