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A Review of Neuroleptic Malignant Syndrome (NMS) and Reported Cases with Olanzapine

Introduction

Neuroleptic malignant syndrome (NMS), the development of severe muscle rigidity and fever, is a serious and potentially fatal complication of drug use. This condition was first documented in France in the 1960's. Since first recognized, the development of NMS has been linked to the use of neuroleptic drugs and other medications. Among antipsychotics, the older typical agents have been implicated as the primary drug-related cause.

In comparison to typical antipsychotics, atypical agents were thought to have less potential for causing NMS. However, with increasing use of atypical antipsychotics, cases of NMS are now being reported. A recent review of clozapine, which was initially thought to be devoid of NMS inducing potential, has documented classic NMS in several patients. Data now indicates an incidence of 0.02-0.5% for emergence of a first episode of NMS among patients using typical antipsychotics, while the incidence in patients on clozapine may be less at 0.01-0.24%. The true incidence of NMS in the newer atypicals is difficult to determine due to the large number of patients who will need to be treated before a real incidence can be elucidated. However, case reports of NMS with the use of risperidone, olanzapine and quetiapine are now appearing in the literature and alert us to the need for vigilance even with agents with lower dopamine blocking potential.

Etiology and Onset of NMS

NMS is thought to occur due to dysregulation of the dopaminergic system within the hypothalamus, nigrostriatal and corticolimbic tracts of the brain. A consequence of this dysregulation is an inability to compensate for increased metabolic activity in the face

of altered central and peripheral heat regulation. The low incidence of initial episodes of NMS (<1%) and the much higher incidence on rechallenge (15-30%) suggests that some patients may be more susceptible to the dopamine blocking effects of neuroleptics and the resulting propensity to develop NMS.

With antipsychotic drugs, the onset of NMS symptoms in susceptible individuals is on average 5-10 days after starting treatment or increasing the dose. Although the range of time to developing NMS has been documented as early as 45 minutes to months into treatment, 90% of NMS cases have occurred within 30 days of initiating or increasing antipsychotic medication.

Diagnosis

Unfortunately, several authors have developed different criteria for the diagnosis of NMS, thus resulting in a variable incidence of reporting. For the purpose of this review, the DSM-IV criteria will be used.

DSM-IV Criteria for NMS

- A. Severe muscle rigidity **and** elevated temperature associated with neuroleptic medication
- B. **Two** or more of the following:
 - Diaphoresis
 - Tachycardia
 - Dysphagia
 - Elevated or labile BP
 - Tremor
 - Leucocytosis
 - Incontinence
 - Mutism
 - Lab evidence of muscle injury (elevated CK)
 - Change in level of consciousness
- C. Symptoms of A&B not due to another substance, neurological or other general medical condition

D. Symptoms A& B are not accounted for by an mental disorder (catatonia)

Common Accompanying Symptoms

Presentation of neuroleptic-induced NMS is heterogeneous, as symptoms range from a “mild” form to severe with life-threatening complications. Common symptoms include psychomotor agitation (which may result in more antipsychotics being given), pallor, sialorrhea and confusion. Laboratory tests often reveal elevations in serum creatinine, blood urea nitrogen, creatine phosphokinase (CK) and liver enzymes. Proteinuria and myoglobinuria may also be present.

Risk Factors for NMS

Various risk factors for developing NMS have been suggested. These include dehydration, organic brain disorders such as mental retardation and various dementias and previous NMS episodes. Drug route and dosing are also important, as rapid dosage titration and the use of parenteral forms of neuroleptics have been implicated as risks. Certain medications are more likely to cause NMS than others. A partial list of medications implicated in causing NMS is presented below:

<u>Neuroleptics</u>	Typical antipsychotics	
	Atypical antipsychotics	
Antidepressants	Amoxapine	Tricyclic antidepressants (rare)
	Monoamine oxidase inhibitors (rare)	Venlafaxine (rare)
Other Dopamine blockers	Metoclopramide	Prochlorperazine
	Droperidol	Reserpine
Others	Lithium (conflicting reports)	
	Tetrabenazine	

NOTE: A rapid decrease or abrupt withdrawal of antiparkinson drugs has been documented as a cause of NMS. Drugs reported include:
 L-dopa, Sinemet
 Dopa agonists: bromocriptine, pergolide, ropinirole
 COMT inhibitors: tolcapone, entacapone

Management of NMS

The mortality rate of NMS is 10 - 20% and the outlook for recovery improves with early intervention and acute hospitalization. If left unnoticed or untreated, symptoms of NMS can progress to acute renal failure and pneumonia with resulting increased morbidity and mortality. Clinicians must be watchful for any signs and symptoms of NMS. As such, monitoring of vital signs and assessment for rigidity are essential, especially early in treatment or during dosage increases.

In cases where NMS is suspected, antipsychotic and anticholinergic drugs need to be discontinued and investigations to identify all possible causes for the symptoms should be initiated. Supportive measures should be instituted immediately as physiologically, patients are often dehydrated and febrile and thus require correction of fluid/electrolyte imbalances and the use of antipyretics. In those who have not responded to supportive treatment in a reasonable period of time, use of dantrolene (skeletal muscle relaxant) and/or bromocriptine (dopamine agonist) can be considered. Unfortunately, these drugs have been reported to prolong the course of NMS in some patients.

