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Neuroleptic Malignant Syndrome: A Review from a Clinically Oriented Perspective

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Abstract: Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening side-effect that can occur in response to treatment with antipsychotic drugs. Symptoms commonly include hyperpyrexia, muscle rigidity, autonomic dysfunction and altered mental status. In the current review we provide an overview on past and current developments in understanding the causes and treatment of NMS. Studies on the epidemiological incidence of NMS are evaluated, and we provide new data from the Canada Vigilance Adverse Reaction Online database to elaborate on drug-specific and antipsychotic drug polypharmacy instances of NMS reported between 1965 and 2012. Established risk factors are summarized with an emphasis on pharmacological and environmental causes. Leading theories about the etiopathology of NMS are discussed, including the potential contribution of the impact of dopamine receptor blockade and musculoskeletal fiber toxicity. A clinical perspective is provided whereby the clinical presentation and phenomenology of NMS is detailed, while the diagnosis of NMS and its differential is expounded. Current therapeutic strategies are outlined and the role for both pharmacological and non-pharmacological treatment strategies in alleviating the symptoms of NMS are discussed.

Keywords: Antipsychotic, drug side-effects, neuroleptic malignant syndrome, psychopharmacology.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an infrequent yet life-threatening condition characterized by delirium, muscular rigidity, fever, and autonomic nervous system dysregulation. Initially described by Delay and colleagues in 1960 [1], shortly after the introduction of antipsychotic medications to psychiatry, its diagnosis represents a significant challenge for clinicians. In addition, there are many aspects regarding its epidemiology, etiopathology and nosology that remain controversial. The present work aims to review current literature about NMS from a clinically-oriented perspective.

EPIDEMIOLOGY

Although NMS is a relatively uncommon side effect, the large number of people who are treated with medications that can cause NMS results in many cases of the disorder, in absolute terms. Prevalence estimates range from 0.167 cases per thousand people [2] to 32.6 cases per thousand people [18]. A meta-analysis that analyzed the epidemiological data available in the literature yielded an overall estimate of 0.991 cases per thousand people [3].

Several reports also provide estimates of the incidence of NMS over a given number of years in various healthcare settings. Pope and colleagues [4] retrospectively reported the incidence of NMS at a psychiatric hospital in Belmont, USA between March 1, 1984 and February 28, 1985. Of the 483 patients who had been treated with antipsychotic medications during this year, 7 patients (1.4%) had definite or suspected diagnoses of NMS [5]. Recognizing the limitations and inaccuracies in retrospective analyses, prospective measures have also been performed, with one report estimating 0.9% incidence over an 18-month period [6], and another reporting a much lower incidence of just 0.07% over a 12-month period [7]. Rates of new cases of NMS diagnosed in academic versus state-run hospitals in the United States appear to be comparable, and in a state hospital in Danvers, USA the incidence of NMS was 0.9% over 2 years [8]. In China and Russia, incidences of NMS are typically reported for longer periods of follow up: one Chinese psychiatric institute reported a rate of 0.12% over 6 years [9], while another report from Russia determined an incidence of 0.02% over a 10-year period [10]. Trends in incidence rates were investigated by Keck and colleagues [11] at the same academic institution where Pope and colleagues had performed their retrospective analysis in 1985. Over a 47-month period, the incidence of NMS was 0.15%, which was comparatively lower than the rate reported by Pope and colleagues five years earlier [4]. This led the group to conclude that new cases of NMS appeared to be declining within the hospital setting, possibly due to increased pharamacovigilance and diagnostic awareness of caregivers [11]. In Australia, cases of NMS resulting from clozapine administration were reviewed in a national database known as the Clozaril Patient Monitoring System (CPMS). A rate of 0.08-0.16% of new cases was obtained in

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the eight months between December 1993 and July 1994 [12]. The authors concluded that the rate of NMS resulting from atypical antipsychotic administration in Australia was similar to the rate resulting from administration of typical antipsychotics, though the presentation of the condition differed slightly (e.g., with less muscle rigidity and much less severe creatinine kinase abnormalities).

In Canada, the Canada Vigilance Adverse Reaction Online (CVARO) database [13] allows Health Canada, healthcare providers, and consumers alike to survey and monitor suspected adverse effects of all approved drugs and medical devices. Reports may be published by hospitals, community groups, the market authorization holder, pharmacists, physicians, as well as other health professionals. Although not all cases of adverse drug reactions are reported, such a tool can enable an estimation of the number of new cases of NMS in Canada to be generated. Thus, we performed a review of suspected cases of NMS resulting from typical and atypical antipsychotic administration using the CVARO database. All reports published between January 1 1965 and September 30 2012 were included, and the keywords used in the search included 'neuroleptic malignant syndrome'. These filters generated a total of 442 results; forty reports were not included since they were not cases of NMS, or were duplicates. NMS associated with atypical antipsychotics is shown in Fig. **1**, and typical antipsychotics in Fig. **2**.

NMS was reported to be associated with the atypical antipsychotics clozapine, olanzapine, risperidone, quetiapine, aripiprazole, paliperidone, asenapine, and ziprasidone, and the typical antipsychotics flupentixol, haloperidol, fluphenazine, thioridazine, chlorpromazine, trifluoperazine, loxapine, periciazine, methotrimeprazine, prochlorperazine, and zuclopenthixol. Interestingly, the number of reports associated with atypical antipsychotics, specifically for clozapine, was much greater than for typicals, with a total of 342 cases reported for atypical antipsychotics, and only 62 cases for typical antipsychotics. Trollor *et al*. [14] performed a similar review of the Australian Adverse Drug Reaction Advisory Committee (ADRAC) database and similarly found that a total of 293 cases were reported between April 1994 and September 2010, of which 234 resulted from atypical antipsychotic administration, and 59 from typical antipsychotics.

