Prophylactic Treatment of Migraine With an Angiotensin II Receptor Blocker
A Randomized Controlled Trial

Erling Tronvik, MD
Lars J. Stovner, PhD
Grethe Helde, RN
Trond Sand, PhD
Gunnar Bovim, PhD

Context There is a paucity of effective, well-tolerated drugs available for migraine prophylaxis.

Objective To determine whether treatment with the angiotensin II receptor blocker candesartan is effective as a migraine-prophylactic drug.

Design and Setting Randomized, double-blind, placebo-controlled crossover study performed in a Norwegian neurological outpatient clinic from January 2001 to February 2002.

Patients Sixty patients aged 18 to 65 years with 2 to 6 migraine attacks per month were recruited mainly from newspaper advertisements.

Interventions A placebo run-in period of 4 weeks was followed by two 12-week treatment periods separated by 4 weeks of placebo washout. Thirty patients were randomly assigned to receive one 16-mg candesartan cilexetil tablet daily in the first treatment period followed by 1 placebo tablet daily in the second period. The remaining 30 received placebo followed by candesartan.

Main Outcome Measures The primary end point was number of days with headache; secondary end points included hours with headache, days with migraine, hours with migraine, headache severity index, level of disability, doses of triptans, doses of analgesics, acceptability of treatment, days of sick leave, and quality-of-life variables on the Short Form 36 questionnaire.

Results In a period of 12 weeks, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan ($P=.001$) in the intention-to-treat analysis (n=57). Some secondary end points also favored candesartan, including hours with headache (139 vs 95; $P<.001$), days with migraine (12.6 vs 9.0; $P<.001$), hours with migraine (92.2 vs 59.4; $P<.001$), headache severity index (293 vs 191; $P<.001$), level of disability (20.6 vs 14.1; $P<.001$) and days of sick leave (3.9 vs 1.4; $P=.01$), although there were no significant differences in health-related quality of life. The number of candesartan responders (reduction of ≥50% compared with placebo) was 18 (31.6%) of 57 for days with headache and 23 (40.4%) of 57 for days with migraine. Adverse events were similar in the 2 periods.

Conclusion In this study, the angiotensin II receptor blocker candesartan provided effective migraine prophylaxis, with a tolerability profile comparable with that of placebo.
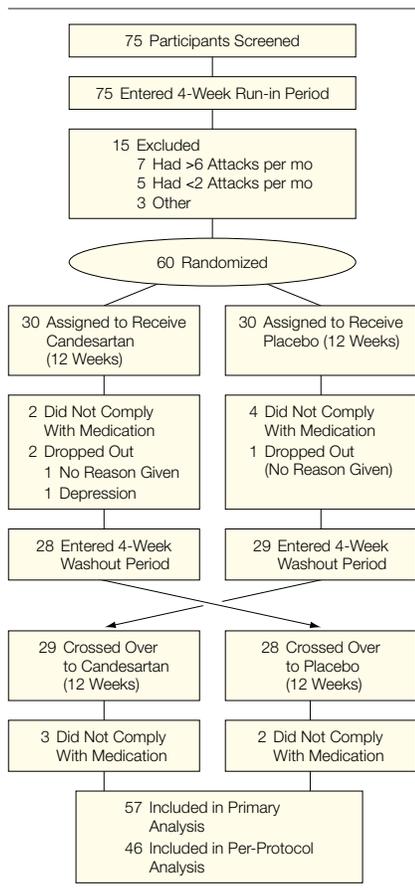
JAMA. 2003;289:65-69   www.jama.com

WORLDWIDE, APPROXI- mately 240 million people have an esti- mated 1.4 billion at- tacks of migraine each year.[1] The effect of this illness on society has been char- acterized by the World Health Organi- zation using the Global Burden of Dis- ease scale,[2] which includes severe migraine in the highest disability class (together with active psychosis, de- mentia, and quadriplegia), emphasiz- ing that this illness represents a seri- ous health problem both for individuals and for society.

Triptans are a major contribution to migraine management, but only about 50% to 60% of patients consistently respond to this type of medication,[3] and in many, it provides only partial relief. Prophylactic treatment is indi- cated if acute treatment alone is inad- equate and if patients experience 2 or more migraine attacks per month. The prophylactic agents available today have limited efficacy and may cause adverse effects not compatible with long-term use.

