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Adinazolam Sustained-Release Treatment of Panic Disorder: A Double-Blind Study

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Two hundred six outpatients with panic disorder and agoraphobia were randomly assigned to receive 4 weeks of treatment with placebo or sustained-release adinazolam under double-blind conditions. Eighty-eight percent of patients receiving drug and 85% of patients receiving placebo remained in the study at week 4. This report describes the "intent-to-treat" analysis of 202 patients who made at least one follow-up visit after randomization at baseline. On the basis of the Clinical Global Impressions-Improvement Scale, 69.7% of the adinazolam-treated patients were much or very much improved compared with 39.6% of the placebo-treated patients at week 4 or endpoint ($p = 0.0001$). At week 4, panic attacks were completely blocked in 57.1% of adinazolam-treated patients and in 39.2% of the placebo-treated patients ($p = 0.009$). Adinazolam sustained-release treatment was statistically more effective than placebo treatment on measures of global improvement, number of panic attacks, SCL-90 phobia severity, main phobia severity, and anticipatory and general anxiety. No drug-placebo differences were found for overall self-rated phobia severity, unexpected or situational panic attacks, or for work, family, or social disability. (J Clin Psychopharmacol 1994;14:255-263)

PANIC DISORDER with agoraphobia can be treated with several different therapies including tricyclic antidepressants,[1] monoamine oxidase inhibitors,[2] benzodiazepines,[3,4] and nonpharmacologic treatments such as cognitive-behavior therapy and panic control therapy.[5] All of these methods reduce the number of panic attacks, decrease anticipatory anxiety, lessen avoidance behavior, and are efficacious in 65 to 75% of treated patients. It is unlikely that any single treatment will establish dominance over the others, at least in the near future. Because patients might have problems tolerating a treatment, fail to respond to a treatment, or not wish to undertake a particular kind of treatment, it is important that we develop a broad range of therapies.

Adinazolam, a triazolobenzodiazepine, is a dimethylamino analogue of alprazolam. Adinazolam produces effects similar to those of other benzodiazepine anxiolytics and different from those of tricyclic antidepressants in animal models, predictive of anxiolytic effects in humans. Unlike benzodiazepines and similar to tricyclics, however, adinazolam possesses antidepressant activity. The antidepressant effects of adinazolam have been studied in clinical trials for depression with or without melancholia.[6-11] Studies also suggested promising activity for the treatment of panic disorder.[12-14] Early trials for depression used a compressed tablet (CT) formulation, which along with the drug's short half-life, resulted in rapid absorption and frequent dosing intervals. A sustained-release (SR) formulation of adinazolam (adinazolam SR; *Deracyn SR*®; Upjohn

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Company, Kalamazoo, MI) was developed so that medication would be effective when dosed just twice a day. Pilot trials of this SR formulation suggested clinical effectiveness in generalized anxiety and panic disorder.[13, 14] The pharmacokinetic and pharmacodynamic effects of adinazolam have been extensively studied in healthy volunteers. The results of these studies, which are important for our understanding of this drug, will be summarized.

Adinazolam is unlike other triazolobenzodiazepines in that it produces an active metabolite, N-desmethyladinazolam (NDMAD), which is a 25-times more potent benzodiazepine receptor agonist than the parent drug.[15] Extensive first-pass hepatic metabolism occurs, and ultimately, over 95% of adinazolam is converted to NDMAD.[16, 17] There is evidence that NDMAD contributes substantially more than does adinazolam to such side effects as sedation, amnesia, and impaired psychomotor performance in healthy volunteers after single oral and intravenous dosing,[18-20] as well as having a uricosuric effect.[20]

A relationship has been found between the level of NDMAD in plasma and decrements on the digit symbol substitution test, in which the EC_{50} corresponded to a level in plasma of 325 ng/mL.[21] With repeated dosing in elderly subjects, adinazolam and NDMAD exhibited linear pharmacokinetics, no accumulation, and only limited impairment of performance and memory.[22]

The pharmacokinetics and pharmacodynamics of adinazolam SR have recently been studied.[23] Advantages were found, relative to the CT formulation of adinazolam, with respect to lower peak levels of parent drug and NDMAD in plasma, less fluctuation, and attenuated psychomotor and sedative effects. These results suggest a more favorable profile for the SR formulation.

