Antiaggressive Effect of Cyproterone Versus Haloperidol in Alzheimer's Disease: A Randomized Double-Blind Pilot Study

David Huertas, M.D., Ph.D.; Juan J. López-Ibor Aliño, M.D., Ph.D.; Juan D. Molina, M.D., Ph.D.; Lorenzo Chamorro, M.D.; Juana Balanza, M.D.; María P. Jiménez, M.D.; and Mercedes Hornillos, M.D., Ph.D.

Objective: Alzheimer's disease (AD) is commonly accompanied by aggressive behavior. In the elderly, effective and safe antiaggressive treatment is lacking. Risks of antipsychotics in this population demand therapeutic alternatives. This randomized, double-blind, pilot trial examined the efficacy and safety of cyproterone in the treatment of agitated AD.

Method: The subjects were 27 elderly patients referred to the University Hospital of Guadalajara Psychogeriatric Clinic diagnosed with AD and associated aggressive behavior (mean Staff Observation Aggression Scale [SOAS] score ≥ 2). Each patient underwent a 15-day washout for psychotropics and then was randomly assigned to receive stable doses of either cyproterone (100 mg/day) or haloperidol (2 mg/day) for 90 days. The primary outcome measure was the SOAS score. This trial was conducted between October 27, 1993, and March 24, 1998.

Results: Of the 27 patients, 19 (70.4%) were women, and the mean age was 80.7 years. The trial was completed by 24 (88.9%) of the subjects (13 in the cyproterone group and 11 in the haloperidol group for 90 days). Three patients (11.1%) dropped out, all after adverse effects in the haloperidol group. Baseline aggression level in the sample was mild (mean SOAS score of 4.48 [SD = 2.04]). Efficacy analyses for all intent-to-treat patients showed that 9 (69.2%) in the cyproterone group achieved complete elimination of aggression at endpoint, in contrast to 2 patients (14.2%) in the haloperidol group ($p = .012$). Ten patients (71.4%) taking haloperidol had adverse events, compared with 4 (30.7%) taking cyproterone ($p = .035$).

Conclusion: Cyproterone showed significantly better efficacy and safety than haloperidol in controlling mild aggression associated with AD. Additional research is needed to confirm if these results can be ratified in a larger study and generalized to patients whose aggression is more severe.

(J Clin Psychiatry 2007;68:439–444)

Received May 8, 2006; accepted Aug. 29, 2006. From the University of Alcalá, Madrid (Drs. Huertas, Chamorro, and Hornillos); the Department of Psychiatry (Drs. Huertas, Chamorro, and Balanza), and the Department of Geriatric Medicine (Drs. Jiménez and Hornillos), University Hospital of Guadalajara, Guadalajara; the Complutense University of Madrid (Drs. López-Ibor Aliño and Balanza); the Institute of Psychiatry and Mental Health, San Carlos University Hospital (Dr. López-Ibor Aliño); University Camilo José Cela and the Department of Psychiatry, Dr. Rodríguez Lafora Hospital (Dr. Molina), Madrid, Spain; and the Linda Pollin Institute, Harvard Medical School, Boston, Mass. (Dr. Huertas).

This investigator-initiated study was supported by a grant from the Social Security Investigation Fund, Spanish National Institute of Health (No. 93/1317).

The authors acknowledge Jan Volavka, M.D., Ph.D., from New York University, for his contributions to the correction of earlier versions of the paper and editorial assistance; and Fernando Carballo, M.D., Ph.D., from the University Hospital of Guadalajara Research Unit (currently employed by the University of Alcalá, Madrid, Spain), who served as project manager from 1993 to 1998, for his support with data analysis and guidance. These individuals disclose no conflict of interest.

The authors report no other significant commercial relationships relevant to the study.

Corresponding author and reprints: David Huertas, M.D., Ph.D., Servicio de Psiquiatría, Hospital Universitario de Guadalajara, Donantes de Sangre s/n, 19002 Guadalajara, Spain (e-mail: davhuertas@inicia.es).

Behavioral disturbances complicate all types of dementia in up to 70% of cases.[1] There is an elevated occurrence of aggression in Alzheimer's disease (AD),[2] mostly in the form of violent resistance to cooperating in daily life activities.

