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Efficacy of Carbamazepine Compared With Other Agents: A Clinical Practice Survey

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Background: To gain an impression of the experience with and efficacy of carbamazepine relative to other agents and relative to its use in treating psychiatric and neurologic disorders in general clinical practice, a survey was distributed in 1988 to psychiatrists practicing in the United States.

Method: The survey was mailed to 9030 members of the American Psychiatric Association (APA) who had expressed an interest in the study and treatment of affective disorders in a 1982 APA survey. The survey sampled clinicians' experience of the efficacy and side effects of carbamazepine in a number of psychiatric and neurologic conditions. Each clinician also provided global impression ratings of the efficacy of a variety of traditional and novel treatments.

Results: Completed surveys were returned by 2543 (28%) physicians. Carbamazepine was reported to be moderately to markedly effective in the following percentage of patients: partial complex seizures, 85.2%; generalized seizures, 82.9%; trigeminal neuralgia, 81.5%; mania prophylaxis, 72.9%; acute bipolar depression, 67.5%; intermittent explosive disorder, 65.2%; acute mania, 62.2%; schizoaffective disorder, 58.8%; other pain syndromes, 51.2%; posttraumatic stress disorder, 48.1%; borderline personality disorder, 43.0%; unipolar depression, 32.2%; schizophrenia, 25.7%; and alcohol withdrawal, 15.9%. About 4.4% of the patients reported were withdrawn from carbamazepine because of side effects.

Conclusion: Carbamazepine was widely used to treat a variety of psychiatric conditions in 1988 and found to be of use in the acute and long-term treatment of bipolar illness. It was rated slightly less effective than lithium, electroconvulsive therapy, or neuroleptics, but more effective than several other agents. The results of the survey highlight many areas in need of further systematic investigation.

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Bipolar disorder is a potentially lethal medical illness characterized by a recurrent, often deteriorating course.[1,2] Lithium has been and remains the drug of choice for treating bipolar disorder, but some patient subgroups demonstrate a high rate of nonresponse. For example, those with dysphoric mania[3–5] or rapid cycling[6–8] frequently show a poor response. In fact, a number of studies[9–16] have demonstrated lithium prophylaxis failure to be approximately 40% in unselected populations. In addition, many bipolar patients have troublesome side effects with lithium or are unable to tolerate its use. Given this experience, clinicians and researchers have sought alternative somatic treatments.

The anticonvulsant carbamazepine has emerged as a well-recognized, second-line treatment option to lithium for refractory bipolar patients.[17] Since much of the early literature concerning the effectiveness of carbamazepine for bipolar patients involved relatively small numbers of patients who were treatment refractory, we were interested in examining the clinical experience with the drug in a broader clinical sample of patients. We wished to gain an impression of the experience with and efficacy of carbamazepine in general clinical practice relative to other agents and relative to its use in other neurologic and psychiatric disorders. We also wished to highlight areas of potential discrepancy between information that existed or was available in the research literature compared with that reported in the clinical experience of physicians who responded to the survey, so that these areas could be targeted for further study and clarification.

In an attempt to address these issues, a survey was designed and distributed in 1988 to psychiatrists practicing in the United States and Puerto Rico who had expressed an interest in affective disorders.

METHOD

A survey was mailed in June and July 1988 to 9030 members of the American Psychiatric Association (APA) who had expressed an interest in the study and treatment of affective disorders in an APA survey conducted in 1982. The first section of the survey sampled clinicians' impressions of the efficacy of carbamazepine in the acute treatment of mania and unipolar and bipolar depression and in the long-term treatment of mania, schizoaffective disorder, schizophrenia, borderline personality disorder, intermittent explosive disorder, alcohol withdrawal, and posttraumatic stress disorder. We also inquired about the efficacy of carbamazepine in the treatment of complex partial seizures, generalized seizures, trigeminal neuralgia, and other pain syndromes. Respondents were asked to provide the number of patients who showed a marked, moderate, mild, unchanged, or unfavorable response to carbamazepine for each condition. Clinicians were also asked to rate their patients' side effects as severe, moderate, or mild, noting the number of patients requiring drug discontinuation.