A multicenter, clinical trial of 4 weeks, with up to 22 weeks of extension treatment (The Upjohn Company protocol M/2300/7400) was designed to evaluate the efficacy and safety of adinazolam SR treatment versus placebo treatment in outpatients with panic disorder with agoraphobia. It was hypothesized that adinazolam SR would be more effective than placebo in reducing the total number of panic attacks and in reducing phobic anxiety, thereby producing greater global improvement. Second, we expected adinazolam SR to produce greater reductions than placebo in the amount and severity of anticipatory and generalized anxiety and in the amount of overall disability experienced by the patient.

In this report, we discuss the efficacy of adinazolam SR treatment versus placebo treatment and the associated side effects during the first 4 weeks of evaluation. Other results from this clinical trial, including long-term efficacy and safety, management of treatment discontinuation, predictors of response, and the importance of drug levels in plasma, will be presented in future reports.

Methods

Study design

This was a parallel, double-blind, flexible-dose 4-week efficacy and safety study with patients randomized to receive either adinazolam SR or matching placebo tablets. At the end of 4 weeks of treatment, eligible patients could enter a 22-week extension phase. The study was conducted at four centers: University of California at Davis, Duke University Medical Center, University of Missouri-Columbia, and University of Wisconsin at Madison. Each center had the study approved by the respective institutional review board. All patients signed an informed consent document approved by the institution review board and The Upjohn Company before entering the study. Patients were recruited via advertisements and public presentations by the investigators. Each center was to provide 50 fully assessable patients. Randomized assignment to treatment groups determined that equal numbers of patients received both treatment possibilities.

Patients who met study criteria and who had not responded to 1 week of single-blind placebo run-in treatment were randomized to receive either active medication or placebo at their baseline visit. Patients returned for evaluations at weeks 1, 2, and 4. A treatment extension of 22 weeks was offered to patients who were judged as responders at week 2 or 4. At the end of a patient's participation in the study, the patient was discontinued from the study medication over a 4-week period and monitored for 2 weeks postdiscontinuation.

Inclusion/exclusion criteria

Patients were required to fulfill all of the following conditions: (1) voluntarily sign written informed consent; (2) be within the age range of 18 to 65 years; (3) meet DSM-III-R criteria for panic disorder with agoraphobia and have at least one panic attack per week for each of 4 weeks before baseline (a panic attack consisted of at least four DSM-III-R recognized symptoms within 10 minutes of onset); (4) be able to take oral medication; (5) use adequate contraception if a female of childbearing potential; (6) agree not to participate in psychotherapy/behavior therapy while in the trial; (7) maintain a diary, attend required clinic visits, provide blood samples for laboratory tests, follow directions, read and understand patient-completed forms; and (8) be free of psychoactive medication for at least 14 days before randomization.

Any of the following conditions at baseline excluded

an individual from the study: (1) pregnancy or lactation; (2) history of epilepsy, seizure (except febrile seizures before age 5), or significant head trauma; (3) presence of acute suicidal ideation; (4) diagnosis of major depression, alcoholism, psychoactive substance abuse, drug-induced psychosis, obsessive-compulsive disorder, hypomania, or paranoia within the last 6 months; (5) history of mania, cyclothymia, psychosis, or dementia within the last 2 years; (6) use of α- or β-blockers, unless the patient was stabilized on such an agent for at least 6 months for nonpanic-related reasons; (7) concurrent generalized anxiety disorder; (8) inability to withdraw from any psychoactive drug; (9) distinctly abnormal laboratory values or uncontrolled physical disease, as determined by the investigator; (10) evidence of hypersensitivity, intolerance, or contraindication to any benzodiazepine or lactose; or (11) previous enrollment in the study.

