Catastrophic Consequences Secondary to Psychotropic Drugs, Part 1

Norman L. Keltner, RN, EdD, CRNP

An integral part of psychiatric nursing is the administration and management of psychotropic drugs (Keltner, 1985; Keltner, Schwecke, & Bostrom, 1995). The centrality of this intervention recently was underscored by the American Nurses Association’s commissioned monograph, entitled *Psychiatric Mental Health Nursing Psychopharmacology Project* (Laraia et al., 1994)

Unfortunately, along with sought-after therapeutic responses to these agents, several serious-to-catastrophic effects occur with sufficient regularity to warrant deliberate vigilance by psychiatric nurses. Serious side effects that may necessitate emergency treatment include cardiovascular effects such as orthostatic hypotension, cardiac conduction blockade, and SA node dysfunction. Neurological effects include extrapyramidal reactions, seizures, delirium, catatonia, ataxia, and glaucoma. Genitourinary effects manifest as urinary retention, nephrotic syndrome, and priapism (Tueth, 1994).

Four catastrophic or potentially fatal syndromes secondary to the use of psychiatric drugs include neuroleptic malignant syndrome (NMS), serotonin syndrome (SS), agranulocytosis, and lithium toxicity. These concerns are the focus of this series. Part 1 focuses on NMS and SS; agranulocytosis and lithium toxicity will be discussed in Part 2 (to appear in the May 1997 issue).

**Neuroleptic Malignant Syndrome**

NMS is a specific, potentially lethal disorder related to usage of dopamine antagonists (Pershing, 1994). NMS is characterized by mental changes, rigidity, hyperthermia, and autonomic dysfunction following exposure to neuroleptic medication (Buckley & Hutchinson, 1995).

The syndrome was first reported in 1960 by Delay, Pichot, Lemperier, Ellisalde, and Peignier. Delay and Deniker (1952) had been credited with introducing the first antipsychotic (chlorpromazine) a decade earlier. The first nursing article to address NMS appeared 25 years later when Keltner and McIntyre (1985) reported the case of a 37-year-old man afflicted with this disorder.

As with other catastrophic consequences, NMS occurs often enough to be considered a significant concern. A morbidity rate of 1% has been mentioned most frequently; however, estimates have ranged to 12.2% when criteria using the “spectrum concept” spread a wider diagnostic net (Buckley & Hutchinson, 1995). Mortality has been estimated between 14% and 30% (Hooper, Herren, & Goldwasser, 1989; Shalev, Hermesh, & Munitz, 1989) estimate that between 1,000 and 4,000 deaths per year in the United States can be attributed to NMS.

Although the actual morbidity and mortality are difficult to discern, a downward trend is occurring. Prospective studies indicating a morbidity rate of 0.07% to 0.15% (Gelenberg, Bellinghausen, Wojcik, Falk, & Sachs, 1988; Keck, Pope, & McElroy, 1991) may reflect the current levels of NMS more accurately; mortality figures have dropped to 11.6% post-1984 (Shalev et al., 1989).

**Pathogenesis of NMS**

As NMS occurs in individuals taking neuroleptics and in those who are withdrawn from antiparkinson dopaminergic agents, a sudden reduction of central nervous system dopamine may be fundamental to its development. For example, a reduction in dopamine has the potential to cause hyperpyrexia, a cardinal symptom of...
NMS, in three interrelated ways (Buckley & Hutchinson, 1995).

First, dopamine receptors in the hypothalamus, the site of temperature regulation, are blocked, and a higher “set point” for core temperature is developed. Second, rigidity associated with decreased dopamine levels, extrapyramidal effects, and parkinsonism increases heat production. Third, anhydrosis, another side effect of neuroleptics, impairs heat dissipation. The combined effect of these physiological changes can cause extreme hyperthermia.

Another hypothesis of NMS development suggests an interaction between dopamine-depleting and serotonin-enhancing activities. When serotonin receptors, located in the hypothalamus, are overabundant and coupled with reductions in dopamine, the result may be high temperatures associated with NMS. Other suggested explanations for NMS development include disordered calcium regulation within skeletal muscle and low serum iron (Buckley & Hutchinson, 1995).

**Causative agents**

NMS is caused by both neuroleptics and non-neuroleptics. As mentioned, withdrawal from antiparkinson dopamine-mimetic agents can have the same effect as neuroleptics, and is conceptually related to neuroleptic-induced NMS. Other non-neuroleptics that have caused NMS include lithium, antiemetics, and antidepressants.

Among neuroleptics, high potency antipsychotics have been implicated most often. In about 50% of NMS cases, haloperidol, a high potency antipsychotic agent, has been prescribed (Caroff & Mann, 1988). Haloperidol, however, is ordered frequently, and its popularity with clinicians partially accounts for this seeming overrepresentation among patients suffering from NMS.

