Clinical Psychopharmacology Seminar

Neuroleptic Malignant Syndrome

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare, but potentially life-threatening adverse effect associated with antipsychotic drugs and other drugs that affect dopaminergic neurotransmission. NMS was first described during early studies of haloperidol in 1960 (Delay et al, 1960). The first report of NMS in English literature was in 1968 (Delay and Deniker, 1968). Since NMS occurs very infrequently, it is extremely difficult to characterize it objectively under controlled conditions. As a result, many uncontrolled reports have been published, sometimes with misleading results. This review will attempt to differentiate and assess the clinical significance of well established features of NMS versus less well established facts.

Interest in NMS has peaked recently, having grown steadily since 1980. Numerous excellent reviews have been published recently that provide comprehensive discussions of NMS (Caroff and Mann, 1993; Dickey, 1991; Ebadi et al, 1990; Heiman-Patterson, 1993).

PATHOGENESIS

There are numerous theories that attempt to explain the pharmacologic mechanism by which NMS occurs (Caroff and Mann, 1993; Dickey, 1991; Ebadi et al, 1990; Heiman-Patterson, 1993; Thornberg and Ereshefsky, 1993). None of these theories satisfactorily explain why NMS only occurs in some patients or why NMS does not always recur even if the patient is re-exposed to the same antipsychotic that originally produced the NMS (Rosebush et al, 1989b). Despite this, most theories attribute most of the clinical features of NMS to dopamine blockade (Caroff and Mann, 1993; Dickey, 1991; Ebadi et al, 1990; Heiman-Patterson, 1993; Thornberg and Ereshefsky, 1993). This is a natural assumption since dopamine antagonists cause NMS and dopamine agonists may be used to treat NMS.

The tremor and rigidity seen in NMS have been linked to nigrostriatal dopamine blockade, an extension of the parkinsonian side effects seen at therapeutic doses of antipsychotics (Heiman-Patterson, 1993; Dickey, 1991). Extreme rigidity, in turn, may contribute to hyperthermia, muscle breakdown, elevated CK, and rhabdomyolysis. Peripherally, antipsychotics also affect intracellular calcium transport resulting in an increased calcium concentration and altered muscle fiber contractility. This effect is reversed by dantrolene (Dickey, 1991). However, there are cases of NMS in which dantrolene administration eliminated fever but had no effect on rigidity (Dickey, 1991).

Central dopamine blockade in the hypothalamus may result in impaired temperature regulation. It has been suggested that dopamine blocking drugs may alter the "set point" of body temperature maintained in the hypothalamus. In addition, the heat dissipating mechanisms affected by the hypothalamus through the autonomic nervous system (e.g. shivering, sweating, and peripheral vasoconstriction or vasodilatation) may be disrupted (Heiman-Patterson, 1993).

ETIOLOGY

Neuroleptic malignant syndrome has been associated with all dopamine blocking drugs (Caroff and Mann, 1993). Clozapine, an antipsychotic that does not exhibit significant antagonism of D2 dopamine receptors, has been thought to be less likely to cause NMS. However, at least fourteen cases of NMS have been attributed to clozapine (Reddig et al, 1992; Sachdev et al, 1995; Thornberg and Ereshefsky, 1993). Likewise, three cases of

NMS have also been attributed to risperidone, another "atypical" antipsychotic (Webster P and Wijeratne C, 1994; Raitasuo V et al, 1994) Metoclopramide, prochlorperazine, promethazine, and droperidol are all dopamine antagonists frequently used as antiemetics and for other reasons. NMS has been attributed to all four of these drugs (Caroff and Mann, 1993). It is recommended that dopamine blocking antiemetics should only be used long-term in patients with a clear indication.

The abrupt withdrawal of dopaminergic drugs has also produced an NMS-like condition in patients with Huntington's disease and Parkinson's disease (Ebadi et al, 1990). Implicated drugs include levodopa, bromocriptine, and amantadine. Not surprisingly, dopaminergic drugs have been studied to treat NMS (Caroff and Mann, 1993; Dickey, 1991; Ebadi et al, 1990; Heiman-Patterson, 1993).

