Relapse of Aggressive and Disruptive Behavior in Mentally Retarded Adults Following Antipsychotic Drug Withdrawal Predicts Psychotropic Drug Use a Decade Later

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Background: Mental retardation is frequently associated with aggression toward self and others. Antipsychotic medications are frequently used as a major treatment of such aggression. However, national and state policies and guidelines are weighted toward stopping or decreasing the doses of these medications whenever possible, although exceptions are permitted. The purpose of this study was to determine if relapse during or after antipsychotic drug withdrawal in mentally retarded adults predicts continuing antipsychotic drug use an average of a decade later.

Method: We report here on a 6- to 13-year (average 10-year) follow-up of 151 institutionalized mentally retarded adults. During the period 1990–1997, the subjects had been prescribed antipsychotic medications to treat maladaptive behaviors, primarily consisting of aggression, disruptive/destructive behaviors, or a combination of these. We compared subjects' psychotropic medication profiles in 2003 as they related to outcome during the earlier period. Our goal was to determine if rapid relapse (a clinically significant increase in maladaptive target symptoms, beginning 3 months or less after antipsychotic drug termination or dosage reduction, that was reversed by antipsychotic drug reinstitution or dosage increases) during or after routine withdrawal of an antipsychotic predicted psychotropic drug use in 2003.

Results: For those individuals successfully withdrawn from antipsychotic medications, 66.3% (55/83) were still psychotropic drug free in 2003. For those who rapidly relapsed during the period 1990–1997 following antipsychotic drug withdrawal or dosage decreases, only 9.0% (5/55) were psychotropic medication free in 2003.

Conclusion: These observations support policies and guidelines indicating that attempts to stop treatment with antipsychotic medications in mentally retarded individuals are worthwhile. However, the results also indicate that eventual discontinuation of antipsychotic medications in institutionalized mentally retarded adults who have previously relapsed upon such withdrawal is unlikely to be successful. Rigid adherence to drug withdrawal policies and guidelines in such individuals should be reconsidered.

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Mental retardation is frequently associated with aggression toward self (self-injurious behavior), aggression toward others, and destructive/disruptive behaviors.[1–4] Psychotropic agents, especially antipsychotic drugs, are a mainstay of treatment for these maladaptive behaviors. Overall, the percentage of mentally retarded individuals treated with psychotropic medications averages between 15% and 25%.[5–10] This percentage is increased to approximately 40% to 50% when challenging behaviors are present[6,7,11] or when institutionalization occurs.[8–10]

However, concern exists about the use of antipsychotic agents in the mentally retarded, in part due to their serious side effects and in part due to differing mind sets and philosophies among professionals.[12–14] Such concerns and associated litigation have led to relatively restrictive federal and state regulations and guidelines on the use of psychotropic drugs in the mentally retarded in the United States.[11,15] Such guidelines include the institution of mandated periodic reviews of cases receiving psychotropic medications, with drug termination being optional, and when such termination is not feasible, determination of the lowest effective dosages.[11,15–19]

Virtually no systematic data are available concerning the long-term evaluation of such policies. However, it is known that a significant number of mentally retarded individuals can successfully be taken off treatment with antipsychotic and other psychotropic medications, al-

though follow-up has generally been for relatively short periods of time.[16,17] In a significant number of cases, intensification of maladaptive aggressive and destructive symptoms rapidly occurs following antipsychotic drug withdrawal or decreasing of dosage, necessitating reinstitution of medications.[20–23]

In the current study, using a retrospective review of records, we evaluated whether successful antipsychotic drug withdrawal predicted continued antipsychotic drug–free status in institutionalized mentally retarded adults and whether episodes of symptom intensification following antipsychotic drug withdrawal predicted subsequent psychotropic drug use an average of a decade later.

The setting of the current study is fortuitous, since it offers extensive psychological/behavioral support to adult mentally retarded individuals in a well-staffed residential facility in which extensive behavioral and educational techniques are applied. It is therefore assumed that with sufficient psychological and behavioral interventions, antipsychotic medication usage reflects recalcitrant maladaptive behaviors such as aggression and self-injurious behavior.