Other causative factors include administration of depot injections or the use of combination therapy. Combining one neuroleptic with another neuroleptic or with lithium increases risk for NMS (Blair, 1990). This is illustrated in a study reported by Persing (1994) in which nearly 50% of the patients with NMS also were taking lithium. Caroff and Mann (1988) found that 96% of patients with NMS developed the disorder within 30 days of initiating treatment. Shalev and Munitz (1986) calculated the mean time from treatment initiation to NMS onset as 4.8 days.

**Risk factors**

Several variables have been identified that place a given patient at higher risk for developing NMS. Although not associated with toxic drug levels, a relationship between NMS development and the loading dose or the rate of increase of the neuroleptic exists. Other risk variables include previous brain injury, a state of exhaustion, increased agitation, and dehydration (Buckley & Hutchinson, 1995; Caroff & Mann, 1993).

**Warning signs**

As noted, the four major symptoms characterizing NMS are mental changes, rigidity, hyperthermia, and autonomic dysfunction. Symptoms occur in this sequence for about 70% of patients experiencing NMS (Velamoor et al., 1994). Mental changes include confusion, delirium, agitation, and catatonia.

Muscle rigidity is global and often associated with a myonecrotic process (Persing, 1994). Essentially, muscles continually held rigid begin to deteriorate, leading to rhabdomyolysis. In turn, serum creatinine phosphokinase (CPK) is released and becomes a good measure of the level of muscle necrosis sustained. The excessive levels of myoglobin can lead to renal failure, the most common cause of death among patients succumbing to NMS (Persing).

Temperatures typically range from 101° to 103° (Blair, 1990), but fevers as high as 108° have been reported (Keltner & McIntyre, 1985). Autonomic dysfunction includes tachycardia, diaphoresis, hypertension, tremulousness, dysphagia, dysarthria, and sialorrhea (Velamoor et al., 1994).

**Management**

Management of this syndrome includes:

- prompt recognition;
- withdrawal of the neuroleptic medication;
- supportive care; and
- administration of a dopamine agonist or a muscle relaxant.

Supportive care activities focus on fever reduction, treatment of secondary infections, sedation, and maintenance.
of respiratory, cardiovascular, and renal function.

The two drugs given most often to counteract the dopamine reduction responsible for NMS are bromocriptine (Parlodel), an antiparkinson dopamineergic agent; and dantrolene (Dantrium), a skeletal muscle relaxant. Bromocriptine acts centrally; dantrolene acts peripherally.

Serotonin Syndrome

Fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), and fluvoxamine (Luvox) are members of a relatively new class of antidepressants referred to as selective serotonin reuptake inhibitors (SSRIs). As the name of this class of drugs suggests, SSRIs selectively increase serotonin bioavailability. This serotonin-enhancing property putatively relieves depression, but also can cause the hyperserotonergic state known as the serotonin syndrome (SS).

This syndrome is characterized by mental changes, altered muscle tone (hyperreflexia, rigidity, myoclonus), hyperthermia, and autonomic dysfunction. Considerable symptomatic overlap occurs between NMS and SS, resulting in diagnostic confusion (Brennan, MacManus, & Howe, 1988).

Serotonin, first isolated and named in 1948 (Rapport, Green, & Page), is subordinated under the monoamine category of neuromodulators and is metabolically “downstream” from the amino acid L-tryptophan (Keltner & Harris, 1994). Serotonin has been linked to several psychiatric disorders, including depression (Schatzberg & Rothschild, 1992), schizophrenia (Meltzer, 1991), and anxiety (Hollister, 1994) as well as several nonpsychiatric problems.

Serotonin syndrome was first described in 1960 by Oates and Sjoerdsma, although the actual term was not coined until 1982 (Insel, Roy, Cohen, & Murphy, 1982). This syndrome, however, has not been widely recognized or understood until recently. The first nursing article addressing this phenomenon appeared much later (Keltner & Harris, 1994).

The similarity of symptoms that exists between NMS and SS is perhaps best illustrated by a letter to the British Journal of Psychiatry in 1988 by Brennan and colleagues, when the term “serotonin syndrome” was not widely known. The letter was entitled 1990. In all, 38 cases, including several deaths, had been reported.

In 1994, Keltner and Harris, following Sternbach’s (1991) model, updated the list with 33 more cases reported (1991 to 1994), again with several deaths having occurred. In their article, Keltner and Harris presented the following case.

A 55-year-old woman (on an MAOI), after taking a single 100-mg dose of sertraline during the evening hours, awoke at 3 AM experiencing shortness of breath, nervousness, and confusion. Her family took her to the hospital where within hours she developed a temperature of 108°F accompanied by seizures.

Over the next 4 days, every treatment effort available at a large teaching hospital was attempted. She died from SS.

