Variables Associated With High Olanzapine Dosing in a State Hospital

Sheila Botts, Pharm.D.; Robert Littrell, Pharm.D.; and Jose de Leon, M.D.

Background: Olanzapine has a U.S. Food and Drug Administration–approved dosing range of 10 to 20 mg/day but is often used at doses exceeding this range. Olanzapine is largely metabolized by cytochrome P450 (CYP) 1A2. Smoking, which induces CYP1A2, is expected to increase clearance of olanzapine by 40%; however, dosage adjustment in smokers is not currently recommended. Additionally, female gender is expected to reduce clearance by 30%. Many institutions target high-dose olanzapine prescribers in an effort to reduce unnecessary drug costs. However, factors such as smoking or gender may necessitate increased doses.

Method: A retrospective review of all patients receiving olanzapine during an inpatient stay at a state psychiatric hospital in Kentucky during 2001 was conducted. Demographic information and smoking status were collected for all patients. Olanzapine doses of > 20 mg/day were considered high doses.

Results: Nine percent (48/522) of olanzapine patients were prescribed high doses. The percentages were similar in women and men (10% vs. 9%, p = .69) and in smokers and nonsmokers (9% vs. 9%, p = .82). Moreover, the mean maximum olanzapine dose was also similar in men and women (15.4 ± 7.2 vs. 14.9 ± 7.3 mg/day, p = .51). The odds of receiving a high dose of olanzapine were increased 2.1 for patients with a schizophrenia spectrum diagnosis (DSM-IV schizophrenia or other psychotic disorder). The odds of receiving a high dose of olanzapine were increased with each incremental increase in length of stay (intermediate length of stay [8–60 days], OR = 5.6; long-term length of stay [> 60 days], OR = 12.0, relative to acute length of stay [< 8 days]).

Conclusions: Neither gender nor smoking status was associated with receiving a high dose of olanzapine. The association of increased length of stay with high dose suggests that treatment resistance may be an important factor in receiving high daily doses of olanzapine.

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Dr. Botts has recently submitted a researcher-initiated proposal to Eli Lilly Research Foundation. During the last 2 years, Dr. Botts has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Janssen. During the last 2 years, Dr. Littrell has served as a consultant for Janssen and on the speakers bureaus of Janssen and Bristol-Myers Squibb. During the last 2 years, Dr. de Leon has been on the advisory boards of Bristol-Myers Squibb and AstraZeneca, received researcher-initiated grants from Eli Lilly Research Foundation and Roche Molecular Systems, Inc, and once delivered a lecture supported by Eli Lilly.

Corresponding author and reprints: Jose de Leon, M.D., Mental Health Research Center at Eastern State Hospital, 627 W. Fourth St., Lexington, KY 40508 (e-mail: jdeleon@uky.edu).

The Schizophrenia Patient Outcomes Research Team recommended doses of antipsychotic medication for schizophrenia between 300 and 1000 chlorpromazine equivalents.[1] Several studies have described factors, including race, that may be associated with high dosing of typical antipsychotics.[2–4] We recently examined excessive dosing of typical antipsychotics in 2 state hospitals and defended the idea that physician biases or unusual prescribing practices may explain some cases of excessive dosing.[5] Additionally, there may be pharmacokinetic reasons to justifiably use high doses of antipsychotics in patients who demonstrate unusually high metabolic capacity due to genetic and environmental reasons. Genetic polymorphic variations associated with ultrarapid metabolism or the presence of inducers, such as smoking or coprescription, may justify some cases of high dosing. Unfortunately, many pharmacoepidemiologic studies do not consider these pharmacokinetic factors when investigating excessive dosing.

The acceptance of atypical antipsychotics as first-line treatment of schizophrenia has changed the prescription of antipsychotics almost completely in U.S. psychiatric hospitals. Atypical antipsychotics are prescribed more frequently than typical antipsychotics, and olanzapine is one of the agents preferred by clinicians. Olanzapine is frequently prescribed at doses higher than 20

mg/day, the highest U.S. Food and Drug Administration–recommended dose for management of schizophrenia. There is very limited published information on the use of doses exceeding 20 mg/day, although some case reports suggest that high doses of olanzapine may be needed in treatment-refractory patients.[6–11] Olanzapine is metabolized by cytochrome P450 1A2 (CYP1A2), flavin-containing monooxygenase, and *N*-glucuronidation[12,13]; however, CYP1A2 is considered the most important pathway.[14] Some medications such as phenytoin and carbamazepine are inducers of olanzapine metabolism, and olanzapine doses of > 20 mg/day may be needed when these medications are coprescribed with olanzapine.[12] Additionally, the clearance of olanzapine is approximately 30% lower in females than males and 40% higher in smokers than nonsmokers.[15] However, dose adjustments based on these factors are not routinely recommended.