Evaluations

Initial screening was done with the Structured Clinical Interview for DSM-III-R (Upjohn Version), (SCID-UP-R).[24] Potential patients were withdrawn from any previous psychoactive medication following good medical practice. Patients were required to be drugfree for 2 weeks before beginning the placebo run-in phase. Within 28 days before randomization, a physical examination, EKG, serum hematology and chemistry assays, and urinalysis were completed. After completion of the 1-week placebo run-in phase and verification of normal laboratory results, and provided panic attacks continued, eligible patients were randomized to treatment. This constituted the baseline evaluation. Patients were instructed in the use of a daily diary for recording symptoms and tablet counts. No systematic behavior therapy was offered, but patients were advised at baseline that they should make efforts to expose themselves to their feared situations. Efficacy and safety evaluations were performed at weeks 1, 2, and 4 after baseline.

Efficacy measures

This study focused on four primary and three secondary efficacy scales. Each of the scales was divided into a number of efficacy measures. These scales can be divided into either clinician- or patient-rated scales.

Primary efficacy measures: observer-rated scales. (1) The Clinical Global Impressions Scale (CGI)[25] includes severity of illness and improvement ratings. The CGI was used to reflect the severity of a patient's panic disorder and agoraphobia and improvement or worsening on relevant dimensions of functioning. Patients were divided into "responders" (those with CGI-Improvement scores of 1 or 2) or "nonresponders" (those with scores of 3 to 7).

(2) The Sheehan Panic and Anxiety Attack Scale (PAAS)[26] measures the frequency (number in past week), duration (minutes), and intensity (0 to 10, 10 = most intense) of both unexpected and situational panic attacks. It also measures the percentage (of waking hours) and intensity (0 to 10, 10 = most intense) of any anticipatory anxiety. The number of patients with zero panic attacks was prospectively selected as the primary efficacy measure.

Primary efficacy measures: self-rated scales. (3) The Phobia Severity Scale (PSS)[26] represents a modification of the Marks Fear Questionnaire,[27] where up to four main phobias are noted on an intensity scale of 0 to 10 (10 = most intense) and an avoidance scale of 0 to 4 (4 = always avoided). A patient's overall disability due to phobias was also rated as to distress and restriction of activities on a visual analog scale of 0 to 10 (10 = maximum discomfort). This primary efficacy measure defined a responder as a patient whose overall phobia disability scale score decreased from baseline by two or more points.

(4) The phobic dimension of the Symptom Checklist-90 (SCL-90)[28] consists of seven items from the SCL-90. Patients rated themselves on a five-point intensity scale for each question. Treatment response was based on a reduction in score of 50% or more relative to baseline.

Secondary efficacy measures: observer-rated scales. (1) The Hamilton Rating Scale for Anxiety[29] provides a total severity score for psychic and somatic symptoms of anxiety and was administered only at baseline and week 4.

(2) The Sheehan Clinician Rated Anxiety Scale (SCRAS)[26] provides a frequency/severity rating of the 13 listed panic attack symptoms in the DSM-III-R. Depersonalization and derealization are split into two separate items; thus, the SCRAS provides a 14-item measure of the 13 DSM-III-R symptoms. Items 15 and 16 provide five-point measures of the frequency and/or severity of situational and unexpected panic attacks during the past week. As such, the SCRAS affords a second measure of panic attack severity, supplementary to the PAAS described above.

Secondary efficacy measures: self-rated scales. (3) The Sheehan Disability Scale[26] measures work, social, and family life disability on three visual analog scales of 0 to 10 (0 = not at all affected, 10 = severely affected).

(4) The main phobia of the PSS was included as a secondary efficacy measure. The patient's main phobia is the phobia reported first on the form. Other listed phobias were not included in this report, because of diminishing endorsement of phobias beyond the first main phobia.

Safety measures

Medical events were recorded by interview (solicited) at each visit. The severity of 35 preselected events was recorded on a four-point scale (none, mild, moderate, severe). A treatment-emergent symptom was defined as an event that occurred for the first time during treatment or worsened, compared with baseline severity, at any visit after baseline.

Medication and dosage

Medication was packaged in individual bottles, sufficient for 1 week's treatment; necessary amounts were dispensed to patients at each visit.

Medication was administered twice a day, starting at one capsule twice daily, and advanced by adding one capsule per day every 3 or 4 days. When there was an odd number of capsules, the larger number was taken in the evening. Doses were advanced until symptoms were abolished or intolerance was experienced. In the event of a medical event, the dose was held constant for a few extra days or reduced to the last tolerated level before again attempting to advance the dose.