METHOD

Subjects

The subject group consisted of profoundly or severely mentally retarded adults (91 men, 60 women; mean age = 48.2 years; age range, 18–81 years) living in a 583-bed residential state institution, the Murdoch Center, located in Butner, N.C. Subjects resided at Murdoch Center during the period 1990–1997 and in 2003, and most had been institutionalized for all of their adult lives. Most had significant medical diagnoses including seizures, cardiac disease, cerebral palsy, strokes, deafness, and blindness. Most of the subjects had been assigned a formal psychiatric diagnosis. In descending order of frequency, the primary DSM-IV diagnoses of these individuals were bipolar disorder, autism, stereotypic movement disorder with self-injurious behavior, intermittent explosive disorder, mood disorder not otherwise specified (NOS), obsessive-compulsive disorder, psychotic disorder NOS, anxiety disorder, behavioral disorder NOS, and oppositional defiant disorder.

All subjects had been treated with conventional antipsychotic medications (thioridazine, chlorpromazine, haloperidol, thiothixene, mesoridazine, trifluoperazine, loxapine, molindone, and perphenazine) alone or in combination with other psychotropic medications (antiepileptic medications used as mood stabilizers, lithium, antidepressants, and benzodiazepines) during the 1990–1997 period. During that time, all had experienced attempts to withdraw conventional antipsychotic medications, and all were reevaluated as to their psychotropic medication profiles in 2003.

The subjects had been prescribed antipsychotic medications alone or with other psychotropic medications to treat maladaptive behaviors, primarily consisting of aggression (hitting, biting, scratching, kicking another, etc.), self-injurious behaviors (hitting, biting, slapping, head banging, etc.), disruptive/destructive behaviors (screaming, throwing objects, overturning furniture, breaking furniture, breaking windows, etc.), or a combination of these behaviors.

Study Design

The study consisted of a review of quarterly or more frequent subject records derived from neurobehavioral review (NBR) conferences. The conferences summarized the psychotropic medications subjects received and the subjects' clinical course during the 1990–1997 period and again in the spring of 2003.[1] The NBR conferences had as a specific focus the making of decisions concerning the administration of psychotropic medications. Although antipsychotic and other psychotropic medication dosage reductions were not mandated, a major consideration of each NBR conference was the evaluation of the feasibility and risk-benefit ratio of such reductions. NBR conferences were conducted on all Murdoch Center residents requiring psychotropic medications for behavioral purposes and consisted of meetings of the subjects' treatment teams.

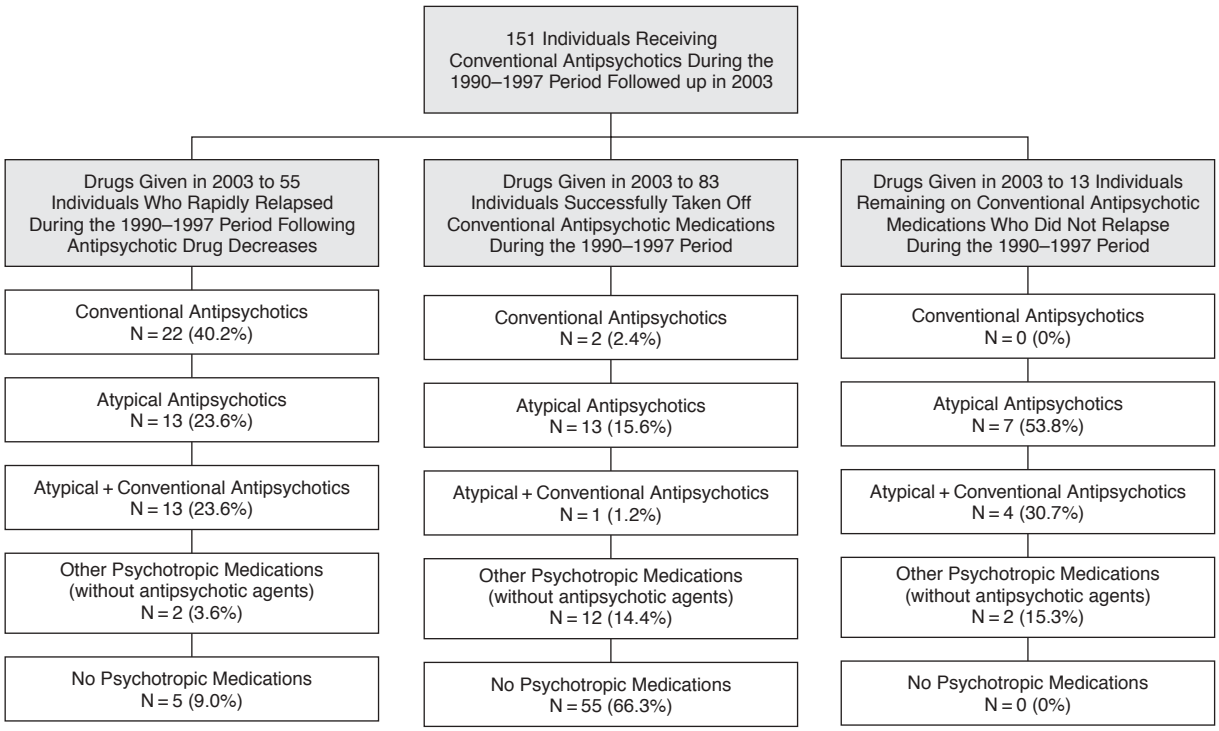
A comparison of the antipsychotic medications and other psychotropic medications administered in 2003 in each subject was conducted as these related to differing outcomes during the 1990–1997 period. The 1990–1997 outcomes were categorized as (1) those individuals who, during the 1990–1997 period, were able to successfully have antipsychotic and other psychotropic drugs terminated (N = 83); (2) those who had a rapid relapse during or after antipsychotic drug withdrawal (N = 55); such rapid relapse consisted of a clinically significant increase in maladaptive target symptoms, beginning 3 months or less after antipsychotic drug termination or dosage reduction, which was reversed by antipsychotic drug reinstitution or dosage increases; and (3) those in whom drugs were not withdrawn and who continued to receive antipsychotic medications up to 1997 (N = 13).

