# *Biological Perspectives*

## Three Potentially Fatal Adverse Effects of Psychotropic Medications

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*He's gone country*
*Everybody's gone country*
*Yeah we've gone country*
*The whole world's gone country*
—Alan Jackson

Psychotropic drugs are in. Even psychiatric nurses who once considered psychotropic drugs a necessary evil or a treatment of last resort, now embrace the inevitability of the times—the fusion of public expectations, third-party considerations, and time constraints. As a result, psychotropic medications have become first-line options in treatment. However, several serious and potentially fatal side effects are related to these agents—for example, neuroleptic malignant syndrome, serotonin syndrome, and agranulocytosis.

All these adverse responses were discovered "after the fact": that is, these effects were not anticipated but were described after patients had developed symptoms or had died. With careful assessments demanded by unacceptable levels of morbidity and mortality, both incidence and death rates have dropped significantly in recent years. Rather than risk allowing these catastrophic consequences to drift to the periphery of practice, we attempt in the following pages to bring the discussions up to date.

### Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially fatal reaction to dopamine blockade caused by antipsychotic and other medications. The majority of these medications are prescribed in the treatment of schizophrenia and work by antagonizing dopamine D2 receptors (Keltner & McIntyre, 1985). Although uncommon, NMS may be fatal if left untreated. Estimates of the incidence of NMS range from 0.5% to 2.4%, and the mortality rate may be as high as 20% in those who are not treated (Reeves, Mack, & Torres, 2001). Persing (1994) identified four cardinal symptoms of NMS: hyperthermia, muscle rigidity, mental status changes, and autonomic instability. NMS most often occurs with high potency antipsychotics. and was first described during clinical trials with haloperidol in 1960 (Reeves, Torres, Liberto, & Hart, 2002). Although haloperidol has been most often implicated, cases also are reported with atypical antipsychotic and other dopamine receptor–blocking medications (Beauchemin, Millaud, & Nguyen, 2002; Harradine, Williams, & Doherty, 2001; Philibert, Adam, Frank, & Carney-Doebbeling, 2001; Solomons, 2002). Ninety-six percent of NMS cases occur within the first 30 days of treatment (Persing), with a duration of 5 to 10 days after antipsychotic medications are discontinued (Lappa et al., 2002).

**Dopamine and NMS.** Dopamine is a catecholamine. It has as its immediate precursor levodopa and is itself a precursor to norepinephrine. Dopamine is synthesized from the amino acid tyrosine, which crosses the blood brain barrier and is converted to levodopa in dopaminergic and noradrenergic neurons. Dopamine's metabolic pathway, then, may be summarized as: tyrosine → levodopa → dopamine → norepinephrine (Keltner, Hogan, & Guy, 2001).

**Pathophysiology of NMS.** Central nervous system dopamine is localized in four specific pathways. Altered functioning in two of these pathways is thought to induce the positive and negative symptoms of schizophrenia. Treatment strategies aimed at manipulating dopamine affect all four tracts. Chemical manipulation of three of these pathways may contribute to NMS (Table 1).

Some of these symptoms of NMS are interrelated. For example, high temperatures may develop and can be exacerbated by massive muscle contraction and

**Table 1. Putative Roles of Dopamine Tracts in Neuroleptic Malignant Syndrome**

| Dopamine Tract | Proposed Effects of Alterations in This Pathway |
|---|---|
| ▪ Nigrostriatal | Rigidity, temperature elevation |
| ▪ Mesocortical | Changes in mental status |
| ▪ Tuberoinfundibular | Temperature dysregulation |

**Table 2. Characteristic Signs and Symptoms of Neuroleptic Malignant Syndrome**

Hyperthermia (to 108°F)

Muscle rigidity
- Dystonias
- Dyskinesias
- Tremors
- Rhabdomyolysis

Mental status changes
- Delirium
- Agitation
- Catatonic features
- Coma

Autonomic instability
- Sinus tachycardia (i.e., 30 beats above baseline)
- Hypertension (i.e., increase of 30 mm Hg systolic, 20 mm Hg diastolic)
- Labile blood pressure
- Tachypnea
- Nausea and vomiting

