Adjunctive Nadolol in the Treatment of Acutely Aggressive Schizophrenic Patients

Edward R. Allan, M.D., Murray Alpert, Ph.D., Cecile E. Sison, Ph.D., Leslie Citrome, M.D., Gabriel Laury, M.D., and Ileana Berman, M.D.

Background: This study assessed the safety and efficacy of nadolol 120 mg/day compared with placebo, when administered adjunctively to neuroleptic in a group of acutely aggressive schizophrenic patients.

Method: Thirty-four male patients enrolled in this double-blind, placebo-controlled trial. The subjects were evaluated with the Brief Psychiatric Rating Scale (BPRS) and the Simpson-Angus Neurologic Rating Scale for extrapyramidal effects. The total BPRS score as well as three factors, thought disturbance, hostility, and activation, was analyzed.

Results: Compared with those who received placebo, the patients taking nadolol showed significant improvement on total BPRS score, particularly on the thought disturbance and activation factors, after the first treatment week ($p = .05$). By the end of the second treatment week, the patients taking placebo also began to show improvement, and the group differences were no longer significant. The patients treated with nadolol showed significantly more improvement on Simpson-Angus scores than those who received placebo ($p = .03$). However, there was no significant correlation between BPRS and Simpson-Angus changes. In the nadolol group, patients with and without akathisia showed no significant difference in their BPRS scores.

Conclusion: These findings suggest that adjunctive nadolol may be useful in the treatment of acutely aggressive schizophrenic patients by inducing a more rapid and consistent decrease of overall psychiatric symptoms and by reducing the extrapyramidal effects. Our results raise the possibility that the mechanism of action of nadolol on psychiatric symptoms in schizophrenic patients may be different from the mechanism of improvement of neuroleptic-induced extrapyramidal symptoms and akathisia. Nadolol may be a helpful adjunctive treatment for schizophrenic patients in general and not just for those with a high hostility level.

(J Clin Psychiatry 1996;57:455–459)

Received Oct. 9, 1995; accepted June 12, 1996. From the Franklin Delano Roosevelt Veterans Affairs Hospital, Montrose (Drs. Allan, Sison, and Laury), the Mount Sinai School of Medicine, New York (Drs. Allan and Laury), the New York University Medical Center, New York (Drs. Alpert and Citrome), the Nathan S. Kline Institute for Psychiatric Research, Orangeburg, N.Y. (Dr. Citrome), and Taunton State Hospital, Harvard Medical School, Boston, Mass. (Dr. Berman).

Supported by a Department of Veterans Affairs Research Advisory Group grant.

The authors thank Abe Sudilovsky for his advice on the study and Demetra Pappas for her suggestions during manuscript preparation.

Reprint requests to: Edward R. Allan, M.D., Psychiatry Service, FDR VA Hospital, Box 100, Montrose, NY 10548.

The management of aggressive schizophrenic patients remains a challenge. A disturbance in noradrenergic arousal mechanisms has been implicated in episodes of aggressive behaviors, and investigators have documented that β-blockers may decrease aggressive or explosive behavior in patients with various psychiatric diagnoses.[1–7] More recently, two controlled, double-blind studies have examined aggressive psychiatric patients and have found that β-blockers may, indeed, cause a reduction in both psychiatric symptoms and aggressive incidents.[5,6] Ratey et al.[6] studied a group of aggressive psychiatric patients in a double-blind trial of adjunctive nadolol, a nonselective β-blocker with a long half-life, and placebo. This group found that nadolol was relatively well tolerated and that patients taking nadolol improved more than those taking placebo. Similarly, our group reported preliminary findings in a heterogeneous group of aggressive patients that suggested that nadolol improved psychiatric symptoms more than did placebo.[5] β-Blockers alone have been used in psychotic symptoms and may have a specific beneficial effect in schizophrenic patients.[8–11] Thus, β-blockers may show therapeutic action on specific schizophrenic signs and symptoms as well as on explosive behavioral dyscontrol.