In our analysis, approximately 39% of NMS cases associated with atypical antipsychotics were in patients who were taking more than one antipsychotic drug; in approximately 42% of these patients, the second and/or third antipsychotic was a typical antipsychotic. Nonetheless, these cases were included in the incidence estimation for atypical-induced NMS for one (or a combination) of the following reasons: i) the atypical antipsychotic was identified by the reporter as the suspected agent, or ii) the atypical antipsychotic was started later and thus was assumed to have precipitated the condition, or iii) the specific co-medicated antipsychotic drugs were not listed (reported as 'other antipsychotic medications'). The frequency of antipsychotic

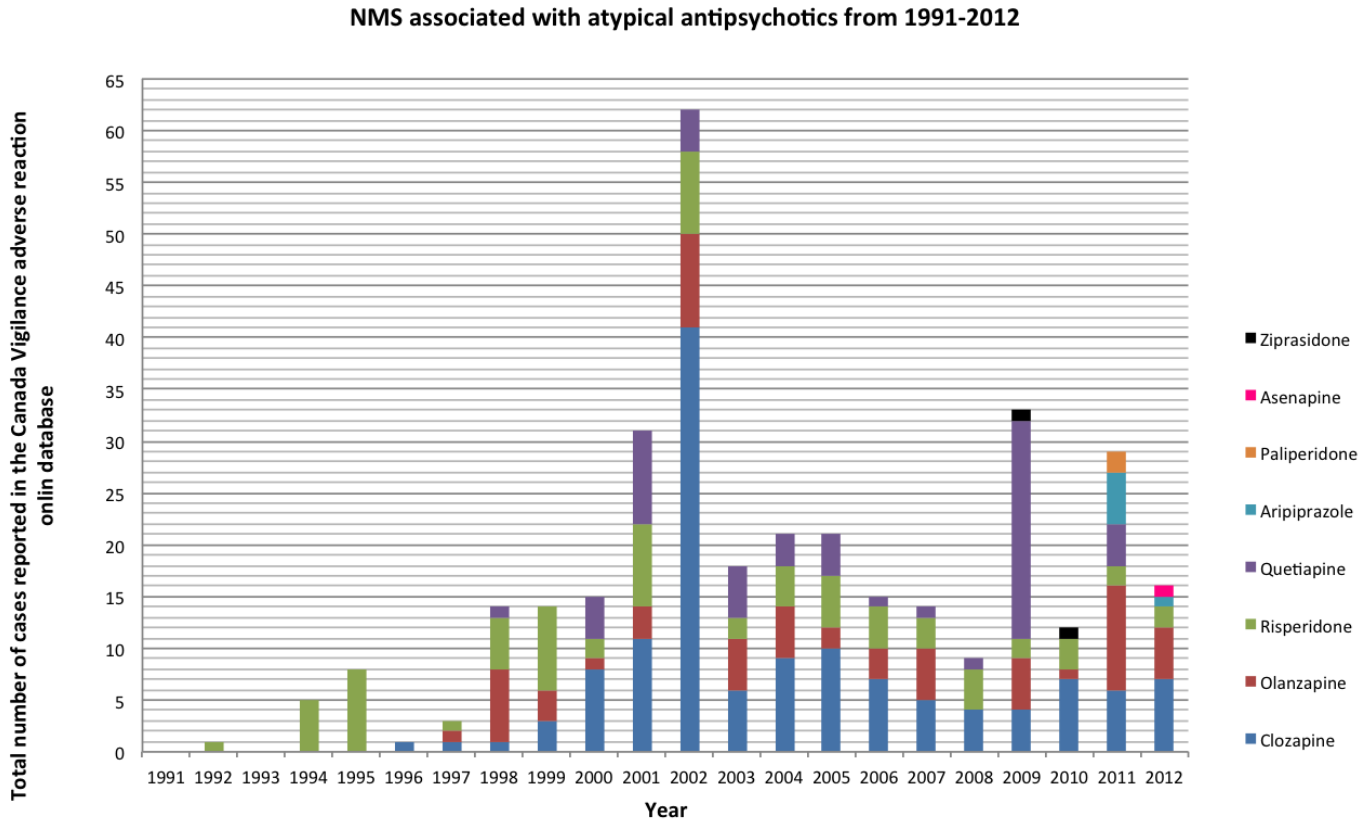

Fig. (1). Number of cases of NMS associated with atypical antipsychotics reported in the Canada Vigilance Adverse Reaction Online Database.