Clozapine is also mainly metabolized by CYP1A2. Several studies have suggested that male gender and smoking are associated with lower plasma clozapine concentrations.[16,17] The effect of gender and smoking on clozapine dosing in the real world is compatible with our knowledge of CYP1A2 physiology.

The *CYP1A2* gene is located in the long arm of chromosome 15. Polymorphisms in the 5'-flanking region in Japanese individuals[18] and in the intron 1 of *CYP1A2 (CYP1A2*1F)* in white individuals[19] have been described. Both polymorphisms do not influence the enzyme baseline activity, but influence the enzyme response to metabolic inducers such as smoking. The *CYP1A2*1F* allele is characterized by a C→A substitution in intron 1 that influences caffeine metabolism, the probe used to test CYP1A2 activity, and is present in 60% of whites.[19] As this polymorphic variation influences inducibility, its effects have been mainly studied in smokers. The polymorphic variation should not have any important effects in nonsmokers unless they are taking CYP1A2 inducers, such as omeprazole. Among smokers, those with *A*/*A* genotype have approximately 60% to 70% more CYP1A2 activity than smokers with *A*/*C* or *C*/*C* genotype.[19]

Polymorphic variations of baseline activity (e.g., poor metabolizer status) have not been described for CYP1A2. However, a recent case of a patient who needed a high dose of clozapine has been interpreted as a possible example of an ultrarapid CYP1A2 metabolizer.[20] In this case, genetic testing was not performed, and there are currently no published descriptions of multiple copies of *CYP1A2* active alleles. By-products of tobacco smoking, such as polycyclic aromatic hydrocarbons, are known inducers of CYP1A2. Medications such as omeprazole and carbamazepine are also thought to induce CYP1A2.[21] In phenotyping studies using caffeine as a substrate, nonsmokers and females tend to show lower CYP1A2 activity.[22,23] In summary, studies of the CYP1A2 substrates caffeine and clozapine suggest that males and smokers may have higher CYP1A2 metabolic capacity and probably need higher doses of CYP1A2 substrates to achieve the same effects. It is logical to assume that if CYP1A2 is a major determinant of olanzapine metabolism, then male patients may need higher doses than female patients and smokers may need higher doses than nonsmokers. A naturalistic study relating olanzapine levels to dosing has suggested that women have lower metabolic capacity than men and that nonsmokers have lower metabolic capacity than smokers.[24]

This study of olanzapine prescription in a state hospital explores the variables associated with high dosing of olanzapine. Based on the assumption that CYP1A2 may be important in olanzapine dosing, it was postulated that male gender and smoking would be associated with the use of high doses of olanzapine. The possible effect of other variables that may be associated with high olanzapine dosing, such as race, concomitant use of CYP1A2 inducers, and treatment-refractory status, was taken into account.

METHOD

Subjects and Variables

All subjects were being treated as inpatients in a state psychiatric hospital. This 160-bed state hospital with approximately 1600 to 1800 annual admissions serves as the primary psychiatric hospital for the severely mentally ill in one third of Kentucky. According to approximations from recent years, patient population characteristics include diagnoses of schizophrenia spectrum disorders in 35%, bipolar disorder in 12%, and major depression in 22%. Fifty-nine percent are male, 41% are female; 87% are white, and 12% are African American. The median length of stay ranges from 6 to 8 days. For this study, we analyzed the prescription of olanzapine in 2001. All patients prescribed olanzapine were identified using the pharmacy database. Olanzapine dosing and patient demographic variables were obtained from a computerized database managed by the University of Kentucky Research and Data Management Center (RDMC). The RDMC, under contract with the Kentucky Department of Mental Health and Mental Retardation, receives, processes, and analyzes monthly performance and outcome measurement data from Kentucky state psychiatric facilities. Additionally, RDMC processes pharmacy data from each of Kentucky's state hospitals.