The medication categories profiled in 2003, based on the above outcomes, were (1) conventional antipsychotic medications, (2) atypical antipsychotic medications, (3) a combination of atypical and conventional antipsychotics, (4) other psychotropic medications (i.e., lithium, antidepressants, mood stabilizers, etc.) given without antipsychotic drugs, and (5) no psychotropic medications.

Data Analysis

Comparisons of the subjects' psychotropic medication profiles for 2003 as these related to outcome during the 1990–1997 period were expressed as absolute numbers

Figure 1. Distribution of Antipsychotic Medications in 2003 in 151 Mentally Retarded Individuals Who Received Conventional Antipsychotic Medications During the 1990–1997 Period[a]



[a]Cases in the 1990–1997 period consisted of individuals receiving antipsychotic medications alone or with other psychotropic medications. In 2003, cases consisted of the latter groups plus individuals receiving other psychotropic medications and individuals receiving no psychotropic medications.

and as percentages of the respective subcategories (Figure 1). Statistical significance ($p < .05$) was determined using 1-sided Fisher exact tests to compare similar medication types across subgroups.

Permission to psychopharmacologically treat had been obtained from each subject's guardian prior to drug administration. Authorization was obtained from the University of North Carolina Medical Institutional Review Board and the Murdoch Center Research Review Committee. The study was carried out in accordance with Declaration of Helsinki standards.

RESULTS

Figure 1 demonstrates the 2003 distribution of psychotropic drugs in 3 subgroups (i.e., those who were successfully withdrawn, those who rapidly relapsed, and those who had not had an attempt made at withdrawal). Results are expressed as the number of cases (N) and the percentage of cases in a given subgroup. Specifically, as shown in Figure 1, 151 individuals still residing at Murdoch Center in 2003 had been receiving conventional antipsychotic medications (alone or in combination with other psychotropic medications) during the 1990–1997 period. During the 1990–1997 period, 55% (N = 83) were successfully withdrawn from antipsychotic medications, 36.4% (N = 55) relapsed upon withdrawal and subsequently had their antipsychotic drug dose increased or treatment restarted, and 8.5% (N = 13) did not have a meaningful withdrawal attempted. An average of a decade later, 39.7% (N = 60) of the total of 151 individuals were psychotropic drug free, 49.6% (N = 75) were still receiving antipsychotic drugs, and 10.5% (N = 16) were receiving other psychotropic medications alone without antipsychotic drugs.

