

# Neuroleptic Malignant Syndrome and Atypical Antipsychotic Drugs

Jambur Ananth, M.D.; Sharat Parameswaran, B.S.; Sarath Gunatilake, M.D.; Karl Burgoyne, M.D.; and Taghrid Sidhom, M.D.

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**Objective:** The incidence of neuroleptic malignant syndrome (NMS) is not known, but the frequency of its occurrence with conventional antipsychotic agents has been reported to vary from 0.02% to 2.44%.

**Data Sources:** MEDLINE search conducted in January 2003 and review of references within the retrieved articles.

**Data Synthesis:** Our MEDLINE research yielded 68 cases (21 females and 47 males) of NMS associated with atypical antipsychotic drugs (clozapine, N = 21; risperidone, N = 23; olanzapine, N = 19; and quetiapine, N = 5). The fact that 21 cases of NMS with clozapine were found indicates that low occurrence of extrapyramidal symptoms (EPS) and low EPS-inducing potential do not prevent the occurrence of NMS and D<sub>2</sub> dopamine receptor blocking potential does not have direct correlation with the occurrence of NMS. One of the cardinal features of NMS is an increasing manifestation of EPS, and the conventional antipsychotic drugs are known to produce EPS in 95% or more of NMS cases. With atypical antipsychotic drugs, the incidence of EPS during NMS is of a similar magnitude.

**Conclusions:** For NMS associated with atypical antipsychotic drugs, the mortality rate was lower than that with conventional antipsychotic drugs. However, the mortality rate may simply be a reflection of physicians' awareness and ensuing early treatment.

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Corresponding author and reprints: Jambur Ananth, M.D., Harbor-UCLA Medical Center, Building F9, 1000 West Carson St., Torrance, CA 90502 (e-mail: jananth@rei.edu, jananth@dmhmsl.state.ca.us).

Neuroleptic malignant syndrome (NMS) is a well-recognized, serious side effect of antipsychotic medications. Pathophysiology of this condition has not been clearly elucidated. A sudden blockade of D<sub>2</sub> dopamine receptors is considered to be a contributing factor for NMS. As this condition generally does not recur when the same drug is re-instituted 4 or more weeks after recovery from the initial episode of NMS,<sup>1,2</sup> a biological matrix congenial to its development has been hypothesized.<sup>3</sup>

Manifestations of this syndrome include symptoms related to 4 major areas: (1) autonomic instability, (2) extrapyramidal symptoms (EPS), (3) hyperpyrexia, and (4) altered mental status.<sup>4</sup> The appearance of these symptoms in patients receiving antipsychotic drugs, alone or in combination, should alert the physician to suspect the diagnosis of NMS. The incidence of NMS is not known, but the frequency of its occurrence with conventional antipsychotic agents has been reported to vary from 0.02% to 2.44%.<sup>5</sup> With conventional antipsychotic drugs, EPS can occur in 89% to 97% of patients during NMS.<sup>6-10</sup> The mean number of days until improvement was shown to be 13 to 15 days<sup>6,11</sup> with conventional antipsychotic agents, and with depot conventional antipsychotic agents, time to improvement was about 17 days.<sup>11</sup> In 66% of cases, the onset of NMS occurred within 2 weeks of the initiation or the last major change in neuroleptic treatment.<sup>6</sup> An increase in creatinine phosphokinase (CPK) levels was seen in over 95% of cases.<sup>7,9,10</sup> Patients with NMS experienced hyperpyrexia, with a mean temperature of 103.0 ± 1.9°F (39.4 ± 1.1°C).<sup>10</sup>

Many predisposing factors have been identified. Males develop the condition more often than females.<sup>6,9,11</sup> Two reviews<sup>10,11</sup> indicated that NMS developed in the early 40s in females and in the early 30s in males. Concomitant lithium use was seen in 58% of cases in one review,<sup>10</sup> but only 16.5% of cases in another.<sup>6</sup> Therefore, the role of lithium in the production of NMS is not conclusive. Mental retardation was seen in about 7% of NMS patients.<sup>6,9</sup>

Atypical antipsychotic agents have the potential to produce NMS as they also block D<sub>2</sub> dopamine receptor blockers. As a result of their low EPS-inducing potential, it has been reported that atypical antipsychotic drug-induced NMS may be qualitatively and quantitatively different from the NMS induced by conventional antipsychotic