There were 538 patient admissions and 522 different patients who were prescribed olanzapine during 2001. For each patient, the highest dose during any 2001 admission was selected for analyses. Table 1 describes demographic and clinical information including the main Axis I discharge diagnosis by the treating psychiatrist. Diagnoses were divided into 3 groups: schizophrenia spectrum disorders (DSM-IV schizophrenia and other psy-

Table 1. Description of Sample and Variables for Patients in a State Hospital Who Were Treated With Olanzapine (N = 522)

Variable	Value
Age, mean (SD), y	41 (14.1)
Olanzapine dose, mg/day	
Mean (SD)	15 (7.3)
Range	2.5–45
Length of olanzapine treatment, d	
Median	9
Percentile, 25th/75th	5/24
Length of stay, d	
Median	13
Percentile, 25th/75th	6/30
Gender, N (%)	
Male	297 (57)
Female	225 (43)
Race, N (%)	
White	482 (92)
African American	40 (8)
Smokers, N (%)	373 (72)
Coprescribed CYP1A2 inducer, N (%)	7 (1)
Olanzapine dose > 20 mg/d, N (%)	48 (9)
30 mg/d	43 (8)
40 mg/d	3 (0.6)
45 mg/d	2 (0.4)
Diagnosis, N (%)	
Schizophrenia spectrum disorders	285 (55)
Mood disorders	133 (25)
Other	104 (20)
Length of olanzapine treatment, N (%)[a]	
Short (< 10 d)	264 (51)
Intermediate (10–18 d)	90 (17)
Long (> 18 d)	168 (32)
Length of hospital stay, N (%)	
Acute (< 8 d)	169 (32)
Intermediate (8–60 d)	266 (51)
Long-term (> 60 d)	87 (17)

[a]The average olanzapine half-life is 35 hours or 1.5 days, and 20% of the subjects had a half-life in the range of 50 hours or 2.5 days.[34] It was assumed that at least 5 to 7 half-lives are required to have certainty of steady state and that the average patient would need to receive the same dose for 10 days or 7 half-lives to reach steady state. Patients who were probably discharged before reaching steady state were classified as having a short length of treatment. Patients who were probably discharged upon reaching steady state, assuming that the dose had not been changed, were classified as having an intermediate length of treatment (range includes the shorter length of 10 days for the average patient and the longer length of 18 days or 7 half-lives of 2.5 days for the 20% who were outliers). The rest of the patients were classified as having a long length of treatment.
Abbreviation: CYP = cytochrome P450.

chotic disorders), mood disorders, and other disorders (Table 1). A proxy-index of refractoriness was defined using the length of stay. The length of stay was classified as acute (< 8 days), intermediate (8–60 days), and long-term (> 60 days).

This categorization of length of stay has some overlap but does not correspond exactly with the unit organization of the hospital. The hospital is composed of 6 units: 1 acute, 2 intermediate, and 3 long-term. The acute unit ideally discharges patients within 7 to 8 days (43%, 226/522 of olanzapine patients), while the intermediate units care for patients who require a longer time for stabilization or who are hospitalized for a typical 60-day court-ordered stay (47%, 244/522). Patients requiring a more lengthy hospitalization are transferred to a long-term unit (10%, 52/522). The length of olanzapine treatment was classified as short, intermediate, or long (Table 1).

Comedication with metabolic inducers at the time of treatment with the highest dose was studied. Phenytoin and carbamazepine, which are known to be metabolic inducers for olanzapine,[12] and omeprazole, a CYP1A2 inducer,[21] were included. Smoking status was treated as a dichotomous variable based on medical chart documentation of a patient as an active smoker.

Statistical Analysis

Doses greater than 20 mg/day were defined as high and considered the dependent variable in the analyses. Several independent variables were considered as determinants of high olanzapine dosing. A priori, it was decided to eliminate from analyses any patient for whom high dosing was explained by the coprescription of any metabolic inducer (phenytoin, carbamazepine, or omeprazole). There were only 7 patients taking these medications, and none were taking high doses. Therefore, no subject was eliminated, and the effect of comedication was not regarded as important in olanzapine dosing in this hospital.