Obvious differences existed in 2003 between the profiles of psychotropic medications given to individuals who in the 1990–1997 period were able to have their antipsychotic medications stopped and those who experienced rapid relapse. As shown in Figure 1, 55 (66.3%) of the 83 individuals who had successfully undergone antipsychotic drug withdrawal in the 1990–1997 period (mean year of antipsychotic withdrawal = 1992) were psychotropic drug free in 2003. Furthermore, only 16 (19.2%) of 83 of those who had successfully been withdrawn from antipsychotic drugs in the 1990–1997 period were still receiving antipsychotic drugs as such in 2003. In addition, for those individuals who became antipsychotic/psychotropic drug free in the 1990–1997 period and yet were receiving psychotropic medications

Table 1. Distribution of Combinations of Antipsychotic and Other Medications During the 1990–1997 Period and in 2003 in Mentally Retarded Individuals

	1990–1997 (N = 151)		2003 (N = 91)[a]	
Medications	N	%	N	%
Conventional antipsychotics				
Conventional(s) alone	85	56.3	10	11.0
Conventional(s) + mood stabilizers	21	13.9	5	5.5
Conventional(s) + lithium	10	6.6	1	1.1
Conventional(s) + antidepressants	9	5.9	0	0.0
Conventional(s) + benzodiazepines	2	1.3	3	3.3
Conventional(s) + mood stabilizers + lithium	7	4.6	3	3.3
Conventional(s) + mood stabilizers + antidepressants	8	5.3	0	0.0
Conventional(s) + mood stabilizers + benzodiazepines	3	2.0	0	0.0
Conventional(s) + lithium + antidepressants	3	2.0	2	2.2
Conventional(s) + lithium + benzodiazepines	3	2.0	0	0.0
Atypical antipsychotics				
Atypical alone	0	0.0	17	18.7
Atypical + mood stabilizers	0	0.0	7	7.7
Atypical + lithium	0	0.0	4	4.4
Atypical + antidepressants	0	0.0	2	2.2
Atypical + mood stabilizers + lithium	0	0.0	1	1.1
Atypical + lithium + antidepressants	0	0.0	17	1.1
Atypical + lithium + benzodiazepines	0	0.0	1	1.1
Conventional + atypical antipsychotics				
Conventional + atypical alone	0	0.0	10	11.0
Conventional + atypical + mood stabilizers	0	0.0	3	3.3
Conventional + atypical + lithium	0	0.0	3	3.3
Conventional + atypical + lithium + antidepressants	0	0.0	2	2.2
Without antipsychotics				
Mood stabilizers alone	0	0.0	6	6.6
Benzodiazepines alone	0	0.0	2	2.2
Mood stabilizers + lithium	0	0.0	2	2.2
Mood stabilizers + antidepressants	0	0.0	5	5.5
Mood stabilizers + benzodiazepines	0	0.0	1	1.1

[a]Does not include 60 individuals who were psychotropic drug free in 2003.

in 2003, a relatively large percentage (12 of 83; 14.4%) were receiving other psychotropic medications alone (selective serotonin reuptake inhibitor antidepressants, valproic acid, topiramate, carbamazepine, lithium, lorazepam, and diazepam) without antipsychotic agents.

In contrast, of those 55 individuals who had rapidly relapsed in the 1990–1997 period (mean year of relapse = 1993), only 5 (9.0%) were psychotropic drug free in 2003, and only 3.6% were receiving other psychotropic agents alone. Conversely, 87.4% were still receiving antipsychotic medications.

Similarly, of those 13 individuals in whom no antipsychotic drug withdrawal was attempted in the 1990–1997 period, none (0%) were psychotropic drug free and 84.5% were receiving antipsychotic drugs in 2003.

Of those still receiving psychotropic medications in 2003, a relatively large percentage of those who had rapidly relapsed in the 1990–1997 period specifically continued to receive conventional antipsychotic medications (thioridazine, chlorpromazine, haloperidol, thiothixene, and perphenazine) or a combination of conventional and atypical antipsychotic agents (atypical antipsychotic agents = olanzapine, risperidone, quetiapine, and clozapine) (35 of 55; 63.6%). For those 13 individuals remaining on treatment with antipsychotic medications in 1997 who did not have their antipsychotic medications decreased during the 1990–1997 period, atypical antipsychotic agents and a combination of atypical and conventional antipsychotic medications were strongly represented in 2003.