The angiotensin-converting enzyme (ACE) inhibitor lisinopril has been found to be an effective prophylactic treatment for frequent migraine at-

tacks.[4] Angiotensin II receptor block- ers provide specific blockade of the re- nin-angiotensin system by competing directly with angiotensin II at its recep- tor, blocking the effects of angiotensin

Figure. Flow of Participants Through the Trial

ache was registered indicated that the risk of headache was about one third lower in patients taking an angiotensin II receptor blocker compared with those taking placebo.[8] Randomized trials of patients with specific headache conditions are needed to prove an effect, however.

The objective of this study was to investigate the use of candesartan as a migraine-prophylactic agent, using a randomized, double-blind, placebo-controlled, crossover design.

METHODS
Study Design and Participants
The study was conducted in the Department of Neurology of the University Hospital of Trondheim, Norway, between January 2001 and February 2002 and followed the guidelines recommended by the International Headache Society (IHS) Committee on Clinical Trials in Migraine[9] with 1 exception. We used the number of headache days as the primary efficacy outcome instead of the recommended "frequency of attacks per 4 weeks." The crossover design was chosen for this single-center study because it requires fewer patients than does a parallel-group design. The study included a 4-week placebo run-in period to verify the frequency of attacks, followed by two 12-week treatment periods separated by 4 weeks of placebo washout. Of the 60 patients included, 57 were recruited from newspaper advertisements and 3 from our outpatient clinic. The protocol and informed consent were approved by the regional ethics committee. Written informed consent was obtained for all patients.

Inclusion criteria were age 18 to 65 years, migraine occurrence with or without aura according to IHS criteria at a rate of 2 to 6 attacks per month, and debut of migraine attacks at least 1 year prior to randomization and before age 50 years.

Exclusion criteria were interval headache not distinguishable from migraine headache; pregnancy, nursing, or inability to use contraceptives in women; decreased hepatic or renal function; hypersensitivity to active substance; previous history of angioneurotic edema;

psychiatric illness preventing full participation; use of daily migraine prophylactics in 12 weeks prior to start of study; having used more than 1 migraine prophylactic prior to study; and cardiac problems or use of diuretics.

Eligible patients underwent physical and neurological examinations, and blood samples were taken for routine hematological and chemistry workups. Medical histories and demographic information were obtained. Participants were instructed to keep headache diaries recording headache duration and severity, level of disability, nausea, vomiting, photophobia/phonophobia, acute medication use, headache characteristics, days of sick leave, and adverse events. In addition, the Short Form 36 (SF-36) quality-of-life questionnaire[10] was completed on each visit.

After a 4-week single-blind placebo run-in period to verify the frequency of attacks, the participants were randomized by a computer-generated randomization scheme to receive either active medication (candesartan cilexetil, one 16-mg tablet daily) or placebo. Patients had a total of 4 visits with a physician: an initial enrollment visit (screening in week 0), a randomization visit (at week 4), and visits after each treatment period (at weeks 17 and 32). In addition, blood pressure was measured and routine blood samples taken by a study nurse 2 weeks after the start of each treatment period. In weeks 12 and 27, participants were telephoned by the study nurse to ensure that possible adverse events were logged. Compliance with treatment was defined as more than 80% of tablets taken as scheduled during each treatment period (determined by tablet count). A summary profile of the trial is presented in the **Figure**. The tablets (active and placebo) that were used in the study had the same size, weight, taste, and appearance to ensure blindness. No specific testing was done to examine if patients could distinguish active drug from placebo, but no patient had used candesartan prior to the study and there was no indication that any of the participants could differentiate between the tablets in the 2 study periods.

II produced by both ACE and non-ACE pathways. Since angiotensin II receptor blockers do not interfere with bradykinin, substance P, or tachykinin metabolism, the usual potential adverse effects associated with ACE inhibitors, such as coughing[5] and angioneurotic edema,[6] are greatly reduced.

Candesartan is a long-acting angiotensin II type 1 (AT_1) receptor blocker with a high affinity for the AT_1 receptor. In clinical studies, this substance has an adverse event profile similar to that of placebo.[7] If the migraine-prophylactic effect of the ACE inhibitor lisinopril is linked to its ability to reduce the level of angiotensin II, angiotensin II receptor blockers could theoretically have the same or better effect on migraine. A recently published meta-analysis involving 12 000 patients who were treated for other conditions but in whom head-

Efficacy Outcomes and Statistical Analysis

The primary efficacy outcome measure was days with headache, recorded by patients in daily diaries. Secondary efficacy outcome measures were hours with headache, days with migraine, hours with migraine, headache severity index (calculated as headache hours multiplied by the reported maximum severity on that day [grades 1-4] and subsequently adding the results for all headache days during the 12 weeks of either treatment period), level of disability (grades 0-3), doses of triptans, doses of analgesics, acceptability of treatment (whether the medication received in each treatment period was something the participant would consider continue using as a prescription), days of sick leave, and health-related quality of life (measured by the SF-36).