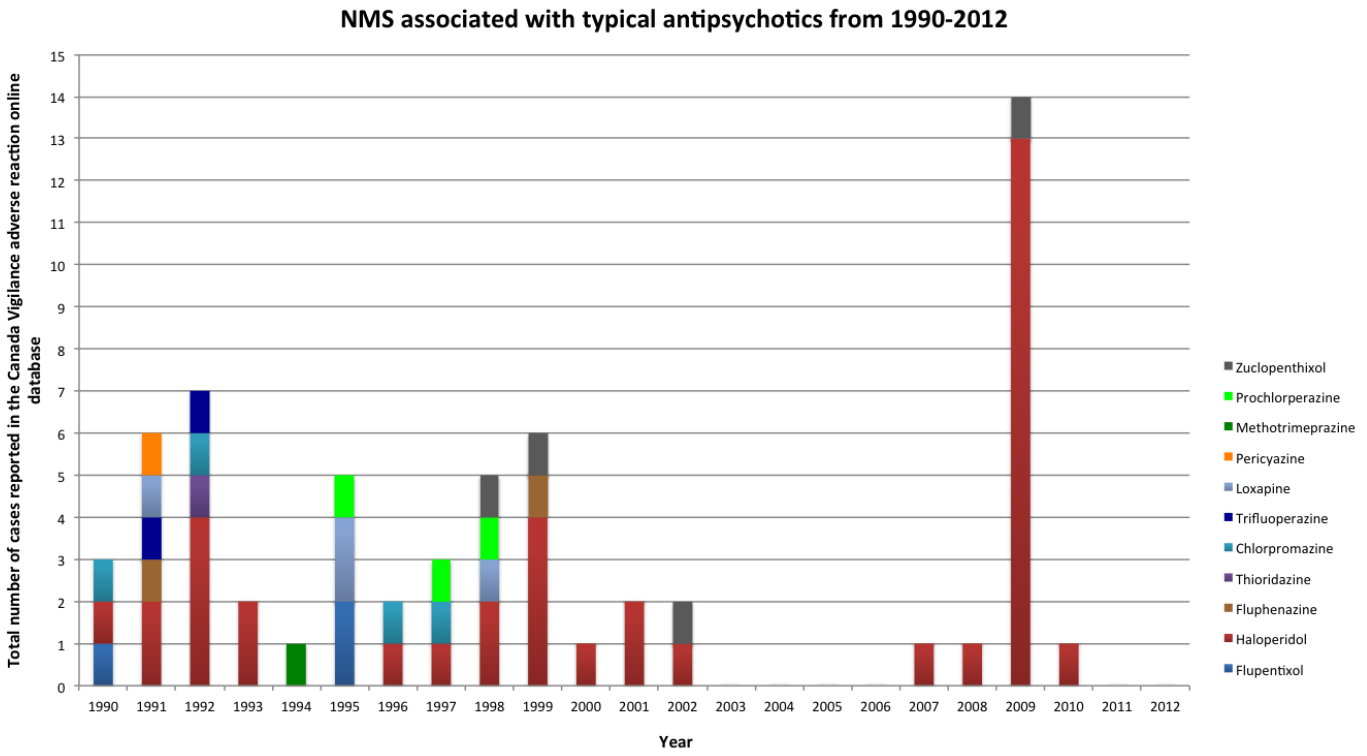

Fig. (2). Number of cases of NMS associated with typical antipsychotics reported in the Canada Vigilance Adverse Reaction Online Database.

polypharmacy in NMS associated with the use of typical antipsychotics was approximately 68%, and almost 72% of these cases were co-medicated with an atypical antipsychotic. Thus there is considerable overlap in these estimations.

Between 1990 and 1999, cases of NMS in our analysis of CVARO associated with typical antipsychotic administration were distributed between multiple different agents, including fluphenazine, flupentixol, loxapine, periciazine, prochlorperazine, methotrimeprazine, chlorpromazine, thioridazine, trifluoperazine, and haloperidol. Since 2000, however, only cases associated with haloperidol have been reported, with the exception of two cases (one in 2002 and another in 2009) that were associated with zuclopenthixol. The peak number of cases occurred in 2009 when thirteen cases were published, all of which were associated with haloperidol.

Conversely, the number of reports for NMS associated with highest number of reports for atypical antipsychotics was in 2002, with forty-one out of sixty-two published reports that year were associated with clozapine. One possible explanation for the significant increase in suspected cases of NMS may be due to the publication of a Canadian Dear Healthcare Professional Letter by Novartis in January of 2002 [15] that warned healthcare providers of the cardiovascular events that were observed to be associated with clozapine, including but not limited to fatigue, flu-like symptoms, fever that is otherwise unexplained, hypotension, arrhythmias, and raised jugular venous pressure. NMS is similarly characterized by fever and autonomic dysregulation. Thus, it may be the case that by being more vigilant for cardiotoxic effects, healthcare providers were also capturing more cases of suspected or definite NMS.

Cases of NMS associated with typical versus atypical antipsychotics also differed in terms of the populations affected. The mean age of patients affected by NMS associated with typical antipsychotics was 45.1 years, and 47.2 for patients affected by NMS associated with atypical antipsychotics. Eighty-eight percent of the atypical cases and 63% of the typical cases affected male patients. Median length of exposure to an antipsychotic prior to the onset of NMS for cases associated with atypicals was 23 days, while the median length of exposure for typical-induced onset was 6 days. Mortality rate was 11% for atypical-induced NMS and 12% for typical-induced.

Initially reported as a condition affecting only people with psychotic disorders treated with antipsychotic drugs, NMS has more recently been reported in a variety of different psychiatric and other medical conditions, consistent with increased use of antipsychotics off label [16, 17], and not only after treatment with antipsychotics but also other psychotropic compounds too. While NMS is reported most commonly in people with schizophrenia, schizoaffective and other forms of psychosis, it has also been observed in other psychiatric conditions, including bipolar disorder, delirium and mental retardation. It can be associated with neurological disorders, such as Parkinson's disease, encephalitis and dementia. Although antipsychotics are the most common type of drugs involved in cases of NMS, other classes of compounds have been reported to cause NMS-like symptoms: these include mood stabilizers, such as lithium

[18, 19] and carbamazepine [20], antidepressants such as paroxetine, sertraline [21], and amitriptyline [22], and antiemetic agents such as metoclopramide [23]. Although these latter cases associated with antidepressants were classified as NMS, alternatively they may have been examples of serotonin syndrome (see 'Differential Diagnoses' below). Finally, the epidemiology of NMS has seen yet an additional challenge with the advent of the newer generation of antipsychotic drugs. Some reports claim that the incidence of NMS has declined with the introduction of atypical antipsychotics [24, 25]. While there is an appealing mechanistic rationale for this claim (i.e. a more balanced dopamine D2 and 5-HT receptor blockade, particularly at the 5-HT2A receptor [26]), the evidence from the current literature is not conclusive in either direction [24]. This is likely due, in part, to publication bias. A historical review of the reporting of NMS in the literature shows that every single antipsychotic compound has a NMS case linked to its administration. These reports are published fairly rapidly after the introduction of the compound in regular clinical use, but then usually decline. Moreover, reports of NMS implicating typical antipsychotics are rare in current literature despite the fact that they are still fairly used worldwide.

RISK FACTORS

Although NMS is often regarded in the literature as an idiosyncratic and unpredictable reaction related to the administration of dopamine antagonists and other compounds, there are a number of risk factors that increase the likelihood of developing NMS. These risk factors can be grouped into four categories (Table **1**), which include pharmacological risk factors (type of drug, pharmacokinetics, polypharmacy); environmental (high ambient temperature, restraint, dehydration); demographic (age, concurrent medical conditions or comorbidity); and genetic liability (history of previous NMS, family history of catatonic disorder, channelopathy).

Table 1. Risk factors, as grouped into distinct categories.