Aggressive behavior in AD patients poses a serious management problem. It causes severe distress to primary caregivers and burnout in nursing staff. It is common that carers ask for medical assistance not because of the memory loss itself, but because of a crisis elicited when the patient becomes aggressive. In addition, patients with agitated dementia are frequently treated with sedative drugs that may contribute to a worsening in cognition and behavior.

Hostility in AD has been associated with a reduction in the prefrontal serotonergic control over behavior[3,4] and with an increase in the subcortical androgenic activity.[5] Testosterone tends to block brain serotonergic control on the expression of aggression.[6] Physical aggression in dementia showed a significant positive correlation with elevated free testosterone in plasma and a negative correlation with estrogen levels.[7,8]

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

Numerous drugs have been investigated in the search for a specific antiaggressive action in dementia with disappointing results in most of the cases.[9] Many psychotropics administered at high doses may reduce aggression through a general sedative effect on behavior. Conventional antipsychotics are frequently prescribed in agitated dementia.[9] However, their benefit is quite limited.[10] The atypical or second-generation antipsychotics have a better tolerability profile than the classical ones, and their antiaggressive effect seems to be independent of both the antipsychotic and sedative effects.[9] Nonetheless, clozapine use is not recommended in elders because of the risks of agranulocytosis, significant anticholinergic effects, and seizures. In spite of the positive data with risperidone[11] and olanzapine[12] in the control of agitated dementia, concerns have arisen about their use in the geriatric population because of the increased risk of cerebrovascular events,[13–16] even though the increased mortality from all atypical antipsychotics in patients with dementia seems to be small and similar to the risk of death among elderly persons receiving conventional antipsychotics.[17,18]

The absence of satisfactory results with the available pharmacotherapies in controlling aggressive behavior in AD motivates investigations of new therapeutic alternatives. Antiandrogens have been used in the treatment of paraphilic sexual violence in all age groups.[19–22] Thus, the effectiveness of cyproterone acetate[23] and of medroxyprogesterone acetate[24,25] has been confirmed in the treatment of elderly men with aggressive hypersexuality. There are also studies on the application of cyproterone to treat nonsexual aggression associated with psychosis[26,27] or dementia.[28] In this sense, several authors have stressed the role of testosterone in the regulation of human aggressive behavior.[29–31]

Collectively, these findings provided an impetus to evaluate the efficacy and safety of cyproterone in controlling aggression associated with AD.

METHOD

The primary objective of the study was to determine if the antiandrogen cyproterone acetate was significantly superior to haloperidol in the control of aggression secondary to AD. The secondary objective of the clinical trial was to compare the safety profile of the 2 products in this particular population.

Bioethics

The study was designed and carried out in accordance with the Helsinki Declaration.[32] The protocol was authorized by the University Hospital of Guadalajara (Guadalajara, Spain) Clinical Research Ethical Committee and by the Spanish Ministry of Health, Division of Pharmacy and Drug Administration, Madrid, Spain. All eligible patients, or their legal representatives when considered incompetent for decision making, signed the informed consent before initiating their participation in the study.

Patient Selection

Eligible patients were required to be 40 years or older, to show a clinical suspicion of dementia (development of cognitive deterioration for greater than 6 months) according to ICD-10[33] criteria; to fulfill the criteria of primary degenerative dementia of the Alzheimer's type in agreement with DSM-III-R[34] requirements as well as with the NINCDS-ADRDA (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association)[35] directives for the diagnosis of possible or probable AD according to the available standards of 1993; and to have evidence of verbal and/or physical aggression associated with AD demonstrated by a mean score on the Staff Observation Aggression Scale (SOAS)[36] ≥ 2 after a 15-day washout for psychotropics.

Excluded were patients with a diagnosis of dementia secondary to another cerebral pathology, patients with a contraindication to treatment with cyproterone or haloperidol, and patients with ethanol abuse or dependency, depression, chronic delusional disorder, schizophrenia, or the need for concomitant psychopharmacologic treatment.

Trial Design

This was an investigator-initiated, randomized, double-blind, parallel-group, 105-day pilot trial conducted between October 27, 1993, and March 24, 1998, at the University Hospital of Guadalajara Psychogeriatric Clinic in Guadalajara, Spain.