There is one case report in the literature were the patient diagnosed with NMS was presumed to have taken > 300 mg of cyclobenzaprine (Flexeril®), a commonly prescribed muscle relaxant, as his only medication. The patients presentation was similar to neuroleptic induced NMS. The authors suggest that this type of reaction in the absence of a neuroleptic may be a hyperthermic reaction and should be classified as a " drug-induced central hyperthermic syndrome" (Theoharides et al, 1995)

INCIDENCE

NMS is very rare (Deng et al, 1990; Keck et al, 1991; Modestin et al, 1992). Estimates of the frequency of NMS in prospective studies range from 0.07% (Gelenberg et al, 1988) to 2.2% (Hermesh et al, 1992; Keck et al, 1989a). Analysis of NMS across studies suggests a frequency of approximately 0.2% (Caroff and Mann, 1993). A number of factors may explain this wide range of frequencies. Diagnostic criteria for NMS varies widely from center to center (Gurrera et al, 1992; Modestin et al, 1992). What is NMS at one site may be severe pseudoparkinsonism at another. Study duration and length of exposure to antipsychotics varies greatly between studies. Clearly, longer studies or studies of patients receiving long-term antipsychotics are more likely to identify more cases of NMS than shorter studies or studies in which the patients only received antipsychotics for a short time. Likewise, antipsychotic dosing practices between sites or over time are likely to affect the reported incidence of NMS. Subjects in studies using higher antipsychotic doses are more likely to identify more cases of NMS (Gelenberg et al, 1988). In one study (Keck et al, 1991), the incidence of NMS declined significantly from 1.1% during a 31 month survey period to 0.15% over a later 47 month period. The authors attributed this decline primarily to enhanced awareness of NMS, earlier treatment, and a reduction in risk factors.

CLINICAL FEATURES AND LABORATORY ABNORMALITIES

Clinical Features. Although there is substantial variability among cases of NMS, most cases commonly exhibit muscle rigidity, hyperpyrexia, altered consciousness, and autonomic instability. The rigidity seen in NMS is often referred to as "lead pipe rigidity" because of the extreme nature of the reaction. In other cases akinesia, dyskinesia, waxy flexibility, and cogwheeling may occur instead or in addition to the classic rigidity (Heiman-Patterson, 1993). The fever seen in NMS is usually exceeds 38°C and sometimes exceeds 41°C (Caroff and Mann, 1993; Heiman-Patterson, 1993). Mental status changes associated with NMS may include stupor, coma, delirium, or catatonia (Caroff and Mann, 1993). Autonomic instability associated with NMS usually includes tachycardia and alterations in blood pressure. Respiratory distress may accompany these signs (Caroff and Mann, 1993). Many atypical cases have also been reported, often lacking one or more of these four classic signs (Caroff and Mann, 1993; Dickey, 1991; Ebadi et al, 1990; Heiman-Patterson, 1993). Variability in severity and diagnostic inconsistency among centers may account for this.

Patients experiencing NMS while taking atypical antipsychotics may present differently than those taking typicals. In a review by Sachdev et al (1995), 40% of patients did not have muscular rigidity. In addition the rise in CK and temperature was milder. The authors concluded that typical NMS does not occur with clozapine and that some patients may have atypical manifestations.

Laboratory Abnormalities. Extreme rigidity leading to muscle necrosis often contributes to elevations in creatine kinase (CK), lactic dehydrogenase (LD), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) seen in NMS (Caroff and Mann, 1993; Gurrera and Romero, 1993). Creatine kinase

elevations, sometimes 100-200 times normal, are seen in most, but not all patients with NMS (Heiman-Patterson, 1993). If the muscle damage is severe enough, rhabdomyolysis and myoglobinuria may and lead to renal failure. Leukocytosis, with or without left shift, is also common. In most cases, the white blood cell count is between 10,000-20,000 although elevations as high as 40,000 have been reported (Addonizio et al, 1987). It is not clear to what extent that concomitant lithium use contributes to leukocytosis.

Rosebush and Stewart (1989) published the details of 24 consecutive cases of NMS occurring among 20 patients they between 1981 and 1987. The diagnosis of NMS was made on clinical grounds in patients receiving an antipsychotic after all other medical explanations were ruled out. Tables 1 and 2 describe the prevalence of the clinical features and laboratory abnormalities observed in these patients.

CLINICAL COURSE

From reviews of case reports, it appears that most cases of NMS occur within the first one to two weeks following initiation of antipsychotic treatment or dose increase (Addonizio et al, 1987; Caroff and Mann, 1988; Shalev and Munitz, 1986). Despite this, NMS may occur at any time during treatment (Addonizio et al, 1987; Caroff and Mann, 1988).

NMS is self-limiting condition once the offending agent has been discontinued. Most sources suggest that NMS will resolve with supportive care within 1-2 weeks (Addonizio et al, 1987; Rosenberg and Green, 1989) unless the patient has been receiving depot antipsychotics. It may take up to one month for NMS to resolve in patients on depot antipsychotics (Addonizio et al, 1987).