Risk Factors	
Category	**Variable**
Pharmacological Treatment	Initial phases of treatment or, change of dosage High dose of AP Parenteral administration (i.v. or i.m.) Polypharmacy Antipsychotic treatment Other compounds: AD, MS, aP
Environmental factors	Physical restraint Dehydration High temperature
Demographics	Age Multimorbidities
Genetic liability	Previous NMS Family history of Catatonic Syndrome Muscle channelopathy

i.v., intravenous; *i.m.*, intramuscular; *AD*, antidepressants; *MS,* mood stabilizers; *AP*, antipsychotics; *aP,* antiparkinsonian

Pharmacological Variables

Although NMS can occur any time during the course of drug treatment, it occurs more frequently during either the initial months of treatment or after a dosage change. In this regard, higher doses of antipsychotic drugs have been correlated with a greater risk of developing NMS. In addition, parenteral routes of administration, either intramuscular or intravenous, have also been associated with greater risk. Nevertheless, NMS has been reported to occur at all standard doses and all routes of administration. Regarding the type of antipsychotic drug, typical (or "first generation") antipsychotics are associated with a higher risk for development of NMS compared to atypical or "second generation", antipsychotics. The common rationale for this hypothesis is related to the higher dopamine D_2 receptor affinity of typical antipsychotics, which have a lower binding dissociation constant from the receptor. Although this hypothesis is appealing, there is no current epidemiological evidence that supports it (as discussed above). Lastly, there are also anecdotal reports that describe polypharmacy as a risk factor for NMS [27]. In particular, either treatment with more than one antipsychotic compound or concurrent administration of an antipsychotic and lithium or carbamazepine has been implicated in several cases of NMS [20, 22].

Environmental Variables

Environmental factors cited in the literature include physical restraint, high external temperature, and dehydratation due to insufficient fluid intake [28]. Together, these variables have the common ability to impair or interfere with heat dissipation, and are therefore consistent with the etiopathogenic pathways presented in Fig. **3**.

Non Modifiable Variables

Major demographic variables for increased risk of NMS include age and medical comorbidity (concurrent medical conditions). Variables that are related to the individual's overall health and resilience, which include advanced age, psychiatric and medical commorbidity can have an important influence on the risk of developing NMS [29]. It is also well established that either prior history of a NMS episode or a personal and/or family history of catatonia is a risk factor for developing NMS [30], which likely reflects in large part a genetic predisposition to NMS of unknown as yet genetic origin [31].

ETIOPATHOGENIC MECHANISMS

With regards to etiopathogenic mechanisms underlying NMS, there are two main postulated hypotheses, which are not necessarily mutually exclusive. Firstly, NMS is traditionally considered to be the result of dopaminergic D2 receptor antagonism in the central nervous system. This receptor antagonism triggers a series of homeostatic responses that raise temperature, create muscular rigidity and impair mental status as a result of autonomic nervous system dysregulation. Secondly, it has recently been postulated that NMS is the result of a toxic effect of the pharmacological

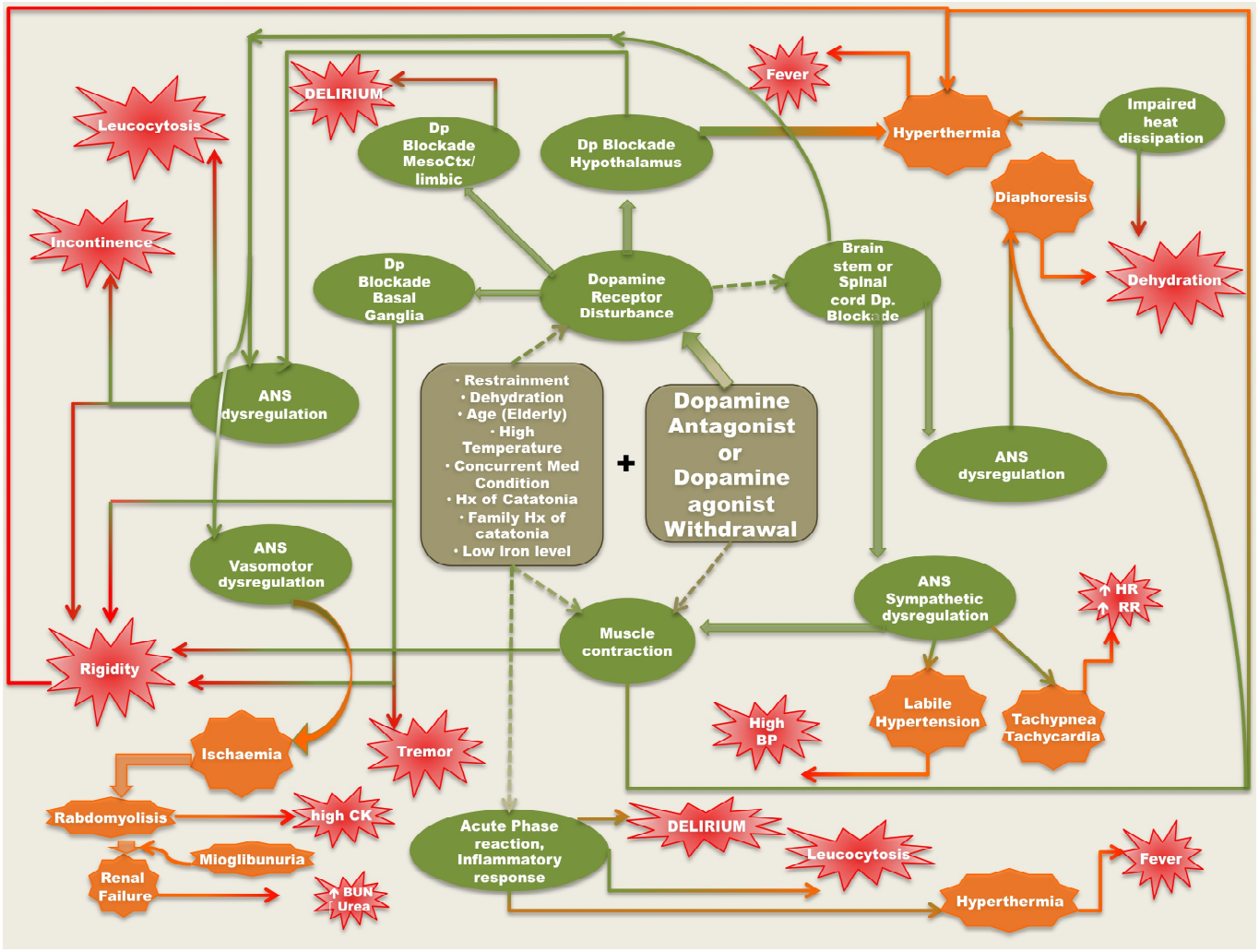

Fig. (3). Etiopathogenesis of Neuroleptic Malignant Syndrome and its clinical manifestations. Khaki-coloured boxes describe risk factors associated with NMS, green ovals describe etiopathogenic mechanisms that lead to pathophysiological changes in orange polygons that result in clinical symptomatology in red stars. Abbreviations: ANS, autonomic nervous system; BP, blood pressure; Dp, dopamine; HR, heart rate; RR, respiration rate.

