

Effects of the Traditional Chinese Herbal Medicine *Yi-Gan San* for Cholinesterase Inhibitor-Resistant Visual Hallucinations and Neuropsychiatric Symptoms in Patients With Dementia With Lewy Bodies

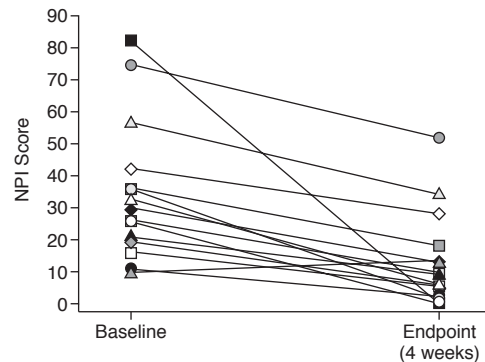
Sir: Dementia with Lewy bodies (DLB) is characterized clinically by progressive and fluctuating cognitive decline, visual hallucinations, and parkinsonism.¹ Some studies have reported that cholinesterase inhibitors are at least partially beneficial for treating patients with DLB.²⁻⁴ However, Shea et al.⁵ reported that cholinesterase inhibitors occasionally caused deterioration of parkinsonian symptoms in patients with DLB. Use of neuroleptics is also considered, but patients with DLB are particularly sensitive to neuroleptics and occasionally experience fatal extrapyramidal symptoms.⁶ Recently, we reported that the traditional Chinese medicine *Yi-Gan San* (YGS) reduced behavioral and psychological symptoms and improved activities of daily living (ADL) in dementia patients.⁷ In that study, YGS was successfully used to treat visual hallucinations in 6 patients with DLB. In the study described here, we expanded on our earlier observations on more generalized neuropsychiatric symptoms by using the Neuropsychiatric Inventory (NPI)⁸ and individual interviews to assess YGS treatment in a sample of patients who had cholinesterase inhibitor-resistant visual hallucinations and other symptoms of DLB.

Method. From January 2004 through February 2005, we enrolled 14 probable DLB patients (9 men and 5 women, mean age = 73.3 years), diagnosed according to the international consensus criteria for DLB,¹ who had visual hallucinations. The patients had taken donepezil for at least 6 months. However, their hallucinations and other psychiatric symptoms were only partially and unsatisfactorily controlled. One 67-year-old woman, also with DLB accompanied by dementia, who stopped taking donepezil because of adverse gastrointestinal effects 2 months before the start of the study was also included. With written consent from the patients or their families, donepezil therapy was discontinued.

After a 1-month washout, we examined global cognitive function using the Mini-Mental State Examination (MMSE),⁹ ADL using the Barthel Index,¹⁰ and behavioral and psychological symptoms using the NPI. These assessments provided baseline values. Patients then received YGS according to the published protocol.⁷ After the 4-week trial, the NPI, the MMSE, and the Barthel Index were administered again. Differences between means for each data set (i.e., NPI, MMSE, and Barthel Index) in patients before and after YGS therapy were assessed using the Student paired t test. A p value of less than .05 was considered significant. Patients and their families were interviewed regarding the details of the visual hallucinations and the time elapsed between the initiation of YGS and disappearance of hallucinations.

Results. As shown in Figure 1, total NPI scores improved significantly, declining from a mean \pm SD of 34.7 ± 21.8 to 13.5 ± 14.5 after 4 weeks of treatment ($p = .0008$, 95% CI = -32.0 to -10.5). The NPI hallucination subscale scores also significantly improved from 7.5 ± 3.3 to 1.5 ± 1.8 ($p < .0001$, 95% CI = -8.0 to -4.1). Twelve of 15 patients reported that their visual hallucinations disappeared within 2 weeks. Barthel Index scores also significantly improved from 76.6 ± 28.3 to 82.2 ± 24.4 ($p = .0027$, 95% CI = 2.3 to 8.9), but MMSE scores did not change significantly (from 17.5 ± 6.8 to 18.6 ± 7.9).