COMPLICATIONS

Untreated or unrecognized cases of NMS may result in numerous complications (see Table 3) (Addonizio et al, 1987; Dickey , 1991; and Ebadi et al, 1990). Despite this, one review of previously published case reports suggested that long-term sequelae are rare, occurring in only four of 120 cases (Shalev and Munitz, 1986). This perspective is confirmed by two long-term follow-up case series involving 16 patients (Levenson and Fisher, 1988; Chen et al, 1991). No significant long-term sequelae were identified in these series.

The frequency of mortality resulting from NMS is difficult to ascertain. Estimates of mortality have ranged as high as 76%, although most reports put it between 10-20% (Shalev et al, 1989). Most studies of this issue have been retrospective reviews of previously published case reports, an approach that may produce misleading results (see discussion below under "Treatment Issues"). In a review by Shalev et al (1989), 202 NMS meeting operational diagnostic criteria were identified between 1959 and 1987. The mortality among these patients was 18.8%. When stratified by date of publication, the mortality rates were 27.7% before 1980, 22.6% from 1980-83, and 11.6% from 1984-87, a statistically significant trend. Predictors of mortality noted in this report are myoglobinuria and rhabdomyolysis. Mortality was 47% and 56% in these patients, respectively.

No cases of mortality were reported from pooled data from five reports of 54 prospectively evaluated NMS cases (Chen et al, 1991; Deng et al, 1990: Gelenberg et al, 1988; Keck et al, 1989a; Rosebush and Stewart, 1989). These data suggest that retrospective reviews of case reports overestimate true NMS mortality, perhaps because fatal cases of NMS are more likely to be reported as a case report than less severe cases.

In children the mortality rates may be higher with rates of 13% for adolescents and 27% for prepubertal youths (Peterson et al 1995). Although no controlled trials are available to confirm these figures.

DIFFERENTIAL DIAGNOSIS

NMS is a diagnosis of exclusion (Caroff and Mann, 1993; Dickey, 1991; Heiman-Patterson, 1993). Numerous other disorders that may mimic NMS in part or whole must be ruled out first (Table 4). Among these diagnoses, acute lethal catatonia (ALC) is of particular interest because it may be indistinguishable from NMS (Caroff and Mann, 1993; Dickey, 1991; Heiman-Patterson, 1993). Before antipsychotics became available, ALC was diagnosed more frequently than it is today (Dickey, 1991). Some have suggested that cases of ALC

have been misdiagnosed as NMS since antipsychotics have become available. Others maintain that antipsychotics are the primary treatment for ALC (Castillo et al 1989), although this, too, is disputed (Caroff and Mann, 1993; Heiman-Patterson, 1993). Castillo et al (1989) have suggested that ALC differs from NMS in terms of onset of symptoms. They suggested that ALC typically begins with a prodrome lasting several days consisting of excitement and agitation, while NMS typically begins with extreme rigidity. The mechanism behind ALC is hypothesized to be an abrupt blockage of dopamine receptors due to negative feedback inhibition. This blockade is thought to be similar to that precipitated by antipsychotic in NMS and is the reason why the two conditions are so similar (Osman and Khurasani, 1994).

The serotonin-syndrome (SS) is another important diagnosis to consider in suspected cases of NMS. The SS is a potentially fatal result from the combination of a monoamine oxidase inhibitor (MAOI) with a serotonin reuptake inhibitor (SRI) (Ciraulo and Shader, 1990). Features of the SS are similar to NMS and include excitement, diaphoresis, rigidity, hyperthermia, tachycardia, and hypertension. Depending on the circumstances of the case involved, the washout period between use of an MAOI and an SRI may range from one to more than five weeks. It is during this washout period that a misdiagnosis of NMS would be most likely, particularly when a patient is seeing more than one physician and complete records are not available.

Various sets of operational criteria to aid in the diagnosis of NMS have been published (Gurrera et al, 1992). Diagnostic criteria for NMS are useful primarily as a research tool to help assure consistent diagnoses of NMS across studies, a recurrent problem in much of the current literature. The practical clinician may find these criteria useful to clarify or solidify the diagnosis of NMS (Gurrera et al, 1992).

RISK FACTORS

Assessing the clinical importance of the many proposed risk factors for NMS is difficult because of the conflicting and uncontrolled nature of the NMS literature. In many cases, it is not apparent if the risk factors are truly related to NMS or if they are simply a confounding variable resulting from some other aspect of the case. Most data suggest the risk of NMS may be minimized through the use of conservative dosing strategies involving a single antipsychotic.