compounds on musculoskeletal fibers, leading secondarily to the full syndrome. In addition to these two leading theories on the etiopathogenesis of NMS, there has been recent interest on the role that acute phase reactants and inflammatory response plays in NMS. Currently, it is unclear whether it is a causal factor or a downstream consequence, but low iron levels have been correlated with NMS and the degree of an inflammatory response [32].

Dopaminergic Receptor Blockade Hypothesis

Dopamine neurotransmission plays a central role in regulating body temperature, mediated in the thermoregulatory centre of the hypothalamus, particularly the anterior pre-optic nucleus [33]. Therefore, antagonism of typical antipsychotics on dopamine receptor-mediated signaling in neurons in the thermoregulatory centre can potentially lead to a dysregulation of thermoregulation [34]. Disrupted dopamine receptor-mediated signaling as a mechanism leading to NMS is consistent with cases described in Parkinson's disease patients who have had their dopamine agonist treatment abruptly withdrawn and subsequently develop NMS [35]. Furthermore, NMS cases reported in patients treated with catecholamine depleting drugs provide further evidence for disrupted dopaminergic signaling as a mechanism underlying NMS [36]. Thus, whether there is a blockade of the postsynaptic receptor, a sudden decrease in postsynaptic receptor stimulation, or a lack of neuro-transmitter, a common factor is the lack of dopaminergic signaling in the thermoregulatory system, which leads to one of the paramount features of NMS: hyperthermia. In addition, altered dopamine neurotransmission in the basal ganglia, which represent a group of subcortical nuclei that regulate motor coordination and muscle tone, may account for other symptoms of NMS. Evidence of a role for disrupted dopamine signaling in motoric pathology comes from Parkinson's disease (PD), where the neurodegeneration of dopamine neurons located in the substantia nigra of the midbrain causes a loss of dopaminergic transmission that

increases muscular tone, causes rigidity, and tremor. Thus, PD individuals are treated with dopamine receptor agonists to restore dopamine signaling and alleviate clinical manifestations. Conversely, individuals treated with typical antipsychotics are at risk of developing Parkinson-like symptoms: tremor, rigidity, and increased muscular tone [37]. Therefore, it is hypothesized that dopamine receptor blockade in the basal ganglia is the pharmacological mechanism underlying rigidity, tremor, and hypertonia observed in NMS. Furthermore, some posit that increased muscular tone, as a secondary symptom of NMS, further increases body temperature contributing to the central hyperthermia generated by disrupted dopamine signaling in the hypothalamus [38].

Musculoskeletal Fiber Toxicity Hypothesis

The view of NMS as a condition caused by toxicity of the musculoskeletal fibers is supported by evidence from clinical similarities between NMS and malignant hyperthermia, the therapeutic response to dantrolene in NMS, and typical antipsychotic drug effects on calcium regulation in skeletal muscular fibers. Malignant hyperthermia is a very rare condition characterized by high body temperature developed after the administration of halogenate anaesthetics. In subjects who develop this condition, it is very characteristic to find an *in vitro* anomalous contractile response by musculoskeletal fibers in response to exposition to halothane or caffeine. Similar results are noted when biopsied muscular fibers from patients who have previously experienced NMS are challenged to halothane or caffeine [39, 40].

Dantrolene is a hydantoin derivative that depresses excitation-contraction coupling in muscle cells by binding to the ryanodine receptor, thus decreasing the intracellular calcium concentration [41]. Initially used for its muscle relaxant properties in neurological conditions that caused spasticity, it was found to be the only compound effective for treating malignant hyperthermia, and afterwards was found to be effective in the treatment of NMS. Thus, it has been posited that the massive calcium entrance into the musculoskeletal fiber is the leading factor to a sustained contraction, and thus rigidity and increased temperature. In support, several *in vitro* studies show that typical antipsychotics, such as chlorpromazine and flufenazine, are capable of mobilizing calcium transport into sarcoploasmic reticulum [42, 43].

CLINICAL PRESENTATION AND DIAGNOSIS

The stereotypical clinical presentation of NMS includes high fever, muscle rigidity, delirium, and dysautonomia (Fig. **3**). Fever is usually very high, without major fluctuations or daily peaks, and not accompanied by chills; therapeutic response to conventional antipyretic drugs is poor. Muscular rigidity is generalized, symmetric, and could present from a mild increase in tone to extreme generalized body rigidity, such as opisthotonos. Focal increases of muscular tone can also be present in the form of blefarospasm, oculogyric crisis, or trismus. Nystagmus, dysphagia, dysarthria, or aphonia can also be present as a result of increased muscular tone. As far as mental status is concerned, delirium is a hallmark symptom of this condition with typical fluctuations in levels of consciousness, disorientation, and psychomotor agitation [44]. Dysautonomia presents as cardiac rate instability, labile hypertension, and extreme diaphoresis. In regard to this latter symptom, profuse sweat may present with a "greasy" quality which makes it quite distinctive from other conditions where diaphoresis is present. Pronounced sialorrhea and urinary incontinence may also be present.

Laboratory results are characterized by high levels of creatine kinase (CK), usually over 600UI/L, and leukocytosis. Increased inflammatory markers, such as C-reactive protein (CRP), fibrinogen, or elevation of erythrocyte sedimentation rate (ESR), are nonspecific findings but almost always present [45]. Other tests may be ordered to aid the differential diagnosis, and are usually negative such as P-LCR analysis, CT scan as well as Zn^{2+} and Mg^{2+} levels. Both electromyography and muscular biopsy usually yield nonspecific results, with minimal capacity to either confirm the presence of NMS or rule out other conditions; therefore, its routine performance is not indicated in workup for NMS unless particular conditions are present.