Figure 1. Effect of *Yi-Gan San* Treatment on Neuropsychiatric Inventory (NPI) Scores in Patients With Dementia With Lewy Bodies (N = 15)^a



^aMean \pm SD NPI score decreased from 34.7 ± 21.8 at baseline to 13.5 ± 14.5 at endpoint; $p = .0008$.

One patient, a 75-year-old woman, discontinued YGS at 1 month because of drowsiness. The other 14 patients have continued to take YGS for 2 to 16 months (mean = 9.0 ± 5.2 months) and remain on the treatment up to the present date. The only recurrence of hallucinations occurred in 2 patients after 1 year of YGS treatment. We have examined the patients' vital signs, neurologic symptoms, liver and renal function, serum electrolyte levels, and blood cell counts every 3 months and noted no values outside normal limits.

Despite a small sample size, these results suggest that YGS may be a safe and well-tolerated treatment for hallucinations and other psychiatric problems among patients with DLB and represents the first of a new class of neurotropic drugs. Larger controlled trials are encouraged.

This research was supported in part by grant #(c)17590592 provided by the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Drs. Iwasaki, Maruyama, Tomita, Furukawa, Nemoto, Fujiwara, Seki, Fujii, Kodama, and Arai report no other financial relationships relevant to the subject of this letter.

REFERENCES

- McKeith IG, Perry EK, Perry RH, for the Consortium on Dementia with Lewy Bodies. Report of the second dementia with Lewy body international workshop: diagnosis and treatment. *Neurology* 1999; 53:902-905
- McKeith I, Del Ser T, Spano P. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000;356: 2031-2036
- Terao T, Shimomura T, Nakamura J. Can donepezil be considered a mild antipsychotic in dementia treatment? a report of donepezil use in 6 patients [letter]. *J Clin Psychiatry* 2003;64:1392-1393
- Campbell S, Stephens S, Ballard C. Dementia with Lewy bodies: clinical features and treatment. *Drugs Aging* 2001;18:397-407
- Shea C, MacKnight C, Rockwood K. Donepezil for treatment of dementia with Lewy bodies: a case series of nine patients. *Int Psychogeriatr* 1998;10:229-238
- Baskys A. Lewy body dementia: the litmus test for neuroleptic sensitivity and extrapyramidal symptoms. *J Clin Psychiatry*

2004;65(suppl 11):16–22

7. Iwasaki K, Satoh-Nakagawa T, Maruyama M, et al. A randomized observer-blind controlled trial of a traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. *J Clin Psychiatry* 2005;66:248–252
8. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:3208–3214
9. Folstein MF, Folstein SE, 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
10. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14:56–61

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Omega-3 Fatty Acids Are More Beneficial in the Depressive Phase Than in the Manic Phase in Patients With Bipolar I Disorder

Sir: We read with interest the recent (June 2005) report by Osher et al.¹ that described the potential effectiveness of omega-3 polyunsaturated fatty acids (PUFAs) in the treatment of bipolar depression.¹ In 1999, Stoll et al.² found that adjunctive treatment with omega-3 PUFAs had a mood-stabilizing effect in patients with bipolar disorder in their 4-month double-blind, placebo-controlled study. In our reexamination of the data reported by Stoll et al., we³ found that all “non-completed” cases (3 of 14 cases) in the omega-3 group developed a manic episode, whereas the depressive symptoms in all but 1 of the non-completed cases (10 of 16 cases), in the placebo group worsened. This observation suggests that omega-3 PUFAs could prevent depression but not mania in patients with bipolar disorders.³ Although several clinical trials support the antidepressant effect of omega-3 PUFAs in unipolar depression,^{4,6} the report by Osher and colleagues¹ is the first (per a MEDLINE search from 1999 through 2005) to support the effectiveness of omega-3 PUFAs in the treatment of bipolar depression, years after the study by Stoll and colleagues was reported.¹ To our knowledge, there have been no reports that describe the effectiveness of omega-3 PUFAs in the acute manic phase of bipolar disorder.