In an attempt to generate a potential cohort of patients experiencing severe hematologic problems, which could be the subject for further studies of markers of vulnerability to this side effect, we asked about patients experiencing severe hematologic reactions. Although we attempted to define these conditions adequately in the survey, subsequent follow-up found that many respondents had indicated the patient had experienced aplastic anemia, for example, when only uncomplicated granulocytopenia was present. Thus, we are unable to provide reliable data on the experience with these severe hematologic side effects in the context of the present report. We also inquired about other untoward side effects and the number of patients experiencing rashes who required drug discontinuation and the number of patients who were restarted on carbamazepine with or without the recurrence of rash.

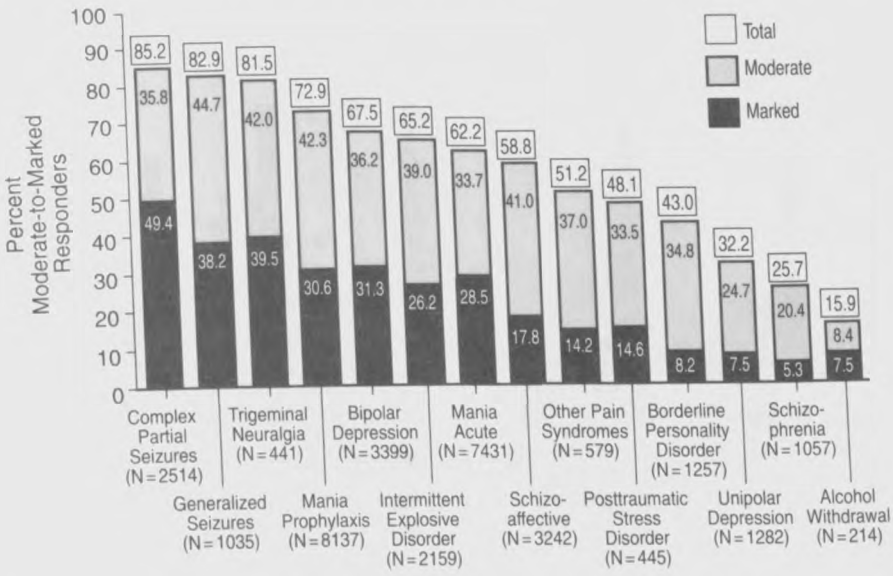
The last section of the survey asked each clinician to provide a global impression of the efficacy of a variety of treatments based on their own clinical experience to date. These treatments included electroconvulsive therapy (ECT), lithium, neuroleptics, carbamazepine, valproate, clonazepam, phenytoin, and calcium channel blockers. Each of these treatments was rated for the following psychiatric conditions: acute mania, acute unipolar depression, acute bipolar depression, prophylaxis of mania, depression, schizoaffective disorder, schizophrenia, borderline personality disorder, intermittent explosive disorder, and alcohol withdrawal. Clinical efficacy was rated on a scale from 5 to 1, where 5 = excellent; 4 = very good; 3 = moderate; 2 = fair; 1 = poor. A rating of 0 was used when the clinician lacked personal experience with a treatment, and this figure was not included in the subsequent average estimates of efficacy. The survey data were entered into the National Institutes of Health mainframe computer, and the Statistical Analysis System (SAS) was used to calculate means, percentages, and other statistics.

RESULTS

Of the 9030 surveys mailed, 2543 (28%) were returned. A total of 1715 clinicians treated at least 1 patient with carbamazepine. The total number of patients treated with carbamazepine as revealed by this survey was 43,565 (median number of patients treated by each physician = 6). The percentage of patients who moderately or markedly improved in response to carbamazepine is illustrated in Figure 1. When we combined moderate and marked responses, we found that the physicians rated 81.5% to 85.2% of patients with trigeminal neuralgia and partial complex and generalized seizures responsive to carbamazepine. This compares with a 72.9% response rate for the use of carbamazepine in the prophylaxis of mania. Remarkably, physicians rated 67.5% of patients moderately to markedly responsive to carbamazepine in the acute treatment of bipolar depression, compared with 62.2% in the acute treatment of mania. As illustrated in Figure 1, successively fewer patients with the following diagnoses were rated responsive: intermittent explosive disorder, 65.2%; schizoaffective illness, 58.8%; other pain syndromes, 51.2%; posttraumatic stress disorder, 48.1%; borderline personality disorder, 43.0%; unipolar depression, 32.2%; schizophrenia, 25.7%; and alcohol withdrawal syndromes, 15.9%.