For each efficacy outcome measure, a candesartan responder was recorded when a symptom reduction of at least 50% was observed in the candesartan period compared with the placebo period, a definition that is in accordance with IHS guidelines[9] and that was used in the lisinopril study.[4] In addition, we recorded those with at least a 50% symptom reduction in the placebo period compared with the candesartan period. Analysis of responders was performed for the total treatment period as well as for the first, second, and third months separately.

The statistical software SPSS version 10.0 (SPSS Inc, Chicago, Ill) was used in the analyses. Prior to the study, we calculated that with a study group of 60 patients, the power to detect a mean placebo-candesartan difference of 0.6 SD (2-sided $\alpha = .05$) would be 93%. To compare end-point variables and to assess carryover or period effects, the Wilcoxon signed rank test was used. The McNemar matched-pairs test was used to compare adverse events. A 2-sided $P < .05$ was considered significant. The number of placebo vs candesartan responders was tested in the subgroup of responders with a binomial test.

RESULTS

Of the 60 patients randomized, there were 3 dropouts; 2 withdrew with no reason given (both in the first period; 1 in the placebo group and 1 in the candesartan group) and 1 withdrew from the study because of depression (first period; candesartan group). Eight were noncompliers with regard to tablet intake but kept a diary for the entire study period. Of these, 1 started a selective serotonin reuptake inhibitor for depression (first period; placebo group), 1 started a β-blocker for supraventricular tachycardia (second period; placebo group), 4 stopped taking tablets because of dizziness (2 in the first period; 1 in the placebo group and 1 in the candesartan group and 2 in the second period; both in the candesartan group), 1 had only a 2-week washout and 1 was noncompliant in both treatment periods. In addition, 3 had days with no diary entries. When patients failed to enter data in their diaries, missing data were imputed from the mean values of that measure for the remaining days of the treatment period.

The intention-to-treat (ITT) analysis was performed on 57 patients, including the 11 noncompliers. The 45 women had a mean (SD) age of 42 (11) years and the 12 men were aged 48 (12) years. Forty-six patients (35 women, mean (SD) age, 42 [12] years; 11 men, age 48 [13] years) completed the study strictly according to protocol.

In the ITT analysis (TABLE 1), differences between candesartan and placebo were significant in favor of candesartan for number of days with headache, headache hours, number of days with migraine, migraine hours, headache severity index, level of disability, doses of triptans, and doses of analgesics. In the per protocol analysis, similar results were observed, with a relative reduction in headache days of 22% ($P = .001$), 25% for headache hours ($P = .001$), 27% for migraine days ($P < .001$), 36% for migraine hours ($P < .001$), 33% for headache severity index ($P < .001$), 33% for

Table 1. Intention-to-Treat Analysis of Efficacy Outcomes in 57 Migraine Patients During 12-Week Treatment Periods

	Outcome, Mean (SD)		Reduction With Candesartan		P Value*
	Candesartan	Placebo	Mean (SD)	Percentage	
Headache days (primary efficacy measure)	13.6 (10.7)	18.5 (12.5)	4.9 (10.6)	26	.001
Secondary efficacy measures					
Headache hours	95.0 (118)	139 (146)	43.9 (105)	31	<.001
Migraine days	9.0 (8.6)	12.6 (8.2)	3.5 (6.4)	28	<.001
Migraine hours	59.4 (66.6)	92.2 (76.8)	32.8 (61.7)	36	<.001
Headache severity index†	191 (249)	293 (290)	102 (210)	35	<.001
Triptan doses	6.9 (10.3)	9.5 (14)	2.6 (10.0)	27	.03
Analgesic doses	12.7 (18.3)	18.9 (30.6)	6.2 (22.0)	33	.02
Disability level	14.1 (15.4)	20.6 (14.3)	6.5 (10.8)	32	<.001
Sick leave days	1.4 (5.2)	3.9 (12.0)	2.5 (8.9)	64	.01

*Calculated by the Wilcoxon signed rank test.
†See "Methods" section of text for explanation of headache severity index.