Eligible patients were evaluated for baseline level of aggression after a single-blind psychotropic washout during 15 days. After a baseline SOAS score ≥ 2 had been confirmed, each patient was randomly assigned to a double-blinded treatment group during 90 days, either with cyproterone (fixed dose of 100 mg/day) or with haloperidol (fixed dose of 2 mg/day). The individual doses of drugs were prepared by the University Hospital of Guadalajara Pharmacy Service, in the form of identical capsules containing a powder base of each of the active ingredients provided by their respective manufacturers together with an authorized excipient. In all cases, the concomitant use of substances with psychotropic effects was prohibited, including benzodiazepines and hypnotic products. All patients had to abstain from any ethanol consumption throughout the study.

Assessments

Data collection points were (1) baseline (after a 15-day washout for psychotropics), (2) mid-treatment

(60-day, after 45 days of treatment), (3) and endpoint (105-day, after 90 days of treatment).

Sociodemographic variables of the sample were collected in a questionnaire (age, gender, and place of residence). The cognitive status of the patients was determined with the Mini-Mental State Examination (MMSE).[37]

Aggression was scored on the SOAS. It is a reporting scale applied by the observer at the actual moment of the aggression episode. It measures 5 differentiated aspects: provocation, the means that are used, the aim of the aggression, consequences for the victim, and the measures adopted to halt the aggression. The global severity of an aggressive event is defined by the sum of the 3 items "Means," "Aim," and "Result." The aggressive episodes are divided into 3 categories: mild (2–5 points), moderate (6–8 points), and severe (at least 9 points). In a recent revision, the scale was demonstrated to be valid and sensitive to change.[38] Other researchers have confirmed the validity of this instrument in measuring aggressive behavior among psychogeriatric patients.[39] In our study, the SOAS evaluation was completed immediately after every episode of aggression by health care staff or the main caretaker of the patient who were previously trained in the understanding and application of the scale. All fulfilled SOAS evaluations of each patient were collected from the caregivers and rated by the clinical investigators at baseline, mid-treatment, and endpoint.

The safety of both study drugs was assessed at each visit by means of medical and neurologic examination, clinical laboratory tests, electrocardiogram, and registration of adverse reactions.

Data Analyses

Mid-treatment (60-day) and endpoint (105-day) analyses of data from all randomly assigned patients who received at least 1 dose of study medication and at least 1 postbaseline assessment were performed. Efficacy analyses were done separately for the intent-to-treat population (27 subjects) and the by-protocol population (24 subjects after 3 dropouts). Safety analysis was based on the intent-to-treat population.

Response was defined for each subject as a reduction ≥ 2 points in the mean after-treatment SOAS score with respect to the subject's mean baseline score (scored before any treatment and after a psychotropic washout). Remission was defined as complete elimination of aggression after treatment (final SOAS score = 0).

The team of statisticians at the University Hospital of Guadalajara Research Unit used Epi Info 5.2 software (Centers for Disease Control, Atlanta, Ga.). The sample was characterized by means of descriptive statistics, expressing the qualitative variables (gender and place of residence) in the form of percentiles, and the quantitative variables (age, baseline MMSE score, baseline SOAS score) with their values of central tendency (mean) and standard deviation (SD). Between-group baseline means in MMSE and SOAS scores were compared using Student t tests (t). The differences in response (reduction of ≥ 2 points from baseline in mean final SOAS score) and remission (final SOAS = 0) rates between treatment groups were calculated applying a χ^2 statistic with Yates correction. To determine a clinically significant difference between treatment groups (effect size), the risk difference (RD) with its corresponding 95% confidence interval (95% CI) was analyzed via 2-tailed Fisher exact probability tests. The incidence of adverse events in each treatment group was described in percentiles. Between-group comparison of safety data was obtained by using a Pearson χ^2 test with its effect size factor (RD with its 95% CI). All statistical tests were interpreted at a 5% significance level (2-tailed) with 80% power.

RESULTS

A total of 27 patients were included in the study, 13 (48.1%) were randomly assigned to be treated with cyproterone and 14 (51.9%) with haloperidol. The trial was completed by 24 subjects (88.9%), and 3 (11.1%) prematurely discontinued the study after adverse reactions to the haloperidol treatment although they were evaluated until 60-day and subsequently classified as dropouts.