Several pharmacodynamic mechanisms have been proposed for the antiaggressive and antipsychotic actions of β-blockers. Some who have studied patients receiving neuroleptics have suggested that the beneficial effect of β-blockers in aggressive psychiatric patients[12–15] may be due to the improvement of akathisia.[16–19] Others, however, have found that β-blockers may decrease psychiatric symptoms and violence through actions on the reticular central nervous system or even through potentiation of

neuroleptic actions.[20–27] β-Blockers have been tried for the treatment of psychotic symptoms directly without neuroleptics rather than adjunctively with neuroleptics.[7,8,11,28,29] These studies show a decrease in psychotic symptoms and suggest that β-blockers act through multiple pathways. Moreover, β-blockers have been shown to improve positive and negative symptoms significantly more than placebo in a group of schizophrenic patients showing no akathisia.[29]

Nadolol acts primarily in the periphery, posing a challenge for alternative hypotheses to explain putative action in schizophrenia and/or aggression. Although the majority of the aggressive patients in psychiatric hospitals have the diagnosis of chronic schizophrenia, there are no studies separately assessing the antiaggressive and antipsychotic effect of such agents in schizophrenic patients. Therefore, we examined the efficacy of nadolol used adjunctively to neuroleptic in acutely aggressive schizophrenic patients admitted to a Psychiatric Intensive Care Unit (PICU).

METHOD

Subjects

The subjects were recruited from those newly admitted (within 1 week) to a PICU because of aggressive behavior or imminent violence (i.e., assaultive behavior toward staff or other patients, destructive behavior directed to objects or self, threat to hurt self or others). Subjects were diagnosed by a psychiatrist (either G.L. or L.C.) and had to meet DSM-III-R criteria for chronic schizophrenia. All patients were treated with neuroleptic medication. To be included in the study, all patients had to be in stable medical condition according to a complete physical examination, electrocardiogram (ECG), and standard laboratory measures. Patients with organic brain syndrome were excluded from the study. Those with asthma, insulin-dependent diabetes mellitus, cardiac failure, or atrioventricular block were also excluded from the study, as well as those with low heart rate (less than 60) and blood pressure (systolic blood pressure below 90 and diastolic blood pressure lower than 60 mm Hg).

Procedure

The study was conducted in our PICU. The PICU[30] is a special unit designed to treat assaultive and suicidal patients and has a high staff-to-patient ratio and ample space to provide buffer zones between patients. Our PICU has a two-step level of care system. The first level involves continuous close observation of acutely suicidal and assaultive patients. Once patients are stabilized, they are transferred to the second level. The second level entails more privileges and less restrictions. The PICU staff is specially trained to recognize potentially violent behavior and promptly intervene to prevent or minimize assaultive and suicidal behavior.

The behavioral structure of the PICU permitted a double-blind comparison with placebo within the medicolegal constraints of a study of potentially violent patients, but required that the study design fit into the average 4-week stay and behavioral program of the PICU.

After providing informed consent, patients received lead-in placebo from 2 to 5 days, and then were randomly assigned to one of two treatment groups. One group began nadolol 80 mg/day for 1 week and then 120 mg/day for the following 2 weeks. Another group received matching placebo. Nadolol or placebo was added to each patient's current psychiatric medication. All subjects were evaluated at baseline and then weekly. The patients were assessed psychiatrically with the Brief Psychiatric Rating Scale (BPRS).[31] Neuroleptic motor effects such as extrapyramidal symptoms and akathisia were assessed using a modified form of the Simpson-Angus Neurologic Rating Scale.[32] In addition, we included a global item (available from the authors upon request) that rated severity of akathisia on a scale of 0 to 4 (normal to severe). Since the aggressive incidents were episodic and rare in the 3 weeks that patients remained in the PICU, to evaluate drug efficacy we utilized clinical scales such as the BPRS rather than counts of aggressive outbursts. In addition, to take a closer look at specific changes in psychiatric symptoms, we analyzed several BPRS factors: activation factor, which included the scores on tension, mannerisms and posturing, and excitement items; hostility factor, composed of the scores on hostility, suspiciousness, and uncooperativeness; and the thought disturbance factor, which included conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content scores. Interrater reliability between the two raters in the BPRS was greater than .8 by interclass correlation analysis.[33]

Vital signs were taken daily before the study medication was given. If blood pressure was below 90/60 mm Hg or pulse less than 60 beats per minute, the subject received single-blind placebo tablets. If placebo was required for more than 3 days for low blood pressure, the patient was removed from the trial.

