Off-Label Use of Antidepressant, Anticonvulsant, and Antipsychotic Medications Among Georgia Medicaid Enrollees in 2001

Hua Chen, M.D., Ph.D.; Jaxk H. Reeves, Ph.D.; Jack E. Fincham, Ph.D.; William K. Kennedy, Pharm.D.; Jeffrey H. Dorfman, Ph.D.; and Bradley C. Martin, Pharm.D., Ph.D.

Received Nov. 22, 2005; accepted Dec. 21, 2005. *From the Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, Houston, Tex. (Dr. Chen); the Department of Statistics (Dr. Reeves), the Department of Clinical & Administrative Pharmacy (Drs. Fincham and Kennedy), and the Department of Agricultural and Applied Economics (Dr. Dorfman), University of Georgia, Athens; and the Division of Pharmaceutical Evaluation and Policy, Pharmacy Practice Department, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock (Dr. Martin).*

Drs. Chen, Reeves, Fincham, Kennedy, Dorfman, and Martin report no significant commercial or other relationships relevant to the subject of this article.

Corresponding author and reprints: Bradley C. Martin, Pharm.D., Ph.D., Division of Pharmaceutical Evaluation and Policy, Pharmacy Practice Department, College of Pharmacy, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205-7122 (e-mail: BMARTIN@uams.edu).

Objectives: To determine the prevalence of and factors associated with the off-label use of antidepressant, anticonvulsant, and antipsychotic medications.

Method: A retrospective analysis of Georgia Medicaid recipients was conducted. Recipients prescribed antidepressant, anticonvulsant, or antipsychotic medications were identified. Logistic regression analysis was used to identify factors associated with off-label use.

Results: A total of 46,976 (75.42%) antidepressant recipients, 38,497 (80.12%) anticonvulsant recipients, and 21,252 (63.62%) antipsychotic recipients received at least 1 of these medications off-label in 2001. The likelihood of receiving off-label medications increased remarkably with advancing age (≥ 65 vs. < 65 years: antidepressant: OR = 5.15, 95% CI = 4.76 to 5.56; anticonvulsant: OR = 4.54, 95% CI = 4.16 to 4.96; antipsychotic: OR = 5.21, 95% CI = 4.82 to 5.63). Although receiving new anticonvulsants launched after 1993 was the strongest predictor (OR = 7.63, 95% CI = 7.07 to 8.23) of receiving off-label anticonvulsant medications, exposure to newer antidepressants and antipsychotics did not confer a higher chance of receiving off-label medications (selective serotonin reuptake inhibitors vs. tricyclic antidepressants: OR = 0.43, 95% CI = 0.40 to 0.45; atypical vs. conventional antipsychotics: OR = 0.76, 95% CI = 0.72 to 0.80).

Conclusions: The off-label use of antidepressant, anticonvulsant, and antipsychotic medications is highly prevalent. Further research to study the effects of off-label use among this high risk subpopulation may be an important step toward defining the scope of and potential for such use.

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Central nervous system (CNS) drugs are one of the drug categories that has been intensively prescribed off-label. Off-label use of CNS drugs can range from 25% to more than 80% of a drug's annual sales.[1] Antidepressants, anticonvulsants, and antipsychotics are the 3 CNS drug categories most commonly prescribed and have ranked among the top 10 therapeutic classes in both U.S. and global sales since 1999.[2] The annual sales of these 3 drug categories increased 40% in the U.S. market from 2000 to 2002.[2] Expanding off-label indications for these 3 drug categories contribute to their increased utilization. Recent literature reported that 40% to 70% of recipients of the second-generation antidepressant, anticonvulsant, or antipsychotic prescriptions received these agents for off-label purposes.[3–10]

It is generally acknowledged that the off-label use of CNS medications is extensive for the pediatric population.[11–13] This prevalence is largely a result of practical difficulties and additional ethical issues when conducting medical research in minor children. However, apart from pediatrics, off-label use evidently plays an important role in adult psychiatry.[7,8,14,15] Although a small proportion of off-label prescription use is based on the "gold standard" of proof from large-scale, carefully controlled clinical trials, many off-label uses may be based on less robust evidence. For instance, atypical antipsychotics, originally approved for the treatment of schizophrenia and mania,

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had been widely used for patients with dementia accompanied by behavioral and psychological symptoms, although their safety and clinical efficacy in the dementia population were uncertain.[8,16] In April 2005, the U.S. Food and Drug Administration (FDA) issued a warning against this use, because clinical studies have shown a higher death rate associated with atypical antipsychotic use compared with dementia patients receiving a placebo.[17] Our previous study also showed that only a modest proportion (19%–57%) of anticonvulsant off-label uses was supported by evidence from randomized, controlled trials.[4] Given that off-label drug use is almost unavoidable in clinical psychiatry, postmarket surveillance and clinical trials targeting patients who are at high risk for receiving off-label CNS medications are necessary to ensure that the benefits of an off-label treatment outweigh its risks. However, because very limited research has addressed this area, the patient and physician factors associated with off-label prescribing remain to be determined.

The aim of the current study was to determine the prevalence of off-label antidepressant, anticonvulsant, and antipsychotic uses in adult Georgia Medicaid enrollees and then to explore patient characteristics (demographic, comorbidities, number of medications filled) and prescriber specialties associated with the off-label uses of these 3 drug categories.

METHOD

Data Source

Data for this study were obtained from computerized Georgia Medicaid administrative claims files containing pharmacy, physician, hospital, and nursing home claims linked by encrypted recipient IDs.

Research Subjects and Cohorts

All Georgia Medicaid enrollees who were 18 years or older as of January 1, 2001, and who had at least 1 antidepressant, anticonvulsant, or antipsychotic prescription filled in 2001 were eligible to be included. Continuous eligibility of 24 months' enrollment in Georgia Medicaid from January 1, 2000, to December 31, 2001, was also required, so that diagnoses preceding the prescription use could be captured to define on- and off-label uses.

Three cohorts were constructed for the recipients of antidepressants, anticonvulsants, and antipsychotics, respectively. Research subjects who received prescriptions from more than 1 drug category were allowed to be entered in multiple study cohorts.