The maximum number of capsules was eight per day. Each capsule contained 15 mg of either adinazolam SR or placebo, thus making the allowed maximum dose of active drug 120 mg/day.

Administration of the study

Before the study, planning meetings were held that included investigators, site coordinators, clinical consultants, and the Upjohn clinical staff. These meetings were under the codirection of Carl Lewis, M.D., Ph.D. (Bristol Myers Squibb Company, formerly of The Upjohn Company), and Michael Liebowitz, M.D. (Columbia University, Clinical Project Consultant). Protocol procedures were discussed. Investigators and coordinators received small-group training in the use of the SCID-UP-R. SCID-UP-R training involved interviewing a patient under direct supervision, as well as observing several others conducting supervised interviews. During the study, semiannual collaborative meetings took place, as well as at least one quality assurance visit to each site by Drs. Lewis and Liebowitz. Additional regular monitoring visits took place throughout the study by the Upjohn clinical staff.

Statistical analysis

It was hypothesized that differences in favor of adinazolam SR would be found on the four primary efficacy measures at weeks 1 and 4. Baseline means were compared using analysis of variance with factors of treatment, investigator, and treatment × investigator interaction, in order to determine if groups differed by site or treatment or in their interaction. Response data at weeks 1 and 4 were analyzed by analysis of covariance with two factors (treatment and investigator) and their interaction, with baseline values serving as covariates. Least squares means or model means (± standard error [SE]) are reported; the reported p values are a reflection of these means and standard errors. Analysis of categorical data was performed by means of χ^2 testing. Repeated-measures analysis of variance yielded results similar to those presented, but we elected to report analysis of means adjusted for baseline at each visit as being easier to interpret and most appropriate for a clinical audience.

We present here the results of actual observed scores and the intent-to-treat analysis, i.e., all patients who returned for at least one follow-up visit after baseline. Scores at the patients' last visit were carried forward for patients dropping out prematurely. The text describes only the last observation carried forward data, because the observed data produced essentially similar findings, except in some cases, the degree of statistical significance was not as strong, whereas in others, it was stronger. The results of both analyses are provided in each table. Only one comparison produced a difference that was statistically significant in one instance but not in the other (see below).

Results

Center effects

Analysis at baseline for center, treatment, and center by treatment effects showed statistically significant differences in baseline severity scores according to center for situational panic attack frequency, unexpected panic attack duration from the PAAS, main phobia severity, and overall phobia severity. Only one of these variables, main phobia severity, proved to be associated with a subsequent treatment effect, which favored adinazolam SR at week 4. Neither baseline treatment differences nor center by treatment interactions were observed for any variable. We therefore pooled data from all sites in the analysis.

Demographics

Two hundred six patients were given randomized medication at their baseline visit. Two hundred two patients returned for at least one postbaseline visit and therefore meet intent-to-treat criteria. The adinazolam SR group had 99 intent-to-treat patients, and the placebo group had 103 intent-to-treat patients. The two groups were well matched on demographic variables. Mean ages (± standard deviation [SD]) for adinazolam SR-treated patients and placebo-treated patients were 36.1 ± 10.8 and 35.5 ± 8.9 years, respectively. Of the

patients in the adinazolam SR group, 34% were men and 66% were women. Of the patients in the placebo group, 33% were men and 67% were women. The ethnic composition of the adinazolam SR group was 98.1% white and 1.9% black. The placebo group was 92.2% white, 3.9% black, 2.9% Hispanic, and 1% other. No differences were observed between treatment groups with respect to symptom ratings based on scores from efficacy scales at baseline (Table 1).

Patient disposition

Of the 99 intent-to-treat adinazolam-treated patients, 12 failed to complete 4 weeks of treatment. Of the 103 intent-to-treat placebo-treated patients, 15 failed to complete 4 weeks of treatment. Reasons for withdrawal from the adinazolam SR group were early completion, i.e., responded and dropped out before week 4 (N = 1), lost to follow-up (N = 1), medical event (N = 2), protocol violation (N = 3), patients withdrew (N = 5). Reasons for withdrawal from the placebo group were early completion (N = 1), lack of efficacy (N = 2), medical event (N = 1), protocol violation (N = 1), patient withdrew (N = 6), other (N = 4). No statistical difference was found in the dropout rates between the two treatment groups ($p = 0.93$).