**Table 3. Risk Factors for Neuroleptic Malignant Syndrome**

- Rapid initiation of antipsychotic
- Rapid increase in antispsychotic dosage
- Prior brain damage/trauma
- Exhaustion
- Electrolyte imbalances
- Concurrent use of tricyclic antidepressants
- Mental retardation
- AIDS dementia

*Source:* Adapted from Lappa et al., 2002; Persing, 1994.

hypermetabolism (Lappa et al., 2002). Rigidity also may cause rhabdomyolysis, which can lead to acute renal failure when kidneys are flooded with myoglobin. Severity is assessed by measurement of creatine phosphokinase (CPK). Renal failure is the most common cause of death in NMS (Persing, 1994).

Mental status changes can be an early sign of NMS and may progress to coma. Changes in mental status may be characterized by delirium, catatonia, and agitation.

Finally, autonomic instability associated with NMS is primarily characterized by sinus tachycardia, changes in blood pressure, tachypnea, and nausea and vomiting (Harradine et al., 2001). A review of these characteristic symptoms of NMS is found in Table 2; risk factors are listed in Table 3.

**Treatment of NMS.** If NMS is suspected, the initial intervention is cessation of antipsychotic medications. Other early interventions often include administration of IV fluids (to correct dehydration and electrolyte imbalances), use of cooling blankets, and administration of aspirin and acetaminophen (Rosebush, 1994). Two medications that are of primary importance in treating NMS are bromocriptine (Parlodel) and dantrolene (Dantrium). Bromocriptine, a dopamine agonist, reverses the hypodopaminergic state that precipitates NMS. Dantrolene, a skeletal muscle relaxer, helps ameliorate the symptoms of muscle rigidity and the resulting muscle breakdown and heat generation (Rosebush). Although serious, an occurrence of NMS is not an absolute contraindication for subsequent therapy with dopamine antagonists. Therapy may be restarted 2 weeks after recovery, but high-potency antipsychotics (e.g., haloperidol, fluphenazine) should be avoided (Persing, 1994). Patients should be monitored closely for signs and symptoms of NMS. Philibert et al. (2001) report that rates of NMS recurrence may be as high as 64% when antipsychotic medications are given within 5 days after symptom resolution. Table 4 summarizes treatment approaches to NMS.

**Patient, family, caregiver, and nursing service education for NMS.** Since most patients receiving antipsychotics reside in the community, educating patients, families, and caregivers (e.g., group-home workers) about NMS becomes an important intervention for reducing morbidity and mortality. All these people should be taught about the four overarching signs and symptoms of NMS (see Table 2) and the importance of taking/administering antipsychotic medications as in-

structed. Dosage increases that are excessive, sudden, or due to patient-clinician miscommunication have led to NMS (Reeves et al., 2001, 2002). These authors illustrate miscommunication with a case in which, after initiation of a haloperidol-to-risperidone switch, the patient continued to take haloperidol from an old bottle, developed a severe case of NMS, and was hospitalized for more than 2 months. The potential for such an occurrence is relatively high in today's outpatient-oriented care model.

Although most patients receiving antipsychotic medications live in the community, these patients are frequently seen by nurses in day treatment, psychopharmacology clinics, or, during times of symptom exacerbation, in hospitals. Hence, nursing's role requires vigilant observation of patients at risk for this syndrome (see Tables 3, 5). Because nursing staff have the advantage of seeing hospitalized patients 24 hours a day, nurses play an important role in recognizing the early signs and symptoms of NMS before it progresses to an advanced stage. In recent years, mortality due to NMS has decreased dramatically and is attributed to early recognition and treatment. Before 1984 mortality was thought to be as high as 25%, but that number has dropped to less than 10% (Lappa et al., 2002; Persing, 1994).

**Table 4. Treatment of Neuroleptic Malignant Syndrome**

- Cessation of dopamine antagonists
- IV fluids
- Cooling blankets
- Aspirin and acetaminophen
- Bromocriptine
- Dantrolene

**Table 5. Strategies for Preventing Neuroleptic Malignant Syndrome**

- Monitor to prevent excessive or sudden drug increases
- Review medication instructions with patient to minimize miscommunications
- Monitor body temperature on routine basis
- Maintain patient hydration
- Monitor electrolytes
- Monitor concurrent administration of agents that can cause NMS

## Serotonin Syndrome

Overheard on the Metro in Washington, DC:

*First teenage girl:* "I'm having a bad day. Nothing is going right."
*Second teenage girl:* "Your serotonin must be low."