Determining Off-Label Prescriptions and Off-Label Recipients

The primary sources for determining labeled indications were the prescription drug leaflets and the *Physicians' Desk Reference* (PDR).[18] Since drug labeling is dynamic in nature, and the approved indications are continuously evolving, we chose to accept all the indications approved by the FDA up to December 2004. Tables 1, 2, and 3 present the labeled indications of all antidepressant, anticonvulsant, and antipsychotic medications. *The International Classification of Diseases,* Ninth Revision, Clinical Modification (ICD-9-CM) definitions of these indications were identified through a comprehensive literature review and ICD-9-CM databases. Table 4 presents the ICD-9-CM codes for each of the labeled indications.

According to the FDA, off-label drug use is the use of a prescription drug for an "indication, dosage form, dose regimen, population, or other use not mentioned in the approved labeling."[19] Owing to the limited availability of information from the Georgia Medicaid database, we did not consider the off-label drug use related to dosage, duration of time, and route of administration. In addition, prescribing an antidepressant, anticonvulsant, or antipsychotic for monotherapy, although it is solely labeled for adjunct therapy, was not considered as off-label use in this

Table 1. Labeled Indications of Antidepressants[a]

Antidepressant	FDA-Approved Indications for Adults
Bupropion	Depression, smoking cessation
Maprotiline	Depression
Mirtazapine[b]	Depression
Nefazodone[b]	Depression
Trazodone	Depression
Venlafaxine[b]	Depression, generalized anxiety disorder, social anxiety disorder (social phobia)
Citalopram[b]	Depression
Fluoxetine[b]	Depression, obsessive-compulsive disorder, bulimia nervosa, panic disorder
Fluvoxamine[b]	Obsessive-compulsive disorder
Paroxetine[b]	Depression, obsessive-compulsive disorder, social anxiety disorder (social phobia), panic disorder, generalized anxiety disorder, posttraumatic stress disorder
Sertraline[b]	Depression, obsessive-compulsive disorder, social anxiety disorder (social phobia), panic disorder, generalized anxiety disorder, posttraumatic stress disorder
Amitriptyline	Depression, depression accompanied by anxiety
Amoxapine	Depression
Clomipramine	Obsessive-compulsive disorder
Desipramine	Depression
Doxepin	Psychoneurosis with depression, depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol), depression and/or anxiety associated with organic disease, psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders
Imipramine	Depression
Nortriptyline	Depression
Protriptyline	Depression
Trimipramine	Depression

[a]All labeled indications were taken from the *Physicians' Desk Reference* (PDR)[18] and prescription drug leaflets and include FDA-approved indications that appeared between PDR editions.
[b]New-generation medications.

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Table 2. Labeled Indications of Anticonvulsants[a]

Anticonvulsant	FDA-Approved Indications for Adults
Acetazolamide	Edema due to congestive heart failure, drug-induced edema, epilepsies (petit mal, unlocalized seizures), chronic simple angle glaucoma, secondary glaucoma, acute angle-closure glaucoma, acute mountain sickness
Carbamazepine	Partial seizures (psychomotor or temporal lobe), generalized tonic-clonic (grand mal) seizure, mild, partial, or generalized seizure
Clonazepam	Seizure disorders, panic disorder
Clorazepate	Anxiety disorder, partial seizures, symptomatic relief of acute alcohol withdrawal
Diazepam	Anxiety disorder, alcohol withdrawal, skeletal muscle spasm, seizure
Divalproex sodium	Mania in bipolar disorder, partial epilepsy, migraine
Ethosuximide	Absence (petit mal) epilepsy
Felbamate[b]	Generalized epilepsy
Fosphenytoin[b]	Short-term parenteral administration, generalized convulsive epilepticus, seizure in surgery
Gabapentin[b]	Partial seizure with epilepsy for patient, postherpetic neuralgia
Lamotrigine[b]	Partial seizure and generalized seizures of Lennox-Gastaut syndrome, bipolar disorder
Levetiracetam[b]	Partial-onset seizures with epilepsy
Lorazepam	Anxiety disorder
Mephobarbital	Sedative for relief of anxiety, tension, and apprehension; anticonvulsant in treatment of grand mal and petit mal epilepsy
Methsuximide	Absence (petit mal) seizure
Oxcarbazepine[b]	Partial seizure with epilepsy
Paraldehyde	Alcohol or drug withdrawal, poisoning by convulsive drug, convulsive episode arising from tetanus, status epilepticus, insomnia
Phenobarbital	Sedative, hypnotic for short-term treatment of insomnia, preanesthetics, long-term anticonvulsants for generalized tonic-clonic seizures and cortical local seizures, emergency control of acute convulsive status epilepticus
Phenytoin	Tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures
Primidone	Tonic-clonic (grand mal) seizure, psychomotor (temporal lobe seizures)
Tiagabine[b]	Partial seizure
Topiramate[b]	Partial seizure, primary generalized tonic-clonic seizures, seizure associated with Lennox-Gastaut syndrome
Valproic acid	Mania in bipolar disorder, epilepsy, migraine
Aonisamide[b]	Partial seizure in epilepsy

[a]All labeled indications were taken from the *Physicians' Desk Reference* (PDR)[18] and prescription drug leaflets and include FDA-approved indications that appeared between PDR editions.
[b]New-generation medications.

Table 3. Labeled Indications of Antipsychotics[a]

Antipsychotic	FDA-Approved Indications for Adults
Clozapine[b]	Severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia, reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders
Haloperidol	Schizophrenic patients who require prolonged parenteral antipsychotic therapy
Loxapine[b]	Schizophrenia
Molindone	Schizophrenia
Olanzapine[b]	Schizophrenia, bipolar mania
Quetiapine[b]	Schizophrenia, acute bipolar mania
Risperidone[b]	Schizophrenia, bipolar mania
Thiothixene	Schizophrenia, psychotic disorder (injection use)
Ziprasidone[b]	Schizophrenia
Chlorpromazine	Schizophrenia, mania, acute intermittent porphyria, intractable hiccups, nausea and vomiting, presurgical apprehension, tetanus
Fluphenazine	Schizophrenia
Mesoridazine	Treatment-resistant schizophrenia
Perphenazine	Schizophrenia, nausea and vomiting
Prochlorperazine	Schizophrenia, severe nausea and vomiting, nonpsychotic anxiety
Promazine	Schizophrenia
Thioridazine	Patients who fail to respond adequately to treatment with other antipsychotic drugs
Trifluoperazine	Schizophrenia, nonpsychotic anxiety
Trifluprom azine	Schizophrenia (acute treatment), nausea and vomiting

[a]All labeled indications were taken from the *Physicians' Desk Reference* (PDR)[18] and prescription drug leaflets and include FDA-approved indications that appeared between PDR editions.
[b]New-generation medications.

study, because our preliminary study found that such use accounts for less than 4% of off-label anticonvulsant use, and it had a great amount of overlap with off-label uses for non–FDA-approved clinical conditions.[4]

An antidepressant, anticonvulsant, or antipsychotic prescription filled in 2001 was categorized as off-label if none of the ICD-9-CM codes the patient received within the 24-month observation period (January 2000–December 2001) could be matched with one of the approved indications of this prescription. Otherwise, the prescription was categorized as on-label.