Dosage

Each tablet of study medication contained 15 mg of either adinazolam SR or lactose placebo. The mean daily doses (±SD) of adinazolam, as calculated from recorded tablet counts, at weeks 1 and 4 were 25.7 ± 5.9 and 84.1 ± 28.6 mg, respectively. This corresponds to a daily average of 1 to 2 tablets at week 1 and 3.5 to 7.5 tablets at week 4. The daily average number of placebo tablets was one to two at week 1 and four to eight at week 4, or 25.0 ± 5.0 and 92.3 ± 27.3 mg equivalents, respectively.

Primary efficacy measures

The results from all four primary efficacy scales are presented in Table 2. Adinazolam SR was not associated with a significant increase in the number of patients with zero panic attacks at week 1 based on the Sheehan PAAS. However, a significant increase ($p = 0.009$) in the number of patients with zero panic attacks was seen at week 4 in favor of adinazolam SR.

On the basis of the CGI-Improvement question, 31 adinazolam SR-treated patients (31.9%) and 17 placebo-treated patients (18.1%) responded to treatment at week 1. Sixty-nine adinazolam SR-treated patients (69.7%) and 40 placebo-treated patients (39.6%) responded to treatment at week 4. The treatment effect was statistically significant at both times ($p = 0.02$ at week 1 and $p = 0.0001$ at week 4).

Results from the CGI-Severity question show that adinazolam SR treatment as compared with placebo

TABLE 1. Mean (±SD) baseline symptom scores

	Adinazolam SR (N = 99)	Placebo (N = 103)
SCRAS[a]		
DSM-III-R panic attack symptoms	36.3 (15.7)	35.8 (14.4)
Sheehan PAAS		
Frequency of unexpected panic attacks (number/wk)	3.30 (6.74)	1.99 (2.73)
Intensity of unexpected panic attacks (scale, 0–10)	3.90 (3.21)	3.61 (2.89)
Duration of unexpected panic attacks (min)	17.4 (27.2)	17.8 (31.0)
Anticipatory anxiety (% of waking time)	39.5 (27.0)	37.6 (27.1)
Anticipatory anxiety (intensity, scale, 0–10)	5.41 (2.34)	5.24 (2.32)
Frequency of situational panic attacks (number/wk)	2.04 (2.50)	2.68 (3.05)
Intensity of situational panic attacks (scale, 0–10)	3.94 (2.89)	4.09 (2.81)
Duration of situational panic attacks (min)	15.3 (26.1)	18.2 (24.4)
Hamilton Rating Scale for Anxiety	18.6 (6.7)	18.5 (6.5)
CGI	4.34 (0.74)	4.33 (0.76)
Phobia rating		
Overall phobia severity (scale, 0–10)	6.93 (2.20)	6.97 (2.35)
Main phobia severity: fear (scale, 0–10)	8.00 (2.11)	7.80 (2.33)
Main phobia severity: avoidance (scale, 0–4)	2.89 (1.07)	2.86 (1.12)
Disability rating		
Work disability[b] (scale, 0–10)	4.39 (2.95)	4.21 (2.77)
Social disability (scale, 0–10)	5.56 (2.68)	5.61 (2.80)
Family life disability (scale, 0–10)	4.15 (2.75)	3.57 (2.82)
SCL-90 Phobia Score[c]	9.34 (6.43)	9.15 (6.63)

[a] Based on items 1 to 14 total.
[b] Adinazolam SR group, N = 83; placebo group, N = 90.
[c] Adinazolam SR group, N = 99; placebo group, N = 102.