Table 2. Responders in the Intention-to-Treat Analysis (n = 57)*

	No. (%)		P Value†
	Candesartan	Placebo	
Headache days	18 (31.6)	1 (1.8)	.001
Headache hours	20 (35.1)	1 (1.8)	<.001
Migraine days	23 (40.4)	2 (3.5)	<.001
Migraine hours	26 (45.6)	1 (1.8)	<.001
Headache severity index	23 (40.4)	2 (3.5)	<.001

*Response defined as a 50% reduction or more in efficacy measure vs placebo.
†Calculated by binomial test in the subgroup of responders.

Table 3. Outcomes in Run-in Period Compared With Candesartan and Placebo Periods (n = 57)

	Outcome, Mean (SD) per 4 Weeks			Reduction From Run-in, %	
	Run-in	Candesartan	Placebo	Candesartan	Placebo
Headache days	8.4 (3.9)	4.6 (3.6)	6.2 (4.2)	45.6	26.3
Migraine days	5.7 (2.9)	3.0 (2.9)	4.2 (2.8)	47.2	26.5
Headache hours	59.1 (50.3)	31.7 (39.3)	46.3 (48.6)	46.4	21.6
Migraine hours	42.8 (34.5)	19.8 (22.2)	30.7 (25.6)	53.8	28.2
Headache severity index*	128 (130)	63.7 (82.9)	97.8 (96.5)	50.4	23.8
Triptan doses	3.8 (4.6)	2.3 (3.4)	3.2 (4.7)	39.2	16.3
Analgesic doses	7.0 (10.0)	4.2 (6.1)	6.2 (10.2)	39.9	12.1
Disability level	9.7 (6.4)	4.7 (5.1)	6.9 (4.8)	51.2	29.0
Sick leave days	1.00 (2.00)	0.47 (1.74)	1.30 (4.00)	53.0	−30.0

*See "Methods" section of text for explanation of headache severity index.

Table 4. Number of Adverse Events in Candesartan and Placebo Periods (n = 57)*

Adverse Events	Candesartan	Placebo
At least 1 symptom	26	27
Symptoms in musculoskeletal system	6	8
Fracture	0	1
Dizziness	11	9
Tendency to faint	0	2
Fatigue	4	2
Upper respiratory tract infection	4	9
Other infection	2	6
Cough	0	1
Cardiac problems	0	1
Gastrointestinal problems	2	3
Rash	1	0
Other	2	2
Total	32	44

*$P > .99$ by the McNemar matched-pairs test of comparison of pooled effects for no adverse events vs at least 1 symptom (2×2 table).

disability level ($P < .001$), 19% for triptan doses ($P = .03$), and 32% for analgesic doses ($P = .02$) (complete data available from the author). The reduction of sick leave days of 44% was marginally nonsignificant ($P = .05$). Treatment was acceptable for 37 of 46 in the candesartan period and 24 of 46 in the placebo period ($P = .001$). Health-related quality of life (SF-36) showed no significant differences.

The percentage of candesartan responders varied from 32% to 46% for the different outcome variables in the ITT analysis (TABLE 2) and from 33 to 48% in the per-protocol analysis. Only 2% to 4% had more than a 50% reduction in each outcome measure with placebo compared with candesartan.

Compared with baseline data (ITT analysis) from the 4-week run-in period (TABLE 3), treatment with candesartan resulted in a 46% relative reduction of days with headache, a 47% relative reduction of days with migraine, a 46% relative reduction of headache hours, and a 54% relative reduction of migraine hours. The relative reduction for these outcomes in the placebo period also ranged from 22% to 28% (Table 3).

During the placebo and candesartan periods, respectively, mean (SD) blood pressures were 126/77 (20/11) mm Hg and 115/70 (16/10) mm Hg ($P < .001$ for systolic and diastolic pressure), and mean (SD) pulse rates were 70 (5) beats/min and 69 (5) beats/min ($P = .76$) There was no significant difference in adverse events between the candesartan and placebo groups (TABLE 4) despite that patients used 16 mg/d of candesartan from the start of the treatment period instead of beginning with the usual starting dose of 8 mg/d. Among the 4 noncompliers who stopped taking tablets because of dizziness, 3 were taking candesartan and 1 was taking placebo. We found no carryover or period effects.