Demographic and Other Baseline Characteristics

The mean age of the sample was 80.7 years (SD = 7.02), with 8 male (29.6%) and 19 female (70.4%) patients. Of those, 18.5% (N = 5) resided in their homes or in the home of a relative, whereas 81.5% (N = 22) were institutionalized in a nursing home. The mean baseline score on the MMSE for the complete sample was 6.89 (SD = 5.07), and the mean baseline SOAS score was 4.48 (SD = 2.04), in the range of mild aggression.

The demographic and baseline clinical characteristics of the patients in each treatment group were homogenous in all parameters except gender, which, in spite of randomization, was distributed unevenly between the groups (p = .047). There were no significant differences between treatment groups with respect to other baseline data (Table 1).

Efficacy Analyses

The results for the intent-to-treat sample are depicted in Table 2 and Figure 1. At mid-treatment (60-day, after 45 days of treatment), the difference in the response rate between groups was not statistically significant. At endpoint (105-day, after 90 days of treatment), 12 (92.3%) of the 13 cyproterone patients responded and 9 (69.2%) remitted, compared with 3 (21.4%) of the 14 haloperidol

Table 1. Sociodemographic and Other Baseline Characteristics of Elderly Patients With Alzheimer's Disease and Associated Aggression

Characteristic	Cyproterone (N = 13)	Haloperidol (N = 14)	t (df = 1)	χ^2 With Yates Correction (df = 1)	p Value
Age, mean (SD), y	81.6 (6.86)	79.9 (7.32)	0.64	NA	.525
Women, N (%)	12 (92.3)	7 (50.0)	NA	3.94	.047
Placed in nursing home, N (%)	11 (84.6)	11 (78.6)	NA	0.01	.926
Baseline MMSE score, mean (SD)	6.9 (5.28)	6.8 (5.08)	0.03	NA	.974
Baseline SOAS score, mean (SD)	3.9 (1.40)	4.9 (2.45)	1.23	NA	.227

Abbreviations: MMSE = Mini-Mental State Examination, NA = not applicable, SOAS = Staff Observation Aggression Scale.

Table 2. Efficacy Analyses for All Intent-to-Treat Patients

Outcome	Cyproterone (N = 13), N (%)	Haloperidol (N = 14), N (%)	χ^2 With Yates Correction (df = 1)	Risk Difference (95% CI) 2-Tailed Fisher Exact Test (df = 1)	p Value
Mid-treatment (60-day)[a]					
Response[b]	8 (61.5)	5 (35.7)	0.91	NA*	.339
Endpoint (105-day)[c]					
Response[b]	12 (92.3)	3 (21.4)	10.99	70.88% (44.96 to 96.80)	.0009
Remission[d]	9 (69.2)	2 (14.3)	6.31	54.95% (23.87 to 86.02)	.012

[a]After 45 days of treatment.
[b]Response = mean SOAS score reduction ≥ 2 points from baseline.
[c]After 90 days of treatment.
[d]Remission = final SOAS score of 0.
*OR (95% CI) = 0.35 (0.05 to 2.16).
Abbreviations: NA = not applicable, SOAS = Staff Observation Aggression Scale.

patients responding and 2 (14.3%) remitting. These group differences were statistically significant (Table 2). Efficacy analyses of the by-protocol sample yielded very similar results (available on request).

The mean MMSE score for the complete sample was 6.11 (SD = 5.54) at mid-treatment and 5.54 (SD = 5.64) at endpoint. Between-group MMSE comparison at these assessment points did not show significant differences (p = .615 and p = .941, respectively).

