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Proposed research diagnostic criteria for neuroleptic malignant syndrome

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Abstract

Many sets of diagnostic criteria have been proposed for neuroleptic malignant syndrome (NMS) but there is a lack of uniformity. No universally agreed criteria exist currently for research purposes, thus making comparisons across studies very difficult. Most of them have flaws and detect too many false-positives based on an over-inclusive definition. The estimates of incidence rates of NMS vary because of differences in the sensitivity threshold of the diagnostic criteria used. A new set of diagnostic criteria is proposed for research purposes. It is hoped that with this set of stringent research diagnostic criteria, future epidemiological, aetiological and treatment research studies on NMS will be more meaningful and comparable across studies. For routine clinical purposes, the clinicians should continue to use their clinical acumen, sound clinical judgement and discretion. To avoid premature aetiological closure and broaden treatment options, we also propose renaming this syndrome descriptively as *drug-induced hyperthermic catatonia* (DIHC).

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Introduction

Different and confusing sets of diagnostic criteria for neuroleptic malignant syndrome (NMS) have been published. There is a lack of agreement on what constitutes NMS. The lack of universally accepted diagnostic criteria is the most serious drawback to understanding of this syndrome (Buckley and Hutchinson, 1995). It is difficult to communicate and compare research findings across studies owing to this lack of agreement on diagnostic criteria. There is no serious and systematic effort to address the ambiguity surrounding the nosologic aspects of NMS. Conceptually, there is a controversy whether NMS represents a drug-induced hyperthermia or a drug-induced catatonia or a combination of both (Blumer, 1997; Caroff et al., 1998; Fink 1995, 1996a; Peele et al., 1998). Detection and diagnosis of NMS are especially difficult in the elderly (Adityanjee et al., 1992; Nierenberg et al., 1991). Natural history of this iatrogenic condition remains controversial (Adityanjee et al., 1989; Velamoor et al., 1994; White and Robins, 1991; Woodbury and Woodbury, 1992). With the exception of psychomotor agitation, there is a limited data on potential clinical risk factors (Berardi et al., 1998). This paper reviews the controversies about the nosology of NMS and suggests research diagnostic criteria that take in to consideration the use of atypical antipsychotics in clinical practice.

NMS was first described by Delay and Deniker (1968) as a syndrome of *pallor* and *hyperthermia*. They described three main groups of symptoms: (1) Hyperpyrexia with temperature between 38 and 40 °C within 24–48 h was considered as the predominant symptom. (2) A group of symptoms including akinesia, stupor or hypertonicity and varying dyskinesias. (3) A group of symptoms referring to the *lungs*, e.g. congestion or infarcts accompanied by dyspnoea and signs of asphyxia. Following this seminal paper others proposed the use of four features, namely hyperpyrexia, rigidity, autonomic dysfunction and altered sensorium (Abbot and Loizou, 1986; Caroff, 1980; Itoh et al., 1979; Shalev and Munitz, 1986; Singh, 1981). The relative weight of each component, in the face of an apparent spectrum of clinical severity remains unclear (Buckley and Hutchinson, 1995). Since laboratories show secondary or non-specific changes and are useful only to exclude other medical conditions, the diagnosis should be made on clinical grounds alone (Abbot and Loizou, 1986;

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Adityanjee et al., 1988; Singh, 1981). Very few authors have touched upon the issue of comparison of diagnostic criteria (Dickey, 1991; Gurrera et al., 1992; Hasan and Buckley, 1998; Modestein et al., 1992).

Review of existing NMS diagnostic criteria

A landmark in the NMS literature was made when Levenson (1985) proposed a set of clinical criteria for NMS. Prior to his publication, the diagnosis of NMS was based on subjective impressions of clinicians. This led to several case reports of questionable diagnostic validity. NMS is only a descriptive syndrome, and the absence of a concrete diagnostic criteria has led to its mis-diagnosis and confounding by other syndromes with a superficially similar clinical profile (Adityanjee, 1987a). Subsequently, other authors have suggested their own diagnostic criteria for NMS (Addonizio et al., 1986; Adityanjee et al., 1988; Caroff et al., 1991; Caroff and Mann, 1993; Friedman et al., 1988; Keck et al., 1989; Lazarus et al., 1989; Nierenberg et al., 1991; Pope et al., 1986a). There has been a tendency to reify the diagnostic criteria though most of them are arbitrary in nature. Some of the proposed diagnostic criteria are based neither on putative aetiology of the subcomponents of the syndrome, nor on a perceived phenomenological similarity amongst the symptoms. Most of the suggested sets of diagnostic criteria come from North America.