Determining the Prevalence of Off-Label Drug Use

Within each cohort, the unit of analysis for computing the prevalence of off-label antidepressant, anticonvulsant, and antipsychotic use was the individual patient who received at least 1 prescription of a certain drug category off-label. The denominator used in this study was all recipients exposed to at least 1 antidepressant, anticonvulsant, or antipsychotic, respectively, during the year 2001.

Determining Patient and Physician Factors Associated With Off-Label Drug Use

A comprehensive list of possible factors associated with off-label prescribing was identified by a survey of published literature and expert opinion. In this study, a MEDLINE search using the combination of MeSH terms *off-label* and (*patient selection*, *physician practice pattern*) was first conducted. However, only a few articles were identified using this search strategy, and most of those articles were not actually related to the off-label treatment selection. Therefore, after consulting a clinical pharmacist in a psychiatric clinic and a neurologist, the

Table 4. ICD-9-CM Codes Assigned to the Labeled Indications of Antidepressants, Anticonvulsants, and Antipsychotics

Labeled Indications	ICD-9-CM Code
Absence (petit mal) seizure	345.0x, 345.2x
Acute intermittent porphyria	277.1x
Alcohol or drug withdrawal	291.0x, 291.3x, 291.8x, 292.0x
Bulimia nervosa	307.51
Convulsive episode arising from tetanus	037.xx, 771.3x, 978.4x, E9484
Depression	296.2x–296.3x
Depression accompanied by anxiety	300.4x
Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol)	291.xx
Depression and/or anxiety associated with organic disease	310.8x, 294.8x
Drug-induced edema	782.3x
Edema due to congestive heart failure	428.xx
Epilepsy	345.xx, 780.39
Generalized anxiety disorder	300.02
Generalized epilepsy	345.0x. 345.1x, 345.2x, 345.3x, 780.39
Intractable hiccups	786.8x, 306.1x
Mania and mania episode in bipolar disorders	296.0x, 296.1x, 296.4x–296.8x
Migraine	346.xx
Nausea and vomiting	787.0x
Nonpsychotic anxiety	300.0x
Obsessive-compulsive disorder	300.3x
Panic disorder	300.01, 300.21
Partial seizure	345.4x, 345.5x
Poisoning by convulsive drug	E858, 780.39
Postherpetic neuralgia	53.19
Posttraumatic stress disorder	309.81
Premenstrual dysphoric disorder	625.4x
Primary generalized tonic-clonic seizures	345.1x, 780.9x
Psychoneurotic patients with depression and/or anxiety	300.0x, 300.4x
Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders	296.xx
Psychomotor (temporal lobe seizures)	345.4x, 345.7x
Schizophrenia	295.xx
Sedative for relief of anxiety, tension, and apprehension	293.xx, 300.xx, 309.xx, 625.4x
Seizure associated with Lennox-Gastaut syndrome	345.01
Skeletal muscle spasm	728.85
Social anxiety disorder (social phobia)	300.23
Status epilepticus	345.3x

Abbreviation: ICD-9-CM = *International Classification of Diseases*, Ninth Revision, Clinical Modification.

authors applied very liberal inclusion criteria to identify and include all potential covariates available in the Medicaid data. This list included patient demographics, diagnosis-related comorbidities, physician specialty, drug classes, and the number of antidepressant, anticonvulsant, and antipsychotic medications filled in the study period (Table 5). In terms of diagnosis-related comorbidities, all mental disorders were included, because antidepressant, anticonvulsant, and antipsychotic medications have been used off-label for various mental disorders. A patient's having a certain mental condition, such as depression with psychotic symptoms, may cause physicians to consider off-label medications. Besides mental disorders, other chronic conditions were also included, given the high prevalence of comorbid mental disturbances associated with these diseases. A list of diagnosis-related comorbidities, which contains detailed classifications of mental and substance-related comorbidities and comparatively general classifications for other diseases[20] and their ICD-9 codes, was obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA).

Statistical Analysis

Three logistic models were estimated for the 3 cohorts (recipients of antidepressants, anticonvulsants, and antipsychotics). A stepwise logistic variable selection procedure was used to identify factors independently associated with the likelihood of patients' receiving a certain drug category off-label. The binary treatment indicator (1 = any off-label use, 0 = labeled use) was modeled according to patients' age, race, gender, comorbidities, type of prescriptions (new generation vs. traditional), and physicians' specialty. The c-statistic (area under receiver operating characteristic curve), proportion of variance explained (R^2), and χ^2 goodness-of-fit test determined model adequacy. All data manipulations and statistical analyses were performed with SAS software (version 8.2, SAS Institute, Inc., Cary, N.C.).

RESULTS

In 2001, 126,685 antidepressant recipients, 87,365 anticonvulsant recipients, and 59,404 antipsychotic recipients were identified from the Georgia Medicaid data. Of these, 62,505 antidepressant recipients, 48,261 anticonvulsant recipients, and 33,536 antipsychotic recipients met the 24-month continuous Medicaid eligibility criterion. After excluding patients younger than 18 as of January 1, 2001, and patients without full Medicaid benefits, the final study sample consisted of 62,289 antidepressant recipients (antidepressant cohort), 48,049 anticonvulsant recipients (anticonvulsant cohort), and 33,406 antipsychotic recipients (antipsychotic cohort). In 2001, 9881 subjects received medications from all 3 drug categories. Table 6 presents the descriptive statistics for the study populations. The majority of the subjects were female, and the average age was between 52 and 54 across the cohorts.