Statistically significant differences existed when the 2003 distributions of psychotropic medications were compared between the group that became psychotropic drug free and the group that rapidly relapsed in the 1990–1997 period. More individuals were psychotropic drug free (Fisher exact test, $p < .00001$) or were receiving other psychotropic medications alone (Fisher exact test, $p < .00001$) in 2003 in the group that had become psychotropic drug free in the 1990–1997 period as compared with the group that relapsed. In contrast, in the group that rapidly relapsed, significantly more individuals were receiving conventional antipsychotic medications (with or without atypical antipsychotic medications) in 2003 (Fisher exact test, $p < .0005$.)

Table 1 demonstrates the distributions of antipsychotic medications given alone and with 1 or more other psychotropic medications during the 1990–1997 period and in 2003. Multiple class polypharmacy occurred in approximately one half of cases during both time periods.

Table 2 demonstrates the distribution of specific antipsychotic medications given in the 1990–1997 period and in 2003. Whereas in the 1990–1997 period all individuals were receiving conventional antipsychotic medications, by 2003, 56% were receiving atypical antipsychotic agents, predominantly olanzapine and risperidone. Significantly, in 2003, a relatively large number were still receiving conventional antipsychotic agents, predominantly thioridazine and haloperidol.

DISCUSSION

Our results demonstrate that approximately 4 out of 10 institutionalized adult mentally retarded individuals in whom a withdrawal from antipsychotic drugs was attempted continued to be psychotropic drug free an average of 10 years later. Short-term follow-up studies of up to 2 years show that a similar percentage of patients, in the short run, can be successfully withdrawn from psychotropic medications (Ahmed et al.,[20] 33%; Branford,[21] 25%; May et al.,[16] 60%).

Thus, since a large number of such withdrawals are successful over a period of many years, our results support attempts at dose lowering or withdrawal of antipsy-

Table 2. Antipsychotic Medications Given to 151 Mentally Retarded Individuals in 1990–1997 and Subsequently Given to the 91 Individuals Still Receiving Antipsychotic Medications in 2003[a]

	1990–1997 (N = 151)		2003 (N = 91)[b]	
Medication	N	%	N	%
Conventional antipsychotics				
Thioridazine	48	31.7	14	15.4
Chlorpromazine	17	11.2	3	3.3
Haloperidol	53	35.0	23	25.3
Thiothixene	10	6.6	5	5.5
Mesoridazine	2	1.3	0	0.0
Trifluoperazine	7	4.6	0	0.0
Loxapine	3	1.9	0	0.0
Molindone	8	5.3	0	0.0
Perphenazine	3	1.9	2	2.2
Atypical antipsychotics				
Olanzapine	0	0.0	20	21.9
Risperidone	0	0.0	28	30.7
Quetiapine	0	0.0	2	2.2
Clozapine	0	0.0	1	1.1

[a]In a number of cases, antipsychotic(s) and other drugs or combinations of antipsychotic drugs were given together in the 1990–1997 period and/or in 2003.
[b]Does not include 60 individuals who were psychotropic medication free in 2003 and who were receiving antipsychotic medications alone or with other psychotropic medications in the 1990–1997 period.

chotic drugs in the mentally retarded. It would therefore certainly seem reasonable to attempt to withdraw antipsychotic and other psychotropic medications in those who have not had such an attempt made previously.

The question exists as to whether or not antipsychotic drugs were necessary in the first place in those mentally retarded individuals who did not relapse upon medication withdrawal. However, we found no obvious differences between the nature or degree of target symptoms in those who did and did not relapse at the time that antipsychotic medications were started or at the time that drug withdrawal was attempted.

Our results also suggest that a significant percentage of institutionalized adult mentally retarded individuals will rapidly relapse when antipsychotic medications are withdrawn, causing a need for rapid reinstitution or increasing the dosage of the antipsychotic medications. Such relapses are clinically significant and may be dangerous to all concerned. They bode poorly for ultimately stopping antipsychotic medications in these previously relapsed individuals. Given the above information, there is an obvious need for more study of what characteristics might be predictive of relapse or continuing stability in the mentally retarded following antipsychotic withdrawal.