Antipsychotic Dose vs Psychomotor Agitation. Antipsychotic dose and psychomotor agitation are intimately linked as NMS risk factors. Patients with NMS tend to receive higher antipsychotic doses, a faster antipsychotic titration rate, and a greater number of IM antipsychotic injections compared to controls (Keck et al, 1989b). The use of IM injection is tantamount to using a higher oral dose since IM antipsychotics have a greater bioavailability than an equivalent oral dose (Davis, 1974). Exhaustion, dehydration, and psychomotor agitation have also been linked to NMS (Dickey, 1991; Caroff and Mann, 1993). In one case series, 18 of 24 patients were agitated before developing NMS (Rosebush and Stewart, 1989). In a case-control study, psychomotor agitation was more common in the NMS patients compared to controls (Keck et al, 1989b). Since agitated patients are more likely to receive a large antipsychotic dose, it is impossible to differentiate the risk associated with each of these factors. It may be that either factor alone, or in combination, predisposes one to NMS. In spite of these data, NMS may occur at low doses in non-agitated patients (Caroff and Mann, 1993).

Antipsychotic Potency. Neuroleptic malignant syndrome is associated with all dopamine blocking drugs (Caroff and Mann, 1993). In two case control studies, potency was not a risk factor for NMS (Keck et al, 1989b, Deng et al, 1990). Some reviews have suggested that high potency antipsychotics, and that haloperidol in particular, may be risk factors (Addonizio et al, 1987; Dickey, 1991; Caroff and Mann, 1993). In one review, haloperidol accounted for 57% of published cases, while chlorpromazine accounted for 24% (Addonizio et al, 1987). These results may be partially explained by the fact that haloperidol is one of most prescribed antipsychotics. In addition, rapid titration to high dose is more common for high potency antipsychotics because of their relative lack of cardiovascular adverse effects compared to low potency antipsychotics.

In children taking antipsychotics 50% of NMS cases were due to high potency drugs. In addition using adults doses in these adolescents may predispose them to NMS (Peterson et al 1995).

Depot Antipsychotics. One case control study has found a link between NMS and depot fluphenazine decanoate (Deng et al, 1990). However, every patient in this study on fluphenazine decanoate was also receiving supplementary oral antipsychotics. In addition, one case control study (Keck et al, 1989) and one review (Glazer and Kane, 1992) of the depot antipsychotic literature have failed confirm this relationship.

Concomitant Medications. Although greater than 50% of reported NMS cases involve concomitant psychotropic drugs, it is not clear that these drugs increase the risk of NMS (Caroff and Mann, 1993; Keck et al, 1989b; Deng et al, 1990). The combination of lithium with an antipsychotic has been widely associated with NMS (Caroff and Mann, 1993; Dickey, 1991). Two case control studies have failed to confirm this association (Keck et al, 1989b; Deng et al, 1990). Keck et al (1989b), have suggested that the use of lithium is simply an indirect reflection of psychomotor agitation and mania (see above).

Genetic Predisposition. There are two case reports that suggest that predisposition to NMS may include a genetic component (Deuschal et al, 1987; Otani et al, 1991). In one report (Deuschal et al, 1987), NMS occurred in a pair of twins. In the other report (Otani et al, 1991), NMS was reported in a mother and her two daughters. Because of this evidence, antipsychotics should be administered cautiously in patients with a family history of NMS.

External Heat Load. High environmental temperatures have been suggested as a risk factor for NMS. One center reported three cases that occurred one during an extreme heat wave (Shalev et al, 1988). These three cases accounted for 4% of all admissions to their hospital over one summer, a remarkable coincidence. Despite this evidence, there is little objective evidence that NMS is caused by high environmental temperatures since NMS has been reported in all extremes of temperature and climate (Caroff and Mann, 1993).

Malignant Hyperthermia. Despite the remarkable clinical similarity between NMS and malignant hyperthermia (MH), there is little evidence that these two disorders are related or that patients with NMS are also at risk for MH. In a review of 48 patients with NMS who also received ECT (and, therefore, anesthesia), no cases of MH occurred (Davis et al, 1991). In studies using the halothane-caffeine contracture tests, an in vitro test used to identify patients who are susceptible to MH, patients with a history of NMS were considered not susceptible to MH (Krivosic-Horber et al, 1987; Adnet et al, 1989; Adnet and Krivosic-Horber, 1990). A recent review by Keck et al (1995) discussed several differences between the two conditions; primarily the fact that neuroleptics fail to trigger hyperthermic responses in MH susceptible patients and that MH does not consistently occur in patients who have a history of NMS and undergo general anesthesia. Despite these data, conservative approaches to ECT anesthesia that do not require the use of succinylcholine in patients with a history of NMS have been described (Parke and Wheatley, 1992; Vallance and McConachie, 1993).