In 2001, 46,976 (75.42%) antidepressant recipients, 38,497 (80.12%) anticonvulsant recipients, and 21,252 (63.62%) antipsychotic recipients received at least 1 of these medications off-label (Figure 1). Table 7 presents the top 5 most-prescribed antidepressant, anticonvulsant, and antipsychotic medications in 2001. The second-generation agents, including selective serotonin reuptake inhibitors (SSRIs), gabapentin, and atypical antipsy-

Table 5. Initial List of Candidate Factors Associated With the Off-Label Use of Antidepressant, Anticonvulsant, and Antipsychotic Medications

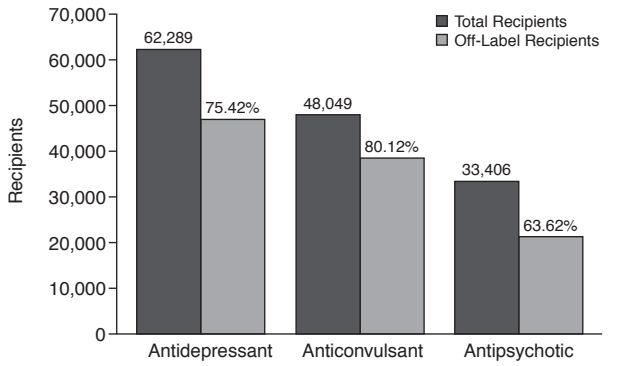
Demographics	ICD-9 Definitions of Diagnosis-Related Comorbidities
Age, gender, race	
Physician specialties	
Psychiatrist vs nonpsychiatrist	
Diagnosis-related comorbidities	
Mental and substance-abuse–related comorbidities	
Acute reaction to stress	308.xx
Adjustment reaction	309.xx
Alcoholic psychoses	291.xx
Alzheimer's disease	290.xx, 331.0x
Bipolar affective disorders	296.4x–296.7x
Cyclothymic disorders	301.13
Depressive disorder, not elsewhere specified	311.xx
Drug psychoses	292.xx
Major depressive disorder	296.2x, 296.3x
Manic disorders	296.0x, 296.1x
Mental retardation	315.xx, 317.xx–319.xx
Neurotic disorders	300.xx
Other mental disorders[a]	302.xx, 306.xx, 307.xx, 310.xx, 316.xx, 648.4x
Other nonorganic psychoses	298.xx
Other organic psychotic conditions, chronic	294.xx
Paranoid/delusional disorders	297.xx
Personality disorders	301.xx, excluding 301.13
Psychoses with origin specified to childhood	299.xx
Schizophrenic disorders	295.xx
Transient organic psychotic conditions	293.xx
Unspecified affective psychoses	296.8x, 296.9x
Other comorbidities	
Anemia	280.0x, 280.1x–281.9x, 285.9x
Asthma	493.xx
Cancer	140.0x–172.9x, 174.0x–175.9x, 179.xx–195.8x, V10.00–V10.69, V10.8–V10.9, 196.0x–199.1x, 200.00–202.38, 202.50–203.01, 203.8x–203.81, 238.6x, 273.3x, V10.71, V10.72, V10.79
Cardiovascular disease	426.10, 426.11, 426.13,426.2x–426.53, 426.6x–426.89, 427.0x, 427.2x, 427.31, 427.60, 427.9x, 785.0x, V45.0, V53.3, 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.0x–428.9x, 401.1x, 401.9x, 402.10, 402.90, 404.10, 404.90, 405.11, 405.19, 405.91, 405.99, 440.0x–440.9x, 441.2x, 441.4x, 441.7x, 441.9x, 443.1x–443.9x, 447.1x, 557.1x, 557.9x, V43.4, 416.0x–416.9x, 417.9x, 093.20–093.24, 394.0x–397.1x, 424.0x–424.91, 746.3x–746.6x, V42.2, V43.3
Chronic pulmonary diseases	490.xx–492.8x, 494.xx, 495.0x–505.xx, 506.4x
Coagulation	286.0x–286.9x, 287.1x, 287.3x–287.5x
Connective tissue disorders[b]	701.0x, 710.0x–710.9x, 714.0x–714.9x, 720.0x–720.9x, 725.xx
Diabetes	250.xx, 357.2x, 362.01, 362.02, 366.41, 648.0x and NOT 648.8x
Epilepsy	345.0x–345.9x
HIV or AIDS	042.xx–044.xx
Hypothyroidism	243.xx–244.2x, 244.8x, 244.9x
Liver diseases	070.32, 070.33, 070.54, 456.0x–456.1x, 456.20, 456.21, 572.3x, 572.8x, V42.7
Other neurologic disorders	331.9x, 332.0x, 333.4x, 333.5x, 334.0x–334.3x, 334.5x–335.9x, 340.xx, 341.1x–341.9x, 348.1x, 348.3x, 784.3x
Nutritional disorders	276.0x–276.9x, 278.0x, 260.xx–263.9x
Paralysis	342.0x–342.12, 342.9x–344.9x
Peptic ulcer disease	531.70, 531.90, 532.70, 532.90, 533.70, 533.90, 534.70, 534.90, V12.71
Renal failure	403.11, 403.91, 404.12, 404.92, 585.xx, 586.xx, V42.0, V45.1, V56.0, V56.8

[a]Other mental disorders: sexual deviations and disorders, physiologic malfunction arising from mental factors, special symptoms or syndromes not elsewhere specified, specific nonpsychotic mental disorders due to organic brain damage, psychotic factors associated with diseases specified elsewhere, mental disorders in pregnancy, antepartum and postpartum.
[b]Connective tissue disorders: Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, etc.
Abbreviations: AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, ICD-9 = *International Classification of Diseases*, Ninth Revision.