Method. We conducted a double-blind placebo-controlled trial, approved by the institutional review board of Taipei City Psychiatric Center, to test the effectiveness of omega-3 PUFAs in the augmentation of existing treatment of acute mania. Eligible participants were newly hospitalized patients in the acute manic phase of bipolar disorder. Written informed consent was obtained before recruitment. Patients were then interviewed and diagnosed according to the DSM-IV diagnostic criteria for bipolar disorder, manic episode, and confirmed to have a minimum score of 20 on the Young Mania Rating Scale (YMRS)⁷ by an experienced psychiatrist (C.-C. Chiu). Excluded were patients who had the mixed type of bipolar disorder, physical illnesses, substance dependence, or other Axis I psychiatric disorders or who were at serious risk of suicide or violence.

After a medication washout period of 2 to 4 days, participants were randomly assigned to either the omega-3 PUFAs group or the placebo group. All patients began to receive a fixed dose of valproate, 20 mg/kg/day, and 5 identical-appearing gelatin capsules twice daily. The identical-appearing gelatin capsules contained concentrated omega-3 fatty acids (eicosapentaenoic acid [EPA, 440 mg] and docosahexaenoic acid [DHA, 240 mg]) for the omega-3 PUFAs group and olive oil for the placebo group. Every capsule was vacuum deodorized and supplemented with tertiary-butylhydroquinone (0.2 mg/g) and tocopherols (2 mg/g) as antioxidants. During the study period, the use of concomitant medications was limited to lorazepam, up to 4 mg/day, for alleviating insomnia, agitation, and restlessness. No psychoactive drug was permitted.

The outcome measurements were the YMRS, the 21-item Hamilton Rating Scale for Depression (HAM-D),⁸ total score on the Positive and Negative Syndrome Scale (PANSS),⁹ and the Clinical Global Impressions Scale-Bipolar Version (CGI-BP),¹⁰ which were rated at weeks 0, 1, 2, 3, and 4. Between-group differences were examined by repeated-measures analysis of variance with time as the repeated factor, treatment group (placebo or omega-3 PUFAs) as the independent factor, and clinical characteristics as the covariates.

Results. Because the use of concomitant antipsychotic medications was prohibited, only 15 patients were enrolled in this study. One of them refused to continue in the study and withdrew the informed consent during the first week. Fourteen patients completed this study.

There were no statistical differences on any clinical characteristics (sex, age, age at illness onset, duration of illness, number of previous episodes, daily valproate dosage, serum levels of valproate, and dosages of lorazepam) between the 2 groups. Mean scores on the YMRS decreased significantly from week 0 to week 4 in both groups (from 36 to 15 in omega-3 PUFAs group, $p < .001$; and from 29 to 7 in the placebo group, $p = .002$). However, YMRS, PANSS, HAM-D, and CGI-BP scores were not statistically different between the 2 groups at weeks 0, 1, 2, 3 and 4, despite the fact that the time factor was taken into consideration in the repeated-measures analysis ($p = .875$).

One subject in the omega-3 PUFA group and 2 subjects in the placebo group reported soft stool or diarrhea. One patient in the placebo group and 2 patients in the omega-3 fatty acid group had body weight gain of more than 5% of baseline weight. These adverse effects could have been caused by valproate treatment.

Our findings suggest that there is no effectiveness produced by adding omega-3 PUFAs to valproate when treating acute bipolar mania. Caution needs be taken when interpreting these preliminary results. The antimanic effect of omega-3 PUFAs could be potentially masked by valproate combination

treatment in a sample this small, since valproate is well studied for acute mania and is generally associated with satisfactory outcomes. The sample size is small because it is difficult to enroll patients in accordance with our protocol that prohibits concomitant antipsychotic medications. In a meta-analysis, Tohen and colleagues¹¹ revealed that most (90.7%) bipolar inpatients receive at least 1 antipsychotic agent for their acute manic illness.