Data Analysis

The BPRS, Simpson-Angus, and akathisia scores for both placebo and nadolol groups were compared using analysis of covariance (ANCOVA) for each treatment week (Weeks 1, 2, and 3) with baseline scores as covariates. For patients who had to be dropped from the study for administrative reasons, we used their last visit scores and carried them forward to the end of the trial.

As these patients were acutely psychotic and highly hostile, some of them required adjustment of their neuroleptic dose. Therefore, we performed an additional ANCOVA to compare chlorpromazine equivalent doses[34] for the two groups at each assessment, using the baseline

chlorpromazine equivalent doses as covariates. We also computed the correlation between chlorpromazine equivalent score at baseline and baseline scores in activation, hostility, and akathisia to see if chlorpromazine equivalent dose could confound the effect of the adjunctive medication on these dependent variables. To see if changes in BPRS and Simpson-Angus scores were correlated, a stepwise multiple regression analysis was done, and baseline scores were entered in the first step. Two-tailed analyses were used to interpret the results.

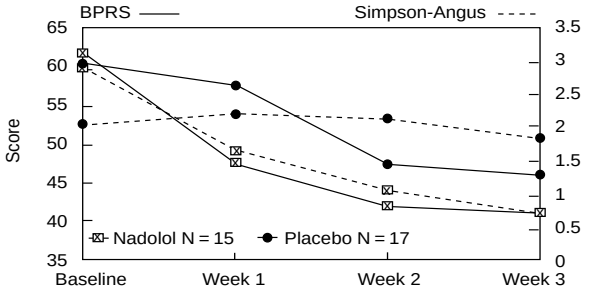
Since it has been suggested that the beneficial effect of β-blockers is due to a reduction of akathisia, in the nadolol group we compared the response between subjects with and without symptoms of akathisia at baseline. Patients who scored less than 2 (normal) on the global akathisia item were included in the group without akathisia (nadolol, N = 11; placebo, N = 14), and those with scores of 2 or more (mild to severe) were included in the akathisia group (nadolol, N = 4; placebo, N = 3). The following results are mean ± SD.

RESULTS

Thirty-four male schizophrenic patients enrolled in the study. Two patients, one from each treatment group, were dropped because of low blood pressure that persisted for more than 3 days. There were no significant age differences between the groups (nadolol mean ± SD age = 40.2 ± 9.0 years; placebo mean age = 38.6 ± 6.9 years). In addition, we found no difference in blood pressure or heart rate. The baseline chlorpromazine equivalence level was not significantly different in the two groups (nadolol mean chlorpromazine equivalent = 1267 ± 1335 mg; placebo mean = 1182 ± 688 mg). Although some patients needed adjustment of their neuroleptic medication, the differences between the nadolol and placebo groups in chlorpromazine equivalent doses were not statistically significant at any time (Week 1: F = 0.02, p = .90; Week 2: F = 0.07, p = .80; Week 3: F = 0.06, p = .80). Correlational analysis indicates that the relationship of chlorpromazine equivalence level to activation, hostility, and akathisia was not significant at any time.

At baseline, the groups did not differ in BPRS scores (nadolol mean score = 62.07 ± 12.83; placebo mean score = 60.88 ± 8.77) (Figure 1). After 1 week of treatment, however, BPRS scores for the nadolol-treated group were significantly lower than for the placebo-treated group (F = 4.05, df = 1,29; p = .05). BPRS scores continued to decrease in the nadolol group. Since the placebo group also began to show improvement, the group differences were no longer statistically significant by the second week (F = 0.11, df = 1,29; p = .70) or at the end of the third week (F = 1.99, df = 1,29; p = .17). Similarly, results of the BPRS factors indicate that after the first week, the nadolol group improved more than the placebo group on the activation factor (F = 4.52, df = 1,31; p = .04) and thought disturbance factor (F = 4.54, df = 1,31; p = .04), but not in the hostility factor (F = 2.19, df = 1,31; p = .15). These differences were not significant by the second week.

Figure 1. Weekly BPRS and Simpson-Angus Neurologic Rating Scale Scores for Each Group*



*Abbreviation: BPRS = Brief Psychiatric Rating Scale. The lower scores show greater improvement.