Others have summarily touched upon the issue of NMS diagnostic criteria (Deng et al., 1990; Harsch, 1987; Kurlan, 1984; Kellam, 1987; Rosebush and Stewart, 1989). None give a precise set of diagnostic criteria but have suggested some essential or primary symptoms for making a diagnosis of NMS. Most important are the criteria proposed by Kellam (1987) and Harsch (1987). Harsch's (1987) criteria are based upon putative aetiology; the symptoms are dichotomized into two primary sets of symptoms: (1) autonomic dysfunction and fever mediated through dopaminergic blockade in the hypothalamus, and (2) rigidity and tremor mediated through dopaminergic blockade in the nigrostriatal system. Harsch's (1987) use of putative aetiology to define the syndrome is a commendable approach. In addition to the above, both Kurlan (1984) and Kellam (1987) independently proposed that NMS is a clinical triad of fever, movement disorder, and altered mentation. Both authors considered fever to be the hallmark of NMS but only Kellam (1987) specified that the degree of fever should be at least 37.5 °C. Kurlan (1984) goes further and states that the three cardinal signs develop concurrently, often in association with other signs of autonomic and neurologic dysfunction. Essentially the same criteria were used by Rosebush and Stewart (1989) who do not specify the extent of fever. Deng et al. (1990) diagnosed NMS in patients with a temperature of 37.5 °C or higher, extrapyramidal signs (muscular rigidity, sialorrhoea or dysphagia), and autonomic signs.

Levenson's criteria

Levenson's (1985) criteria (Appendix 1) are based on a pragmatic clinical approach analogous with the Ducket Jones diagnostic schema for rheumatic heart disease with a dichotomy of clinical features into major and minor criteria. His diagnostic criteria are flexible enough to account for clinical diversity and allow episodes without either muscular rigidity or hyperthermia to be characterized as NMS (Levenson, 1985). His criteria give undue diagnostic importance to raised CPK levels as one of the major diagnostic criteria (Adityanjee, 1991; Roth et al., 1986). Levenson (1986) modified these criteria to eliminate minor elevations of CPK (less than 1000 U/l) as a major manifestation. Despite their limitations, Levenson's criteria remain the most useful and sensible in routine clinical practice as they allow a diagnosis of NMS in patients being treated with atypical antipsychotics where rigidity is usually absent (Goates and Escobar, 1992). An analogous flexible diagnostic approach, similar in concept to those used in rheumatic heart disease, has been adopted by Nierenberg et al. (1991).

Addonizio et al.'s criteria

Addonizio et al. (1986) adopted a *spectrum approach* to the diagnosis of NMS. They used a symptom checklist of 10 signs and symptoms to identify NMS (Appendix 2). The presence of five symptoms within the same 48-h period was used to identify an episode. The absence of fever (< 37.5 °C) or extrapyramidal symptoms (EPS) precluded the diagnosis of NMS. Non-specific findings like leucocytosis (more than 10 800 cells/cm) and elevated CPK (more than 83 U/l) was given equal importance as were altered sensorium and autonomic dysfunction, in diagnosing NMS. Their criteria allow characterization as milder variants of NMS which hitherto would have been diagnosed as EPS. Thus, diagnostic flexibility was based on the premise that NMS is a continuous syndrome of physiological reactions to neuroleptics (Addonizio et al., 1986). For example, a patient with a fever of 37.5 °C, rigidity, tremor, elevated CPK of 84 U/l and leucocytosis (more than 10 800 cells/cm) would qualify as NMS under this schema even though the patient is fully awake and alert with no evidence of autonomic dysfunction. Their definition of NMS was so over-inclusive that they ended

up identifying 12.2% of their neuroleptic-treated patients as having NMS (Addonizio et al., 1986).

Pope et al.'s criteria

Pope et al. (1986a) developed an operational criteria to reflect the consensus of the various published reviews at that time. Their criteria require simultaneous presence of fever in absence of other known aetiology (37.5 °C), EPS and autonomic dysfunction (Appendix 3). These criteria allowed them to make a retrospective diagnosis of probable NMS in the absence of rigidity or fever. They subsequently, revised these criteria by raising the fever threshold to 38 °C (Keck et al., 1989). This modification does make the criteria more restrictive than those proposed originally.