Table 6. Demographic Characteristics of Antidepressant, Anticonvulsant, and Antipsychotic Cohorts (recipients)

				Race, N (%)		
Cohort (recipients)	N	Mean Age, y	Female, N (%)	White	Black	Other
Antidepressant	62,289	53.97	47,831 (76.79)	32,964 (52.92)	21,713 (34.86)	7612 (12.22)
Anticonvulsant	33,406	52.14	21,876 (65.49)	15,663 (46.89)	14,512 (43.44)	3231 (9.67)
Antipsychotic	48,049	52.46	32,691 (68.04)	25,533 (53.14)	17,068 (35.52)	5448 (11.34)

Figure 1. The Prevalence of Antidepressant, Anticonvulsant, and Antipsychotic Off-Label Use



chotics had replaced the traditional agents as the most popularly prescribed antidepressant, anticonvulsant, and antipsychotic medications. Gabapentin was found to be the medication most commonly used off-label. Nearly all gabapentin recipients (98.04%) received the drug for clinical conditions other than partial epilepsy or postherpetic neuralgia in 2001.

Tables 8, 9, and 10 present the logistic regression results for the recipients of antidepressant, anticonvulsant, and antipsychotic medications, respectively. Multivariate models revealed that patient demographic factors, especially age, were strong predictors for the likelihood of receiving off-label medications. The recipients 65 years or older were 4 to 6 times more likely to receive an off-label prescription than those less than 65 years of age (antidepressants recipients: OR = 5.15, 95% CI = 4.76 to 5.56; anticonvulsants recipients: OR = 4.54, 95% CI = 4.16 to 4.96; antipsychotics recipients: OR = 5.21, 95% CI = 4.82 to 5.63). Whites were consistently more likely to receive off-label medications than nonwhites (antidepressant recipients: OR = 1.15, 95% CI = 1.10 to 1.20; anticonvulsant recipients: OR = 1.71, 95% CI = 1.62 to 1.80; antipsychotic recipients: OR = 1.89, 95% CI = 1.79 to 1.99).

The results of the logistic regression analyses also demonstrate that exposure to newer generation agents did not always confer a higher risk of receiving off-label medications. For anticonvulsant recipients, receiving new agents launched after 1993 was the strongest indicator (OR = 7.63, 95% CI = 7.07 to 8.23) of receiving off-label anticonvulsant medications. However, patients exposed to SSRIs (OR = 0.43, 95% CI = 0.40 to 0.45) or atypical antipsychotics, especially clozapine (OR = 0.20, 95% CI = 0.16 to 0.23), were associated with a lower likelihood of receiving medications off-label compared with patients exposed to tricyclic antidepressants or conventional antipsychotics, respectively.

The association between physician specialties and off-label drug use was found to be inconsistent across the cohorts. Antipsychotic recipients who were seeing a psychiatrist during the study period seemed to be more likely to receive antipsychotic medications off-label (OR = 1.44, 95% CI = 1.31 to 1.58). Nevertheless, for antidepressant (OR = 0.85, 95% CI = 0.80 to 0.91) and anticonvulsant (OR = 0.25, 95% CI = 0.24 to 0.27) recipients, seeing a psychiatrist was associated with a lower likelihood of receiving these 2 drug categories off-label.

Many diagnoses-related comorbidities also had factor impacts on the likelihood of receiving off-label medications. Renal failure was the only disease that was associated with a greater likelihood of receiving all 3 drug categories off-label (antidepressants: OR = 1.43, 95% CI = 1.24 to 1.64; anticonvulsants: OR = 1.77 95% CI = 1.49 to 2.10; antipsychotics: OR = 1.84, 95% CI = 1.52 to 2.24). Major depressive disorder was found to be associated with greater likelihoods of receiving both anticonvulsant (OR = 1.40, 95% CI = 1.28 to 1.52) and antipsychotic (OR = 2.1, 95% CI = 1.94 to 2.27) medications off-label. Additionally, patients with mental retardation (OR = 2.50, 95% CI = 2.31 to 2.71), Alzheimer's disease (OR = 2.10, 95% CI = 1.78 to 2.48), neurologic disorders such as paralysis (OR = 2.18, 95% CI = 1.79 to 2.66), and psychoses due to different reasons were more likely to receive off-label antipsychotics than patients without these conditions, while patients with schizophrenia (OR = 1.69, 95% CI = 1.55 to 1.84) and pain problems associated with diabetes or joint diseases were more likely to be prescribed anticonvulsants off-label than patients without these conditions.

DISCUSSION

This study confirmed the previous finding that off-label use of antidepressant, anticonvulsant, and antipsychotic medications is highly prevalent.[3–10] Among the 3 drug categories under investigation, anticonvulsants, especially gabapentin, were the drug category most frequently prescribed off-label, followed by antidepressants and antipsychotics. Although the off-label use of second-generation CNS agents has been frequently mentioned in the recent literature, the results of this study demonstrate that these new-generation agents, except for gabapentin, are generally used less often for off-label purposes than traditional agents.

The high rate of off-label drug use is due to many factors. The long and expensive drug approval process required by the FDA is regarded as one of the major barriers that discourage drug manufacturers from pursuing the approval of off-label uses. The most striking example is for 2 commonly used antidepressant drugs, clomipramine and fluvoxamine, which are not even indicated for depression in the United States.[18] Also, with ever-growing off-label prescribing in real practice, drug manufacturers often lack financial incentives to conduct clinical trials for

Table 7. Prevalence of Off-Label Uses of Top 5 Prescribed Antidepressants, Anticonvulsants, and Antipsychotics in 2001

Drug Category	Drug Name	Number of Recipients With at Least 1 Prescription	On-Label	Off-Label	% Off-Label
Antidepressant	Sertraline[a]	14,077	4700	9377	66.61
	Amitriptyline	11,724	2191	9533	81.31
	Paroxetine[a]	11,000	3647	7353	66.85
	Fluoxetine[a]	10,588	3518	7070	66.77
	Trazodone	9748	3358	6390	65.55
Anticonvulsant	Gabapentin[a]	11,540	226	11,314	98.04
	Lorazepam	10,233	1171	9062	88.56
	Phenytoin	9898	4933	4965	50.16
	Divalproex sodium	8495	3606	4889	57.55
	Diazepam	6160	1278	4882	79.25
Antipsychotic	Risperidone[a]	12,970	4307	8663	66.79
	Olanzapine[a]	11,161	5392	5769	51.69
	Haloperidol	5371	2556	2815	52.41
	Quetiapine[a]	4521	1840	2681	59.30
	Prochlorperazine	1925	685	1240	64.42

[a]New-generation agents.