It is logical to assume that the reason that mentally retarded individuals who relapsed in the 1990–1997 period continued to receive antipsychotic medications in 2003 was due to an ongoing need for antipsychotic medications. However, since our current data do not reflect a systematic appraisal of behavioral relapse (or stability) using formal behavioral observations or rating scales, it is possible that the decisions to continue antipsychotic medications in 2003 occurred because of physician and staff preferences, rather than patient need. We believe this is unlikely, since the nature of most of the documented relapses of a subset of our subjects was dramatic, as we have described previously.[24] Furthermore, we noted that 85% of those who relapsed in the 1990–1997 period and were still receiving antipsychotic agents in 2003 had again relapsed following a later attempt or attempts to decrease their doses of antipsychotic agents (D.S.J., unpublished observations, 2005). For the 13 individuals in whom antipsychotic drug withdrawal did not occur in the 1990–1997 period, all subsequently had drug withdrawal attempts made, and all subsequently relapsed.

It would appear that the long-term outcome of our subject group differs from that occurring in schizophrenic individuals. Attainment of antipsychotic drug–free status without relapse over a period of years is highly unlikely in schizophrenic populations. In addition, although transition from conventional to atypical antipsychotic drugs often did occur, our results suggest that many mentally retarded adults remain on treatment with conventional antipsychotic medications, alone or in combination with atypical antipsychotic medications. Such contemporary use of conventional antipsychotic medications is supported by the relative equivalence and safety of conventional and atypical antipsychotic medications in treating schizophrenic patients. Such results were noted in the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[25] and differ from other reports suggesting that atypical antipsychotic drugs, given to schizophrenics, are somewhat more effective than conventional ones.[26] It is furthermore possible that, as with our mentally retarded subject group, some schizophrenic patients may be more effectively treated with conventional antipsychotic agents or a combination of conventional and atypical antipsychotics. This possibility has not generally been explored in the psychopharmacologic literature.

With respect to the other limitations and considerations of our study, the administration of antipsychotic drugs was not randomized and was not blinded, and our subjects were limited to adult individuals with very low intelligence quotients. In addition, our study did not include the exploration of the pharmacologic outcomes in mentally retarded individuals receiving only non-antipsychotic psychotropic medications during the 1990–1997 period or the outcomes of those who were discharged from the Murdoch Center during the 1990–1997 period. Furthermore, our subjects consisted of institutionalized inpatients with a high degree of structure available to them. Our success in discontinuing antipsychotic medications also may have been due in part to the sophisticated behavioral controls used in our setting. Antipsychotic drug

withdrawal in an outpatient or group home setting may be a very different process, due to a relative lack of available structure and treatments.

CONCLUSIONS AND IMPLICATIONS FOR POLICY

A large percentage of our adult mentally retarded subjects were successfully taken off antipsychotic medications for a period averaging 10 years and did not relapse. Our results thus affirm the wisdom of federal and state guidelines and regulations mandating attempts to discontinue antipsychotic and/or other psychotropic medications or to find the lowest effective doses. However, a significant number of individuals did rapidly relapse upon antipsychotic medication withdrawal, leading to serious maladaptive behaviors and the uninterrupted use or reinstitution of antipsychotic medications. Current guidelines do allow exceptions to a policy of psychotropic medication withdrawal in the mentally retarded. However, our data suggest that a change in emphasis in the regulations and guidelines concerning antipsychotic drug reduction and withdrawal should occur. Guidelines should be reconsidered to incorporate, in adult mentally retarded individuals prone to withdrawal-induced relapse, just how unlikely it is that psychotropic drug–free status can be attained. The importance of potential harm to patients and staff following relapse should lead to a more balanced perspective. Careful scrutiny of previous records for medication withdrawals is indicated to break the cycle of relapse and violence, and caution should occur in instituting medication withdrawals.

Guidelines should reflect the observation that for individuals with multiple previous relapses, less aggressive withdrawal strategies are indicated. At the least, attempts at withdrawal in such individuals should be performed slowly, with great caution, and with frequent observations, so that when such reduction attempts occur, any intensification of symptoms can be identified and treated rapidly and effectively.

Drug names: carbamazepine (Equetro, Carbatrol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), diazepam (Valium and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), loxapine (Loxitane), molindone (Moban), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), topiramate (Topamax), trifluoperazine (Stelazine and others), valproic acid (Depakene and others).

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