**Table 1. Demographics and Diagnosis of Patients With Atypical Antipsychotic Drug–Induced Neuroleptic Malignant Syndrome<sup>a</sup>**

Variable	Clozapine	Risperidone	Olanzapine	Quetiapine	Total
Number of patients	21	23	19	5	68
Males, N	17	13	13	4	47
Females, N	4	10	6	1	21
Age, mean ± SD, y	40.2 ± 17.1	48.3 ± 22.0	48.5 ± 20.3	37.6 ± 13.7	45.0 ± 19.7
Dosage, mean ± SD, mg/d	318 ± 299	4.3 ± 3.1	9.7 ± 2.3	412.5 ± 317	
Primary psychiatric diagnosis, N					
Schizophrenia and other psychoses	19	13	13	4	49
Mood disorders	1	4	4	0	9
Other or unknown	1	6	2	1	10
Mental retardation	3	2	3	1	9
Concomitant psychiatric prescriptions, N					
Benzodiazepines	3	4	9	4	20
Benzotropine	3	6	3	0	12
Other antipsychotics	2	3	4	2	11
Antidepressants	2	4	3	0	9
Valproate	3	2	3	1	9
Lithium	1	3	3	0	7
Other	4	3	2	0	9
None	11	9	7	0	27
Patients with physical illnesses, N	4	10	7	2	23
Patients with prescriptions for physical illnesses, N	5	4	7	2	18

<sup>a</sup>Patients identified by MEDLINE database search in January 2003.<sup>14–73</sup>

drugs.<sup>12</sup> However, the nature and consequences of such differences have not been clearly elucidated. This article will review the published cases of NMS associated with atypical antipsychotic drugs, their manifestations, and response to treatment.

## METHOD

### Data Sources

The case reports were collected by conducting a MEDLINE search in January 2003, using the term *neuroleptic malignant syndrome*, limiting the search to English-language publications, and scrutinizing the references in each of the retrieved publications.

### Study Selection and Data Synthesis

The nature of the symptoms and the severity of the cases associated with atypical antipsychotics were analyzed to ascertain whether there were qualitative and quantitative differences in psychopathology between these cases and the cases involving conventional antipsychotic drug–induced NMS. For the purpose of our review, standard NMS diagnostic criteria<sup>13</sup> were not initially employed in case selection, in order to ensure the inclusion of any cases with atypical presentation. In all of the case reports used, the antipsychotic agent being administered was the primary suspected cause of NMS. The outcome of NMS was measured by noting the increase in CPK, admission to the intensive care unit, days to recovery from NMS, and/or death. The patient variables that were analyzed were age, sex, concomitant physical illness, antipsychotic drug involved and its dose, and administration of other medications. The results were tabulated for all atypical antipsy-

chotic drugs as well as for each drug separately. The confounding variables that might have contributed to the occurrence of NMS, such as dehydration or hyponatremia, were also scrutinized when available in the case reports.

## RESULTS

### NMS Associated With Atypical Antipsychotic Drugs in General

Our MEDLINE research yielded 68 cases (21 females and 47 males) of NMS associated with atypical antipsychotic drugs that met DSM-IV criteria (Table 1).<sup>14–73</sup> The mean age of the patients was 45 years, with a standard deviation (SD) of 19.7 and a median value of 41 years. When NMS occurred, the dose of the atypical antipsychotic medication prescribed was increasing in 31, decreasing in 2, stable in 32, and unknown in 3 patients. The primary diagnoses noted were schizophrenia (N = 35), schizoaffective disorder (N = 11), bipolar disorder (N = 7), dementia (N = 5), other psychosis (N = 3), depression (N = 2), and unknown or unclear (N = 5). Twenty-seven of these 68 patients treated with atypical antipsychotics received no other concomitant psychiatric medications; the remaining 41 patients received concomitant psychiatric medications as follows: benzodiazepines (N = 20), benzotropine (N = 12), antidepressants (N = 9), valproate (N = 9), lithium (N = 7), other conventional antipsychotic drugs (N = 11), others (N = 9).

Forty-five of the 68 patients had no major physical illness. In the remaining 23 patients, the following physical illnesses were noted: hypertension (N = 8), infectious disease (N = 5), other cardiovascular disease (N = 4), diabetes mellitus (N = 3), and other physical illness (N = 19).