In most psychiatric and neurologic patient subgroups, about 4% to 5% were reported to have discontinued carbamazepine because of side effects (range, 1.4%–11.5%); a total of 1912 patients (4.4%) were taken off carbamazepine treatment because of side effects. The clinicians who responded to the survey reported that 616 (1.4%) of the carbamazepine-treated patients experienced serious side effects, 3035 (7.0%) experienced moderate side effects, and 11,511 (26.4%) experienced mild side effects. A total of 377 clinicians reported that 904 patients had a rash, which is 2.1% of the patients treated with carbamazepine. Of 904 patients who had a rash, 209 were restarted on the drug. Of these, 83 (39.7%) were reported to have a recurrence of the rash, which is notable in that 126 (60.3%) did not experience a recurrence of the rash upon rechallenge with carbamazepine. The 11 severe cutaneous reactions reported included exfoliative dermatitis (N = 2), Stevens-Johnson syndrome (N = 7), aggravation of psoriasis (N = 1), and severe cellulitis (N = 1). Among other side effects listed by clinicians were hepatitis (N = 39) and hyponatremia (N = 10). Weight gain was reported as a problematic side effect in only 5 patients.

ıre 1. Moderate-to-Marked Clinical Efficacy of Carbamazepine: Survey of United States Psychiatrists, 1988*



N = total of patients rated for each disorder.

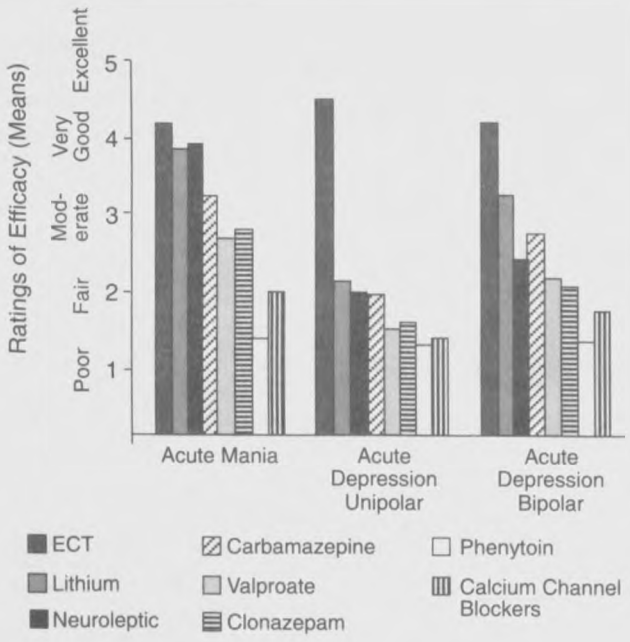
The comparative clinical efficacy of carbamazepine with conventional agents (ECT, lithium, and neuroleptics) and other novel treatments (valproate, clonazepam, phenytoin, and calcium channel blockers) is of considerable interest and summarized in figures 2A–C. The three conventional treatments were rated as close to "very good" when employed in acute mania. Carbamazepine received an average of moderate efficacy for the treatment of acute mania, with valproate and clonazepam ranking in the fair-to-moderate range. As expected, ECT was ranked as the best modality for the treatment of unipolar and bipolar depression, with lithium being rated as moderately efficacious in bipolar depression but only fair in unipolar depression.

In long-term or prophylactic treatments, as summarized in Figure 2B, lithium (followed by carbamazepine) was rated as most effective in the prophylaxis of mania, while ECT and lithium were rated as the best treatments but with lesser degrees of efficacy in the prophylaxis of depression (we did not ask about antidepressants). Neuroleptics were rated as the most effective treatment for schizoaffective and schizophrenic illness. Carbamazepine was rated as fair to moderate in schizoaffective illness and only fair in schizophrenia, as were most of the other treatments. As summarized in Figure 2C, no agent was reported to be particularly effective in the treatment of borderline personality disorder, although neuroleptics and carbamazepine received the highest rating. Carbamazepine was rated as the most effective drug in the treatment of intermittent explosive disorder. The benzodiazepine clonazepam was rated as the most efficacious drug of those listed in the treatment of alcohol withdrawal syndrome.