The group treated with active drug had lower Simpson-Angus scores than the placebo group (see Figure 1). After the first week of treatment, the differences between the two groups were not statistically significant (F = 1.27, df = 1,29; p = .27). At Week 2, however, the nadolol group showed a trend toward reduction in Simpson-Angus scores compared with the placebo group (F = 3.91, df = 1,29; p = .06), and at Week 3, the patients taking nadolol had significantly lower scores on the Simpson-Angus (F = 5.57, df = 1,29; p = .03). The two groups did not differ significantly in the global akathisia item during any of the weekly assessments.

The BPRS scores did not differ significantly in patients with (N = 4) and without (N = 11) akathisia after treatment with nadolol (F = 0.97, p = .35). A stepwise multiple regression was used to examine whether improvement on the BPRS was associated with improvement on the Simpson-Angus. We found no significant relationship between changes in Simpson-Angus and BPRS scores for the group treated with nadolol during any of the weekly assessments while controlling for baseline scores (Week 1: F to add = 0.02, p = .88; Week 2: F to add = 0.73, p = .41; Week 3: F to add = .09, p = .76).

DISCUSSION

The results from this study are consistent with earlier reports that β-blockers, including nadolol, are safe and effective as adjunctive treatment to neuroleptic in aggressive schizophrenic patients. In contrast to some data indicating that large amounts of β-blockers are needed to obtain a therapeutic effect in such populations, our findings suggest that relatively low doses may also be effective. These lower doses are less frequently associated with risk

of side effects or interactions with other medications. With doses of 80 to 120 mg/day of nadolol, excessive hypotensive action was not a problem.

It appears that the effects of nadolol were synergistic with the behavioral program, accelerating the improvement curve without changing its nature. Compared with patients treated with placebo, those treated with nadolol had a faster improvement of their psychiatric symptoms. The BPRS scores for patients treated with nadolol decreased significantly more than for those treated with placebo during the first week and continued to decrease throughout the study. During the second and third weeks, those patients taking placebo also showed some improvement in BPRS scores. Although patients taking nadolol continued to improve, the group differences were no longer significant. Like previous reports, our findings suggest that, compared with placebo, nadolol was more effective in the treatment of neuroleptic-induced extrapyramidal symptoms (EPS). Although in an earlier study[5] of a heterogeneous sample of aggressive psychiatric patients treated with nadolol we reported that Simpson-Angus and BPRS changes were directly correlated, in the present report, with only schizophrenic patients, these changes did not correlate significantly. In fact, the pattern of changes on the Simpson-Angus was different from that on the BPRS; the group receiving active adjunctive treatment showed increasing divergence from the placebo group over time. On the basis of these findings, we may question whether the mechanism of action of nadolol on psychiatric symptoms is different from the mechanism of improvement of neuroleptic-induced EPS. Support for this hypothesis is provided by the finding that the reduction in BPRS score was partly due to a decrease in the thought disturbance factor, which included scores from conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content items.

The antipsychotic and antiaggressive mechanism of action may be related to the effects of β-blockers on various neurotransmitters in the brain. Animal studies have suggested that the designation *β-blockers* is a misnomer and that, in fact, these agents interact with dopaminergic, serotonergic, and noradrenergic receptors.[35–39] It has been suggested that propranolol may selectively block the dopamine receptors in the limbic system and therefore may have an antipsychotic effect.[35,36] One study observed a decrease in norepinephrine levels in schizophrenic patients successfully treated with a β-blocker.[37] In addition, a number of studies found that nonselective β-blockers have a significant 5-HT receptor blockade activity[38,39] that could be responsible for both the antipsychotic and antiaggressive effects. Nadolol minimally penetrates the blood-brain barrier,[40] and so the question remains how a peripherally acting agent can affect the central nervous system processes involved in psychosis. It has been written that schizophrenics may be in a state of "hyperarousal."[41–43] A peripherally acting drug may work through feedback and feedforward loops between peripheral, somatic, and autonomic sites and brain areas to influence central processes such as cognition and emotion. Such links between bodily processes and the brain have been written about by both earlier and more recent writers interested in mind-body relationships.[44,45] Nadolol has been found to reduce levels of aggression in heterogeneous groups of psychiatric patients.[5,6]

Our findings should be viewed with caution, since β-blockers have been shown to increase plasma neuroleptic levels.[46] A further increase of neuroleptic level, however, is unlikely to have produced the symptom improvement seen in our group, since our patients initially had received adequate or even high doses of neuroleptics (doses of more than 1000 mg of chlorpromazine equivalent units). Also, if blood levels were significantly altered by pharmacokinetic action, one might expect increased neuroleptic adverse experiences. In fact, we found a significant difference between treatment groups by the third week.