Sex. While some reviews suggest that NMS is twice as common in males (Dickey, 1991), others suggest that antipsychotics are used differently between the sexes (Caroff and Mann, 1993). Men may be more likely to receive a higher antipsychotic dose if they are perceived as more threatening by their caregivers.

Age. NMS has been reported in all age groups and does not differentiate between NMS patients and controls (Keck et al, 1989b; Caroff and Mann, 1993). There have been 55 case reports on NMS in children reported in the literature (Latz and McCracken, 1992; Peterson et al, 1995; Steingard et al, 1992). The clinical presentation in children and adolescents is similar to adults.

Diagnosis. NMS may occur in any patient exposed to an antipsychotic, regardless of diagnosis (Caroff and Mann, 1993). In one case series, only one of 20 NMS patients were schizophrenic, and 14 of them had and affective illness (Rosebush and Stewart, 1989). In another series, 11 of 12 cases of NMS were schizophrenics (Deng et al, 1990).

History of NMS. Patients with a history of NMS are at increased risk for NMS. This issue is discussed in detail below under "Antipsychotic Rechallenge."

TREATMENT

Treatment Issues. The most difficult mystery to solve about NMS is the mystery of rational treatment. Since NMS occurs so rarely, it is impossible to perform a study under ideal circumstances, a double-blind, placebo-controlled trial. As a result the clinician is left with the dilemma of trying to evaluate less objective forms of research. The most popular research method used to study NMS is an analysis of previously published case reports, a case report analysis (Addonizio et al, 1987; Caroff and Mann, 1988; Davis et al, 1991; Rosenberg and Green, 1989; Sakkas et al, 1991; Shalev and Munitz, 1986; Shalev et al, 1989). In a case report analysis (CRA), the authors of the report attempt to identify a comprehensive collection of NMS cases. As the study sample, these cases of NMS are analyzed and classified in an attempt to characterize various aspects of NMS. In studies that use this approach to evaluate treatment efficacy, cases are characterized and analyzed by the use of a specific treatment such as bromocriptine, dantrolene, or amantadine compared to supportive care alone (Davis et al, 1991; Rosenberg and Green, 1989; Sakkas et al, 1991; Shalev et al, 1989).

Case report analyses should be evaluated very carefully with constant attention to potential biases that may have been introduced as a result of the research design. One large problem is the lack of diagnostic consistency among reports. A "comprehensive review" of published cases of NMS may vary from 67 cases (Rosenberg and Green, 1989) to 734 cases (Davis et al, 1991; Sakkas et al, 1991). One study used operational diagnostic criteria to identify NMS cases (Shalev et al, 1991). Another study included cases if they were "consistent with NMS" (Rosenberg and Green, 1989). In other reports, no mention was made of how a case of NMS was identified (Davis et al, 1991; Sakkas et al, 1991).

Another difficulty associated with evaluating CRAs is the lack of randomly allocated treatments or specific treatment protocols. Furthermore, the motivation that resulted in the publication of each individual case report must be assessed. A number of limitations of samples created from case reports have been identified (Rosenberg and Green, 1989): 1) more severe cases may be more likely to receive specific treatments over supportive care; 2) cases with a good outcome to specific treatment may be reported more frequently than cases with a poor outcome; 3) more severe cases may be reported more frequently; 4) "classic" cases or, conversely, more atypical cases may be reported more frequently; 5) year of treatment may affect outcome since mortality has declined over the past decade; 6) treatment sites vary from case to case, and so do, probably, approaches to treatment. Because of all of these variables, the study populations in CRAs can hardly be considered "normal."

Despite each of these caveats, most clinicians will choose to use a specific treatment such as bromocriptine, dantrolene, or amantadine because it is unlikely that any of these drugs will cause any significant toxicity compared to the NMS, and they may be at least partially effective. Furthermore, the possibility of an unfavorable outcome and legal liability if treatment is not provided may influence many clinicians to use a specific treatment.

