Published in final edited form as:
Am J Geriatr Psychiatry. 2009 September ; 17(9): 744–751. doi:10.1097/JGP.0b013e3181ab8c61.

PRAZOSIN FOR THE TREATMENT OF BEHAVIORAL SYMPTOMS IN ALZHEIMER'S DISEASE PATIENTS WITH AGITATION AND AGGRESSION

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Abstract

Objectives—Agitation and aggression in Alzheimer's disease (AD) is a major cause of patient distress, caregiver burden, and institutionalization. Enhanced behavioral responsiveness to central nervous system norepinephrine release may contribute to the pathophysiology of agitation and aggression in AD. Prazosin, a nonsedating generic medication used for hypertension and benign prostatic hypertrophy, antagonizes norepinephrine effects at brain postsynaptic alpha-1 adrenoreceptors. This pilot study examined the efficacy and tolerability of prazosin for behavioral symptoms in patients with agitation and aggression in AD.

Design—Double-blind, placebo controlled, parallel group study.

Setting—A university AD center and a nursing home in Seattle.

Participants—Twenty-two nursing home and community dwelling participants with agitation and aggression and probable or possible AD (mean age 80.6 ± 11.2).

Intervention—Randomization to placebo (n=11) or prazosin (n=11). Medication was initiated at 1mg/day and increased up to 6mg/day using a flexible dosing algorithm.

Measurements—The Brief Psychiatric Rating Scale (BPRS) and Neuropsychiatric Inventory (NPI) at weeks 1, 2, 4, 6, and 8. The Clinical Global Impression of Change (CGIC) at week 8.

Results—Participants taking prazosin (mean dose 5.7 ± 0.9mg/day) had greater improvements than those taking placebo (mean dose 5.6 ± 1.2mg/day) on the NPI (mean change -19 ± 21 versus -2 ± 15, X^2=6.32, df=1, p=0.012) and BPRS (mean change -9 ± 9 versus -3 ± 5, X^2=4.42, df=1, p=0.036) based on linear mixed effects models, and the CGIC (mean 2.6 ± 1.0 versus 4.5 ± 1.6, Z=2.57, p=0.011 [Mann-Whitney test]). Adverse effects and blood pressure changes were similar between prazosin and placebo groups.

Conclusion—Prazosin was well tolerated and improved behavioral symptoms in patients with agitation and aggression in AD.

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No disclosures to report.

This research was presented in part as a poster at the 11th International Conference on Alzheimer's Disease and Related Disorders, Chicago, Illinois, July 2008.

Keywords

agitation; dementia; prazosin; norepinephrine

OBJECTIVE

Dementia-related agitation and aggression describes a cluster of behaviors that includes irritability, uncooperativeness with care, anger outbursts, verbal and physical aggression, and pressured motor hyperactivity. These behaviors frequently emerge as chronic clinical problems during the course of Alzheimer's disease (AD).(1-3) Agitation and aggression increases caregiver burden in both the home and long term care setting, is distressing to patients and others in the patient's environment(4, 5) and is a frequent precipitant of long term care placement.(6) Treatment guidelines recommend the use of atypical antipsychotics to reduce agitation and aggression when nonpharmacological approaches have failed(7-9); however, these drugs are only modestly effective for agitation, nonresponders are common, and emergent adverse effects such as sedation often occur.(10-15) Furthermore, the atypical antipsychotics modestly increased the risk for stroke and death in randomized clinical trials in patients with dementia,(16) and the FDA has now issued a black box warning regarding the risk of prescribing atypical and typical antipsychotics to elderly persons with dementia.(17) Thus, the development of more effective and safer pharmacologic approaches for the treatment of agitation and aggression in AD is an important clinical goal.(18)

A potential pharmacological target for such drug development is the central nervous system (CNS) noradrenergic system. Neurobiologic studies in the clinic and in postmortem brain tissue suggest that enhanced responsiveness to norepinephrine (NE) at the alpha-1 adrenoreceptor (AR) may contribute to the pathophysiology of dementia-related agitation and aggression.(19-22) Prazosin is a centrally acting generic alpha-1 AR antagonist used for decades to treat hypertension and benign prostatic hypertrophy urinary symptoms. It is the only clinically available alpha-1 AR antagonist that readily crosses from the blood into brain; it has been demonstrated specifically to block CNS alpha-1 ARs when administered peripherally.(23, 24) In an open label study of persons with AD and treatment-resistant agitation, prazosin administration was associated with substantial reduction in agitation without hypotension or other significant adverse effects.(25) Here, we present positive results of a pilot double-blind placebo-controlled trial of prazosin for agitation and aggression in AD.