Nine patients had mental retardation. Fifty patients were not prescribed any drugs for the treatment of physical illnesses. Concomitant medications in the remaining 18 patients were antibiotics (N = 6), H<sub>2</sub> receptor blockers (N = 4), docusate (N = 4), diuretics (N = 3), bronchodilators (N = 3),  $\beta$ -blockers (N = 2), steroids (N = 2), levothyroxine (N = 2), and 1 each of oral contraceptives, enalapril, morphine, omeprazole, cisapride, nitroglycerin, nifedipine, prazosin, and clonidine.

The mean number of days from the initiation or last major change of the atypical antipsychotic agent to the onset of NMS was 120 days (SD = 386, median = 10 days), and in 62% of cases the onset of NMS occurred within 2 weeks. Although the average duration to the onset of NMS appears to be larger than that with conventional antipsychotic drugs, the large standard deviation and the substantially lower median value show these data to be consistent with previous reports. The mean maximum measured level of CPK was 5958 U/L (SD = 13,999; median = 1445 U/L). The mean maximum temperature was 38.8°C (SD = 1.21, median = 38.6°C).

Whether atypical antipsychotic drug-induced NMS manifests EPS less often than conventional antipsychotic drug-induced NMS was evaluated, based on the fact that atypical antipsychotic drugs are known to generally produce fewer EPS.<sup>74</sup> Fifty-three patients (78%) exhibited EPS during NMS. The mean number of days until recovery was 9.97 days (SD = 11.2, median = 7). Nineteen patients were rechallenged with atypical antipsychotic drugs. These data are described in a subsequent paragraph. Basically, by comparing these data with data for NMS associated with conventional antipsychotic drugs as detailed above, atypical antipsychotic drug-induced NMS manifestations were shown to be of similar nature and severity as those produced by conventional antipsychotic drugs. Three patients, 1 receiving olanzapine and 2 receiving risperidone, died as a result of NMS.

### NMS Associated With Olanzapine

In December 2002, olanzapine represented 27.76% of the U.S. market for antipsychotic medications (IMS Data TRx Share, Dec. 2002<sup>75</sup>). There were 19 case reports of NMS with olanzapine,<sup>14-32</sup> consisting of 6 female and 13 male patients. The mean age of the population was 48.5 years (SD = 20.3). The mean daily dose of olanzapine was 9.7 mg (SD = 2.3). At the time when NMS occurred, the dose was increasing in 8 cases, stable in 10, and unknown in 1.

The primary patient diagnoses were schizophrenia (N = 10), schizoaffective disorder (N = 3), bipolar disorder (N = 3), depressive disorder (N = 1), and unknown or unclear (N = 2). Concomitant psychiatric medications were benzodiazepines (N = 9), lithium (N = 3), valproate (N = 3), bupropion (N = 3), antidepressants (N = 3), other antipsychotics (N = 4; levomepromazine, cloza-

pine, haloperidol, and risperidone), and other (N = 2; phenytoin and carbidopa). Seven patients received no concomitant medications.

Medical illnesses noted included diabetes mellitus (N = 2), hypertension (N = 2), and 1 each of obesity, congestive heart failure, pulmonary sarcoidosis, chronic obstructive pulmonary disease (COPD), sleep apnea, hypothyroidism, gallbladder stones (without cholecystitis), carcinoma of the sigmoid colon, multinodular goiter, urinary tract infection, rheumatic arthritis, peptic ulcer disease, glaucoma, and pneumonia. Twelve patients had no medical illness. Three patients had mental retardation. The medical prescriptions taken were docusate (N = 2), antibiotics (N = 2), antacid agent (N = 3), and 1 each of furosemide, triamcinolone, salmeterol, enalapril, morphine, betaxolol, and levothyroxine. Twelve patients were taking no medical prescriptions.

The mean number of days from the initiation of or the last major change in olanzapine to the onset of NMS was 135 days (SD = 321). The mean maximum measured level of CPK was 6421 U/L (SD = 10,776). The mean maximum measured temperature was 38.8°C (SD = 1.4). The number of olanzapine-treated patients exhibiting EPS during NMS was 13 (68%). The mean number of days for recovery from NMS was 7.5 days (SD = 6.2). Of the 5 patients (26%) rechallenged with atypical antipsychotics, 4 tolerated the drug without recurrence of NMS symptoms. Atypical antipsychotic medications used in these rechallenges were olanzapine (N = 3), quetiapine (N = 1), and ziprasidone (N = 1). One patient died of NMS, although this patient had numerous preexisting physical illnesses.