Supportive Care. Discontinuation of the causative agent is the single most important step in treating NMS (Caroff and Mann, 1993). While success has been reported with continued treatment of psychosis with an antipsychotic in some cases (Goldwasser et al, 1989), most other reports suggest this may be associated with a poorer outcome (Davis et al, 1991; Gelenberg et al, 1988; Keck et al, 1991) Other support should be administered as needed. Fluid replacement, fever reduction, and support of cardiac, respiratory, and renal function is commonly necessary. Likewise, complications such as pneumonia, renal failure, and thromboembolism should be monitored for. Hemodialysis may be necessary in the event of renal failure.

Pharmacologic Treatments. There are two common pharmacologic approaches used to treat NMS. Dopaminergic drugs such as bromocriptine or amantadine are used to counteract the presumed dopamine blockade that produces the symptoms of NMS. Dantrolene is a skeletal muscle relaxant that is used to treat malignant hyperthermia, a condition that bears striking clinical resemblance to NMS. Dantrolene presumably acts to decrease rigidity and, possibly, fever.

Rosenberg and Green (1989) compared supportive care, bromocriptine, and dantrolene in a CRA of 67 NMS patients identified between 1977 and 1987. Cases were included in this analysis if they included age sex, diagnosis, signs and symptoms of NMS, mode of treatment, and either response time (time until the patient's symptoms improved) or resolution time (time until all symptoms disappeared). Sixty-five of the cases were attributed to an antipsychotic or metoclopramide. The remaining two cases were related to abrupt dopamine

agonist withdrawal. The mean response time was 6.8 days for supportive care alone, 1.0 day for bromocriptine, and 1.7 days for dantrolene ($p<0.0005$ for both treatments compared to supportive care alone; see table 4). The mean resolution time was 15.8 days for supportive care alone, 9.9 days for bromocriptine, and 9.0 days for dantrolene ($p<0.1$, a nonsignificant trend for each specific treatments compared to supportive care alone; see table 5).

In a study of similar design published by Sakkas et al (1991), a total of 734 cases of NMS were identified in a literature search who were treated with supportive care alone or bromocriptine, dantrolene, or amantadine alone or in combination with other specific treatments. The authors of this study attempted to "identify every published case on NMS" for inclusion in their CRA. The diagnostic criteria used to identify cases of NMS were not reported. The three measures of efficacy used in this study were the reporting clinician's opinion of improvement rate, recurrence of NMS following discontinuation of specific treatment, and mortality. Among these three outcomes measures, recurrence of NMS following discontinuation of a specific treatment is the most useful because these are the only cases that include an objective measure of the specific treatments' effects, i.e. recurrence of fever, rigidity, etc. The clinician's opinion as an outcomes measure is less useful because of the uncontrolled biases in each original case report (see "Treatment Issues" above). The comparison of mortality rate between supportive care alone and a specific treatment is difficult because this study included every known case of NMS. Many of the historical cases were almost certainly treated differently than modern cases since identification and treatment of NMS has improved in the past 10-15 years. In addition, since supportive care has probably improved over the years since NMS was first reported, inclusion of older cases in the analysis would tend to make supportive care alone appear less effective than specific treatments that have only been used in recent years. The results of this study are summarized in Table 6.

In the Shalev et al (1989) analysis of mortality among previously published case reports, mortality was no different between supportive care (7/52, 13.5%) and any specific treatment of bromocriptine, dantrolene, or amantadine, alone or in combination (4/43, 9.3%). These data suggest that specific treatments have no effect on mortality. Unfortunately, the small number of actual fatalities and the limitations of the CRA study design make any firm conclusion impossible.

There is one study that contradicts the widely held notion that specific treatments for NMS are more effective than supportive care alone (Rosebush et al, 1991). In this analysis of 20 consecutive referrals, the decision to use supportive care alone was based on the prescriber's familiarity of the specific treatment literature. There was no randomization, blinding, or treatment protocol. The mean duration of NMS symptoms in the supportive care only group ($n = 12$) was 6.8 days compared to 9.9 days for the eight patients who received bromocriptine and/or dantrolene ($p < 0.05$). There was a trend for more severe medical illness among the patients who received a specific treatment. These results led the authors to suggest that specific treatments may actually worsen outcome. In another interpretation, however, one might surmise that the patients who received bromocriptine and/or dantrolene received them specifically because they were more ill or because they had a more severe case of NMS.