Assessment of NMS, Laboratory Workup

The most important steps in making an accurate diagnosis of NMS are to obtain a good clinical history, as well as conduct a detailed physical exploration by organs and systems. In particular, it is very important to gather a detailed and comprehensive drug history, collecting information about all the medications, the duration, the dose, route of administration, and sequence of drug administration. In addition to the clinical history, a comprehensive initial laboratory workup is also needed. This laboratory workup must provide information needed to rule out serious conditions affecting the central nervous system (CNS), such as infections or inflammatory processes, although some authors consider lumbar puncture and/or CNS neuroimaging "second line" tests (see Table **2**). Also, the laboratory workup should assess the severity of the condition, including its effects on other systems and organs (i.e. kidney and liver function tests, pH and hydro-electrolytic balance). Thirdly, the laboratory workup should help to establish the diagnosis as well as to monitor how the condition evolves (eg. complete blood count [CBC] and creatine phosphokinase **[**CPK]). A basic workup is summarized in Table **2**.

It is worthwhile considering several issues related to the workup. Firstly, it should be noted that CPK increase is usually above 1,000 UI/L (it can actually get as high as 100,000 UI/L) when NMS develops. This point is important, particularly as other conditions that increase CPK, such as physical restrain or intramuscular administration of drugs, can also increase CPK. However, those conditions usually cause CPK increases that are below 600 UI/L. Noteworthy, CPK monitoring serves not only for diagnostic purposes, but also for monitoring the condition, since levels of CPK must decrease over time as the condition improves. Finally, it should be noted that routine muscular biopsy is not indicated for diagnosing NMS, and should only be performed when a strong suspicion about a different condition is causing the muscular problem.

Table 2. Workup.

Basic tests or first line
CBC and differential
Hydroeletrolytic equilibrium (Zn^{+}, Ca^{2+}, Mg^{2+} included)
Liver function tests
Creatinine, BUN, urea
Serial CPK, troponin
Urinanalysis
CSF analysis[a]
CNS imaging (CT or MRI)[a]

CBC, complete blood count; *BUN*, blood urea nitrogen; *CPK*, creatine phosphokinase; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *MRI*, magnetic resonance imaging

[a]Some authors consider these as second line tests, nonetheless they are highly useful for differential diagnosis

Complications

Provided proper management is being implemented, NMS usually resolves over the course of 3 to 14 days unless complications develop. NMS is a condition associated with significant morbidity, and, remarkably, a 10% mortality rate. This morbidity and mortality is caused by serious complications that occur as a result of NMS. In this regard, the most frequent serious complications are pulmonary infections, caused by broncho-aspiration, as well as acute kidney failure caused by myoglobinuria [46]. Disseminated intravascular coagulation and multiorgan failure have also been described [47, 48]. Finally, as a result of the autonomic nervous system involvement, reversible dilated myocardiopathy (also known as Takotsubo myocardiopathy) may also occur [49].

Diagnostic Criteria

As there is no pathognomonic sign or "gold standard" diagnostic test, NMS is diagnosed according to diagnostic criteria. Several attempts have been made since the mid-1980s to standardize the diagnostic criteria for NMS. These include criteria put forth by Levenson and colleagues [50], Pope and colleagues [4], Addonizio and colleagues [51], Adityanjee & Aderbigbe [52], and most recently, the DSM-5 [4]. In Table **3** the differences and similarities are presented in detail. These tools differ in the flexibility they afford in diagnosing NMS: for instance, Levenson's criteria [50] do not include antipsychotic administration as a criterion, while Lazarus' criteria [53] do, and Pope and colleagues [4] justify hyperthermia, what many groups consider to be a distinct symptom of NMS, to be nonessential when using retrospective methods of diagnosis. All sets of criteria indicate that it is necessary to rule out other conditions that present with a similar cluster of symptoms, and most groups consider muscle rigidity and hyperthermia as cardinal symptoms for the differential diagnosis.

Presentations of NMS that do not meet DSM criteria, and specifically that completely lack or have milder forms of hyperthermia and/or muscle rigidity, are often classified as 'atypical NMS'. Atypical cases have been observed to occur more frequently with the use of atypical antipsychotic drugs, such as clozapine [12], aripiprazole [54], or paliperidone [55]. The concept of atypical NMS as an independent condition has traditionally been challenged, since there is considerable overlap between the diagnostic criteria of NMS and several of the potential adverse effects of antipsychotic drugs [56] which may also include cardiovascular and metabolic complications [57, 58, 59]. Picard and colleagues [56], however, argue that evidence from a number of case reports published between 1980-2000 support the diagnostic validity of atypical NMS, and that in most cases, the difficulty lies in distinguishing between prodromal or impending typical NMS, and true atypical NMS.

Diferential Diagnosis

As mentioned above, the differential must include conditions in which muscle rigidity and/or hyperthermia are prominent. Thus, CNS infections, lithium intoxication, heat shock, lethal catatonia, central anticholinergic syndrome, and malignant hyperthermia are some of the conditions to be ruled out in the differential diagnosis. A comparison table is presented to detail differences and contrast these conditions (Table **4**). Serotonin syndrome (SS) deserves particular attention with regards to the differential diagnosis. Serotonin syndrome is a condition characterized by the presence of changes in mental status, agitation, clonus, hyperreflexia, and hyperthermia as a result of toxic and excessive serotoninergic stimulation [60]. As in NMS, it is a clinical diagnosis with no diagnostic test available. Given the degree of overlapping clinical presentation, is not surprising then that SS can be mistaken as NMS [61]. This may account for some reports in the literature that describe NMS as result of antidepressant treatment. Furthermore, it has been suggested that the concurrent administration of an antidepressant with an antipsychotic drug may increase the risk of NMS due to serotoninergic transmission interfering with dopaminergic transmission [62]. This is not a trivial point as the most effective treatment for SS is cyproheptadine [63- 65], which is a serotonin receptor antagonist, and there is no role for dantrolene, biperidene, or bromocriptine in the therapeutic management of SS, and vice versa. In this regard, an individual who presents with fever and muscle rigidity, and who has the antecedent of exposure to both antipsychotic and antidepressant drug treatment, poses a serious diagnostic challenge and a therapeutic dilemma [66]. No particular set of criteria to address this particular differential diagnosis has been developed yet.