Adityanjee et al.'s criteria

The most restrictive definition of NMS has been by Adityanjee et al. (1988) (Appendix 4). Their criteria require simultaneous presence of fever of at least 39 °C, lasting for more than 24 h, in the absence of any concurrent medical cause, altered sensorium (in the form of confusion, clouding of consciousness, disorientation, mutism, stupor or coma) independently documented by at least two observers along with muscular rigidity and autonomic dysfunction. They did not equate non-specific features like restlessness or agitation with altered sensorium as some others have done. They cautioned against the routine clinical use of the spectrum approach and considered elevation in serum CPK levels and leucocytosis as supportive features only, and not of diagnostic value (Adityanjee et al., 1988). O'Dwyer and Sheppard (1993) also suggest that elevation of CPK is a non-specific finding, particularly in patients who become pyrexial on neuroleptics. Use of CPK as a diagnostic criterion may lead to overdiagnosis of NMS (O'Dwyer and Sheppard 1993). Indeed, there has been an over-reliance on the estimation of creatine kinase as a potential diagnostic marker for NMS (Buckley and Hutchinson, 1995). The criteria proposed by Adityanjee et al. (1988) take into account these issues and are designed to minimize the false-positive cases (Adityanjee, 1991). Their criteria, however, cannot identify episodes of NMS (in the absence of muscular rigidity) in patients being treated with atypical antipsychotics, etc.

Friedman et al.'s criteria

Friedman et al. (1988) adopted a spectrum approach to the diagnosis of NMS. Based upon the clinical profile, they assigned different thresholds of diagnostic certainty. They devised the following working definitions. *Possible NMS*, any one of the following: (1) a visit to an emergency room, or an emergency neurologic evaluation; (2) fever of 38 °C without other explanation; (3) altered mental state; (4) extrapyramidal syndrome; (5) incontinence; (6) CPK elevation not due to trauma. *Probable NMS*, all of the following: (1) fever (temperature of 38 °C without other explanation); (2) altered mental state; (3) severe EPS. The criteria for definite NMS are as for probable NMS plus a response to bromocriptine, dantrolene, and/or carbidopa/L-dopa, or probable NMS resulting in death with a negative autopsy (including the brain). This was a bold hierarchical approach with some limitations. The diagnostic criteria for possible NMS appeared too broad. The diagnosis of definite NMS requires treatment response as a precondition; this forbids the diagnosis of definite NMS in patients with self-limiting episodes with cessation of neuroleptics and supportive management only. However, the efficacy of specific treatment for NMS has not been validly established and proven (Rosebush and Stewart, 1989; Sakkas et al., 1991). Therefore, any reliance on treatment response as an essential criteria for definite diagnosis is too controversial to be of any practical clinical use.

Criteria of Caroff's group

Lazarus et al. (1989) initially proposed a set of criteria which require treatment with neuroleptics within 7 d of onset of an episode. Their approach is neither descriptive nor theoretical as their criterion (4) is an arbitrary, heterogeneous conglomeration of extrapyramidal signs and symptoms, autonomic dysfunction, altered sensorium and abnormal laboratory results (Appendix 5). On the other hand muscle rigidity (another EPS) has been retained separately as an essential feature along with fever. The authors do not give any rational justification for proposing yet another set of diagnostic criteria which is neither eclectic nor based on putative aetiology. The same criteria essentially have been presented elsewhere by this group in variously modified versions (Caroff et al., 1991; Caroff and Mann, 1993).

Clinical issues in the diagnosis of NMS

The estimates of incidence rates of NMS vary widely because of varying definitions and differences in the sensitivity threshold of the diagnostic criteria (Adityanjee, 1987b, 1988; Adityanjee et al., 1988, In Press; Gurrera et al., 1992; Kellam, 1990; Modestein et al., 1992). This is not an unusual phenomenon, as a similar situation holds

true for the incidence and prevalence rates of other side-effects of neuroleptics, such as tardive dyskinesia (Woerner et al., 1991). The absence of a common vocabulary not only hampers research on comparisons between populations in terms of incidence, course and natural history, risk factors, treatment response and long-term outcome, it also leads to avoidable confusion in the clinical literature. The next section will deal with some of these issues.

Forme frustes/atypical forms

These variant forms of NMS, without fever or with delayed fever, or without muscular rigidity, have been described by various authors (Baker and Chengappa, 1995; Clarke et al., 1988; Hynes and Vickar, 1996; Lev and Clark, 1994; Levenson, 1985; Misiaszek and Potter, 1985; Nierenberg et al., 1991; Weinberg and Twerski, 1983; Wong, 1996). These atypical forms have been variously termed as formes frustes (Shalev and Munitz, 1986), milder variant NMS (Addonizio et al., 1986; Haggerty et al., 1987), benign NMS (Mezaki et al., 1989) and atypical NMS (Bernstein, 1979; Misiaszek and Potter, 1985). Addonizio et al. (1986) reported that these milder variants of NMS resolve without discontinuation of neuroleptics and questioned their being called 'malignant syndrome'. While they suggested that there should be a very strict criteria for NMS, Adityanjee et al. (1988) also agreed that there could be milder forms of NMS, according to them, these milder forms could be prevented from becoming a 'fulminant form'. Two out of the three cases they described had milder symptoms; these symptoms were completely aborted on the discontinuation of antipsychotics (Adityanjee et al., 1988). Similar cases, labelled as incipient NMS, were reported by Velamoor et al. (1990). Dickey (1991) views the presence of atypical or incomplete forms of NMS as the main reason behind various proposals for diagnostic criteria. Some suggest that adherence to a rigid diagnostic paradigm may inhibit prompt clinical diagnosis and treatment (Nierenberg et al., 1991). The concept of incomplete forms of NMS could not be supported in prospective studies (Modestein et al., 1992).