Pathogenesis

Whereas NMS is related to dopamine antagonism, SS is related to a hyperserotonergic state. Both neurotransmitters affect temperature regulation in the hypothalamus; dopamine lowers temperature and serotonin raises temperature (Keltner & Harris, 1994). Therefore, drugs that block dopamine as well as those that enhance serotonin tend to raise body temperature. When an imbalance between these two neurotransmitters occurs, an increase in temperature can develop (Nimmo, Kennedy, Tullett, Blyth, & Dougall, 1993). Further, a hyperserotonergic state causes a relative hypodopaminergic state and thus may account for the overlapping symptoms of SS and NMS (Bodner, Lynch, Lewis, & Kahn, 1995).

Causative agents

SS is caused following the use of serotonergic agents, either alone or in combination with MAOIs (Bodner et
Drug combinations reported to cause serotonin syndrome

<table>
<thead>
<tr>
<th>Drug</th>
<th>When combined with</th>
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<tbody>
<tr>
<td>L-tryptophan</td>
<td>Fluoxetine, MAOIs, clomipramine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>MAOIs</td>
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<tr>
<td>Clomipramine</td>
<td>Alone, MAOIs, moclobemide*</td>
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<tr>
<td>Moclobemide*</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>L-dopa</td>
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<tr>
<td>Meperidine</td>
<td>MAOIs</td>
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<tr>
<td>Phenelzine</td>
<td>Ecstasy (street drug)</td>
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<tr>
<td>Dextromethorphan</td>
<td>MAOIs</td>
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<tr>
<td>Sertraline</td>
<td>MAOIs, nortriptyline</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Buspirone, paroxetine</td>
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<tr>
<td>Fluvoxamine</td>
<td>Alone</td>
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*an investigational drug

| Table |

The Table lists some drug combinations reported to cause SS (Bodner et al.; Reeves & Bullen, 1995).

Risk factors

The major risk factor associated with SS is the combination of serotoninergic agents with an MAOI. Therefore, MAOIs should not be administered with these drugs. Additionally, a definite washout period must be observed when switching from one to the other.

The length of time for the washout will differ depending on the direction of the switch. If changing from an MAOI to fluoxetine, a 14-day washout period should be observed (Cain, 1992; Ooi, 1991). Conversely, if switching from fluoxetine to an MAOI, at least 5 weeks must elapse because of the long half-life (7 to 9 days) of fluoxetine (Keltner & Harris, 1994).

Signs of SS

Serotonin syndrome is characterized by mental changes, altered muscle tone, autonomic dysfunction, and hyperthermia. Examples of each follow:

- Mental changes: agitation, restlessness, confusion, discoordination, hypomania, coma, seizures.
- Altered muscle tone: myoclonus, tremor, shivering, rigidity, hyperreflexia.
- Autonomic changes: hypertension, hypotension, tachycardia, diaphoresis.
- Hyperthermia: as pointed out in the brief case study, can reach 108°F; however, temperatures usually are lower and can be normal.

Distinguishing SS From NMS

NMS and SS can present an almost identical clinical picture. Knowledge of a few distinguishing characteristics can aid in making a differential diagnosis (Keltner & Harris, 1994; Kline, Mauro, Scala-Barnett, & Zick, 1989; Nimmo et al., 1993). They are noted in the following.

1) The most important point is drug history. Neuroleptics cause NMS and serotonimetics cause SS.

2) SS tends to develop within hours of taking serotonergic drugs; NMS usually takes 3 to 9 days (Kline et al., 1989) with a 4.8 day mean (Shalev & Munitz, 1986).

3) NMS has more pronounced rigidity, greater autonomic dysfunction, and more pallor.

4) SS has more pronounced hyperreflexia, restlessness, unsteady gait, and myoclonus.

5) Hyperthermia, diaphoresis, rhabdomyolysis, disseminated intravascular coagulation, and acute renal failure occur with approximately the same intensity in both disorders.

Management

Effective treatment of SS begins with withdrawal of the offending agent(s) followed by focusing on symptom management. Treatment usually includes controlling elevated temperature, seizures, myoclonus, and hypertension.

Supportive measures include the use of intravenous fluids, antipyretics, and cooling devices (Bodner et al., 1995; Sternbach, 1991). Myoclonus and rigidity can be treated with clonazepam (Klonopin), benzotropine (Cogentin), and lorazepam (Ativan), although their efficacy is not established (Bodner et al.). Anticonvulsants should be used for seizures and nifedipine (Procardia) has been used to treat SS-related hypertension (Sternbach). Finally, the serotonin receptor antagonists methysergide and cyproheptadine have been found to shorten the duration of SS (Bodner et al.; Lappin & Auchincloss, 1994).

Summary

The use of psychotropic drugs has dramatically changed the lives of many; yet, as often occurs with technological advances, negative out-
comes can be encountered. Potentially fatal reactions to neuroleptic drugs and serotonin-enhancing agents (e.g., antidepressants) have been presented in Part 1, with the intent of alerting and informing psychiatric nurses. Part 2 will complete this series on catastrophic consequences of psychotropic drugs with a discussion of agranulocytosis and lithium toxicity.

References


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