Electroconvulsive Therapy (ECT). Two CRAs studying the efficacy of ECT for NMS have been published (Mann et al, 1990; Davis et al, 1991). ECT has been used to treat NMS because of the clinical similarities between NMS and acute lethal catatonia (ALC) and because of the anecdotal reports of the dramatic effect of ECT for ALC (Caroff and Mann, 1993). In the Mann et al CRA (1990), ECT was considered effective in 20 of 27 cases and partially effective in three cases. Two patients in this series developed serious cardiovascular complications during ECT, cardiac arrest in one and ventricular fibrillation in the other. It may be that NMS patients are a minority who are predisposed to serious cardiovascular complications during ECT, a rare occurrence, typically. Conversely, it is possible that these patients were reported primarily because of the severity of their complications, a bias of case report literature. In the Davis et al CRA (1991), 24 of 29 cases improved with ECT. Three of these patients improved despite continued antipsychotic treatment. Of the five nonresponders, all continued to receive antipsychotics. Of interest, the patients' psychiatric illnesses frequently improved along with their NMS symptoms during ECT.

Treatment Recommendations. Bromocriptine and dantrolene are the two most widely studied specific treatments for NMS (Table 7). Choice of a specific drug should be centered on the patient. Bromocriptine is

an inexpensive oral drug, which, by nature of its dopaminergic pharmacology, directly opposes the effect of antipsychotics. However, this same effect may also worsen a patient's psychosis. Dantrolene, while inexpensive orally, is extremely expensive as an injection. Dantrolene injection should be reserved for patients who cannot receive oral drugs, and they should be switched to oral dantrolene as soon as reasonable. The most serious adverse effect of dantrolene is severe hepatotoxicity that occurs following prolonged exposure high doses. This is rarely a problem in NMS. There is no evidence that there is any difference in efficacy between oral bromocriptine and oral or intramuscular dantrolene (Rosenberg and Green, 1989; Sakkas et al, 1991). Likewise, there is no evidence that combining two or more specific treatments improves response (Sakkas et al, 1991). Combinations are only recommended if a single agent has failed.

Caroff and Mann (1993) suggest ECT as a treatment alternative in cases where differentiation between ALC and NMS is difficult, in cases in which pharmacologic treatment has failed, and in resolved cases of NMS in which antipsychotic rechallenge is inadvisable despite continued psychosis.

RECHALLENGE

Data from reviews of previously published case reports suggest that patients with a history of NMS have a 30-50% risk of recurrence of NMS following antipsychotic rechallenge (Pearlman, 1986; Caroff and Mann, 1988; Susman and Addonizio, 1988; Wells et al, 1988). In one review (Wells et al, 1988), the elapsed time between the resolution of the symptoms of NMS and antipsychotic rechallenge was related to recurrence. The NMS recurrence rate was 63% (7/11 patients) if the antipsychotic was reintroduced within 5 days of the resolution of the initial episode of NMS. The recurrence rate dropped to 30% (10/33 patients) if more than five days elapsed. Of interest, four of seven cases were successfully rechallenged using the same antipsychotic that initially caused the NMS. Likewise, Susman and Addonizio (1988) reported a higher recurrence rate if rechallenge occurred before complete resolution of NMS symptoms. Caroff and Mann found that the NMS recurrence rate dropped from 30% to 15% if a low potency antipsychotic was used to rechallenge. However, this may be due to the use of lower equivalent doses with low potency antipsychotics compared to high potency antipsychotics because of cardiovascular side effects associated with low potency antipsychotics.

In one case series, 13 of 15 patients were successfully rechallenged with an antipsychotic (Rosebush et al, 1989). However, five patients (33%) experienced recurrence on the first rechallenge. Rechallenge was successful in every case in which two weeks elapsed following the episode of NMS and rechallenge. Likewise, successful rechallenge was more likely if lower dose was used at rechallenge. One patient was successfully rechallenged on the same regimen initially associated the episode of NMS. The sample in this study was too small to evaluate the effect of antipsychotic potency on NMS recurrence.

Rechallenge Recommendations.

There are many NMS patients that will continue to require an antipsychotic. The following recommendations may help prevent recurrence of NMS.

1.Reassess the indication for the antipsychotic. 2.Wait two weeks after resolution of NMS before rechallenge. 3.Rechallenge with a different chemical class antipsychotic and/or a different potency. 4.Use the lowest dose possible. Titrate slowly. 5.Consider alternative treatments such as such as benzodiazepines for agitation. Benzodiazepines may be effective alone for agitation, or, if given in combination with an antipsychotic, they will allow for a lower antipsychotic dose. 6.Avoid the long-acting depot antipsychotics haloperidol decanoate and fluphenazine decanoate since patients with a history of NMS are at higher risk for NMS in the future and because and episode of NMS may last up to one month when associated with these dosage forms.