The results of this preliminary randomized controlled trial along with the results of the open-label study by Osher et al.¹ support our previous hypothesis that omega-3 PUFAs might be more beneficial in the depressive phase than in the manic phase of bipolar disorder.³

The work was supported by grants NSC 89-2314-B-109-005, 92-2314-B-109-003, and 93-2320-B-039-001 from the Taiwan National Science Council; grant DOH 94F044 from Taiwan Department of Health; and grant DMR-92-017 from China Medical University Hospital, Taichung, Taiwan.

Drs. Chiu, Huang, Chen, and Su report no other financial relationship relevant to the subject of this letter.

REFERENCES

- Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *J Clin Psychiatry* 2005;66:726-729
- Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407-412
- Su KP, Shen WW, Huang SY. Are omega3 fatty acids beneficial in depression but not mania? [letter] *Arch Gen Psychiatry* 2000;57:716-717
- Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* 2002;159:477-479
- Su KP, Huang SY, Chiu CC, et al. Omega-3 fatty acids in major depressive disorder: a preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol* 2003;13:267-271
- Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* 2002;59:913-919
- Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry* 1978;133:429-435
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-276
- Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res* 1997;73:159-171
- Tohen M, Zhang F, Taylor CC, et al. A meta-analysis of the use of typical antipsychotic agents in bipolar disorder. *J Affect Disord* 2001;65:85-93

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Hypotension Secondary to the Combination of Intramuscular Olanzapine and Intramuscular Lorazepam

Sir: An intramuscular (IM) formulation of olanzapine was approved by the U.S. Food and Drug Administration (FDA) in March 2004 for the treatment of agitation associated with schizophrenia and bipolar I disorder.¹ The package insert for IM olanzapine reports significant incidence of orthostatic hypotension in one third of nonagitated patients with schizophrenia who were treated with the maximum recommended dosage of olanzapine IM (three 10-mg doses administered 4 hours apart).¹ Forty-nine adverse events, 29 of which were deemed serious and 8, fatal, were reported in Europe.² In response, Eli Lilly Canada released a Dear Healthcare Professional letter in September 2004 warning of adverse events with IM olanzapine.² A similar letter was also distributed to health care professionals in Europe.³ The letters warn against the coadministration of IM olanzapine and parenteral benzodiazepine agents. No such letter was sent out in the United States, nor are we aware of any case reports in the literature to date of clinically significant hypotension resulting from administration of IM olanzapine. We report a case in which concomitant administration of IM olanzapine and IM lorazepam resulted in clinically significant hypotension in an acutely psychotic patient.

Case report. Mr. A, a 46-year-old African American man with paranoid schizophrenia, had a history of multiple lengthy admissions complicated by paranoid delusions about oral medications. He typically required initial treatment with injectable antipsychotics. In a previous admission (Oct. 2004), he was court ordered to receive IM olanzapine, which was effective and which he tolerated without adverse effects. He received 19 doses over a 10-day period before he was successfully switched to oral olanzapine and discharged to the community.

In a subsequent admission (June 2005), police brought Mr. A to the hospital after he threatened a local utility worker with a gun. Mr. A was paranoid and reluctant to answer questions, and he voiced concerns that members of the medical staff were imposters involved in a plot against him. He appeared to be responding to internal stimuli, whispering to unseen persons, but denied visual or auditory hallucinations. He became agitated and threatening when informed he would be admitted. Olanzapine, 10 mg IM, was administered in the urgent care center to facilitate transfer to an inpatient unit. Approximately 30 minutes after the injection of olanzapine, Mr. A was still agitated, and lorazepam, 2 mg IM, was given. Prior to the injections, his blood pressure was 124/74 mm Hg. Within 4 hours of receiving lorazepam, his blood pressure dropped to 80/37 mm Hg. He was lethargic and complained of dizziness. Two hours later, his blood pressure was 66/30 mm Hg, and fluids were administered. Despite hydration, he remained hypotensive and symptomatic with subsequent readings of 105/61, 98/53, and 90/49 mm Hg. Twelve hours later, his blood pressure returned to baseline at 122/64 mm Hg. He was rechallenge with IM olanzapine alone and his blood pressure was unaffected at 118/72 mg. He received 4 additional doses of IM olanzapine without incident. As his symptoms resolved, he agreed to take oral medications and was switched to oral olanzapine.