To assess the onset of the antimigraine effect, we compared the number of responders in each month of the 2 treatment periods (eg, month 1 in the candesartan period compared with month 1 in the placebo period). A treatment effect was observed during the first month (21/57 responders taking candesartan and 7/57 responders taking placebo) and remained relatively stable throughout the second (17/57 vs 7/57) and third (20/57 vs 6/57) months.

COMMENT

In our study, candesartan reduced the number of headache days, migraine days, and migraine hours compared with placebo, and 32% to 46% of patients were responders with at least a 50% reduction on at least 1 of the efficacy outcomes. We used number of headache days as a primary efficacy outcome instead of the recommended "attacks per 4 weeks" because we considered number of headache days to be a more robust and conservative parameter. Use of triptans may make it difficult to distinguish between separate attacks, and the participants would also have had to record exactly when each headache started and stopped. Since our headache diary was already quite extensive, we feared that this might cause an even higher dropout rate.

A comparison between candesartan and other drugs used for migraine prophylaxis is difficult to perform because of differences in design and end points. Many studies also report results as differences from baseline instead of in comparison with placebo. β-Blockers, calcium channel blockers, and valproic acid are the medications used as first-line migraine-prophylactic therapies.[11] In a meta-analysis of propranolol, 160 mg/d, for prophylaxis of migraine including 53 studies (both open and controlled) and 2403 patients, Holroyd et al[12] reported a relative improvement of 33% with regard to headache index with active medication compared with placebo, which is similar to the results of the present study (33% in the per-protocol analysis and 35% in the ITT analysis). In comparative studies, no significant differences in headache indexes were found for flunarizine, the most thoroughly investigated calcium channel antagonist, compared with the β-blockers propranolol or metoprolol.[13] In a recent multicenter controlled trial in which flunarizine was compared with propranolol, 160 mg/d, there was a 59% reduction of mean number of hours with migraine during flunarizine and propranolol treatment com-

pared with the run-in period.[14] This treatment effect is on the same order of magnitude as that of the present study (54%). For valproate, a double-blind, placebo controlled study showed a reduction in migraine hours of 38% compared with placebo,[15] and we found a reduction of 36% for this outcome. Double-blind, placebo-controlled studies of valproate based on comparison to baseline also show a relative reduction of migraine frequency of 30% to 40%.[16]

Our comparison with baseline (run-in) headache frequency showed substantial effects of both candesartan and placebo. A meta-analysis quantifying the placebo response of prophylactic therapy in migraine demonstrated a mean (SD) reduction in migraine attacks of 16.8% (12.7%) (95% confidence interval, 10.9%-22.6%) in the placebo groups.[17] Our placebo response was somewhat larger than anticipated. One explanation may be that many patients volunteer for migraine treatment studies at a time when their disorder is at a higher level than usual. Baseline comparisons may therefore give too optimistic results.

The mechanism of action of candesartan as a migraine prophylactic is not yet known. The main rationale for the present trial was the positive effect of the ACE inhibitor lisinopril in migraine prophylaxis.[2] Candesartan reduces the effects of angiotensin II, which has several effects that may be relevant to migraine, such as direct vasoconstriction, increased sympathetic discharge, and adrenal medullary catecholamine release. In addition to its traditional role as a circulating hormone, angiotensin is also involved in local functions through activity of tissue renin-angiotensin systems that occur in many organs, including the brain (both systemic and presumptive neurally derived angiotensin).[18] Acting through the AT_1 receptor in the brain, angiotensin modulates cerebrovascular flow[19] and has effects on fluid and electrolyte homeostasis, autonomic pathways, and neuroendocrine systems. It is thought that angiotensin II modulates both potassium channels and calcium activity in cells.[18] Angiotensin II

has also been shown in rat brains to increase the level of both dopamine and the main serotonin metabolite, 5HIAA, and to exert a significant influence on the tonic modulation of pineal melatonin synthesis.[20,21]

In addition, angiotensin II has been shown to activate nuclear factor kappa B, which is associated with increased expression of inducible nitric oxide synthase.[22,23] These effects of angiotensin II may be targets for further research on the pathogenesis of migraine.

Several characteristics of candesartan may make it suitable as a migraine prophylactic drug. In this study, the incidence of adverse effects attributable to candesartan was similar to that for placebo, and it has no significant drug interactions.[24] In contrast with β-blockers, candesartan does not affect pulse rate, is not associated with sexual dysfunction and can be used safely in patients with asthma.[25] The incidence of cough, which is a common adverse effect of ACE inhibitors, is low.[24]

Our findings suggest that the angiotensin II receptor blocker candesartan might be a useful agent for migraine prophylaxis. Larger studies to confirm our results are warranted.