SUMMARY

NMS is rare but serious adverse effect associated with dopamine blocking drugs. The classic features of NMS include extreme rigidity, fever, autonomic instability, and mental status changes. The most important risk

factors associated with NMS are a high antipsychotic dose, rapid dose titration and psychomotor agitation. Early recognition and treatment of NMS will minimize complications. Supportive care combined with immediate discontinuation of the causative agent is the primary treatment of NMS. In addition, specific drug treatments such as bromocriptine or dantrolene are frequently used. If possible, it is important to allow a period of two weeks after an episode of NMS has completely resolved before reinitiating antipsychotic treatment. Use of a different antipsychotic may minimize the risk of recurrence of NMS.

Table 1. Prevalence of the Clinical Features of NMS

Clinical Feature	Prevalence (%)
Fever	24/24 (100%)
Tachycardia	24/24 (100%)
Delirium	24/24 (100%)
Diaphoresis	24/24 (100%)
Rigidity	23/24 (96%)

Muteness

23/24 (96%)

Tremulousness

22/24 (92%)

Movement disorder

14/24 (58%)

Incontinence

13/24 (54%)

Hypertension

10/24 (42%)

Labile blood pressure

8/24 (33%)

Dyspnea

7/24 (29%)

Rash

7/24 (29%)

Diffuse slowing on EEG

7/7 (100%)

From: Rosebush and Stewart 1989

Table 2. Prevalence of Laboratory Abnormalities Associated with NMS

Laboratory Abnormality

Dehydration

22/24 (92%)

Elevated CK

21/23 (91%)

Elevated LD

20/22 (91%)

Elevated AST

19/23 (83%)

Elevated ALT

13/22 (59%)

Elevated ALP

5/24 (21%)

Low Iron Concentration

19/20 (95%)

Leukocytosis

18/24 (75%)

Thrombocytosis

9/16 (56%)

Proteinuria

21/23 (91%)

Myoglobinuria

16/24 (67%)

CSF Protein

7/19 (37%)

From: Rosebush and Stewart 1989

Table 3. Complications of NMS

Medical Complications

Cause of Death

Aspiration pneumonia

respiratory arrest

Renal failure

Pneumonia

Cardiac arrest

Pulmonary embolism

Seizures

Sepsis

Sepsis

Hepatorenal failure

Pulmonary embolism

Disseminated intravascular coagulation

Pulmonary edema

Rhabdomyolysis

Respiratory failure

From: Addonizio et al 1987; Dickey 1991; and Ebadi et al 1990

Table 4. Differential Diagnosis of NMS
Infections
Tumors
Trauma
Seizures
Acute Lethal Catatonia
Malignant Hyperthermia
The Serotonin Syndrome
Anticholinergic Delirium
Severe Parkinsonism
Heat Stroke
Dystonic Reactions

Table 5. Results from Rosenberg and Green (1989)

Treatment

Response Time (days)

Resolution Time (days)

Supportive Care Alone

6.8 (n = 5)

15.8 (n = 8)

Bromocriptine

1.0* (n = 15)

9.9 (n = 22)**

Dantrolene

1.7* (n = 10)

9.0 (n = 9)***

Note: sample sizes vary from group to group based on which details were found in the original case report.
*p < 0.0005 compared to supportive care alone
**p = 0.09 compared to supportive care alone
***p = 0.07 compared to supportive care alone

Table 6. Results from Sakkas et al (1991)

Treatment

Improvement Rate (Clinician's Opinion)

Relapse Rate Following Removal of Specific Treatment

Mortality Rate

Amantadine

63% (n = 19)
29% (n = 7)
6% (n = 17)*

Bromocriptine Alone

94% (n = 54)
18% (n = 17)
8% (n = 51)**

Dantrolene Alone

79% (n= 58)
6% (n = 35)
9% (n = 58)**

Supportive Care Alone

Not applicable
Not applicable
21% (n = 438)
*p = 0.23 compared to supportive care alone
**p < 0.05 compared to supportive care alone

Table 7. Comparison of Bromocriptine and Dantrolene
Drug
Mechanism of Action
Dosage
Acquisition Cost
Adverse Effects

Bromocriptine

Dopamine Agonist

7.5-40 mg/day po in divided doses

$5.00/day

Psychosis, hypotension, nausea

Oral Dantrolene

Muscle Relaxant

4-8 mg/kg/day in divided doses

$5.00/day

Hepatotoxicity

Intravenous Dantrolene

Muscle Relaxant

2-3 mg/kg/day initially; max 10 mg/kg/day

$400.00/day

Hepatoxicity

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