Chapter 7
Treatment of Panic Disorder in Older Adults: A Pilot Study Comparison of Alprazolam, Imipramine, and Placebo

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Type of Study Parallel group, double-blind, placebo-controlled, flexible-dose pilot study

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Objectives To gather pilot data in older patients with panic disorder (DSM-III-R) to begin to determine the efficacy of imipramine and alprazolam [1].

Methods This study recruited 25 community-dwelling adults ≥55 years of age to participate in an 8-week parallel group, double-blind, placebo-controlled, flexible-dose pilot study of alprazolam, or imipramine for panic disorder. Subjects completed a pre-screen questionnaire, and those who were likely to fulfill study criteria

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were clinically interviewed using the structured clinical interview for DSM-III-R-Patient Version and Mini-Mental State Exam (MMSE). Inclusion criteria included age ≥55 years who met DSM-III-R criteria for panic disorder with or without agoraphobia (n = 25; 23 females, 2 males).

Exclusion criteria included bipolar disorder, schizophrenia or other psychosis, borderline personality disorder, obsessive-compulsive disorder, or cognitive impairment (MMSE ≤23). Subjects with alcohol or other substance abuse/dependence within prior 6 months or concurrent treatment with anxiolytics or concurrent treatment for anxiety with another clinician were also excluded. Finally, patients with active unstable medical, metabolic, or cardiopulmonary conditions were also excluded.

In this 8-week study, participants completed a 2-week washout period and were then randomized to receive, in a double-blind fashion, alprazolam, imipramine, or placebo. Subjects were assessed on an outpatient basis by a psychiatrist or psychiatry fellow for clinical response and need for medication adjustment weekly for the first 4 weeks, biweekly for weeks 6–8 (week 8 = endpoint), and at withdrawal of drug (week 10).

Subjects could receive medication up to four times daily to mimic clinical prescribing of alprazolam, starting with one nightly capsule (alprazolam 1 mg, imipramine 25 mg, or placebo) and increasing to one capsule twice daily after 3 days if tolerated. Dose increases occurred at weekly visits with a target dose of ten capsules, or the maximum beneficial dose not limited by side effects, by week 4. To mimic real-world practice of flexibility in dosing, the dose per capsule was reduced to 0.5 mg in alprazolam and 10 mg in imipramine after the first 14 subjects completed the study. Mean doses for subjects were 2.87 mg/day (SD = 1.66, range 1–6) for alprazolam and 77.5 mg/day (SD = 59.4, range 10–200) for imipramine.

The primary outcome measures in this study were global change ratings using Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Physicians' Global Impression (PGI) ratings, and average number of panic attacks per week from self-reported daily panic diaries.

The small sample size prevented statistical analyses between the groups, so only descriptive data were reported.

Results Twenty-five participants were randomized in the study, eight to the alprazolam group, ten to the imipramine group, and seven to the placebo group. The baseline mean age and mean age of panic onset were 62.75 years and 34.88 years for subjects in the alprazolam group, 61.30 years and 38.11 years for those in the imipramine group, and 59.29 years and 38.00 years for participants in the placebo group. The mean number of panic attacks per week in the month before treatment was similar among groups (alprazolam 2.38, imipramine 3.60, and placebo 3.2). Comorbid diagnoses and dependent measures of depressed mood (HAM-D) and anxiety (HAM-A) were grossly comparable across groups as well.

Of the 25 patients randomized to the 3 treatment groups, 4 dropped out during week 1, 1 dropped out during week 2, and 1 dropped out during week 3. Six of the

seven dropouts were from the placebo group and one from the imipramine group. With the dropout rate approaching 25%, the investigators terminated the study early.