On the basis of the available data on CYP1A2 activity, it was hypothesized that male gender and smoking would be associated with high doses. To consider the effect of diagnoses, the presence of schizophrenia spectrum disorder was considered. The level of unit (acute, intermediate, or long-term) and the length of stay and olanzapine treatment were measured as ordinal variables with 3 levels as previously described. Other variables considered to be of potential importance as independent variables were race and geriatric age (age > 65 years). As in our prior study,[5] univariate analyses were conducted first, followed by multivariate analyses (logistic regression) (see Table 3). Odds ratios (ORs) with 95% confidence intervals (CIs) were computed from 2-way cross-tabulations for univariate analyses. Significant independent variables were then introduced in a logistic regression with high dosing as the dependent variable. The advantage of logistic regression was that the OR corresponding to an association between high olanzapine dosing and a variable was adjusted for the effect of the other variables in the logistic model. The Statistical Package for Social Sciences (SPSS Inc.; Chicago, Ill.) was used for calculations. The Hosmer-Lemeshow goodness-of-fit test was used to test the fitness of the logistic models.[25] All models described in this article fit well.

Further analysis of olanzapine dosing as a continuous variable was used to verify whether the independent variables had a significant effect on olanzapine dosing. Mean olanzapine doses were compared using independent-sample t tests or 1-way analysis of variance (ANOVA) (see Table 2). For the discussion of effect sizes, the classical nomenclature defined by Cohen[26] was used.

RESULTS

Variables With Nonsignificant Odds Ratios in Univariate Analyses

Neither gender nor smoking status was significantly associated with high olanzapine doses. Forty-eight (9%) of 522 patients treated with olanzapine were prescribed high doses, and the percentages of women and men with high doses were almost identical (10% vs. 9%, respectively; p = .69). Similarly, there were no significant effects of gender on mean olanzapine doses (Table 2). The percentages of nonsmokers and smokers with high doses were almost the same (9% for both; p = .82). Neither race nor geriatric age was significantly associated with high olanzapine doses.

Significant Variables in Univariate Analyses and Logistic Regression

As Table 3 shows, schizophrenia spectrum diagnosis, unit, length of stay, and treatment were significantly associated with high doses of olanzapine in the univariate analyses. When these 4 variables were introduced in logistic regression, the unit effect and the length of treatment were no longer significant.

Effects of Individual Prescribers

To explore the effect of individual psychiatric prescribers, the doctors of the acute unit were compared to identify any physicians prescribing high doses more frequently than their peers. Similar procedures were used in the intermediate and long-term units. One of the 5 physicians on the acute unit appeared to be an outlier since 11% of the physician's patients were prescribed high doses versus 0% to 5% in the rest of the physicians. This effect was lost in the logistic regression analysis including schizophrenia spectrum diagnosis and length of stay as confounding variables.

Similarly, 1 of the 5 physicians on the intermediate units appeared to be an outlier; 22% of the physician's patients were prescribed high doses versus 5% to 9% in the rest. The effect of this psychiatrist was significant when a logistic regression was calculated by including schizophrenia spectrum diagnosis (length of stay was not significant in the intermediate unit) as a confounding variable in the patient sample of these units (for the outlier physician, OR = 3.5, CI = 1.6 to 7.9, p = .003). The long-term units had 3 physicians with prescription rates of high doses ranging from 17% to 30%. One was an outlier with 0%.

Significant Variables in Schizophrenia Patients

Length of stay, unit acuity, and long duration of olanzapine treatment were significantly associated with high doses of olanzapine in the univariate analyses restricted to schizophrenic patients. The effect of unit level and long duration of olanzapine treatment was no longer significant in the logistic regression after correcting for length of stay (for stays of 8–60 days, OR = 4.8, CI = 1.1 to 21.3, p = .04; for stays of > 60 days, OR = 10.8, CI = 2.3 to 49.7, p = .002).