METHODS

Study participants

Study participants were residents at the Caroline Kline-Galland Home (n=12), which is a 250-bed community skilled nursing facility in Seattle, or were community-dwelling patients recruited through the University of Washington Alzheimer's Disease Research Center (n=10), enrolled 2005 through 2007. Eligible participants had probable or possible AD by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria, and exhibited agitation and aggression at least twice weekly for two weeks, with a score of 4 (moderate) or more on at least one of the following Brief Psychiatric Rating Scale (BPRS) items: anxiety, tension, hostility, uncooperativeness, or excitement.(26, 27) Previously prescribed psychotropic and general medications were continued during the trial provided doses had been stable for at least 4 weeks.

Exclusion criteria included supine systolic blood pressure <110, orthostatic hypotension (≥ 20 mmHg drop in systolic BP following 2 minutes of standing posture), and concurrent administration of other alpha-1 AR antagonists. Further exclusions included uncontrolled

persistent distressing psychotic symptoms (hallucinations, delusions), current delirium, current depression, or history of bipolar disorder or schizophrenia. Also excluded were participants with unstable medical conditions that could have contributed to cognitive or behavioral impairment, such as acute infection, electrolyte imbalance, thyroid disease, and renal or hepatic failure. The University of Washington Human Subjects Committee IRB approved this study. After study procedures were fully explained, written informed consent was obtained from a legally authorized representative and, when possible, the patient.

Design

This was an 8-week, randomized, single-site, parallel group study of placebo vs. prazosin. Randomization was accomplished through a computer generated randomization schedule and was blocked for setting (nursing home or community dwelling). All participants and research personnel were blinded to treatment arm with the exception of the pharmacist. Prazosin was titrated using a flexible dose algorithm, starting with 1mg qhs and increased by increments of 1 to 2 mg every 3 to 7 days up to a maximum of 2mg qam and 4mg qhs. Increases in dosage were made by the study prescriber (psychiatrist or physician assistant) if target behaviors were not markedly improved and there were no adverse effects attributable to prazosin. The study medication prescriber was blinded to the treatment condition but monitored the participant's blood pressure and possible adverse effects.

Outcome measures

The primary outcome measures were the Clinical Global Impression of Change (CGIC) and change from baseline scores in the Neuropsychiatric Inventory (NPI) and BPRS.(27-29) The NPI is a 12 item scale that assesses the frequency and severity of psychiatric and behavioral disturbances in dementia patients, such as agitation, psychosis, and mood disturbance. NPI item scores are based on informant report and scaled from 0 to 12, with higher values indicating greater behavioral disturbance. The BPRS is an 18-item scale that rates psychiatric symptoms, including mood, psychotic, anxiety, and motor symptoms. Each item ranges from 1 to 7, with higher scores indicating more severe psychiatric symptoms. The Clinical Global Impression of Change was used as a global estimate of behavioral status, and employs a 7 point scale where 1 indicates "markedly improved," 4 indicates "no change," and 7 indicates "markedly worse." Secondary outcome measures included the emergence of side effects, changes in blood pressure, and the Lawton-Brody Physical Self-Maintenance Scale (PSMS), which monitors changes in functional status by assessing items such as feeding, ambulating, toileting, and dressing.(30)

All outcome measures were assessed by an experienced research nurse who was blinded to study medication, blood pressure, and side effects. The blind rater assessed the NPI, BPRS, and PSMS at baseline and at weeks 1, 2, 4, 6, and 8, and assessed the CGIC at week 8 or at the last visit if the participant withdrew from the study early.

Statistical Analysis

We used a modified intent-to-treat approach, where we included all participants with at least one follow-up outcome measure in our statistical analyses. The main outcomes of interest were total BPRS score, total NPI score, and CGIC rating. Differences in CGIC (only 1 measure per participant) by treatment group were determined using the Mann-Whitney test. Mean changes from baseline in BPRS and NPI scores by treatment group at each follow-up visit (up to 6 follow-up visits) were computed. A single summary measure of the mean change in BPRS and NPI scores for each treatment group across the course of study was estimated by calculating the mean of each participant's follow-up measures, subtracting this mean from the baseline value, and then from these values, calculating group means and standard deviations. Differences in BPRS and NPI by treatment group were evaluated using linear mixed effects

models, with behavior score as the dependent variable; treatment group, time of measurement (pre-treatment vs. post-treatment) and the interaction between them as the fixed effect covariates; and participant identifier as a random effect. The primary effect of interest was the treatment group x time of measurement interaction, which represents the difference in post- vs. pre-treatment change by treatment group. All p-values from the linear mixed effects models reported below are based on the significance of the likelihood ratio chi-square test with one degree of freedom (df) for the treatment group x time of measurement interaction. Analyses of the secondary outcomes, PSMS score and blood pressure, were conducted using linear mixed effects models as described above. Summary measures in the text are presented as means ± standard deviations (SDs) unless otherwise noted. A significance level of 0.05 was used for all analyses. The analyses were carried out using R 2.6.1 and Stata 10 (College Station, Texas). (31)