As shown in Table 7.1, the number of panic attacks per week, measured by self-reported panic diaries, decreased from baseline to posttreatment in the alprazolam,

Table 7.1 Panic disorders outcomes after treatment with alprazolam, imipramine, and placebo

		Alprazolam		Imipramine		Placebo	
		Baseline	Posttreatment	Baseline	Posttreatment	Baseline	Posttreatment
N		8	8	10	9	7	1
Outcome	*Measure*						
Mean panic attacks per week (SD)	Panic diary	2.38 (2.39)	0.00 (0.00)	3.60 (4.22)	0.13 (0.35)	3.29 (3.09)	0.00[a]
Physician's mean global ratings (SD)	PGI question #1	3.00 (0.89)	1.75 (1.04)	3.40 (1.27)	1.70 (0.95)	3.50 (0.71)	3.33 (2.08)[b]
Physician's mean global clinical impression (SD)	PGI question #2	–	1.50 (0.76)	–	2.30 (1.36)	–	4.00 (2.16)[c]
Mean therapeutic effects of medication (SD)	PGI question #3	–	4.50 (0.76)	–	3.70 (1.10)	–	2.50 (1.73)[c]
Physician's mean rating of minimal severity of side effects (SD)	PGI question #4	–	0.88 (0.99)	–	0.80 (0.63)	–	0.67 (1.16)[b]
Physician's mean anxiety rating score (SD)	HAM-A	17.86 (11.74)	3.87 (5.62)	13.40 (6.24)	5.30 (3.65)	20.00 (10.00)	15.00 (10.55)[c]
Physician's mean depression rating score (SD)	HAM-D	14.00 (7.79)	3.88 (6.11)	11.40 (6.77)	3.20 (2.39)	12.71 (5.38)	9.00 (7.44)[c]

SD standard deviation
[a]Using one subject, last available data point
[b]Using three subjects, last available data point
[c]Using four subjects, last available data point

imipramine, and placebo groups, although there was only a single placebo participant at the completion of the study. Physician's mean global rating (PGI question #1), a measure of symptoms severity, for alprazolam, imipramine, and placebo groups were higher at week 1 when compared to the posttreatment period. The physician's mean anxiety rating score, as measured by the HAM-A, and mean depression rating score, as measured by the HAM-D, were also lower in the posttreatment period for all groups when compared to baseline.

Conclusions Findings suggest comparable efficacy for alprazolam and imipramine in the short-term treatment of panic disorder in adults ≥55 years old. The results also suggested that the effective dose for alprazolam and imipramine for older female adults might be about half of the usual effective dose for younger adults.

Strengths of the Study

1. The study was randomized, double-blind, and placebo controlled.
2. Medication dosing design was flexible.
3. All participants were older adults ≥55 years old.
4. The authors do not overstate their results, recognizing that the conclusions that can be drawn are limited due to the very small sample size.

Limitations of the Study

1. A very small sample size of 25 participants divided over 3 groups meant that only descriptive statistics could be provided with no statistical analyses between groups or intent-to-treat analyses performed.
2. A short treatment period of 8 weeks leaves the question of whether alprazolam leads to tolerance in the elderly unanswered.
3. The recruitment process was through self-referral.
4. The study assessed on the basis of Jadad score indicates that this was low-quality study with a score of 2 out of 5 [2].

Questions Yes (1) No (0)	**Was the study described as random?**	**Was the randomization scheme described and appropriate?**	**Was the study described as double-blind?**	**Was the method of double blinding appropriate? (Were both the patient and the assessor appropriately blinded?)**	**Was there a description of dropouts and withdrawals?**	**Total score Range of score quality 0–2, low 3–5, high**
Score	1	0	1	0	0	2

5. While described as a double-blinded study, no reference was made regarding how blinding was maintained. Also, no CONSORT statement flowchart was provided to adequately assess dropouts and withdrawals at time of recruitment as well as after study enrollment. The number of dropouts per group was provided, but no patient reported reasons.
6. Twenty-three of 25 persons in the study are women, and 24 of 25 persons in the study are white, both limiting generalizability of the study.
7. Details of random sequence generation and allocation concealment were not provided.
8. There was a 25% dropout rate and 6 of 7 patients in the placebo group withdrew early.
9. The study medications were provided by Upjohn Company, the maker of alprazolam, and conflicts of interest are unstated.
10. The short study duration of 8 weeks limits ability to assess for multiple known adverse effects of benzodiazepine use in elderly, such as dizziness, sedation, cognitive impairment, and hip fractures [3–5].

Take-Home Points Although relatively low doses of alprazolam and imipramine were tolerable and reduced self-reported and physician rated anxiety in older adults with panic disorder, generalizability of this study is severely limited by its small size and short duration.

Practical Applications of the Take-Home Point Among older adults with panic disorder, alprazolam and imipramine appear to be efficacious in the short term.

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