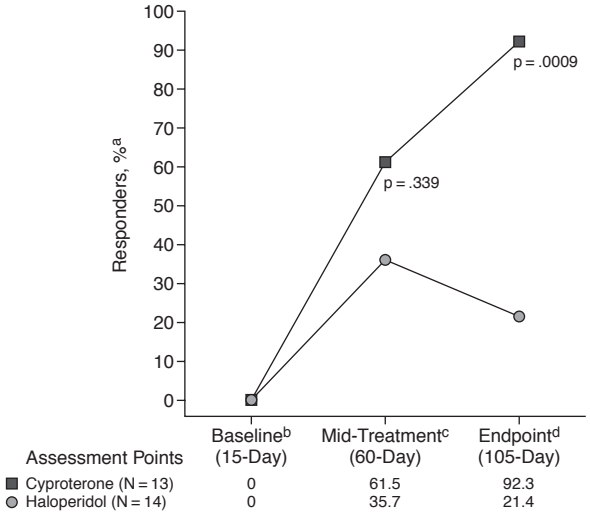
Safety Evaluation

The results of safety assessments are summarized in Table 3. Three patients (11.1%) discontinued the trial early. All were in the haloperidol group and left the study because of adverse reactions (1 parkinsonism, 1 corrected QT interval [QTc] prolongation, and 1 exfoliative dermatitis), whereas in the cyproterone group there were no discontinuations. In the intention-to-treat population (N = 27), the total number of patients with adverse events at endpoint in the haloperidol group was 10 (71.4%) (5 showed parkinsonism, 2 sedation, 1 QTc prolongation, 1 dry mouth, and 1 exfoliative dermatitis) as compared with 4 (30.8%) of the subjects in the cyproterone group (2 patients displayed fatigue, 1 anxiety, and 1 mild hyperbilirubinaemia without any other significant data indicating liver failure or cholestasis). No patient under cyproterone treatment showed symptoms, signs, or analytic data of a genotoxic effect on hepatocytes. The analysis of the difference in safety between treatment groups showed a significantly higher risk of adverse reactions with haloperidol than with cyproterone (Table 3).

DISCUSSION

Using a rigorous study design, the main hypothesis of the study was confirmed. The results demonstrate that cyproterone was superior to haloperidol in terms of reduction and complete elimination of mild aggression associated with AD. These findings are consistent with previous studies demonstrating a role of testosterone in the modulation of aggressive behavior.[5–9,29–31] It is noteworthy that even though the antiaggressive effect of cyproterone has been reported for isolated cases of mental retardation, childhood psychosis, and schizophrenia,[26,27] and for 19 patients with severe dementia in an open-label preliminary study,[28] its use in the control of aggressive behavior secondary to dementia has not yet been systematically investigated. On the other hand, the low efficacy of haloperidol found in our study population is consistent with the data presented in the meta-analysis by Schneider et al.[10] The MMSE mean score got worse throughout the 105 days of study for both groups, as would be expected from the natural evolution of AD. Hence, the improvement in behavior cannot be attributed to a clinical improvement in the state of dementia.

Figure 1. Between-Group Comparison of Response Rates at Mid-Treatment and Endpoint for All Intent-to-Treat Patients



[a]Response = Mean Staff Observation Aggression Scale score reduction of 2 points or more from baseline.
[b]After a 15-day washout for psychotropics.
[c]After 45 days of treatment.
[d]After 90 days of treatment.

Table 3. Safety Analysis for All Intent-to-Treat Patients at Endpoint

Adverse Event	Cyproterone (N = 13), N (%)	Haloperidol (N = 14), N (%)
Parkinsonism	0	5 (35.7)
Sedation	0	2 (14.3)
QTc prolongation	0	1 (7.1)
Dry mouth	0	1 (7.1)
Exfoliative dermatitis	0	1 (7.1)
Fatigue	2 (15.4)	0
Anxiety	1 (7.7)	0
Mild hyperbilirubinaemia	1 (7.7)	0
Total*	4 (30.8)	10 (71.4)

*χ^2 (Pearson test) = 4.46, risk difference (95% CI) = 40.66% (6.16 to 75.16), df = 1, p = .035.
Abbreviation: QTc = corrected QT interval.

The second hypothesis was also confirmed, although in a less conclusive manner. The treatment with cyproterone was significantly safer and better tolerated than the treatment with haloperidol. None of the subjects had to leave the protocol in the cyproterone group, while in the haloperidol group, 3 subjects had to discontinue due to adverse events. The between-group difference in discontinuation did not reach statistical significance, probably because of the small sample size. There were significantly more adverse events in the haloperidol than in the cyproterone group. One patient taking cyproterone developed mild elevation in bilirubin concentrations at endpoint. Since there were no other significant clinical or laboratory abnormalities indicating liver failure or cholestasis, the patient's discontinuation was not deemed necessary by a geriatrician.