We scored this event using the Naranjo Causality Scale,⁴ a validated tool used to estimate the probability that an adverse drug reaction was caused by a suspected agent. This event rated a 6, which indicates a probable adverse drug reaction (score > 9 indicates a definite adverse drug reaction; 5-8, probable ad-

verse drug reaction; 1–4, possible adverse drug reaction; 0, doubtful adverse drug reaction).⁴ The combination of IM antipsychotics and benzodiazepines is widely used to treat acute psychotic agitation and is considered safe. This case identifies a potentially harmful drug interaction between 2 agents that are likely to be used in combination. Whether this is actually an interaction or just an additive effect of the 2 medications is unclear. It is also not known what effects other sedative agents known to decrease blood pressure, such as alcohol or oral benzodiazepines, have on parenteral olanzapine. There is a need for warning statements advising against the administration of the combination of IM olanzapine and IM benzodiazepines until more data are published.

Drs. Zacher and Roche-Desilets report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Zyprexa IntraMuscular [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2004
2. Eli Lilly and Company. Important Safety Information Regarding the Correct Use of Zyprexa Intramuscular. Dear Healthcare Professional Letter (Canada). September 7, 2004
3. Moran M. Zyprexa IM caution issued in some countries but not US. *Psychiatr News* 2005;40:1–6
4. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–245

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Placebo Response in Psychotic Depression

Sir: I read with interest the report by Simpson et al.¹ in the May 2005 issue of the *Journal*. While it is always gratifying to learn of the practical applications of one's research,^{2,3} the authors may be overinterpreting the significance of their open-label observations on the basis of a misconception of the placebo response in psychotic depression. The authors compared their observations with 2 historical studies^{4,5} that found "a low placebo response rate with psychotic depression."^{1(p601)} However, these 2 studies were single-blind placebo run-ins of short duration (5 days to 2 weeks). A better comparison would have been with the only study to assess the placebo response rate in psychotic depression using a double-blind placebo-controlled paradigm,⁶ in which a 28% to 31% placebo response rate was observed in an 8-week study of hospitalized patients.

Curiously, the authors observed, using a last-observation-carried-forward repeated-measure analysis, a 75% decrease in Hamilton Rating Scale for Depression scores, but not in Brief Psychiatric Rating Scale scores, with mifepristone treatment. This is the opposite of what one would have expected on the basis of the hypothesis that the hypercortisolemia in psychotic depression is playing a role in the development of the psychosis, but not necessarily the depression.^{2,3}

As the authors point out, the study has several problems, including lack of placebo control, a nonblind paradigm, lack of weekly ratings on all measures, no statistical tests to assess interrater reliability, and no systematic collection of side effect data. In addition, no standardized instrument was used for diagnosis despite the fact that psychotic depression is very

difficult to diagnose and is often confused with other psychiatric disorders.^{7–9}

The authors should be commended for undertaking a study in this severely ill patient population. However, without standardized diagnostic instruments or a placebo control, the results should be interpreted with caution. Furthermore, without any hypothalamic-pituitary-adrenal axis measures in the study, the statement by the authors that their observations indicate "a resetting of the glucocorticoid system that impacts the expression of psychotic depression"^{1(p601)} must be viewed as pure speculation. Future studies of medications for which governmental approval for the treatment of psychotic depression is being sought must include a standardized diagnostic instrument as well as a double-blind placebo-controlled study paradigm.