Who hasn't heard that the key to a good mood is adequate levels of serotonin? The very popular selective serotonin reuptake inhibitors (SSRIs), as their descriptive name suggests, are molecularly configured to do just that—increase serotonin levels. These agents have gained a reputation for being relatively "safe" drugs and are popular because they have fewer side effects than most older antidepressant drugs. For several years now, however, it is clear that boosting serotonin is not without complications. A very serious consequence of serotonin enhancement, serotonin syndrome (SS), has proved fatal in a number of instances. Since the first episode of SS in 1960 (Oates & Sjoerdsma, 1960) there have been hundreds of reports; the actual incidence of this syndrome, however, is unknown. It is thought that SS is underreported or misreported because of confusion with NMS (Mason, Morris, & Balcezak, 2000; Sternbach, 1991). Further, while some cases of SS have indeed produced a fatal effect, many cases are mild, detected early, and go unreported.

**Serotonin and SS.** Serotonin (5-hydroxytryptamine [5 HT]), an indolamine, is derived from the amino acid tryptophan and synthesized in the raphe nuclei as follows: tryptophan → 5-hydroxytryptophan → serotonin (McKenry & Salerno, 1998). Mason et al. (2000) remind us that only 2% of the body's supply of serotonin is in the central nervous system. Ninety percent is found in the gut, and the remaining 8% in blood platelets. Serotonin is important in modulating psychiatric states

**Table 6. Characteristic Signs and Symptoms of Serotonin Syndrome**

**Hyperthermia** (to 108°F, though usually lower and sometimes normal)

**Altered muscle tone**
- Myoclonus
- Tremor
- Shivering
- Rigidity
- Hyperreflexia

**Altered mental status**
- Agitation
- Restlessness
- Confusion
- Uncoordination
- Hypomania

**Autonomic changes**
- Hypertension
- Hypotension
- Tachycardia
- Diaphoresis

*Source:* Adapted from Mason et al., 2000; Rodomski et al., 2000, Sternbach, 1991.

(aggression, anxiety, depression) and biological functions (appetite, emesis, migraine, pain, sleep, temperature regulation). Manipulation of serotonin affects these psychological states and biological functions.

**Pathophysiology of SS.** Signs and symptoms of SS can be grouped into four inclusive categories that are almost identical to those of NMS—hyperthermia, altered muscle tone, mental status changes, and autonomic instability (Table 6). Left untreated, SS can lead to coma, seizures, high fever, metabolic acidosis, rhabdomyolysis, disseminated intravascular coagulation, and renal failure (Radomski, Dursun, Reveley, & Kutcher, 2000). These signs, symptoms, and conditions result from a hyperserotonergic state frequently linked to treatment with SSRIs. SS may develop when SSRI monotherapy is prescribed or when other drugs are given concomitantly with SSRIs. Elevated serotonin levels develop due to interference with SSRI metabolism (i.e., cytochrome P450 enzyme system inhibitors), inhibition of monoamine oxidase metabolism of serotonin, prevention of serotonin reuptake, or other mechanisms related to drug/drug interactions (Kuszmar, Blasiole, & Schwartz, 1998). Particularly troublesome SSRI-drug combinations include those with serotonin agonists, monoamine oxidase inhibitors (MAOIs), lithium, levodopa, meperidine, and tricyclic antidepressants (Mason et al., 2000; Sternbach 1991; Weitzel & Jiwanlal, 2001). Further, non-SSRI monotherapy and non-SSRI drug combinations also have caused SS (Table 7 shows drugs and drug combinations implicated in SS). Finally, a number of street drugs are known to elevate serotonin and cause SS, including LSD, cocaine, and Ecstasy. Research has identified many different types of serotonin receptors (Mason et al., 2000; Weitzel & Jiwanlal, 2001). SS is thought to be caused by the excess stimulation of 5-$HT_{1A}$ receptors and perhaps $5HT_2$ receptors (Mason et al.; Radomski et al., 2000; Sternbach, 1991).