DISCUSSION

While a large number of psychiatrists returned the completed survey in a fashion that allowed for a coding of results, the total represented only 28% of the number of surveys distributed in 1988. As such, the typicality of the experience with carbamazepine and other agents at that time can only be grossly estimated. The results of the survey may be biased by a greater number of returns from psychiatrists with either highly positive or negative experiences with these agents, or there may be a particular bias in their review and experience with treatment efficacy. Nonetheless, a variety of factors suggests that the survey was, in fact, responded to in a generally valid fashion. As a whole, the estimates of the efficacy of carbamazepine in the treatments for which it is approved (seizure and pain disorders) were highly consistent with those reported in the literature when more systematic and controlled assessment techniques were used. There were few surprises in the assessments of the efficacy of the neuroleptics for the conditions for which they are either approved or most commonly used. Finally, the results reported in this survey for the utility of carbamazepine in a variety of neuropsychiatric patients, particularly those with bipolar affective disorder, were highly convergent with those based on more systematic assessments reported in the literature. Several of these points will be elaborated on in more detail below, but taken together, they suggest that the average

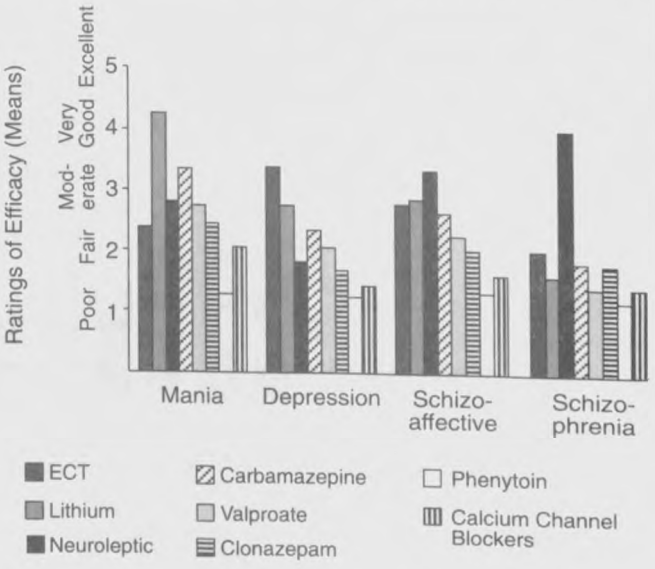
Figure 2A. Clinical Impressions of Efficacy of Acute Treatments*



*Number of physicians rating treatment effectiveness for each diagnosis:

	Acute Mania	Unipolar Depression	Bipolar Depression
ECT	1171	1795	1429
Lithium	2305	1659	2100
Neuroleptic	2277	1561	1711
Carbamazepine	1084	532	815
Valproate	318	137	208
Clonazepam	756	270	363
Phenytoin	205	136	128
Calcium channel blockers	264	100	130

Figure 2B. Clinical Impressions of Prophylactic Treatments*



*Number of physicians rating treatment effectiveness for each diagnosis:

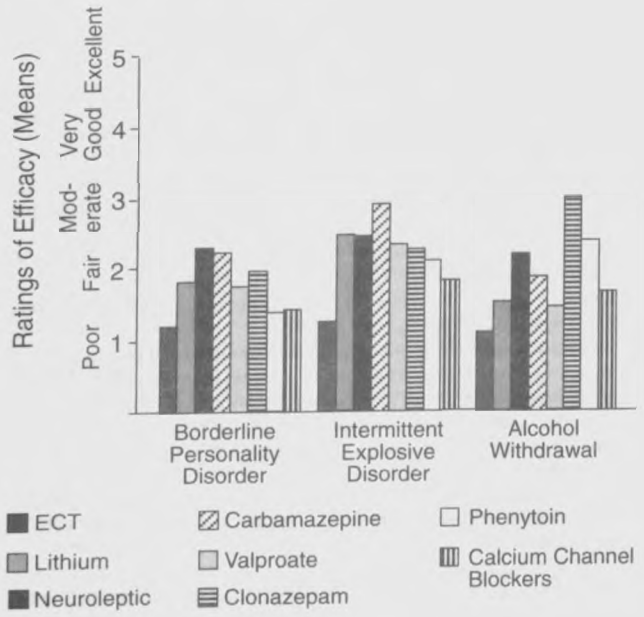
	Mania	Depression	Schizo-affective	Schizo-phrenia
ECT	522	1243	857	849
Lithium	2327	1990	1938	1290
Neuroleptic	1858	1430	2076	2178
Carbamazepine	1251	679	838	519
Valproate	286	154	171	100
Clonazepam	513	279	326	291
Phenytoin	128	119	110	113
Calcium channel blockers	171	102	88	70