Author Affiliations: Department of Neurology and Clinical Neurophysiology, Norwegian University of Science and Technology, Trondheim, Norway.

REFERENCES

1. Phillips P. Migraine as a woman's issue—will research and new treatments help? *JAMA*. 1998;280(23):1975-1976.
2. *Challenges for the 21st Century: A Gender Perspective on Nutrition Through the Life Cycle.* ACC/SCN symposium report, nutrition policy paper 17; November 1998:82. Available at: http://acc.unsystem.org/scn/Publications/NPP/npp17.pdf. Accessed May 12, 2002.
3. Ferrari MD, Roon KI, Lipton RB, et al. Oral Triptans (serotonin 5-HT agonists) in acute migraine treatment. *Lancet*. 2001;358:1668-1675.
4. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril). *BMJ*. 2001;322:19-22.
5. Lalloo UG, Barnes PJ, Chung KF. Pathophysiology and clinical presentations of cough. *J Allergy Clin Immunol*. 1996;98:S91-S96.
6. Pillans PI, Coulter DM, Black P. Angiooedema and urticaria with angiotensin converting enzyme inhibitors. *Eur J Clin Pharmacol*. 1996;51:123-126.
7. Stoukides CA, McVoy HJ, Kaul AF. Candesartan cilexetil: an angiotensin II receptor blocker. *Ann Pharmacother*. 1999;33:1287-1298.
8. Etminan M, Mitchell A, Levine MA, et al. Efficacy of angiotensin II receptor antagonists in preventing headache. *Am J Med*. 2002;112:642-646.
9. Tfelt-Hansen P, Block G, Dahlof C, et al. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia*. 2000;20:765-786.
10. Ware JE, Gandek B, for the IQOLA Project Group. The SF-36 health survey: development and use in mental health research and the IQOLA project. *Int J Mental Health*. 1994;23:49-73.
11. Limmroth V, Michel MC. The prevention of migraine. *Br J Clin Pharmacol*. 2001;52:237-243.
12. Holroyd KA, Penzien DB, Cordingley GE. Propranolol in the management of recurrent migraine: a meta-analytic review. *Headache*. 1991;31:333-340.
13. Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. Available at: http://www.aoa-net.org/MembersOnly/hcprevent.pdf. Accessed May 12, 2002.
14. Diener HC, Matias-Guiu J, Hartung E, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses. *Cephalalgia*. 2002;22:209-221.
15. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. *Cephalalgia*. 1992;12:81-84.
16. Mathew NT. Antiepileptic drugs in migraine prevention. *Headache*. 2001;41:S18-S24.
17. van der Kuy PH, Lohman JJ. A quantification of the placebo response in migraine prophylaxis. *Cephalalgia*. 2002;22:265-270.
18. Allen AM, Moeller I, Jenkins TA, et al. Angiotensin receptors in the nervous system. *Brain Res Bull*. 1998;47:17-28.
19. Nishimura Y, Ito T, Saavedra JM. Angiotensin II AT_1 blockade normalizes cerebrovascular autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats. *Stroke*. 2000;31:2478-2486.
20. Mendelsohn FA, Jenkins TA, Berkovic SF. Effects of angiotensin II on dopamine and serotonin turnover in the striatum of conscious rats. *Brain Res*. 1993;613:221-229.
21. Baltatu O, Afeche SC, Jose dos Santos SH, et al. Locally synthesized angiotensin modulates pineal melatonin generation. *J Neurochem*. 2002;80:328-334.
22. Reuter U, Chiarugi A, Bolay H, Moskowitz MA. Nuclear factor-kappa B as a molecular target for migraine therapy. *Ann Neurol*. 2002;51:507-516.
23. Lorenzo O, Ruiz-Ortega M, Suzuki Y, et al. Angiotensin III activates nuclear transcription factor-kappa B in cultured mesangial cells via AT_2 receptors. *J Am Soc Nephrol*. 2002;13:1162-1171.
24. Kirk JK. Angiotensin-II receptor antagonists: their place in therapy. *Am Fam Physician*. 1999;59:3140-3148.
25. Tanaka H, Teramoto S, Oashi K, et al. Effects of candesartan on cough and bronchial hyperresponsives in mildly to moderately hypertensive patients with symptomatic asthma. *Circulation*. 2001;104:281-285.