The results from this study suggest that nadolol may be a helpful and well-tolerated adjunctive treatment for both aggressive schizophrenic patients and schizophrenic patients without significant levels of hostility. It is interesting that thought disturbance improved while the hostility factor of the BPRS did not. This finding suggests that the peripherally acting β-blocker, perhaps by reducing peripheral arousal, somehow had a stronger effect on cognitive mechanisms than on agitation. Since the hostility factor showed no significant improvement while the thought disturbance factor improved more in patients taking nadolol than placebo, one could wonder if nadolol may be a helpful adjunctive treatment for schizophrenic patients in general and not just for those with a high hostility level. It is important to note that patients were still quite psychotic at the end of treatment. Treatment was targeted on patient aggressiveness, and aggressiveness and psychosis can be orthogonal to each other; a psychotic patient may or may not be aggressive and vice versa. Additional studies are necessary to assess the effect of β-blockers to confirm our findings.

Drug names: nadolol (Corgard), propranolol (Inderal and others).

REFERENCES

1. Yudofsky S. The use of beta-blockers in the treatment of aggression. Psychiatric Letters 1988;6:15–24
2. Yudofsky S, Williams D, Gorman J. Propranolol in the treatment of rage and violent behavior in patients with chronic brain syndromes. Am J Psychiatry 1981;138:218–220
3. Ratey JJ, Morrill R, Oxenkrug G. Use of propranolol for provoked and unprovoked episodes of rage. Am J Psychiatry 1983;140:1356–1357
4. Volavka J. Can aggressive behavior in humans be modified by beta-blockers? Postgrad Med 1988;29:163–168
5. Alpert M, Allan ER, Citrome L, et al. A double-blind placebo-controlled study of adjunctive nadolol in the management of violent psychiatric patients. Psychopharmacol Bull 1990;26:367–371