Table 8. Independent Factors Associated With the Off-Label Use of Antidepressants Identified From the Stepwise Logistic Variable Selection Procedure

Factor	Off-Label[a] (Total N = 45,909)	On-Label[a] (Total N = 15,282)	Odds Ratio	95% CI	p Value
Age (≥ 65 vs < 65)	17,088 (37.2)	867 (5.7)	5.149	4.764 to 5.564	< .0001
Race (white vs nonwhite)	24,350 (53.0)	7687 (50.3)	1.150	1.099 to 1.204	< .0001
Gender (male vs female)	11,336 (24.7)	2909 (19.0)	1.549	1.465 to 1.638	< .0001
Prescription class (SSRI vs tricyclic)	25,939 (56.5)	11,163 (73.0)	0.428	0.404 to 0.453	< .0001
Prescription class (other second-generation antidepressant vs tricyclic)	16,008 (34.9)	7485 (49.0)	0.550	0.518 to 0.584	< .0001
Physician specialty (psychiatrist vs nonpsychiatrist)	3955 (8.6)	2615 (17.1)	0.853	0.797 to 0.914	< .0001
Number of drugs, mean (SD)	1.333 (0.651)	1.719 (0.94)	0.900	0.869 to 0.932	< .0001
Manic disorders	95 (0.2)	179 (1.2)	0.432	0.321 to 0.581	< .0001
Transient organic psychotic conditions	384 (0.8)	397 (2.6)	0.775	0.649 to 0.926	.0049
Other organic psychotic conditions, chronic	1134 (2.5)	306 (2.0)	0.826	0.698 to 0.977	.0259
Paranoid/delusional disorders	138 (0.3)	139 (0.9)	0.714	0.529 to 0.964	.0279
Other nonorganic psychoses	1364 (3.0)	1091 (7.1)	0.868	0.782 to 0.963	.0076
Adjustment reaction	494 (1.1)	1396 (9.1)	0.212	0.189 to 0.239	< .0001
Personality disorders	181 (0.4)	543 (3.6)	0.465	0.378 to 0.571	< .0001
Neurotic disorders	2951 (6.4)	6535 (42.8)	0.173	0.164 to 0.183	< .0001
Other mental disorders	1213 (2.6)	1278 (8.4)	0.698	0.632 to 0.771	< .0001
Alcoholic psychoses	1169 (2.5)	1437 (9.4)	0.634	0.572 to 0.703	< .0001
Drug psychoses	1135 (2.5)	1853 (12.1)	0.617	0.560 to 0.681	< .0001
Alzheimer's disease	1426 (3.1)	252 (1.6)	0.792	0.667 to 0.941	.0079
HIV or AIDS	483 (1.1)	365 (2.4)	0.746	0.631 to 0.882	.0006
Epilepsy	856 (1.9)	715 (4.7)	0.838	0.737 to 0.953	.0071
Asthma	2883 (6.3)	2605 (17.0)	0.811	0.756 to 0.871	< .0001
Cardiovascular disease	15,874 (34.6)	7719 (50.5)	0.762	0.726 to 0.800	< .0001
Connective tissue disorders	1368 (3.0)	928 (6.1)	0.891	0.803 to 0.989	.0302
Hypothyroidism	1713 (3.7)	1435 (9.4)	0.814	0.745 to 0.890	< .0001
Nutritional disorders	4894 (10.7)	4189 (27.4)	0.730	0.687 to 0.776	< .0001
Peptic ulcer disease	886 (1.9)	781 (5.1)	0.882	0.780 to 0.997	.045
Renal failure	1200 (2.6)	398 (2.6)	1.425	1.239 to 1.640	< .0001

[a]Values are N (% total) unless otherwise stated.
Abbreviations: AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, SSRI = selective serotonin reuptake inhibitor.

new indications, particularly for low-prevalence disease states and for products nearing patent expiration or that are off patent. Government research institutes couldn't possibly fund clinical trials to investigate the multitude of off-label uses in the prescription drug marketplace, nor could the FDA review all possible uses. The agency has neither the financial resources nor the personnel to review each use.

Off-label drug use is legal in the medical community and sometimes is essential to giving patients optimal medical care. The FDA acknowledges that "good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgement."[21] However, the regulation of off-label drugs is still a complicated and controversial area, because most off-

Table 9. Independent Factors Associated With the Off-Label Use of Anticonvulsants Identified From the Stepwise Logistic Variable Selection Procedure

Factor	Off-Label[a] (Total N = 37,156)	On-Label[a] (Total N = 10,030)	Odds Ratio	95% CI	p Value
Age (≥ 65 vs < 65)	12,310 (33.1)	687 (6.8)	4.544	4.159 to 4.964	< .0001
Race (white vs nonwhite)	20,277 (54.6)	4571 (45.6)	1.708	1.620 to 1.800	< .0001
Gender (male vs female)	11,150 (30.0)	3943 (39.3)	0.742	0.701 to 0.784	< .0001
Physician specialty (psychiatrist vs nonpsychiatrist)	4430 (11.9)	3166 (31.6)	0.253	0.237 to 0.270	< .0001
Prescription class (new generation vs conventional)	14,295 (38.5)	1625 (16.2)	7.628	7.071 to 8.230	< .0001
Number of drugs, mean (SD)	1.42 (0.757)	1.53 (0.811)	0.745	0.718 to 0.772	< .0001
Acute reaction to stress	158 (0.4)	133 (1.3)	0.680	0.518 to 0.894	.0058
Alcoholic psychoses	1212 (3.3)	931 (9.3)	0.561	0.502 to 0.626	< .0001
Alzheimer's disease	1121 (3.0)	235 (2.3)	0.811	0.678 to 0.971	.0227
Bipolar affective disorders	1361 (3.7)	999 (10.0)	0.364	0.326 to 0.405	< .0001
Drug psychoses	1401 (3.8)	759 (7.6)	1.216	1.081 to 1.368	.0011
Major depressive disorder	3366 (9.1)	1331 (13.3)	1.397	1.282 to 1.524	< .0001
Mental retardation	3083 (8.3)	1662 (16.6)	0.663	0.614 to 0.716	< .0001
Neurotic disorders	3286 (8.8)	2886 (28.8)	0.253	0.235 to 0.272	< .0001
Other nonorganic psychoses	1482 (4.0)	694 (6.9)	1.145	1.019 to 1.287	.023
Other organic psychotic conditions, chronic	959 (2.6)	311 (3.1)	0.775	0.655 to 0.917	.003
Schizophrenic disorders	3995 (10.8)	1230 (12.3)	1.689	1.551 to 1.839	< .0001
Unspecified affective psychoses	564 (1.5)	402 (4.0)	0.727	0.617 to 0.856	.0001
Cardiovascular disease	11,951 (32.2)	4272 (42.6)	0.781	0.736 to 0.828	< .0001
Coagulation disorders	489 (1.3)	306 (3.1)	0.742	0.621 to 0.886	.001
Connective tissue disorders	1138 (3.1)	332 (3.3)	1.455	1.254 to 1.689	< .0001
Diabetes	6123 (16.5)	1598 (15.9)	1.232	1.142 to 1.329	< .0001
Hypothyroidism	1448 (3.9)	721 (7.2)	0.814	0.728 to 0.909	.0003
Liver diseases	302 (0.8)	131 (1.3)	1.367	1.070 to 1.747	.0124
Neurologic disorders other than paralysis	639 (1.7)	473 (4.7)	0.710	0.611 to 0.824	< .0001
Nutritional disorders	4411 (11.9)	2312 (23.1)	0.734	0.682 to 0.791	< .0001
Paralysis	1314 (3.5)	847 (8.4)	0.575	0.518 to 0.639	< .0001
Renal failure	1044 (2.8)	225 (2.2)	1.768	1.490 to 2.097	< .0001