Table 2. Maximum Olanzapine Doses in a State Hospital Population According to Subgroups (N = 522)

Variable	Olanzapine Dose (mg/d), Mean ± SD	p
Men vs women	15.4 ± 7.2/14.9 ± 7.3	.51[a]
Smokers vs nonsmokers	15.1 ± 7.2/15.1 ± 7.4	.91[a]
Schizophrenic vs nonschizophrenic	16.5 ± 7.7/13.5 ± 6.3	< .001[a]
Length of hospital stay		< .001[b]
Acute (< 8 d)	11.9 ± 5.5	
Intermediate (8–60 d)	15.9 ± 7.0	
Long-term (> 60 d)	19.0 ± 8.4	

[a]Independent-sample t test.
[b]One-way analysis of variance. All post hoc tests were highly significant: patients with stays > 60 days had significantly higher mean doses than patients with stays of 8 to 60 days and patients with stays of < 8 days, and patients with stays of 8 to 60 days had significantly higher mean doses than patients with stays of < 8 days.

Table 3. Univariate Analyses and Logistic Regression of High Olanzapine Dosing in a State Hospital (N = 522)

	Univariate Analyses			Logistic Regression[a]		
Variable	OR	95% CI	p	OR	95% CI	p
Schizophrenia	2.7	1.4 to 5.3	.003	2.1	1.0 to 4.1	.04
Length of hospital stay						
Acute (< 8 d)[b]	…	…	…	…	…	…
Intermediate (8–60 d)	6.2[b]	1.9 to 20.9	.003	5.6	1.7 to 18.9	.005
Long-term (> 60 d)	14.4	4.1 to 50.4	< .001	12.0	3.4 to 42.4	< .001
Unit						
Acute[c]	…	…	…	…	…	…
Intermediate	2.8	1.3 to 5.9	.007	NS	NS	NS
Long-term	5.1	2.0 to 13.2	.001	NS	NS	NS
Length of olanzapine treatment						
Short (< 10 d)[d]	…	…	…	…	…	…
Intermediate (10–18 d)	1.2	0.42 to 3.6	NS	NS	NS	NS
Long (> 18 d)	4.8	2.3 to 9.6	< .001	NS	NS	NS

[a]Hosmer-Lemeshow goodness of fit: $\chi^2 = 0.2$, df = 4, p = .99.
[b]This is the reference group for this variable. The OR for stays of 8 to 60 days compared stays of 8 to 60 days with stays of < 8 days. The OR for stays of > 60 days compared stays of > 60 days with stays of < 8 days.
[c]This is the reference group for this variable. The OR for intermediate units compared intermediate units with acute unit. The OR for long-term units compared long-term units with acute unit.
[d]This is the reference group for this variable. The OR for intermediate compared intermediate with short. The OR for long compared long with short.
Abbreviation: NS = not significant.

DISCUSSION

Limitations and Strengths of the Study

We are unaware of any similar pharmacoepidemiologic studies of high dosing in a large sample of patients taking olanzapine. This prescription pattern reflects the

prescribing in one hospital and by a specific group of psychiatrists who have been working in this city for some time. Replication studies in other hospitals and outpatient departments are needed. Clinical response was not studied, and it was assumed that longer hospitalizations reflected refractoriness. It is possible that some patients, particularly in the acute unit, may have been discharged before reaching steady state; however, this is current clinical practice in U.S. hospitals. In our study, the length of olanzapine treatment had no effect on the odds of receiving high-dose olanzapine after correction for length of stay. The lack of a measurement of number of cigarettes smoked by smokers is a limitation, but information from another study in our hospital in 74 patients taking olanzapine suggested that the number of cigarettes had no significant effect on olanzapine dosing.[27] The lack of measure of weight is a limitation, but we believe that weight is probably not an important factor for several reasons: (1) in the present sample, the discharge diagnosis of obesity did not predict high olanzapine dose; (2) in a sample that included 74 patients taking olanzapine, the correlation between weight and olanzapine dose was very low ($r = -0.1$)[27]; and (3) in our prior study on high dosing of typical antipsychotics,[5] we found that controlling high dose by weight did not make a difference in the analyses.

Besides these obvious limitations shared with any similar naturalistic study, this study has some obvious strengths, including the large and representative sample and the availability of a computerized database that allowed tracking of olanzapine dosing during hospitalization. Prior studies of high dosing, including ours,[5] have typically included a cross-sectional sampling of dosing. In the present study, we were able to select the highest dose for each patient during 1 or several hospitalizations in 1 year.

Significant Variables in Olanzapine Dosing

As some case reports suggest,[6–11] it appears that, in this hospital, the main predictor of the use of high doses is refractory illness. The effect sizes were rather large in the logistic regression and ANOVA. These large effect sizes were also found when analyses were restricted to the schizophrenic sample.