As to the potential risk of cyproterone in high doses to induce hepatotoxicity[40,41] or a genotoxic effect on hepatocytes,[42,43] the data have not been conclusive. The studies of clinical follow-up in large groups of patients that were administered cyproterone show an overall good tolerability and safety profile.[20,44–46] The use of cyproterone in the geriatric population presents potential disadvantages such as the appearance of depression[46] or adynamia,[47] although their frequency and intensity are not very significant. In addition, liver function and glucose metabolism should be controlled. Impotence and azoospermia do not represent a significant risk in the male population with AD.

In accordance with the meta-analysis by Lonergan et al.,[1] our results advise against the chronic use of haloperidol in patients with agitated dementia, while the antiaggressive effect of cyproterone shows promise in the long-term treatment of these patients.

The study has certain limitations. The small sample size could limit the external validity of the research. Even though the differences found with 27 patients were significant, the study should be replicated with a larger sample. One of the consequences of the small sample size was the gender imbalance between the treatment groups that occurred in spite of randomization. The mild level of baseline aggression in the sample may also represent a limitation of the study, because it is unclear if the results would generalize to patients whose aggression is more severe.

CONCLUSION

The results of the present clinical trial demonstrate that the treatment with cyproterone produces a noticeable reduction of aggression secondary to AD. The antiaggressive effects of cyproterone were not related to sedative or antipsychotic properties of the medication, nor to a clinical improvement in the state of dementia. This suggests a specific action on the aggressive behavior. In addition, the safety profile of cyproterone in our population was satisfactory, and significantly superior to haloperidol. No patient experienced serious adverse reactions or had to discontinue the protocol because of intolerance of cyproterone. There were no signs of severe hepatotoxicity or of hepatic or mammary genotoxicity. Further controlled clinical trials with larger group sizes and higher baseline aggression levels are needed to confirm these findings.