Following an NMS episode, a patient requiring antipsychotic treatment may be re-challenged no sooner than two weeks after the signs and symptoms of NMS have resolved. In re-challenging a patient, one might consider an alternative neuroleptic or dopamine blocking agent that is less likely to cause NMS. The increased risk of developing NMS on re-challenge requires vigilance in monitoring for early signs and symptoms as well as starting with a low dose and increasing very slowly.

Review of olanzapine-associated NMS cases

As mentioned previously, the presentation of NMS can vary from a well-defined set of symptoms to an atypical presentation. The latter may be due to unique transmitter properties of the drug. Recently, NMS case reports have appeared in the literature with the use of olanzapine and these will be reviewed below.

Olanzapine Case Reports of NMS

Pt	Diag-Nosis	Age Sex	Olanzapine (mg)	Other concomitant Drugs	Max. CK	Prev.NMS	Other Risk Factors	Outcome
1 +/-	Sz	40 F	5mg x14d 10mg x 5d	Clozapine 400mg/d x 3 yrs	36,000	No	MR	D/C olanzapine & clozapine Rechallenge (4 mo later) olanzapine 2.5mg ↑q7d → 10mg Successful
2 *	Sz	22 M	5mg x 2d 10mg x 2d	No	1832	Yes Haldol/ Nozinan	No	Resolved No rechallenge
3 ⇒	SA	69 M	5 mg x 2d	Li, VPA, Diazepam	4150	Yes Risperidone /Li	Time since last NMS	Resolved No rechallenge
4 *	MR	21 M	Dose ↑ to 12.5 mg in 12 days	Clonazepam Benztropine	6030	Yes Haldol x 2	MR	Resolved No rechallenge
5 ⇒	Sz	60 F	10mg x 1d	--	1239	No	Haldol 6-10mg/d D/C day prior	Died—"due to inadequate treatment"
6 ⇒	BD	67 M	10mg /d x 5 mos	VPA	762	No	Dehydrated Liver mets	Resolved No rechallenge
7 *	SA	70 F	5mg x 2d 10mg x 2d	--	1573	Yes Zuclopenthixol Chlorprothixene	No (6mos after last NMS)	Resolved No rechallenge
8 ⇒	Sz	48 M	5mg x 3d 10mg x3 d	Haldol LA 25 d prior to Olanz.	2899	No	No	Resolved No rechallenge
9 *,#	Sz	37 M	5 mg x1d 2.5 mg x 1d 7.5 mg x3 d	--	704	Yes Thioridazine	NMS 7days prior To starting olanzapine	Resolved Rechallenged 2.5mg →↑5mg/d successful.
10 ⇒	Sz	78 F	10mg/d x 2.5yr	Levo-mepromazine 50mg x2 yr	35020	No	UTI Dehydrated	Resolved Rechallenged 2 wks later,same drugs & dosage à 6 d later NMS
11 ⇒	D	85 M	10mg x 7d	Haldol x3 (24-48hr prior) Nefazodone	49	No	unknown	Resolved. No rechallenge (? serotonin syndrome)
12 ⇒	Sz	30 M	Unknown	Unknown	Unknown	Yes CPZ/Haldol	Unknown	Resolved
13 +/-	BD	63 F	10mg/d x 3 mos	Lithium (refused most Doses)	6182	Yes Haldol Fluphenazine	Dehydrated ↑ FBS	Resolved No rechallenge

⇒Met DSM IV criteria for NMS

Sz - Schizophrenia
SA—Schizoaffective

*Mild to mod rigidity only +/- No documented rigidity # No fever

D—Depression BD--Bipolar
MR –Mental Retardation

Comparison of these 13 case reports is difficult, due to incomplete information and lack of adherence to a standard. It can be seen that ~ 6 reports did not meet the strict criteria of DSM IV for the diagnosis of NMS. Further complicating the picture is the fact that concurrent or recently discontinued medications could have partially contributed to the onset of NMS. However, the case studies do show a few interesting points. Development of NMS early in the course of treatment and with rapid dose increases is similar to that seen with typical antipsychotics. Combination treatment with more than one antipsychotic may also contribute to the risk of NMS. Olanzapine was used in several cases in which NMS had previously occurred with typical antipsychotics and the risk of recurrence was still illustrated. Unfortunately, the cases of successful use of olanzapine in patients with a prior history of NMS are not published, so it is difficult to tell if the risk continues in the 15-30% range. It is of interest to note that 7 of the cases occurred in patients aged 60 years or older. The lack of severe rigidity in 6 of the cases does suggest that an “atypical” NMS may be a presentation seen with olanzapine—or it could be that the early identification of NMS prevented it progressing to a full NMS.

Whether atypical antipsychotics have a different incidence or presentation of NMS requires data from much larger treatment populations. This will probably require years to accumulate. In the interim, the use of olanzapine still warrants monitoring for symptoms of NMS and should be used carefully in patients with a previous history of NMS as these patients may be particularly susceptible to recurrence even with the use of antipsychotics with lower dopaminergic blocking capabilities.

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