**Treatment of SS.** While there is no standardized treatment of SS, early detection, discontinuation of the serotonergic drug, and supportive care are critical. Laboratory tests cannot detect SS; serotonin blood levels usually are within normal limits (Kuszmar et al., 1998). As with NMS, lab values can detect some complications of SS, including disseminated intravascular coagulation and rhabdomyolysis. (See Table 8 for a comparison of NMS and SS.)

Treatment is often supportive and can range from antipyretics and intravenous fluids to neuromuscular blockade, mechanical ventilation, and external cooling (Mason et al., 2000). Pharmacological interventions include treating myoclonus and rigidity with clonazepam, lorazepam, or benztropine (Keltner, 1997a). Attempts to counter elevated serotonin are achieved by using serotonin antagonists such as chlorpromazine, methysergide, and cyproheptadine. Benzodiazepine administration provides a more indirect approach to serotonin inhibition since gamma aminobutyric acid receptors modulate serotonergic neurons.

**Table 7. Drugs and Drug Combinations That Have Caused Serotonin Syndrome**

1. Venlafaxine and mirtazapine
2. Tramadol and sertraline
3. SSRI and 5-HT3 receptor antagonist
4. Olanzapine
5. Mirtazapine and fluoxetine
6. Mirtazapine monotherapy
7. Fluvoxamine and mirtazapine
8. Linezolid
9. Tramadol and fluoxetine
10. Dexamphetamine and venlafaxine
11. Atypical antipsychotics
12. Ecstasy
13. Metoclopramide and SSRI
14. Cyproheptadine
15. Moclobemide and citalopram
16. Venlafaxine and trazodone
17. Fluvoxamine
18. 5-HT2A antagonism
19. Fluoxetine
20. Paroxetine and risperidone
21. Tandospirone and trazodone
22. Moclobemide and citalopram
23. Meridia combined with merperidine or fentanyl
24. Clomipramine after withdrawal of clozapine
25. Sertraline
26. Nortriptyline and selegiline
27. Citalopram or sertraline
28. Buspirone added to fluoxetine
29. Sertraline and metoclopramide
30. Trazodone to nefazodone
31. Nefazodone and fluoxetine
32. Venlafaxine following amitriptyline
33. Fluoxetine and moclobemide
34. Paroxetine and risperidone
35. Clozapine and SSRI
36. Paroxetine and moclobemide
37. Erythromycin and sertraline
38. Sertraline, buspirone, and loxapine
39. Clomipramine
40. Fluvoxamine
41. Meperidine
42. Fluoxetine plus tramadol
43. Dothiepine hydrochloride
44. Ayahuasca preparations and SSRIs
45. Carbamazepine and sertraline
46. Venlafaxine
47. Mirtazapine and fluoxetine

*Editor's note:* For a list of references for this table, contact the author: Keltnern@son.uab.edu

**Table 8. Comparing NMS and Serotonin Syndrome**

| | NMS | SS |
|---|---|---|
| Drug history | Usually an antipsychotic | Serotonin-enhancing agent |
| Onset | Days to weeks | Minutes to hours |
| Pathophysiology | Hypodopaminergic state | Hyperserotonergic state |
| Hyperthermia | More likely (90%) | Less likely (46%) |
| Muscle tone | More rigidity, greater rhabdomyolysis | More hyperreflexia, restlessness, myoclonus |
| Mortality | Higher than SS | Lower than NMS |
| Autonomic dysregulation | More than SS | Less than NMS |
| Resolution | On average 5–10 days | On average <24 hours |

*Sources:* Fisher & Davis, 2002; Keltner, 1997a, Mason et al., 2000; Sternbach, 1991.

**Patient, family, caregiver, and nursing service for SS.** Patients, families, caregivers, and nursing personnel should be aware of the signs and symptoms of SS. The patient should be taught the importance of asking healthcare professionals about the use of over-the-counter drugs (e.g., St. John's Wort) or dietary supplements. Another

safeguard for patients includes the suggestion to provide a list of current medications when seeing more than one prescribing clinician. In addition, patients and families should be taught that certain foods such as cheese, milk, poultry, and red wine contain tryptophan, which is serotonergic and may put them at risk for SS.