RESULTS

Participants

Of the 33 patients screened for the study, 9 did not meet inclusion and exclusion criteria. The remaining participants were randomized to prazosin (n=12) and placebo (n=12). One participant from each treatment arm dropped out due to hypotension before a follow-up assessment could be performed, leaving 11 participants on prazosin and 11 participants on placebo who had at least one follow-up assessment available for analysis.

The overall completion rate was 54%, and did not differ between the two groups. During the 8 week follow-up period, four additional participants in the prazosin group dropped out. Reasons were: moving to a new nursing home for two participants, lower extremity edema for one participant, and continuing agitation for one participant. During the 8 week follow-up period, five participants in the placebo group dropped out. Reasons were: continuing agitation for 3 participants, lower extremity edema for one participant, and rash for one participant.

Table 1 summarizes the baseline characteristics for participants with at least one follow-up assessment available for analysis. Baseline age, MMSE scores, gender distribution, and setting (community dwelling and nursing home) were similar between the two groups. One participant in the placebo group was African American, and all other participants were Caucasian. The number of psychotropic medications taken during the study was also similar between the two groups (prazosin group, 2.4 per patient; placebo group, 2.0 per patient). Specifically, of the 22 participants with follow-up visits, 9 were receiving atypical antipsychotics, 12 cholinesterase inhibitors, 5 memantine, 11 antidepressants, 1 buspirone, 6 benzodiazepines, 3 divalproex, and 1 propranolol. All subjects had at least one major medical diagnosis, most commonly chronic cardiovascular disease, osteoarthritis, or a gastrointestinal disorder.

The mean dose of study medication was 5.7 ± 0.9mg/day for the prazosin group and 5.6 ± 1.2mg/day for the placebo group.

Behavioral and Functional Outcome Measures

Participants who were taking prazosin had greater improvement in all three primary behavioral outcome measures than those taking placebo (Table 2). For those participants who completed the study, there were greater improvements in the prazosin over placebo groups as measured by the NPI (-13 ± 23 versus 5 ± 21) and the BPRS (-9 ± 8 versus 3 ± 5). A calculated group mean that incorporates scores for completers plus noncompleters with at least one follow-up measure also shows improvements in the prazosin versus placebo group in the NPI (-19 ± 21 versus -2 ± 15) and the BPRS (-9 ± 9 versus -3 ± 5). When analyzed using a linear mixed effects model, differences in both measures were statistically significant (NPI, X^2=6.32, df=1,

p=0.012; BPRS, X^2=4.42, df=1, p=0.036). For global behavioral status measured by the CGIC, all the participants taking prazosin either remained the same or improved, while six of the 11 participants taking placebo had some worsening. The differences in CGIC between the prazosin and placebo group were statistically significant (mean 2.6 ± 1.0 versus 4.5 ± 1.6, Z=2.57, p=0.011 [Mann-Whitney test]).

The mean scores for NPI subitems in the prazosin group are as follows: delusions (baseline 2.9 ± 3.5, last observed 0.9 ± 1.6), hallucinations (baseline 1.1 ± 2.5, last observed 1.0 ± 2.5), agitation/aggression (baseline 8.6 ± 2.4, last observed 5.0 ± 3.7), depression/dysphoria (baseline 3.7 ± 4.2, last observed 3.4 ± 4.5), anxiety (baseline 4.7 ± 3.3, last observed 2.1 ± 2.8), euphoria/elation (baseline 1.3 ± 2.6, last observed 1.2 ± 1.7), apathy/indifference (baseline 5.7 ± 4.5, last observed 2.9 ± 4.4), disinhibition (baseline 3.5 ± 3.6, last observed 1.1 ± 1.9), irritability/lability (baseline 4.2 ± 3.5, last observed 2.5 ± 3.1), aberrant motor behavior (baseline 4.8 ± 5.1, last observed 2.9 ± 3.2), nighttime behavior (baseline 2.0 ± 2.5, last observed 3.2 ± 3.1), and appetite/eating change (baseline 2.7 ± 3.8, last observed 2.0 ± 2.6).