### NMS Associated With Risperidone

In December 2002, risperidone represented 28.23% of the U.S. market for antipsychotic medications (IMS Data TRx Share, Dec. 2002<sup>75</sup>). Our literature search yielded 23 cases of NMS associated with the use of risperidone,<sup>33-54</sup> consisting of 10 female and 13 male patients. The mean age of the patients who developed NMS was 48.3 years (SD = 22.0). The mean dose of risperidone was 4.3 mg daily (SD = 3.1). At the time when NMS occurred, the dose of risperidone was increasing in 10 patients, decreasing in 1, stable in 11, and unclear in 1 case.

The diagnoses of patients who developed NMS were schizophrenia (N = 7), schizoaffective disorder (N = 4), bipolar disorder (N = 3), depression (N = 1), dementia (N = 4), other psychosis (N = 2), and unknown or unclear (N = 2). Concomitant medications included bupropion (N = 6), lithium (N = 3), valproate (N = 2), benzodiazepines (N = 4), other antipsychotics (N = 3; haloperidol, trifluoperazine, and sulpiride), antidepressants (N = 4), and others (N = 3).

Ten patients had medical illnesses which included hypertension (N = 5), COPD (N = 2), heart disease (N = 2),

and 1 each of diabetes, coronary artery disease, sickle cell trait, asthma, peptic ulcer disease, and benign prostatic hypertrophy. Two patients had mental retardation. Four patients received medications for physical illnesses. Two patients had a previous history of NMS.

The mean number of days to the onset of NMS was 46.3 days (SD = 134). The mean maximum measured level of CPK was 9209 U/L (SD = 21,199). The mean maximum measured temperature was 38.8°C (SD = 1.27). The number of risperidone-treated patients who manifested EPS during NMS was 21 (91%). The mean number of days for recovery was 12.7 (SD = 16.0). Of the 3 patients rechallenged with risperidone, 1 developed NMS again. Two male patients, aged 82 and 67 years, on risperidone treatment died. The 82-year-old male patient developed NMS 5 days after initiating risperidone, with increased EPS, urinary incontinence, diaphoresis, and fever. He died a week later of pneumonia. The 67-year-old male patient developed NMS 3 days after initiating risperidone at 1 mg b.i.d. Manifestations included severe EPS, seizures, fever, confusion, and kidney failure.

#### NMS Associated With Clozapine

In December 2002, clozapine represented 4.87% of the U.S. market for antipsychotic medications (IMS Data TRx Share, Dec. 2002<sup>75</sup>). Twenty-one cases in the literature of NMS with clozapine were identified,<sup>55-68</sup> with 4 female and 17 male patients. The mean age of the patients was 40.2 years (SD = 17.1). The mean dose of clozapine was 318 mg daily (SD = 299). The dose of clozapine at the time NMS was noted was increasing in 11 cases and stationary in 10.

Primary patient diagnoses were schizophrenia (N = 15), schizoaffective disorder (N = 3), bipolar disorder (N = 1), other psychosis (N = 1), and unknown or unclear (N = 1). Concomitant psychiatric medications were not used in 11 cases. Among the other 10 patients, medications used were valproate (N = 3), other antipsychotics (N = 2), bntropine (N = 3), benzodiazepines (N = 3), antidepressants (N = 2), lithium (N = 1), and others (N = 4).

Seventeen patients had no physical illnesses. In the remaining patients, the following illnesses were seen: infectious disease (N = 3), hypertension (N = 1), and Crohn's disease (N = 1). Three patients had mental retardation. Medications for physical illnesses were prescribed to 5 of the 21 patients. These included antibiotics (N = 3), H<sub>2</sub> blockers (N = 2), and 1 each of docusate, clonidine, and chlorthalidone.

The mean duration to the onset of NMS was 218 days (SD = 628). CPK during NMS was 1571 U/L (SD = 2196). The mean temperature was 38.7°C (SD = 1.1). The number of clozapine-treated patients exhibiting EPS during NMS was 15 (71%). The mean duration for recovery was 10.7 days (SD = 10.5). Eleven patients were rechallenged with atypical antipsychotic drugs, and 9 did not develop

any recurrence of NMS symptoms. Atypical antipsychotic drugs employed for rechallenge were clozapine (N = 7), olanzapine (N = 2), and risperidone (N = 2). No deaths occurred among the cases of NMS with clozapine.