6. Ratey JJ, Sorgi P, O'Driscoll GA, et al. Nadolol to treat aggression and psychiatric symptomatology in chronic psychiatric inpatients: a double-blind, placebo-controlled study. J Clin Psychiatry 1992;53:41–46
7. Ratey J, Gordon A. The psychopharmacology of aggression: toward a new day. Psychopharmacol Bull 1993;9:65–73
8. Sheppard GP. High-dose propranolol in schizophrenia. Br J Psychiatry 1979;134:470–476
9. Lindstrom LH, Persson E. Propranolol in chronic schizophrenia: a controlled study in neuroleptic-treated patients. Br J Psychiatry 1980;137: 126–130
10. Pugh CR, Steinert J, Priest RG. Propranolol in schizophrenia: a double-blind, placebo controlled trial of propranolol as an adjunct to neuroleptic medication. Br J Psychiatry 1983;143:151–155
11. Manchanda R, Hirsh SR. Does propranolol have an antipsychotic effect? a placebo-controlled study in acute schizophrenia. Br J Psychiatry 1986; 148:701–707
12. Adler LA, Reiter S, Corwin J, et al. Neuroleptic-induced akathisia: propranolol versus benztropine. Biol Psychiatry 1988;23:211–213
13. Dupuis B, Catteau J, Dumon JP, et al. Comparison of propranolol, sotalol, and betaxolol in the treatment of neuroleptic-induced akathisia. Am J Psychiatry 1987;144:802–805
14. Hermesh H, Molcho A, Munitz H. Successful propranolol therapy for neuroleptic-induced akathisia resistant to anticholinergic and benzodiazepine drugs. Clin Neuropharmacol 1988;11:369–372
15. Irwin M, Sullivan G, Van Putten T. Propranolol as a primary treatment of neuroleptic-induced akathisia. Hillside Journal of Clinical Psychiatry 1988;10:244–250
16. Lipinski JF, Keck PE, McElroy SL. Beta-adrenergic antagonist in psychosis: is improvement due to treatment of neuroleptic-induced akathisia? J Clin Psychopharmacol 1988;8:409–416
17. Crowner ML, Douyon R, Convit A, et al. Akathisia and violence. Psychopharmacol Bull 1990;26:115–117
18. Keckich WA. Neuroleptics: violence as a manifestation of akathisia. JAMA 1978;240:2185
19. Schulte JL. Homicide and suicide associated with akathisia and haloperidol. American Journal of Forensic Psychology 1985;6:3–7
20. Ritrovato CA, Weber SS, Dufresne RL. Nadolol in the treatment of aggressive behavior associated with schizophrenia. Clin Pharmacol 1989; 8:132–135
21. Sorgi PJ, Ratey JJ, Polakoff S. β-Adrenergic blockers for the control of aggressive behaviors in patients with chronic schizophrenia. Am J Psychiatry 1986;143:775–776
22. Grizenko N, Vida S. Propranolol treatment of episodic dyscontrol and aggressive behavior in children. Can J Psychiatry 1977;33:776–778
23. Mattes JA. Metoprolol for intermittent explosive disorder. Am J Psychiatry 1985;142:1108–1109
24. Yudofsky S, Silver JM, Schneider SE. Pharmacological treatment of aggression. Psychiatric Annals 1987;17:397–405
25. Fenster PE. Update on beta-adrenergic blockers. Pharmacy and Therapeutics 1992;17(1):46–57
26. Weinstock M, Weiss C, Gitter S. Blockade of 5-hydroxytryptamine receptors in the central nervous system by beta-adrenoreceptor antagonists. Neuropsychopharmacology 1977;16:273–276
27. Weinstock M, Weiss C. Antagonism by propranolol of isolation-induced aggression in mice: correlation with 5-hydroxytryptamine receptor blockade. Neuropharmacology 1980;19:653–656
28. Jefferson JW. β-Adrenergic receptor blocking drugs in psychiatry. Arch Gen Psychiatry 1974;31:681–691
29. Eccleston D, Fairbairn AF, Hassanyeh F, et al. The effect of propranolol and thioridazine on positive and negative symptoms of schizophrenia. Br J Psychiatry 1985;147:623–630
30. Allan E, Brown R, Laury G. Planning a psychiatric intensive care unit. Hosp Community Psychiatry l988;39:81–83
31. Overall JE, Gorham DR. Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
32. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;45(suppl 212):11–19
33. Shrout P, Fleiss J. Intraclass correlation uses in assessing rater reliability. Psychol Bull 1979;86(2):420–428
34. Davis J. Comparative doses of and costs of antipsychotic medications. Arch Gen Psychiatry 1975;48,181–190
35. Weisel F. Effects of high dose propranolol treatment on dopamine and norepinephrine metabolism in regions of rat brain. Neurosci Lett 1976;2: 35–38
36. Weisel F. Effects of the isomeric forms of propranolol on central monoamine metabolism in regions of rat brain. Prog Neuropsychopharmacol 1977; 1:83–89
37. Sternberg DE, van Kammen DP, Lake CR, et al. The effect of pimozide on CSF norepinephrine in schizophrenia. Am J Psychiatry 1081;138: 1045–1051
38. Middlemiss DM, Buxton D, Greenwood D. Beta-adrenoceptor antagonists in psychiatry and neurology. Pharmacol Ther 1981;12:419–437
39. Lader M. β-Adrenoceptor antagonists in neuropsychiatry: an update. J Clin Psychiatry 1988;49:213–223
40. McDevitt DG. Comparison of pharmacokinetic properties of beta-adrenoceptor blocking drugs. Eur Heart J 1987;8(suppl M):9–14
41. Zahn TP. Studies of autonomic psychophysiology and attention in schizophrenia. Schizophr Bull 1988;14:205–208
42. Dawson M, Nuechterlein K. Psychophysiological dysfunction in the developmental course of schizophrenic disorders. Schizophr Bull 1984;10: 204–232
43. Spohn HE, Patterson T. Recent studies of psychophysiology in schizophrenia. Schizophr Bull 1986;5:581–611
44. James W. What is an emotion? Mind 1884;9:188–205
45. Damasio A. Descartes' Error: Emotion, Reason and the Human Brain. New York, NY: Putnam; 1994
46. Silver J. Elevation of thioridazine plasma levels by propranolol. Am J Psychiatry 1986;143:1290–1292