Baseline PSMS scores for both groups were similar at baseline (prazosin 25 ± 7, placebo 24 ± 8). Changes in PSMS scores were not different between the two groups (prazosin mean change -4 ± 8, placebo mean change -6 ± 10; [X^2=1.19, df=1, p=0.3, linear mixed effects model]).

Safety

Prazosin was generally well-tolerated and adverse effects were similar between the prazosin and placebo groups (Table 3). Baseline systolic and diastolic blood pressures were similar between the two groups at baseline (prazosin vs. placebo in units of mmHg: systolic, 134 ± 15 vs. 127 ± 15; diastolic, 74 ± 12 vs. 73 ± 11). Estimated mean change in systolic blood pressure from baseline averaged over the duration of the study in the prazosin group was -2 ± 18 mmHg and in the placebo group was 1 ± 19mmHg. Neither treatment group had any appreciable change in average diastolic blood pressure (0 ± 8 mmHg for both). There was no evidence of differences in blood pressure change over study duration by treatment group from the linear mixed effects model (X^2=0.49, df=1, p=0.5 for systolic, X^2=0.06, df=1, p=0.8 for diastolic). One study participant in the prazosin group reported an episode of dizziness on standing; there were no other episodes of blood pressure related symptoms.

CONCLUSIONS

This study provides preliminary support for the efficacy of the alpha-1 AR antagonist prazosin as a novel treatment for behavioral symptoms in AD patients with agitation and aggression. Improvements in both the NPI and BPRS were significantly and substantially greater with prazosin than placebo. The onset of improvement with prazosin was rapid and the clinical significance of improvement was supported by CGIC ratings. The magnitude of behavioral improvement with prazosin in this study was comparable to that of atypical antipsychotics in previous randomized controlled trials.(10, 13, 14, 32, 33)

Because there is substantial loss of NE producing locus ceruleus (LC) neurons in AD, it may seem counterintuitive that reducing the CNS postsynaptic response to NE by prazosin would produce behavioral improvement. However, compensatory upregulation of surviving LC neurons that sustain age-appropriate enhanced levels of CNS NE outflow in AD is supported by multiple postmortem brain tissue as well as clinical studies.(19, 20, 34) In addition to the compensatory upregulation of presynaptic noradrenergic outflow in AD, there is also increased density of postsynaptic alpha-1 AR in LC projection areas in prefrontal cortex and hippocampus.(21, 22) This upregulation of postsynaptic alpha-1 AR is associated with aggressive behavior antemortem.(35) That antagonism of brain alpha-1 AR by prazosin

reduces behavioral symptoms in AD is therefore consistent with the complex neurobiology of brain adrenergic system changes in AD.

The potential contribution of increased NE responsiveness at CNS alpha-1 AR to the pathophysiology of behavioral symptoms in AD may explain the efficacy of atypical antipsychotics for agitation and aggression. In vitro studies in human postmortem brain tissue demonstrate that alpha-1 AR antagonism of the atypical antipsychotics is more potent or similarly potent to dopamine D2 receptor antagonism. Quetiapine is clearly more potent at the alpha-1 AR than at the dopamine D2 receptor (Kd = 8.1 for the alpha-1 AR versus 770 for the D2 receptor, with lower Kd values indicating higher potency).(36) Olanzapine, risperidone and ziprasidone are comparably potent at the alpha-1 AR and dopamine D2 receptor.(36)

Recently, representatives from academic medical centers, the pharmaceutical industry, the FDA, the NIH, the nursing home industry, and patient advocacy groups created a consensus statement stressing the need for medications to treat agitation related to dementia and the drawbacks of current off-label atypical antipsychotic use.(18) Several consensus guidelines and position statements recommend using atypical antipsychotics when nonpharmacological approaches have failed, but they caution prescribers about the increased side effect burden and risks involved, including the FDA “black box warning” for risk of cerebrovascular events and mortality in patients with dementia.(7, 8, 37) The CATIE-AD study showed that side effects, such as sedation, extrapyramidal symptoms, and confusion, often offset efficacy of atypical antipsychotics for patients with AD with agitation and aggression.(12) It has been hypothesized that sedation caused by antipsychotics may increase morbidity and mortality in frail elderly dementia patients.(11, 38) Prazosin is a promising treatment alternative because it is rarely sedating.