TABLE 2. Treatment effects on primary efficacy measures

Variable	All subjects	Completers
Zero panic attacks[a]		
Week 1		
Adinazolam SR	33.3% (96)	33.0 (90)
Placebo	23.1% (95)	24.1 (83)
p value[b]	NS[c]	NS
Week 4		
Adinazolam SR	57.1% (98)	61.4 (88)
Placebo	39.2% (101)	41.3 (75)
p value	0.009	0.011
CGI-Improvement[a]		
Week 1		
Adinazolam SR	31.9% (31)	34.4% (31)
Placebo	18.1% (17)	20.7% (17)
p value	0.02	0.045
Week 4		
Adinazolam SR	69.7% (69)	76.1% (67)
Placebo	39.6% (40)	44.6% (33)
p value	0.0001	0.0001
CGI-Severity of Illness (Mean score ± SE)		
Week 1		
Adinazolam SR	3.9 ± 0.1	3.8 ± 0.1
Placebo	4.0 ± 0.1	4.0 ± 0.1
p value	NS	NS
Week 4		
Adinazolam SR	3.2 ± 0.1	3.1 ± 0.1
Placebo	3.6 ± 0.1	3.5 ± 0.1
p value	0.007	0.0133
Overall phobia score (Mean score ± SE)		
Week 1		
Adinazolam SR	6.1 ± 0.2	6.1 ± 0.2
Placebo	6.0 ± 0.2	6.1 ± 0.2
p value	NS	NS
Week 4		
Adinazolam SR	4.9 ± 0.2	4.3 ± 0.3
Placebo	4.7 ± 0.2	4.6 ± 0.3
p value	NS	NS
SCL-90 Phobia Scale[a]		
Week 1		
Adinazolam SR	25.8% (93)	27.7% (83)
Placebo	22.4% (96)	25.7% (70)
p value	NS	NS
Week 4		
Adinazolam SR	61.4% (96)	68.7% (83)
Placebo	38.9% (95)	38.6% (70)
p value	0.002	<0.001

[a] % Responders.

[b] *p* values for zero panic attacks, CGI improvement, and SCL-90 phobia scale were based on χ^2 testing, 1 degree of freedom. Other *p* values were based on least squares means analysis of covariance.

[c] NS, not significant.

treatment significantly lowered the score at week 4 but not at week 1. The SCL-90 phobia dimension subscale did not indicate a greater treatment effect for adinazolam SR than for placebo at week 1 but did indicate a significant treatment effect at week 4 for adinazolam SR. Mean overall phobia scores from the PSS were not significantly different between treatments at week 1 or 4.

Other indicators of efficacy retrieved from the PAAS deal with unexpected panic attacks, situational panic attacks, and anticipatory anxiety. At week 1, the mean (±SE) number of unexpected panic attacks for adinazolam SR-treated and placebo-treated patients, respectively, were 2.0 ± 0.4 and 3.2 ± 0.4; mean intensity scores were 2.5 ± 0.2 and 2.9 ± 0.2, respectively; and mean duration of attack was 17.3 ± 3.8 and 17.5 ± 3.8 minutes, respectively. Differences between treatment groups at week 1 were not statistically significant. At

week 4, the mean number of unexpected panic attacks for adinazolam SR-treated and placebo-treated patients, respectively, were 1.3 ± 0.3 and 1.8 ± 0.3; mean intensity scores were 1.8 ± 0.2 and 2.2 ± 0.2, respectively; and mean duration was 12.0 ± 5 and 18.6 ± 4.5 minutes, respectively. None of these were statistically significant.

At week 1, the mean (±SE) number of situational panic attacks for adinazolam SR-treated and placebo-treated patients, respectively, were 1.7 ± 0.2 and 1.0 ± 0.1; mean intensity scores were 2.6 ± 0.2 and 2.9 ± 0.3, respectively; and mean duration was 12.4 ± 2.3 and 14.0 ± 2.3 minutes, respectively. At week 4, the mean number of situational panic attacks for adinazolam SR-treated patients and placebo-treated patients were 1.1 ± 0.2 and 1.1 ± 0.2, respectively; mean intensity scores were 1.9 ± 0.2 and 2.2 ± 0.2, respectively; and the mean duration was 7.7 ± 3.1 and 13.1 ± 3.1 minutes, respectively. None of the differences were statistically significant.

At week 1, the mean amount (percentage of waking hours) of anticipatory anxiety for adinazolam SR-treated and placebo-treated patients, respectively, was 27.1 ± 1.8 and 34.9 ± 1.9% ($p = 0.005$). Mean anticipatory anxiety intensity scores were 4.1 ± 0.2 and 4.8 ± 0.2, respectively ($p = 0.02$). At week 4, the mean amount (percentage of waking hours) of anticipatory anxiety for adinazolam SR-treated patients and placebo-treated patients, respectively, was 22.0 ± 2.0 and 29.7 ± 2.0% ($p = 0.009$). Mean anticipatory anxiety scores were 3.3 ± 0.2 and 4.3 ± 0.2, respectively ($p = 0.003$).