Nosological Entity of NMS

A controversial issue is whether NMS is a condition that should be considered as an independent entity, or is rather a malignant form of catatonia (i.e. represents the extreme severity of catatonic syndrome). The former argument is supported by those authors who see the dopaminergic receptor blockade as the specific etiopathogenic mechanism that causes the condition, and the response to dopaminergic agonists as further confirmatory evidence for that. On the other hand, Taylor and Fink are amongst the many scholars who argue that NMS is a form of malignant catatonia.

Table 3. Comparison of diagnostic criteria.

Levenson Criteria (1985)	Pope Criteria (1986)	Addonizio Criteria (1987)	Lazarus Criteria (1989)	Adityanjee & Aderibigbe Criteria (1999)	DSM-5 Criteria (2013)
All three major, or two major and four minor criteria suggest a high probability of NMS. **Major Criteria:** 1. Hyperthermia 2. Rigidity 3. Elevated CPK (usually > 1000 UI/L) **Minor Criteria:** 1. Altered consciousness level 2. Tachycardia 3. Labile arterial pressure 4. Tachypnea 5. Diaphoresis 6. Leukocytosis	Allows for prospective and retrospective diagnoses. **Prospective diagnoses** (all three required): 1. Hyperthermia (oral temperature >37.5°C) 2. EPS with at least two of the following: lead-pipe muscular rigidity, cogwheeling, sialorrhea, oculogyric crisis, retrocollis, opisthotonos, trismus, dysphagia, choreiform movements, dyskinetic movements, festinating gait, flexor-extensor posturing 3. Autonomic dysfunction with two or more of the following: hypertension (>20mmHg rise in diastolic above baseline), tachycardia (>30 beats/min above baseline), tachypnea (>25 respirations/min), prominent diaphoresis, incontinence **Retrospective diagnoses** (if one of the three criteria above are not documented, a probable diagnosis is still permitted if both of the following criteria are met): 1. Clouded consciousness (e.g., delirium, mutism, stupor, coma) 2. Leukocytosis (>15,000 WBC/mm^3) CPK >300 U/mL	1. Hyperthermia 2. Rigidity 3. Dystonia 4. Blood pressure elevation (>140mmHg systolic, >90mmHg diastolic, or both) 5. Tachycardia 6. Diaphoresis 7. Elevated CPK 8. Leukocytosis	Requires all three major criteria, plus three minor criteria. **Major Criteria:** 1. Neuroleptic administration in past 7 days 2. Hyperthermia 3. Rigidity **Minor Criteria:** 1. Altered consciousness 2. Tachycardia 3. Labile arterial pressure 4. Tachypnea 5. Elevated CPK or myoglobinuria 6. Leukocytosis	Classifies diagnoses according to Type I, II, III, and IV subclasses of NMS. Also indicates use of rating scales to measure symptom severity for research purposes. **Type I (Classical NMS):** 1. Must be induced by oral or parental ingestion of typical or atypical neuroleptic, dopamine depleter/ antagonist, or a psychoactive agent in past 2 weeks, or by intramuscular administration of a neuroleptic in past 8 weeks; may also be induced by withdrawal of antiparkinsonian or anticholinergic agent in the past 1 week 2. Altered consciousness (rated on the Glasgow Coma Scale) 3. EPS (rated on the Simpson-Angus Rating Scale) 4. Hyperthermia (oral temperature >38.5°C for at least 48 hours) 5. Autonomic dysfunction, with at least two of the following: tachycardia (>100 beats/min), tachypnea (>25 respirations/min), blood pressure fluctuations (at least 30mmHg change in systolic, or 15mmHg change in diastolic) 6. Diaphoresis 7. Incontinence 8. Any two of the following: elevation in CPK, leukocytosis, low serum iron levels, elevation of liver enzymes, myoglobinuria **Type II (Atypical NMS):** 1. Must be induced by the same agents as Type I NMS (above) 2. Altered consciousness 3. Hyperthermia 4. Autonomic dysfunction 5. Any one of the following: elevation in CPK, leukocytosis, low serum iron levels, elevation of liver enzymes, myoglobinuria Note that EPS is not necessary for Type II NMS. **Type III (Impending/threatened/ incipient/aborted NMS):** Induced by exposure to either typical or atypical neuroleptic, but condition does not meet criteria for either Type I or II; otherwise strongly suspected to be NMS. **Type IV (miscellaneous conditions as NMS):** Includes miscellaneous conditions resulting from withdrawal of antiparkinsonian agents, or exposure to psychostimulants, or dopamine depleters/antagonists	1. Hyperthermia (oral temperature >38.0°C on at least 2 occasions) 2. Rigidity 3. CPK >4-times the upper limit 4. Changes in mental status (delirium, altered consciousness) 5. Autonomic activation, including: tachycardia (>25% above baseline), diaphoresis, blood pressure elevation (systolic or diastolic ≥25% above baseline), or fluctuation (≥20mmHg diastolic change or ≥25mmHg systolic change), urinary incontinence, pallor, tachypnea (>50% above baseline)

DSM, Diagnostic and Statistical Manual; *CPK*, creatinine phosphokinase; *EPS*, extrapyramidal symptoms; *WBC*, white blood cells

Table 4. Differential diagnoses.

NMS Differential Diagnosis	
Diagnosis	**Key differential characteristics**
Central anticholinergic syndrome	No rigidity, CPK levels normal
Lithium toxic encephalopathy	No fever, CPK levels are normal
Malignant hyperthermia	There is history of anesthesia with fluoronade anesthesics
Heat shock related to neuroleptics	No diaphoresis, no rigidity
Heat shock	No diaphoresis, no rigidity; History of heat and sun exposition
CNS Infection	Abnormal CSF, usually there is neurological focality
Lethal Catatonia	Semiology can be very similar but there is no history of neuroleptic administration
Serotonin Syndrome	CPK levels are normal; no leukocytosis; no rigidity, but clonus and hyperreflexia are present

CPK, creatinine phosphokinase; *CNS*, central nervous system; *CSF*, cerebrospinal fluid.