Dr. Rothschild reports no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Simpson GM, El Sheshai A, Loza N, et al. An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* 2005;66:598–602
2. Schatzberg AF, Rothschild AJ, Langlais PJ, et al. A corticosteroid/dopamine hypothesis for psychotic depression and related states. *J Psychiatr Res* 1985;19:57–64
3. Schatzberg AF, Rothschild AJ. The roles of glucocorticoid and dopaminergic systems in delusional (psychotic) depression. *Ann N Y Acad Sci* 1988;537:462–471
4. Glassman AH, Roose SP. Delusional depression: a distinct clinical entity? *Arch Gen Psychiatry* 1981;38:424–427
5. Chan CH, Janicak PG, Davis JM, et al. Response of psychotic and nonpsychotic depressed patients to tricyclic antidepressants. *J Clin Psychiatry* 1987;48:197–200
6. Rothschild AJ, Williamson DJ, Tohen MF, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *J Clin Psychopharmacol* 2004;24:365–373
7. Rothschild AJ, Phillips KA. Selective serotonin reuptake inhibitors and delusional depression [letter]. *Am J Psychiatry* 1999;156:977–978
8. Rothschild AJ. Challenges in the treatment of depression with psychotic features. *Biol Psychiatry* 2003;53:680–690
9. Rothschild AJ, Winer J, Flint A, et al. Accuracy of the diagnosis of psychotic depression at four academic medical centers. In: *New Research Abstracts of the 158th Annual Meeting of the American Psychiatric Association*; May 21–26, 2005; Atlanta, Ga. Abstract NR 291:22

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Drs. Simpson and Kingsbury Reply

Sir: We thank Dr. Rothschild for his comments on our recent article and for the opportunity to respond to his criticisms. We do not believe that we overinterpreted the significance of our results.

Dr. Rothschild quotes his own 2 identical studies,¹ which included some 30 sites. However, the remission rate ranged from 8% with placebo to 23% with the active combination of drugs. In the first trial, the response rate was 28% with placebo and 64% with active treatment, i.e., olanzapine plus fluoxetine, ($p = .004$). In the second trial, the response rate with placebo was 32%, and the response rate with active treatment was 48%. In the second trial, the response rate with active treatment did

not differ significantly from the response rate with placebo. Our study showed a 75% response rate and a 55% remission rate with mifepristone. Although Dr. Rothschild comments that the HAM-D showed a 75% reduction but not the BPRS, both the HAM-D and the BPRS scores decreased significantly from baseline ($p < .001$ for both).² We think these changes demonstrate more than a placebo response.

The question of diagnosis is an interesting one. Each subject's diagnosis was independently confirmed using DSM-IV criteria by an experienced psychiatrist at each of the 2 sites.² In a previous study at one of the sites,³ 32% of patients with psychotic depression responded to 8 weeks of sertraline as opposed to 68% of nonpsychotic patients, with 32% of nonpsychotic and 68% of psychotic depression patients eventually receiving ECT. The number of responders approximates the placebo response rate in Dr. Rothschild's study, but is very different from the results with mifepristone in our study.²

Dr. Rothschild's final paragraph baffles us. He writes, "The statement by the authors that their observations indicate 'a resetting of the glucocorticoid system' must be viewed as pure speculation." What we clearly wrote was, "If replicated, these findings would suggest a resetting of the glucocorticoid system. . . ."^{2(p601)}

The study referred to in this letter was an investigator-initiated and investigator-funded study, including purchase of the medication.