**Clozapine-Induced Agranulocytosis**

Agranulocytosis, a potentially fatal adverse reaction to clozapine (Clozaril) administration, is defined as a white blood cell (WBC) count <1,000 cells/$mm^3$ or an absolute neutrophil count of <500/$mm^3$ (Keltner, 1997b), is linked to clozapine (Clozaril) administration and is potentially fatal. The incidence of clozapine-induced agranulocytosis occurs at a rate of 1% to 2% of patients treated (Clozaril, 1998). Clozaril has high affinity for the D4 dopamine receptor. It also blocks D1 dopamine receptors in the limbic system and has antihistaminic (greatest affinity), antimuscarinic, antiadrenergic, and antiserotinergic effects (Rudolf, Grond, Neveling, & Heiss, 1997). Clozapine, widely regarded as the most effacious therapy for the treatment of schizophrenia, has been shown to produce a significant improvement in 30% to 60% of schizophrenic patients unresponsive to traditional antipsychotics.

Additionally, reduced incidence of extrapyramidal side effects (EPSEs) and tardive dyskinesia have been reported with clozapine therapy (Theodoropoulou et al., 1997). The link between clozapine and agranulocytosis was first identified in the 1970s. From a group of 35,000 Finnish patients receiving treatment with clozapine, 18 developed agranulocytosis. Of this group, 9 patients died of severe infections (Alphs & Anand, 1990). Because of the substantial risk for this potentially fatal adverse reaction, the drug manufacturer, Novartis, distributes clozapine only in countries having national blood monitoring systems and has requirements for physician monitoring of WBCs as well. In the United States, this service is known as the Clozaril National Registry (CNR). The CNR requires that patients have blood drawn weekly for the first 6 months of treatment, and biweekly thereafter for patients with stable WBC counts. The CNR (Clozaril, 1998) ensures prescription safety including:

- Consistent blood monitoring for early detection of leukopenia
- Immediate cessation of clozapine treatment if leukopenia occurs
- Exclusion from drug rechallenge if clozapine-induced agranulocytosis occurs, and, in accordance with the "no blood, no drug" policy,
- Immediate discontinuation of treatment in cases of noncompliance with the blood monitoring system.

Although exact mechanisms remain obscure, several theories exist for clozapine induced agranulocytosis. As described by Feldman (1996), these include:

- Cytotoxic effect exhibited on marrow cells by the clozapine metabolite desmethylclozapine
- Suppressed release of granulocyte-stimulating factor (GSF), resulting in hematological imbalances
- Formation of antibodies toxic to blood neutrophils
- Clozapine-induced agranulocytosis typically develops within the first 1 to 3 months of use, with significant risk reduction after 6 months of use (Guest & Soko-luk, 1998).

Once clozapine is withdrawn, recovery to pretreatment WBC levels usually occurs rapidly (=1 week) (Guest & Sokoluk). Within the therapeutic range, dosage levels do not correlate positively with increased incidence; however, risk increases with age, females are more frequently affected than males, and some ethnic groups (e.g., Jewish patients) are more susceptible than others (Lieberman et al., 1990; Mendelowitz, Gerson, Alvir, & Lieberman, 1995).

**Treatment considerations.** Agranulocytosis is reversible and not fatal if treated (Gaszner, Makkos, & Kosza, 2002). Treatment for clozapine-induced agranulocytosis consists of immediate cessation of the drug and administration of granulocyte-stimulating factors (GSF). Research shows that early introduction of GSF may shorten the duration of agranulocytosis by half (Gerson, 1994). In cases of severe agranulocytosis, treatment with granulo-

cyte-colony-stimulating factor or granulocyte macrophage-colony-stimulating factor may be necessary (Feldman, 1996). Because of the mandated blood draws, nursing implications are relatively straightforward. Patients must be educated on the importance of compliance, including drug adherence, as well as continuous monitoring. Patients also must be taught to report temperature elevations and flu-like symptoms to the prescribing healthcare provider.

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**Search terms**: *Agranulocytosis , neuroleptic malignant syndrome, psychotropics, serotonin syndrome*