A schizophrenia spectrum diagnosis was associated with high olanzapine doses. The comparison of percentages of doses that were and were not high and the comparisons of mean doses suggested that schizophrenia diagnosis had medium effect sizes in olanzapine dosing.

The effect of the unit appears to be mainly explained by the different levels of length of stay, since this effect disappeared in the logistic regression. The influence of specific psychiatrists in prescribing high olanzapine doses in this hospital ranged from no significant effect to medium effect sizes in the different units. The most clear outlier, a physician in the intermediate unit, provided a corrected OR within the physicians of that unit of 3.5 (CI = 1.6 to 7.9). That OR was not different from the effect of the long-term unit (vs. intermediate unit), OR = 1.8 (CI = 0.83 to 4.1). The physician prescribed high doses to 22% of patients versus 17% to 30% for 3 of the 4 physicians in the long-term unit. This physician in the intermediate unit does not seem like an outlier when compared with the long-term unit physicians.

Lack of Significance of Smoking and Gender in Olanzapine Dosing

Olanzapine dosing did not follow the predicted pattern of other CYP1A2 substrates. Neither gender nor smoking had an effect on olanzapine dosing in this population. We provide 2 hypotheses of why gender and smoking did not determine olanzapine dosing in this hospital. It is possible that olanzapine is a typical CYP1A2 substrate and that men and smokers do in fact metabolize olanzapine faster, but that this effect is obscured by the statistical "noise" of the system, particularly the refractoriness of the patient. Against this interpretation is the fact that this "noise" allowed us to verify the effect of schizophrenia, something that we expected to find according to our prior study of typical antipsychotics.[5]

Alternatively, it is possible that CYP1A2 may not be as important in olanzapine metabolism as it is in caffeine or clozapine metabolism. In the clinical setting, it is difficult to miss the effect of smoking on clozapine[16,17] or caffeine dosing.[28] It may be that olanzapine metabolism by glucuronidation (e.g., UDP-glucuronosyltransferase enzymes [UGTs]) obscures the typical CYP1A2 pattern. Recent information[13,29] suggests that the role of UGTs in olanzapine metabolism may have been underestimated.[14] With the influence of UGTs, it is likely that only variables that influence both CYP1A2 and UGT function will significantly affect olanzapine metabolism. Ideally, one would like to provide some clinical guidance as to the effect of UGTs in olanzapine metabolism. Many psychopharmacologic agents, including several antipsychotics, are metabolized by UGTs.[13] The key issue is probably the percentage of the total metabolism explained by UGTs and which specific UGT may be involved. The possibility that UGT1A4 may metabolize olanzapine has recently been described,[30] but this enzyme has not been well studied.

Some general information is known about UGTs. In contrast to CYP isozymes, UGTs probably have lower levels of specificity and greater substrate overlap.[13] Similar to CYPs, smoking can induce some UGTs and not others. Unfortunately, information on which UGTs are induced by smoking is preliminary.[13] Like CYPs, some UGTs have polymorphic variations that may explain racial differences in metabolism.[13,31,32] These differences may have significant clinical effects, at least for nicotine metabolism, since epidemiologic studies suggest that African Americans appear to have slower nicotine metabolism

than whites.[33] One may consider these ideas on the relative influence of UGTs and CYP1A2 on olanzapine metabolism to be speculative, but they are worth further consideration.

Ours is the first pharmacoepidemiologic study of high dosing in atypical antipsychotics. Our negative findings of a lack of major influences of gender and smoking on olanzapine dosing in the real world call for new studies of olanzapine metabolism (including metabolic studies of the role of UGTs). Replication studies are needed to verify that high olanzapine dosing is mainly driven by refractory illness (and schizophrenia diagnosis). If these positive findings are replicated, it may be time to further evaluate, with double-blind studies, the use of lower olanzapine doses in more acute patients and the use of even higher doses than have been used in prior double-blind studies[34] of treatment-refractory patients.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine and others), clozapine (Clozaril, Fazaclo, and others), olanzapine (Zyprexa), omeprazole (Nexium, Prilosec, and others), phenytoin (Cerebyx, Dilantin, and others).

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