[a]Values are N (% total) unless otherwise stated.

label uses have not been adequately tested for safety and effectiveness. It is a challenge for regulators to protect patients' safety without interfering with physicians' practice and the pharmaceutical industry's First Amendment rights.

In this study, the odds of receiving antidepressant, anticonvulsant, or antipsychotic medication off-label were found to increase dramatically with advancing age. This finding may be explained by some highly prevalent mental disorders, such as dementia, among elderly Medicaid recipients, many of whom reside in a long-term care facility. It is very common for senior patients to develop psychosis with delusions or hallucinations, depression, anxiety, and/or behavior problems as complications of degenerative dementia. The estimated prevalence of neuropsychiatric disturbance in dementia ranges from 60% to 80% at any one time, and the lifetime risk is almost 100%.[22] At present, there is not any FDA-approved medication available for the treatment of these problems. Most often, antidepressants were prescribed to control depressive symptoms, while antipsychotic drugs were used for behavioral and psychological symptoms in dementia.[8,16,23] Logistic regression analysis also revealed that whites were more likely to receive antidepressant, anticonvulsant, and antipsychotic medications off-label than nonwhites. Although the Medicaid population generally has low socioeconomic status, this disparity may still be explained by the different health care accessibility between races. While the mental illnesses themselves are prevalent to the same relative degree in minority and white populations, the literature has shown that the impact of the mental disorders is notably more significant for minority populations, chiefly because minorities are less likely to receive mental health care.[24]

The comorbidity profile of off-label recipients observed in this study is generally consistent with the literature.[3,8–10,25] For instance, patients with mental retardation were more likely to receive off-label antipsychotics, while patients with schizophrenia were more likely to receive off-label anticonvulsants. In general, almost all off-label antipsychotic prescriptions were written for persons with mental disorders or substance abuse–related conditions. In contrast, off-label anticonvulsants were used more often for the pain problems associated with diabetes and joint diseases. This difference in prescribing patterns may partially explain why seeing psychiatrists is associated with a greater likelihood of receiving antipsychotics off-label and a smaller likelihood of receiving anticonvulsants off-label, since only patients with mental disorders or substance abuse–related diseases would be seeking help from psychiatrists, whereas patients with pain problems or other neurologic disorders are usually treated by other physicians. Therefore, it is unlikely for a psychiatrist to write an off-label anticonvulsant prescription for patients with pain problems such as diabetic neuralgia.

Table 10. Independent Factors Associated With the Off-Label Use of Antipsychotics Identified From the Stepwise Logistic Variable Selection Procedure

Factor	Off-Label[a] (Total N = 20,482)	On-Label[a] (Total N = 12,126)	Odds Ratio	95% CI	p Value
Age (≥ 65 vs < 65)	7948 (38.8)	1027 (8.5)	5.209	4.820 to 5.629	< .0001
Race (white vs nonwhite)	10,683 (52.2)	4340 (35.8)	1.889	1.791 to 1.992	< .0001
Gender (male vs female)	6548 (32.0)	4781 (39.4)	0.834	0.788 to 0.881	< .0001
Prescription class (atypical except clozapine vs conventional)	8262 (40.3)	6170 (50.9)	0.757	0.716 to 0.800	< .0001
Prescription class (clozapine vs conventional)	136 (0.7)	537 (4.4)	0.191	0.156 to 0.234	< .0001
Physician specialty (psychiatrist vs nonpsychiatrist)	1808 (8.8)	931 (7.7)	1.441	1.312 to 1.583	< .0001
Number of drugs, mean (SD)	1.313 (0.641)	1.551 (0.814)	0.828	0.797 to 0.860	< .0001
Major depressive disorder	3046 (14.9)	1825 (15.1)	2.100	1.944 to 2.268	< .0001
Manic disorders	88 (0.4)	230 (1.9)	0.497	0.377 to 0.656	< .0001
Bipolar affective disorders	942 (4.6)	1671 (13.8)	0.491	0.446 to 0.541	< .0001
Unspecified affective psychoses	402 (2.0)	684 (5.6)	0.661	0.572 to 0.764	< .0001
Other organic psychotic conditions, chronic	1252 (6.1)	279 (2.3)	1.723	1.478 to 2.010	< .0001
Paranoid/delusional disorders	141 (0.7)	277 (2.3)	0.469	0.370 to 0.593	< .0001
Other nonorganic psychoses	1548 (7.6)	2101 (17.3)	0.570	0.526 to 0.618	< .0001
Psychoses with origin specified to childhood	223 (1.1)	48 (0.4)	2.715	1.945 to 3.790	< .0001
Adjustment reaction	555 (2.7)	385 (3.2)	1.452	1.250 to 1.685	< .0001
Personality disorders	259 (1.3)	400 (3.3)	0.671	0.557 to 0.807	< .0001
Neurotic disorders	2177 (10.6)	2305 (19.0)	0.852	0.787 to 0.921	< .0001
Cyclothymic disorders	15 (0.1)	5 (0.0)	3.913	1.341 to 11.421	.0125
Depressive disorder, not elsewhere specified	1688 (8.2)	1699 (14.0)	0.878	0.803 to 0.959	.004
Other mental disorders	776 (3.8)	596 (4.9)	1.138	1.003 to 1.290	.044
Drug psychoses	730 (3.6)	1214 (10.0)	0.696	0.623 to 0.777	< .0001
Other alcohol- and drug-related psychoses	915 (4.5)	1384 (11.4)	0.674	0.608 to 0.748	< .0001
Alzheimer's disease	1541 (7.5)	211 (1.7)	2.100	1.779 to 2.479	< .0001
HIV and AIDS	197 (1.0)	183 (1.5)	1.420	1.137 to 1.773	.002
Mental retardation	2945 (14.4)	1162 (9.6)	2.500	2.305 to 2.711	< .0001
Cancer	784 (3.8)	391 (3.2)	1.236	1.073 to 1.423	.0033
Cardiovascular disease	5870 (28.7)	4298 (35.4)	0.865	0.814 to 0.920	< .0001
Connective tissue disorders	391 (1.9)	236 (1.9)	1.427	1.190 to 1.712	.0001
Diabetes	2735 (13.4)	2127 (17.5)	0.894	0.830 to 0.964	.0036
Hypothyroidism	677 (3.3)	756 (6.2)	0.790	0.699 to 0.893	.0002
Nutritional disorders	2049 (10.0)	2158 (17.8)	0.702	0.646 to 0.762	< .0001
Renal failure	398 (1.9)	199 (1.6)	1.844	1.521 to 2.235	< .0001
Paralysis	524 (2.6)	150 (1.2)	2.179	1.785 to 2.660	< .0001