Interpretation of the results in this study is limited by the small sample size and the high dropout rate during follow-up. For these reasons, we presented data at each time-point, avoided last observation carried forward summaries for primary outcome measures, and did not perform a formal exploratory analysis of subitems in the NPI and BPRS. In the prazosin group, many NPI subitems had lower mean scores at last observation than at baseline, suggesting that not only agitation and aggression, but other behavioral symptoms might respond. However, without a formal NPI and BPRS subitem statistical analysis, we can not conclude which specific psychiatric or behavioral symptoms improved with prazosin. The improvements in total NPI and BPRS scores, however, do suggest overall behaviors improve with prazosin, providing rationale for future larger studies where efficacy can be more clearly demonstrated and the needed analysis of specific behavioral domains can be undertaken.

Another potential limitation to this study is that the optimal dose for prazosin was not clearly established, since most participants tolerated well the highest dose provided in this study. Future trials can investigate whether doses higher than 6mg/day may be optimal. Follow-up in this study also ended after eight weeks. Previous studies of propranolol and atypical antipsychotics that include longer observational periods indicate that behavioral improvements may not persist long-term.(39, 40) Longer follow-up in future studies would better establish long-term efficacy.

In summary, this study showed statistically and clinically significant differences favoring prazosin over placebo in behavioral outcome measures, and prazosin was well-tolerated. These data suggest that this medication may be effective for behavioral symptoms in patients with dementia-related agitation and aggression, and support the need for future studies to establish efficacy of prazosin.

Acknowledgments

This research was supported by grants from the NIA (AG005136, AG018644), the Joan Alhadeff Alzheimer's Disease Research Fund, and the Department of Veterans Affairs Mental Illness Research, Education, and Clinical Center Special Fellowship in Advanced Psychiatry.

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Table 1

Baseline Characteristics

Characteristic	Prazosin n=11	Placebo n=11	All n=22
Age (years)[a]	83.2 ± 11.5	78.1 ± 10.8	80.6 ± 11.2
MMSE (score)[a,b]	9.3 ± 6.6	14.0 ± 12.0	11.4 ± 9.3
Female/male	4/7	5/6	9/13
Nursing home/community dwelling	6/5	6/5	12/10

[a] mean ± standard deviation

[b] Six participants were unable to cooperate with testing: 2 Prazosin, 4 Placebo

Table 2

Behavioral Responses to Prazosin versus Placebo: Behavior Scores Presented as Mean ± Standard Deviation

	Baseline (n=22)	Change from baseline for participants remaining at each time point					Mean group change[a]	Test statistic[b]	P[b]
		Week 1 (n=22)	Week 2 (n=19)	Week 4 (n=15)	Week 6 (n=13)	Week 8 (n=13)			
N									
Prazosin	11	11	10	8	7	7			
Placebo	11	9[c]	9	7	6	6			
NPI									
Prazosin	49 ± 16	-20 ± 19	-16 ± 23	-16 ± 25	-15 ± 24	-13 ± 23	-19 ± 21	X^2=6.32	.012
Placebo	43 ± 18	-5 ± 17	-2 ± 21	4 ± 17	-1 ± 14	5 ± 21	-2 ± 15		
BPRS									
Prazosin	45 ± 8	-9 ± 8	-8 ± 10	-7 ± 13	-7 ± 9	-9 ± 8	-9 ± 9	X^2=4.42	.036
Placebo	44 ± 7	-3 ± 7	-5 ± 7	-2 ± 6	-3 ± 8	3 ± 5	-3 ± 5		
CGIC									
Prazosin							2.6 ± 1.0	Z=2.57	.011
Placebo							4.5 ± 1.6		

[a] For the NPI and BPRS, mean group change was determined by calculating the mean of each participant's follow-up measures, subtracting this mean from the baseline value, and then from these values, calculating group means and standard deviations. This reflects a group change for participants who had at least one follow-up measure. For the CGIC, the mean is shown.

[b] For the NPI and BPRS, the likelihood ratio chi-square test (df=1) for the significance of the post- vs. pre-treatment change x treatment group interaction from linear mixed effects models of behavior score on treatment group and time of treatment (pre vs. post). For the CGIC, the Mann-Whitney test.

[c] 2 subjects were not present for their 1 week visit but did return for subsequent visits.

Table 3

Adverse Experiences

	Prazosin	Placebo	All
Sedation	3	3	6
Confusion	1	4	5
Lower extremity edema[a]	1	2	3
Hypotension[b]	2	1	3
Headache	0	2	2
Cough	2	0	2
Hallucinations	1	1	2
Dizziness on standing	1	0	1
Rash[c]	0	1	1

[a] One participant in each group terminated from the study early because of edema

[b] One participant in each group terminated from the study early because of hypotension; one participant in the prazosin group had hypotension resolve when concomitant antihypertensive medications were adjusted

[c] One participant in the placebo group terminated from the study early because of rash