Drug names: clozapine (FazaClo, Clozaril, and others), medroxyprogesterone acetate (Provera and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. Cochrane Database Syst Rev 2002:CD002852
2. Jost BC, Grossberg GT. The evolution of psychiatric symptoms in Alzheimer's disease: a natural history study. J Am Geriatr Soc 1996;44: 1078–1081
3. Lanctot KL, Herrmann N, Eryavec G, et al. Central serotonergic activity is related to the aggressive behaviors of Alzheimer's disease. Neuropsychopharmacology 2002;27:646–654
4. Lai MK, Tsang SW, Francis PT, et al. Reduced serotonin 5-HT1A receptor binding in the temporal cortex correlates with aggressive behavior in Alzheimer disease. Brain Res 2003;974:82–87
5. Huertas D. Agresividad en las Disfunciones Cerebrales. In: Huertas D, López-Ibor Aliño JJ, Crespo Hervás MD, eds. Neurobiología de la Agresividad Humana. Barcelona, Spain: Ars Médica; 2005:77–99
6. Birger M, Swartz M, Cohen D, et al. Aggression: the testosterone-serotonin link. Isr Med Assoc J 2003;5:653–658
7. Orengo CA, Kunik ME, Ghusn H, et al. Correlation of testosterone with aggression in demented elderly men. J Nerv Ment Dis 1997;185:349–351
8. Orengo CA, Kunik ME, Molinari V, et al. Do testosterone levels relate to aggression in elderly men with dementia? J Neuropsychiatry Clin Neurosci 2002;14:161–166
9. Volavka J, Citrome L, Huertas D. Update on the biological treatment of aggression. Actas Esp Psiquiatr 2006;34:123–135
10. Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38: 553–563
11. Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:134–143
12. Street JS, Clark WS, Kadam DL, et al. Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer's dementia. Int J Geriatr Psychiatry 2001;16 (suppl 1):S62–S70
13. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry 2004;161:1113–1115
14. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. CMAJ 2002;167:1269–1270
15. Wooltorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. CMAJ 2004;170:1395
16. Bullock R. Treatment of behavioural and psychiatric symptoms in dementia: implications of recent safety warnings. Curr Med Res Opin 2005;21:1–10
17. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medication. N Engl J Med 2005;353:2335–2341
18. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943
19. Laschet U, Laschet L, Fetzner HR, et al. Results in the treatment of hyper- or abnormal sexuality of men with antiandrogens [abstract]. Acta Endocrinológica 1967;119(suppl):54
20. Neumann F, Kalmus J. Cyproterone acetate in the treatment of sexual disorders: pharmacological base and clinical experience. Exp Clin Endocrinol 1991;98:71–80
21. Krueger RB, Kaplan MS. Depot-leuprolide acetate for treatment of paraphilias: a report of twelve cases. Arch Sex Behav 2001;30:409–422
22. Czerny JP, Briken P, Berner W. Antihormonal treatment of paraphilic patients in German forensic psychiatric clinics. Eur Psychiatry 2002;17: 104–106
23. Davies TS. Cyproterone acetate for male hypersexuality. J Int Med Res 1974;2:159–163
24. Cooper AJ. Medroxyprogesterone acetate (MPA) treatment of sexual acting out in men suffering from dementia. J Clin Psychiatry 1987;48:368–370
25. Weiner MF, Denke M, Williams K, et al. Intramuscular medroxyprogesterone acetate for sexual aggression in elderly men [letter]. Lancet 1992;339:1121–1122
26. Thibaut F, Kuhn JM, Colonna L. A possible antiaggressive effect of cyproterone acetate [letter]. Br J Psychiatry 1991;159:298–299
27. Thibaut F, Colonna L. Cyproterone acetate in the treatment of aggression [letter]. Am J Psychiatry 1992;149:411
28. Caparros-Lefebvre D, Dewailly D. Preliminary pilot study of cyproterone acetate for the treatment of aggressive behavior associated with severe dementia. Rev Neurol (Paris) 2005;161:1071–1078
29. Christiansen K, Knussmann R. Androgen levels and components of aggressive behavior in men. Horm Behav 1987;21:170–180
30. Christiansen K. Behavioural effects of androgen in men and women. J Endocrinol 2001;170:39–48
31. Rubinow DR, Schmidt PJ. Androgens, brain and behavior. Am J Psychiatry 1996;153:974–983
32. World Medical Association. Declaration of Helsinki. In: Beauchamp TL, Walters L, eds. Contemporary Issues in Bioethics, 3rd ed. Belmont, Calif: Wadsworth Publishing Company; 1989:421–423
33. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Geneva, Switzerland: WHO; 1992
34. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987
35. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944
36. Palmstierna T, Wistedt B. Staff observation aggression scale, SOAS: presentation and evaluation. Acta Psychiatr Scand 1987;76:657–663
37. Folstein M, Folstein S, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
38. Nijman HL, Palmstierna T, Almvik R, et al. Fifteen years of research with the Staff Observation Aggression Scale: a review. Acta Psychiatr Scand 2005;111:12–21
39. Shah A, De T. The relationship between two scales measuring aggressive behavior among continuing-care psychogeriatric inpatients. Int Psychogeriatr 1997;9:471–477
40. Murphy BJ, Collins BJ. Severe hepatitis and liver failure induced by cyproterone acetate [letter]. Aust N Z J Med 1996;26:724
41. Giordano N, Nardi P, Santacroce C, et al. Acute hepatitis induced by cyproterone acetate. Ann Pharmacother 2001;35:1053–1055
42. Watanabe S, Yamasaki S, Tanae A, et al. Three cases of hepatocellular carcinoma among cyproterone users [letter]. Lancet 1994;344:1567–1568
43. Rüdiger T, Beckmann J, Queisser W. Hepatocellular carcinoma after treatment with cyproterone acetate combined with ethinylestradiol [letter]. Lancet 1995;345:452–453
44. Kaiser E, Gruner HS. Liver structure and function during long-term treatment with cyproterone acetate. Arch Gynecol 1987;240:217–223
45. Rabe T, Feldmann K, Heinemann L, et al. Cyproterone acetate: is it hepato- or genotoxic? Drug Saf 1996;14:25–38
46. Regidor PA, Speer K, Regidor M, et al. Long-term side-effects following cyproterone acetate containing therapy in gynecology. Zentralbl Gynakol 2000;122:268–273
47. Goldenberg SL, Bruchovsky N. Use of cyproterone acetate in prostate cancer. Urol Clin North Am 1991;18:111–122

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Alzheimer's Disease and Related Disorders section. Please contact Eric M. Reiman, M.D., at Eric.Reiman@bannerhealth.com.