Secondary efficacy measures

The mean Hamilton Rating Scale for Anxiety score was significantly lower at week 4 for the adinazolam SR group as compared with the placebo group (10.9 ± 0.6 vs. 13.3 ± 0.6, $p = 0.013$).

The mean total SCRAS score at week 1 was significantly lower for the adinazolam SR group than the placebo group (10.5 ± 0.4 vs. 12.1 ± 0.4; $p = 0.015$). This difference was also significant at week 4 (8.4 ± 0.5 vs. 10.1 ± 0.5; $p = 0.034$). Situational panic attacks were compared at weeks 1 and 4 for adinazolam SR and placebo and did not differ at either time. At week 1, mean scores for adinazolam SR and placebo were 1.0 ± 0.1 versus 1.1 ± 0.1, respectively; at week 4, mean scores were 0.6 ± 0.1 versus 0.7 ± 0.1, respectively. Unexpected attacks were also compared between treatment groups at weeks 1 and 4. Mean unexpected attack scores at week 1 for adinazolam SR and placebo were 0.9 ± 0.1 versus 1.0 ± 0.1, respectively; at week 4, mean scores were 0.5 ± 0.1 versus 0.9 ± 0.1 ($p = 0.02$).

The main phobia fear scores at week 1 did not differ between the adinazolam SR group and the placebo group (6.7 ± 0.2 vs. 6.0 ± 0.2, respectively). There was a significant difference at week 4 in favor of adinazolam SR (5.1 ± 0.2 vs. 5.8 ± 0.2; $p = 0.04$). Phobic avoidance was not significantly different between treatment groups at week 1 (2.4 ± 0.1 vs. 2.5 ± 0.1, adinazolam SR vs. placebo, respectively) but was significantly lower in the adinazolam SR group at week 4 (1.8 ± 0.1 vs. 2.1 ± 0.1; $p = 0.03$). The completer analysis for this last measure failed to demonstrate a statistically significant difference (0.5 ± 0.31 vs. 0.7 ± 0.1; $p = 0.07$).

Mean scores of disability at week 4 revealed no statistically significant effect for adinazolam SR treatment over placebo treatment with respect to social, work, or family life disability. Adinazolam SR treatment showed a trend toward significance on the measure of social disability with a p value of 0.081.

Medical events

Treatment-emergent medical events that differed significantly in incidence between treatment groups are as follows. Adinazolam SR-treated patients had a significantly greater incidence of fatigue (46.1 vs. 34.0%; $p = 0.01$), incoordination (40.2 vs. 20.4%; $p = 0.0003$), and sedation (71.6 vs. 39.8%; $p = 0.0001$) than did placebo-treated patients. Placebo-treated patients had a significantly greater incidence of palpitations (33.0 vs. 14.7%; $p = 0.003$) and sleep disorders (36.9 vs. 16.7%; $p = 0.001$) than did adinazolam SR-treated patients.

Effect size

One way to measure the actual difference made by a particular treatment is to calculate the effect size. The effect size was calculated by use of the following formula: (mean change for adinazolam SR divided by the standard deviation of change for adinazolam SR) minus (mean change for placebo divided by the standard deviation of change for placebo). When this was done, comparing adinazolam SR and placebo on the four primary efficacy measures (CGI, SCL-90, PSS, and number of panic attack–free patients), the respective effect sizes were 0.37, 0.31, 0.15, and 0.31. These values may be taken to reflect the modest, yet probably meaningful, contribution of drug therapy to outcome. Effect sizes are regarded as strong when they are greater than 0.8 to 1.0.[30]

Discussion

This study has demonstrated the short-term therapeutic efficacy of adinazolam SR relative to placebo after 4 weeks of treatment in 202 outpatients with panic disorder and agoraphobia. Efficacy was found on five major parameters in accordance with prediction. Adinazolam SR reduced the number of patients who experi-

enced panic attacks, as well as reducing phobic avoidance (SCL-90 and main phobia avoidance), global illness severity, and anticipatory and general anxiety. Significant drug effects were found at week 1 on global improvement and DSM-III-R panic attack severity. No treatment effects were found for disability or for overall phobia severity. Whether these could be explained as a result of the short duration of the trial, or are due to some other cause, could not be ascertained.