estimates of treatment efficacy by the bulk of the respondents, as well as the way the clinicians responded to the survey based on their diagnoses and global assessments, reflected generally representative opinions in the field at the time and appropriate interpretation of the questions raised in the survey.

In relationship to the results reported in this survey and in more systematic studies in the literature, it is of interest that the 62.2% moderate-to-marked response rate in acute mania revealed in this survey is highly convergent with the 70% response rate reported in 19 controlled studies of carbamazepine (reviewed by Post[8]) in the treatment of acute mania. Somewhat surprising, however, is the grading of 67.5% moderate-to-marked response in the treatment of acute bipolar depression. Excellent responses were observed in 42% of the treatment refractory bipolar depressed patients treated with carbamazepine alone under double-blind conditions.[18] These results suggest the potential importance of further study of the acute antidepressant efficacy of carbamazepine, particularly in the treatment of bipolar depressed patients. In the case of mania prophylaxis studies, the 72.9% moderate-to-marked response rate compares with a 72% moderate-to-marked response rate in the seven controlled studies reviewed by Post,[17] and a 65% response rate (344 of 526 patients) reported in the uncontrolled studies and case reports in the literature. It is also of considerable interest that the data from this survey match the assessment of successive decreases in efficacy of carbamazepine when one moves from pure bipolar illness to schizoaffective and then to schizophrenic illness, as reported by Okuma et al.[19]

In spite of the estimates of moderate-to-marked (62.2%) efficacy of carbamazepine in acute mania, it was not viewed as being as effective as either ECT, lithium, or neuroleptics for this indication in the global clinical impressions ratings filled out by clinicians in the second part of the survey; yet carbamazepine was rated slightly more favorably than either valproic acid or clonazepam. It should be noted that the experience with valproate was based on a relatively small number of physicians' responses (318 for valproate versus 1084 for carbamazepine), as valproate[20–22] was not as widely used as carbamazepine in 1988. The respondents reported the

Figure 2C. Clinical Impressions of Somatic Treatments in Other Chronic Mental Illnesses*



*Number of physicians rating treatment effectiveness for each diagnosis:

	Borderline Personality Disorder	Intermittent Explosive Disorder	Alcohol Withdrawal
ECT	377	209	156
Lithium	1227	1075	313
Neuroleptic	1809	1335	729
Carbamazepine	580	726	143
Valproate	116	121	59
Clonazepam	365	334	315
Phenytoin	133	304	255
Calcium channel blockers	62	74	48

relative inefficacy of the calcium channel blockers, with an average rating just less than fair (1.9), although a number of open and double-blind clinical trials have reported substantial efficacy (particularly for verapamil and nimodipine) in mania.[23–26] The reasons for this discrepancy remain to be elucidated, but could lie in verapamil's clinical overlap with lithium and failure to work in lithium-nonresponsive patients; the divergence suggests the need for further study of the acute and prophylactic efficacy of this class of compounds in bipolar illness. In spite of early reports of the efficacy of phenytoin in a variety of psychiatric syndromes including acute mania,[27–29] few systematic studies of this compound have been reported recently, and our experience was negative for five patients studied in a double-blind fashion (Post RM. 1988. Unpublished data). These experiences are consistent with the fact that few of the 205 physicians responding to the question on the efficacy of phenytoin consider this drug to be very effective in the treatment of acute mania.

The role of the benzodiazepine clonazepam clearly requires further study to adequately delineate its profile of clinical efficacy, particularly in the acute[30–32] and prophylactic[33] treatment of affective illness. Results of the current clinical experience survey do little to clarify the situation in relation to clonazepam, although it is apparent that it was fairly widely used in 1988 and is likely to continue to be widely used as an adjunctive treatment in current clinical practice.