#### NMS Associated With Quetiapine

In December 2002, quetiapine represented 18.78% of the U.S. market for antipsychotic medications (IMS Data TRx Share, Dec. 2002<sup>75</sup>). Five cases of NMS attributable to this drug have been reported in the literature,<sup>69-73</sup> with 4 males and 1 female. The mean age of these patients was 37.6 years (SD = 13.7). The mean dose of quetiapine was 412.5 mg daily at the time when NMS occurred (SD = 317). The dose of quetiapine at the time of NMS was constant in 1 case, decreasing in 1, increasing in 2, and unknown in 1.

The primary diagnoses were schizophrenia (N = 3), schizoaffective disorder (N = 1), and dementia (N = 1). Concomitant psychiatric medications included benzodiazepines (N = 4), other antipsychotics (N = 2), and valproate (N = 1). The patients exhibited no physical illnesses, except 1 patient with hypothyroidism. One patient had mild mental retardation. Medical prescriptions were limited to levothyroxine in 1 patient and oral contraceptives in another.

The mean number of days to the onset of NMS was 7 days (SD = 5.0). The mean maximum measured level of CPK was 7926 U/L (SD = 8313). The mean maximum temperature was 38.5°C (SD = 0.86). Four of the 5 patients exhibited EPS during NMS. The mean number of days until recovery was 5.8 days (SD = 2.77). All patients recovered without sequelae. None were rechallenged with atypical antipsychotic drugs.

#### Treatment of NMS

As a result of NMS, 6 patients were treated in a medical unit. Of the 6, 4 were receiving olanzapine. Thirteen patients were seen in the emergency room, and 12 patients were admitted to the intensive care unit. Of the 12, 5 each were receiving risperidone and olanzapine; the other 2 were receiving clozapine. Five patients, 2 receiving clozapine and 3 receiving olanzapine, required intubation or ventilation. Twenty-three patients received bromocriptine or dantrolene, while 31 patients did not receive either agent (Table 2). Bromocriptine, a dopamine agonist, and dantrolene, an oxidative phosphorylation decoupler and muscle relaxant, are useful in reducing hyperpyrexia due to rhabdomyolysis and restoring autonomic stability, although their effectiveness in treatment remains undetermined.<sup>6,76</sup>

#### Rechallenge With Atypical Antipsychotic Drugs

Of the 68 patients, antipsychotic rechallenge with atypical antipsychotic drugs was attempted in 19 patients: 11 on clozapine, 5 on olanzapine, and 3 on risperidone

Table 2. Neuroleptic Malignant Syndrome (NMS) Severity and Outcome<sup>a</sup>

Variable	Clozapine	Risperidone	Olanzapine	Quetiapine	All Antipsychotics
Time to onset of NMS, mean ± SD, d	218 ± 628	46.3 ± 134	135 ± 321	7.0 ± 5.0	120 ± 386
Creatine phosphokinase, mean ± SD, U/L	1571 ± 2196	9209 ± 21,199	6421 ± 10,776	7926 ± 8313	5958 ± 13,999
Temperature, mean ± SD, °C	38.7 ± 1.1	38.8 ± 1.27	38.8 ± 1.4	38.5 ± 0.86	38.8 ± 1.21
Patients with EPS, N (%)	15 (71%)	21 (91%)	13 (68%)	4 (80%)	53 (78%)
Time to recovery, mean ± SD, d	10.7 ± 10.5	12.7 ± 16.0	7.5 ± 6.2	5.8 ± 2.77	9.97 ± 11.2
Patients rechallenged, N (%)	11 (52%)	3 (13%)	5 (26%)	0	19 (28%)
Rechallenges with the same drug, N	7	1	3	0	11
Successful rechallenges, N	9	2	4	0	15
Patient deaths, N	0	2	1	0	3
Dantrolene and bromocriptine use, N					
Dantrolene only	2	2	2	0	6
Bromocriptine only	2	4	2	0	8
Both dantrolene and bromocriptine	2	4	3	0	9
Neither dantrolene nor bromocriptine	12	7	9	3	31
Unknown	3	6	3	2	14
Treatment settings and procedures, N					
Taken to a medical unit	1	0	4	1	6
Seen in the Emergency Room	3	7	3	0	13
Taken to the Intensive Care Unit	2	5	5	0	12
Intubation and/or ventilation	2	0	3	0	5