[a]Values are N (% total) unless otherwise stated.

The strength of the statistical associations in this study establishes clear service implications. As the likelihood of receiving off-label antidepressants, anticonvulsants, and antipsychotic medications was 4 to 6 times higher among patients 65 years or older than among those younger than 65 years, recognition of the vital role of postmarket surveillance and clinical studies targeting off-label use among the senior population is essential. The elderly are a group of patients in whom drug effects are influenced by age-related changes in pharmacokinetics, pharmacodynamics, and homeostasis, which render them more susceptible to adverse drug reactions.[26] Since the risk/benefit ratios of most off-label uses are uncertain, using drugs in accordance with evidence to support benefit should be especially stressed among the senior population. It is also important to note that, besides patients' age, renal disease is another factor that consistently affects the likelihood of receiving antidepressant, anticonvulsant, and antipsychotic medications off-label. The epidemiologic literature has shown that a substantial proportion of the end-stage renal disease (ESRD) population has comorbid psychiatric disorders.[27] Subsyndromal depressive syndromes, for example, are likely in about 25% of the individuals with ESRD, and major depression in 5% to 22% of this population. Although clinical experience suggests that the majority of psychotropic medications can be safely used with an ESRD patient, remarkably few data are available on the metabolism and efficacy of these agents in patients with renal impairment. Given the enormous prevalence of comorbid renal and psychiatric disorders, more outcomes research is imperative to help psychiatric consultants and nephrologists to manage this substantial patient population.

The main limitation of this study is the potentially different understanding regarding off-label use between clinicians and researchers. For instance, none of the antipsychotic medications has been approved for relieving the psychotic symptoms in mental disorders other than schizophrenia and bipolar disorders. Nevertheless, using an antipsychotic for depression patients with psychotic symptoms is usually regarded as labeled treatment in clinical practice but was categorized as off-label in this study. The operational definition of labeled indications adopted in the study strictly followed the drug informa-

tion from the PDR and drug leaflets. This definition may be narrower than clinicians' common definition. Therefore, the estimates derived from this study, though generally consistent with other literature, may slightly inflate the prevalence of off-label use for some medications. Moreover, the data source employed is an administrative database, and, as such, it is associated with the limitations that affect all administrative databases, including over/under coding, coding errors, missing codes, and lack of direct links between diagnosis codes and prescriptions. Because of the poor understanding and social stigma carried by mental disorders, undercoding is common for these diseases. The undercoding among patients with depression and anxiety, Alzheimer's disease, and related dementia has been reported in both inpatient and outpatient settings.[28–30] Therefore, our methodology, which relies solely on ICD-9-CM code to identify diagnosis, may not have fully captured patients with certain conditions. This undercoding may have skewed the results toward overestimating the rate of off-label drug use. To mitigate the potential impact of undercoding and missing codes, we expanded the study window to a 2-year period to identify ICD-9-CM codes for labeled indications in the year prior to, in addition to the year of, the claim for an antidepressant, anticonvulsant, or antipsychotic prescription. Finally, the ICD-9-CM definitions of mental disorders used in the study were collected from other published claims studies and may not agree exactly with those adopted in physician offices. The misclassification of off-label and on-label uses was another potential issue in the study.

CONCLUSIONS

The off-label use of antidepressant, anticonvulsant, and antipsychotic medications is highly prevalent. Further research to study the effects of off-label use of these 3 drug categories in high-risk subgroups, especially the geriatric population, may be an important step toward better defining the scope of and potential for such use.

Drug names: acetazolamide (Diamox and others), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), clozapine (Clozaril, FazaClo, and others), desipramine (Norpramin and others), diazepam (Valium and others), divalproex sodium (Depakote), doxepin (Sinequan and others), ethosuximide (Zarontin and others), felbamate (Felbatol), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), fosphenytoin (Cerebyx), gabapentin (Neurontin and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal), levetiracetam (Keppra), lorazepam (Ativan and others), loxapine (Loxitane and others), methsuximide (Celontin), mirtazapine (Remeron and others), molindone (Moban), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), paroxetine (Paxil, Pexeva, and others), phenytoin (Dilantin, Phenytek, and others), primidone (Mysoline and others), prochlorperazine (Compazine, Compro, and others), protriptyline (Vivactil), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thiothixene (Navane and others), tiagabine (Gabitril), topiramate (Topamax), trazodone (Desyrel and others), trifluoperazine (Stelazine and others), trimipramine (Surmontil), valproic acid (Depakene and others), venlafaxine (Effexor), ziprasidone (Geodon), zonisamide (Zonegran and others).

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