Although the benzodiazepines are most widely used in the treatment of alcohol withdrawal syndromes, clonazepam was rated as only moderately effective. Interestingly, carbamazepine was rated by 143 physicians as relatively poorly to fairly effective in the treatment of alcohol withdrawal syndromes, even though older Scandanavian[34–36] and more recent United States[37] literature exist suggesting its acute and long-term efficacy. Given the potential abuse liability of the benzodiazepines, adequate elucidation of the role of carbamazepine (which does not share this abuse liability) in the treatment of alcohol and benzodiazepine[38–41] withdrawal syndromes would be of clinical importance.

The results of this survey support the general view that psychopharmacologic approaches to borderline personality disorder leave much to be desired. Neuroleptics and carbamazepine were the most highly ranked drugs in terms of efficacy, but rating of these agents just reached into the fair range. These data are of interest in light of the more systematic studies of Cowdry and Gardner[42] who viewed carbamazepine as the most effective agent among the neuroleptic trifluoperazine, the benzodiazepine alprazolam, and the monoamine oxidase inhibitor (MAOI) tranylcypromine, compared with placebo in the treatment of behavioral dyscontrol symptoms in patients with borderline personality disorder. At the same time, in Cowdry and Gardner's study,[42] carbamazepine was not rated by patients as a very effective antidepressant, while tranylcypromine received much higher subjective improvement ratings. The data from the study by Cowdry and Gardner[42] plus the data from other trials reporting the effectiveness of carbamazepine in treating impulsive or violent behavior[43–46] are consistent with the rating of carbamazepine as the most effective of the somatic treatments listed for intermittent explosive disorder.

While carbamazepine appears to have been generally well tolerated by the 43,565 patients who were reported to have been observed during treatment with this agent, some 1912 patients (4.4%) discontinued carbamazepine because of side effects, including severe hematologic and dermatological reactions. About 2% of patients experienced a rash while taking carbamazepine. This is generally comparable with the frequently cited figure of carbamazepine-produced rash on the order of 3%,[47] but is much lower than the 12% incidence of rash observed

in our clinical experience in the treatment of patients at the National Institute of Mental Health (NIMH) (Kramlinger KG, Phillips KA, Post RM. 1993. Unpublished observations). The safety of re-exposure to carbamazepine after the experience of a cutaneous reaction is uncertain. Reports on retreatment have demonstrated results varying from no rash recurrence[48] to recurrence of other symptoms without rash[49] and, most commonly, recurrence,[50–54] often with a more rapid onset than that observed during the first exposure to carbamazepine. It is of interest that of the 209 patients retreated with carbamazepine following the emergence of a rash, about 60% did not experience a recurrence. This raises the question of whether some patients can be re-exposed to carbamazepine without the use of steroids, but it would appear that this should be done only with considerable caution, as the potential for severe dermatological reactions upon re-exposure clearly exists. Moreover, a recent report of Murphy et al.[55] reaffirms the earlier reported experience of Vick[56] indicating that many patients can be either continued on carbamazepine or retried on the drug under the cover of short-term use of prednisone. However, Hampton et al.[57] reported a case where systemic allergy was evident in that the patient showed a fever and other symptoms, and these systemic manifestations were not adequately suppressed by prednisone treatment.

While it appears that carbamazepine was widely used in the treatment of a variety of psychiatric conditions in 1988 and found, in particular, to be of use in the acute and long-term treatment of bipolar illness, this survey highlights the need for further research in a variety of areas. Even though bipolar illness afflicts approximately 1% of the population of the United States, it remains a highly understudied illness. Few NIMH-sponsored treatment trials for patients with bipolar illness have been conducted in the past several years. Chemical and biological predictors of response should be sought. The results of this large clinical practice survey, while consistent with the more formal existent literature on the use of carbamazepine and related anticonvulsants in the treatment of bipolar disorder, clearly highlight many areas in great need of further research. In addition, it is clear that a more adequate delineation of the use of these agents in other neuropsychiatric indications is also required.

Drug names: alprazolam (Xanax), carbamazepine (Tegretol and others), clonazepam (Klonopin), nimodipine (Nimotop), phenytoin (Dilantin and others), prednisone (Delta-Dome and others), tranylcypromine (Parnate), trifluoperazine (Stelazine), valproic acid (Depakene and others), verapamil (Calan and others).

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