<sup>a</sup>Patients identified by MEDLINE database search in January 2003.<sup>14-73</sup>

treatment. Of these, 9 on clozapine (82%), 4 on olanzapine (80%), and 2 on risperidone (67%) were rechallenged successfully, and recurrence of NMS symptoms was observed only in 4. Eleven patients were rechallenged with the same atypical antipsychotic drug that caused NMS: 7 on clozapine, 3 on olanzapine, and 1 on risperidone treatment.

### Deaths Attributed to NMS

There were 3 deaths, 1 in the olanzapine group (a 60-year-old woman) and 2 in the risperidone group (67- and 82-year-old men). All 3 manifested EPS during NMS. CPK levels ranged from 823 to 1239 U/L. Temperature ranged from 38°C to 43°C. The patient on olanzapine therapy had numerous physical illnesses (diabetes, sarcoidosis, COPD, sleep apnea, congestive heart failure, hypertension, and obesity) that may have contributed to the outcome, while the other 2 did not.

### CONCLUSIONS

The review of the case reports indicates that atypical antipsychotic agents can cause NMS, even severe enough to cause mortality in some instances. The occurrence of NMS with atypical drugs and particularly with clozapine is intriguing. Clozapine binds loosely to the D<sub>2</sub> dopamine receptors and EPS generally do not occur with this drug, irrespective of the dosage employed. The fact that 21 cases of NMS with clozapine were noted in our review, despite its demonstrably low market share, indicates that low EPS-inducing potential does not prevent the occurrence of NMS and that D<sub>2</sub> dopamine receptor blocking is unlikely to be the sole mechanism responsible for NMS. As noted in previous reports, factors other than D<sub>2</sub> block-

ing have an important part to play in the pathophysiology of NMS.<sup>77-79</sup>

One of the cardinal features of NMS has been reported to be a rapid and an increasing manifestation of EPS. The conventional antipsychotic drugs produce EPS during 95% or more of NMS cases. In fact, EPS is a classical clinical component of this syndrome. It is reported that EPS increases at the time of the occurrence of NMS. With atypical antipsychotic drugs, the incidence of EPS during NMS is approximately of similar magnitude. There have been reports that EPS is not manifested often in NMS associated with atypical antipsychotic drugs. In our survey, EPS was a finding in 78% of patients. Even the NMS patients receiving clozapine manifested EPS frequently. While it is proven that atypical antipsychotic drugs produce EPS less often, EPS is still a part of the clinical picture of NMS, even with atypical antipsychotic drugs.

Is NMS associated with atypical antipsychotic drugs less severe? Any answer to this question is speculative. Of the 68 cases that we reviewed, 12 patients were treated in the intensive care unit and 23 were treated with dantrolene and/or bromocriptine, indicating the severity of the disease. However, the mortality of only 3 of the 68 patients indicates a lower rate than has been seen previously.<sup>8</sup> On the other hand, the mortality rate of NMS as a result of conventional antipsychotic drugs is also decreasing. As physicians are increasingly aware of this condition and thereby recognize and treat it rapidly, the mortality rate may be a reflection of physicians' awareness and ensuing early treatment.

*Drug names:* benzotropine (Cogentin and others), betaxolol (Betoptic, Kerlone, and others), bromocriptine (Parlodel and others), carbidopa (Lodosyn, Stalevo, and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril and others), dantrolene (Dantrium),

enalapril (Vasotec and others), furosemide (Lasix and others), haloperidol (Haldol and others), levothyroxine (Synthroid, Levoxyl, and others), lithium (Eskalith, Lithobid, and others), morphine (Kadian, Oramorph, and others), nifedipine (Adalat, Procardia, and others), nitroglycerin (Minitran, Nitrostat, and others), olanzapine (Zyprexa), omeprazole (Nexium, Prilosec, and others), phenytoin (Dilantin and others), prazosin (Minipress and others), quetiapine (Seroquel), risperidone (Risperdal), salmeterol (Advair and Serevent), triamcinolone (Kenacort, Aristocort, and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

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