This argument is well supported by the fact that NMS presents with the clinical features of a catatonic syndrome with the addition of severe autonomic nervous system dysregulation, responds very well to the same treatments as catatonic syndrome (e.g. ECT), and that NMS-like presentations are well documented before the development of antipsychotics [67].

THERAPEUTIC MANAGEMENT

Non Pharmacological Measures

Once a presumptive diagnotic impression is suggested by the clinical history and semiological findings, the single most critical strategy in the therapeutic management of NMS is to discontinue the suspected pharmacological compound. There is little rationale for delaying discontinuation, even with regards to obtaining laboratory results for CPK or other indices: it is not necessary to delay discontinuation in order to seek confirmatory evidence as part of a more suggestive clinical picture. One should immediately discontinue the potentially harmful compound upon suspicion of NMS.

Other non-pharmacological maneuvers to consider are those related to the risk factors discussed above, which should target the environmental conditions that might predispose or worsen the condition. Specifically, a comfortable ambient temperature not higher than 21-23º C will allow better heat dissipation. In this regard, physical measures to control temperature such as application of wet cold cataplasms have not been systematically evaluated, but are a low-cost and very low-risk measure to apply. Another important general consideration is to assess the general nutritional and hydration state so that appropriate corrective procedures can be applied. Finally, it is very important to keep in mind that fluctuation in the level of consciousness is accompanied with an impaired deglutory reflex, and therefore, increased risk for aspiration pneumonia, which is associated with a significant mortality rate. In this regard, it has been demonstrated that a low-cost and low-risk measure that significantly reduces the risk of aspiration pneumonia is to adopt a semi-recumbent positioning (defined as elevation of the head of the bed to 45 degrees) [68]. Physical restraint may be necessary but should be used discreetly since it has been associated with increased risk for NMS as mentioned above [28].

Suportive Treatment

After the suspected drug has been discontinued and the aforementioned non-pharmacological strategies have been deployed, general supportive management and non-specific pharmacological treatment should be put in place. Nasal gases administering oxygen at a fiO2 in the range of 24-28% are necessary. Any hydroelectrolytic imbalance or pH alteration should be corrected. In this regard, maintaining a slightly alkalotic pH benefits the excretion of myoglobinuric detritus, which can be supplemented by administering loop diuretic compounds. In order to control labile hypertension, calcium blockade antihypertensives are the compound of choice since, based on the musculoskeletal toxicity hypothesis, they may exert a beneficial effect at the musculoskeletal fiber as well. Administration of low-weight heparins to prevent the occurrence of pulmonary thromboembolism completes a comprehensive treatment of this condition.

Specific Pharmacological Treatment

This is a controversial topic as randomized controlled trails are lacking and recommendations are based on consensus and expert opinion. In this regard, one group of scholars would be more inclined to treat this condition with just supportive treatment and who would not add specific drugs as a first line treatment. On the other hand, there is another group who strongly emphasize the need of starting specific pharmacologic treatment as soon as possible [69, 70].

The evidence available supporting the use of different treatment regimes is based on case series and expert opinion and consensus. The three main drug options available are:

dantrolene, bromocriptine, and biperiden [70, 71]. Dantrolene is a hydantoin derivate that causes muscle relaxation by inhibiting calcium release by the endoplasmic reticulum, and consequently decreases intracellular calcium availability. Thus, its use is consistent with the musculoskeletal toxicity, and the therapeutic experience in treating malignant hyperthermia. Dantrolene is administered intravenously at a dose of 1-10 mg/kg body weight or per os at 50-600mg qd. Bromocriptine as well as other dopamine receptor agonists such as l-dopa, amantadine, apomorphine and lisuride have been used in clinical trials, based on the dopamine blockade hypothesis of NMS as an etiopathogenic pathway. Most of the research has been performed with bromocriptine, versus rather sporadic cases described for the other compounds. The recommended dose for bromocriptine is starting with 2.5mg TID and increased 2.5-7.5 mg per day up to a maximum of 45mg qd. Monitoring for adverse side effects such as nausea, vomiting, or mental status worsening should be in place. Finally, anticholinergic drugs have been tested based on their capacity to increase dopaminergic neurotransmission, with little impact on muscle rigidity or hyperthermia. A series of case studies showed that the fastest resolution of NMS was achieved first by bromocriptine followed by dantrolene. Both drugs resulted in a remission of NMS far faster than supportive treatment in isolation; furthermore, there are some authors who support the concurrent use of both compounds [71].

Other therapeutic options that have been successfully tested are lorazepam and electroconvulsive therapy (ECT), which support the notion of NMS as a particular case within the catatonic syndrome spectrum of disorders [72].

NMS and Recurrence

Most individuals who suffer a NMS episode are in need of chronic antipsychotic drug treatment. Therefore, the occurrence of a NMS episode poses a significant dilema, since the ocurrence of one episode of NMS is a risk factor for developing subsequent episodes [73]. In this regard, prescription of low-potency dopaminergic receptor antagonists is advised as well as slower titration patterns, or avoiding parenteral administration of antipsychotic drugs [74]. Given the wide array of pharmacological options, rechallenge with the same compound should be avoided, and even the option of chronic ECT as an alternative for treatment should be considered.

FINAL REMARKS

Although NMS is a relatively infrequent condition, it requires timely and accurate diagnosis and treatment because of its life-threatening implications. Better recognition and monitoring of its symptoms by clinicians is needed, especially early on in the course of antipsychotic treatment and when switching from one antipsychotic medication to another, and alternative forms of pharmacological and non-pharmacological treatment for both the underlying psychosis disorder and NMS should be considered when patients present with NMS. Finally, in order to develop a better understanding of this serious condition and to improve care and service to patients and clients, clinicians should be encouraged to update public national databases so that all mental health practitioners may benefit from these experiences.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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