More detailed analysis of the PAAS revealed no significant differences between treatments with respect to frequency, intensity, or duration of either unexpected or situational panic attacks at weeks 1 and 4. However, analysis of the individual SCRAS items 15 (situational panic attacks) and 16 (unexpected panic attacks) showed a significant treatment effect in favor of adinazolam SR at week 4 for unexpected attacks, consistent with the PAAS finding that adinazolam SR produced a greater number of patients with zero attacks at week 4.

Our results compare well with previous trials of alprazolam and adinazolam CT in panic disorder,[3, 12] which found that 50% of alprazolam patients and 28% of placebo patients were free of panic attacks after 4 weeks of treatment.[3] In a previous study of adinazolam CT, Pyke and Greenberg[12] found a 79% response rate. Drug effects were not found on all measures, and the effect size was modest, although we cannot say that is any less than the effect size of other drugs in panic disorder, because these data are not customarily given.

In accounting for outcome, we may need to consider additional variables, one of which is readiness for change. We do know, from other analyses of our data, that patient "readiness to change" was a strong determinant of outcome in a linear regression model to predict outcome (Beitman BD, and associates, unpublished observation). Thus, other variables need to be taken into account as we explain outcome in this study. Perhaps, in placebo-controlled drug trials, a drug's advantage over placebo is amplified among individuals who are more "ready to change," i.e., contemplators as opposed to precontemplators, using the terminology of DiClemente and Prochaska.[31] These individuals may be at a point where their potential for recovery or their innate recuperative power is greater than in precontemplators, and they can take greater advantage of an active treatment when one is offered to them. This is an important area for further study.

Other considerations

There are some important considerations to remember when reviewing the results of this 4-week study. During the trial, a number of patients did respond to placebo, a reminder that the placebo response in panic disorder cannot be ignored. It is possible that the effects of repeated visits, which constitute a form of exposure therapy for agoraphobic patients, could be therapeutic to some degree. We do not believe that our very minimal exposure instructions at the baseline visit produced a significant therapeutic effect but acknowledge that we did not rate this. Spontaneous remission may account for some improvement in both groups.

Study medication compliance was checked by diary records, tablet counts, and a blood test for the illicit use of other benzodiazepines.[32] Benzodiazepine use was 5.0% or less and 15.5% or less, respectively, for the active and placebo groups at any week during the short term phase of the study. Details concerning this analysis are presented elsewhere.[33]

This report is limited in that it is only concerned with the short-term (4-week) treatment phase of the study. Issues beyond the scope of this report include the association of placebo with improvement, the question of whether the therapeutic effects persist during long term treatment, the question of whether additional drug effects appear later in treatment (e.g., improvement on disability scales, or larger effect sizes), the question of whether placebo responders are more likely to relapse later on, discontinuation and withdrawal effects, pharmacokinetics and levels of adinazolam SR and NDMAI in plasma, and subsequent relapse rates. Some of these questions will be answered in forthcoming reports by our group.

Conclusions

This study demonstrated the therapeutic effectiveness of adinazolam SR relative to placebo in the short term (4-week) treatment of 202 outpatients with panic disorder with agoraphobia. Adinazolam SR effectively reduced the number of patients with panic attacks and reduced phobic avoidance and overall severity of illness. Some evidence suggests an earlier onset of antipanic effect (the SCRAS at week 1) and a later onset of antiphobic effect (the main phobia severity and SCL-90 ratings at week 4). No treatment effects were found for the patient's general disability due to panic disorder or for overall phobia severity. This lack of effect may possibly be because of the short duration of the trial or some other as-yet-unascertained cause. Adinazolam SR was well tolerated. Sedation, incoordination, and fatigue occurred significantly more often in the adinazolam SR group than in the placebo group, a profile that is similar to that seen with other benzodiazepines.

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