Drs. Simpson and Kingsbury report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Rothschild AJ, Williamson DJ, Tohen MF, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *J Clin Psychopharmacol* 2004;24:365-373
2. Simpson GM, El Sheshai A, Loza N, et al. An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* 2005;66:598-602
3. Simpson GM, El Sheshai A, Rady A, et al. Sertraline as monotherapy in the treatment of psychotic and nonpsychotic depression. *J Clin Psychiatry* 2003;64:959-965

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Clonidine-Induced Gynecomastia and Hyperprolactinemia in a 6-Year-Old Child

Sir: Clonidine, an α_2 -adrenergic receptor agonist, has been used in children with attention-deficit/hyperactivity disorder (ADHD).¹ Although there are several reports of gynecomastia and hyperprolactinemia induced by antihypertensive agents,² to my knowledge there is no report of gynecomastia associated with clonidine treatment.

Case report. A 6-year-old boy presented in 2004 with a 1-year history of hyperactivity, inattentiveness, irritability, and easy distractibility. He fulfilled DSM-IV criteria for ADHD, for which treatment with methylphenidate, 20 mg/day was started, which led to no improvement. After 3 months, methylphenidate

was replaced by clonidine. The initial clonidine dose was 0.1 mg/day, and over a 3-week period the dosage was increased to 0.3 mg/day.

The patient's personal history revealed that, at the age of 4 years, he had experienced a single attack of generalized tonic-clonic seizure. Since then, he had been taking sodium valproate 100 mg/day continually with no further seizure attacks or adverse reactions. He had no family history of either neurologic or endocrinologic disorders.

At week 4 of clonidine therapy (0.3 mg/day), his mother noticed a swelling in both of his breasts. She did not, however, reveal this to the physician, as she thought it was normal. At the end of 8 weeks of clonidine therapy, at a regularly scheduled appointment, the patient's mother revealed this swelling to the treating psychiatrist. Local breast examination confirmed gynecomastia, 3 cm in diameter and 3 cm in height, with mild tenderness and without galactorrhea. The patient's serum prolactin level was found to be 37.5 mg/mL (normal range, 1.5-19.0 mg/mL). Further organic workup, including a computed tomographic scan of the head and a thyroid profile, revealed no further abnormalities. A possibility of clonidine-induced gynecomastia was considered, and clonidine was gradually tapered and stopped while treatment with sodium valproate, 100 mg/day, was continued. Within 3 weeks of stopping clonidine, there was marked reduction in the patient's gynecomastia, and his serum prolactin level decreased to within the normal range (7.0 mg/mL).

In our case, gynecomastia emerged while the patient was on treatment with clonidine and sodium valproate. Withdrawal of clonidine alone resulted in a return of his serum prolactin level to within the normal range and the disappearance of gynecomastia. This outcome suggests that clonidine was the only causative agent for gynecomastia. The exact underlying mechanism of this reaction is difficult to explain.

A computer search (PubMed; keywords: *clonidine*, *hyperprolactinemia*, and *gynecomastia*; range of dates: 1975 to 2005) and a manual search revealed no description of hyperprolactinemia and gynecomastia appearing as side effects of clonidine in children. However, I found 1 case report of persistent postpartum galactorrhea with hyperprolactinemia that accompanied treatment with clonidine; both galactorrhea and hyperprolactinemia disappeared when clonidine treatment was stopped.³

It is difficult to speculate about and generalize our findings on the basis of a single case report. Data on the side effects of chronic clonidine administration are sparse. Further systematic studies are required to discover endocrine disturbances associated with clonidine treatment in children with ADHD.

Dr. Mendhekar reports no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Biederman J, Spencer T, Wilens T. Evidence-based pharmacotherapy for attention-deficit hyperactivity disorder. *Int J Neuropsychopharmacol* 2004;7:77-97
2. Mosenkis A, Townsend RR. Gynecomastia and antihypertensive therapy. *J Clin Hypertens (Greenwich)* 2004;6:469-470
3. Heim J, Massart C, Auvray E, et al. Post-partum galactorrhea with hyperprolactinemia persistent during a clonidine treatment [in French]. *Sem Hop* 1979;55:1933-1934

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