Mode of onset and natural history

Medicine has long made use of the concept of stage in approaching the investigation of pathologic phenomenon (Carr, 1983). The term stage implies a point in a process, a temporal progression in a definite direction or towards some arbitrary end. It is, therefore, well-suited to the phenomenon of disease process that progress in time from onset to an outcome (Carr, 1983). Indeed, stages are generally identified clinically by means of intra-individual differences that occur over time (Carr, 1983). NMS is an acute illness which develops progressively over 1–3 d (Dickey, 1991). White and Robins (1991) reported a series of five cases in whom a catatonic state preceded the onset of NMS. A number of authors consider catatonia to be either a harbinger of impending NMS or a predisposing factor (Dent, 1995; Fricchione, 1985; Raja et al., 1994; White and Robins, 1991). Similarly, others have suggested EPS or confusion as prodromal symptoms (Clarke et al., 1988; Van Putten et al., 1988; Velamoor et al., 1992). Woodbury and Woodbury (1992) proposed five discrete stages in the progression towards NMS, with the first and second stages involving development of extrapyramidal reactions and neuroleptic-induced catatonia respectively. These authors based their schema on the suggestion of Fricchione (1985) that neuroleptic-induced catatonia can progress to NMS if not treated appropriately. Changes in either mental status or rigidity were the initial manifestation of NMS in 82.3% of cases ($n = 340$) with a single presenting sign and were significantly more likely to be observed before hyperthermia and autonomic dysfunction (Velamoor et al., 1994). Discontinuation of neuroleptics during this prodromal phase may abort an impending NMS episode (Adityanjee et al., 1988; Caroff et al., 1991, Velamoor et al., 1994). Systematic examination of early signs and the progression of symptoms in NMS may be worthwhile to facilitate prompt recognition and interventions to abort the syndrome in its incipient state (Velamoor et al., 1994). Based on the clinical severity of complications, Taniguchi et al. (1997) classified the cases into three types: (i) mild, with no complications; (ii) moderate with only respiratory disturbance; and (iii) severe, with respiratory disturbance and renal failure. The issues of natural history during and after recovery from acute episode and relationship with original psychotic illness have been discussed by Adityanjee et al. (1989).

Impact of atypical antipsychotic agents

The first case report linking clozapine to NMS appeared more than a decade ago (Pope et al., 1986b). This was followed by another case in which NMS was presumed to have resulted from a combination of clozapine and carbamazepine (Muller et al., 1988). A series of case reports have suggested that clozapine alone can cause NMS (Anderson and Powers, 1991; Das Gupta and Young, 1991; Goates and Escobar, 1992; Miller et al., 1991; Nopoulos et al., 1990). Some of the patients did not develop the full-blown classical picture of NMS as they did not have muscle rigidity (Anderson and Powers,

1991; Das Gupta and Young, 1991; Goates and Escobar, 1992; Miller et al., 1991; Nopoulos et al., 1990; Thornberg and Ereshefsky, 1993). The patients in other reports had confirmed typical NMS; their symptoms included muscle rigidity which was associated with clozapine (Anderson and Powers, 1991; Das Gupta and Young, 1991; Miller et al., 1991; Reddig et al., 1993). Goates and Escobar (1992) highlighted the fact that criteria suggested by Levenson (1985) and Pope et al. (1986a) allow diagnosis of NMS in the absence of rigidity/EPS if several additional minor criteria are present. Others question the diagnosis of atypical NMS on clinical grounds in these cases (Hasan and Buckley, 1998; Weller and Kornhuber, 1993, 1996). Typical NMS can occur with clozapine and its incidence may be as common as with classic neuroleptics (Hasan and Buckley, 1998; Sachdev et al., 1995; Tsai et al., 1995). Clozapine rechallenge in a case or previous NMS with typical neuroleptics resulted in recurrence of NMS (Illing and Ancill, 1996). A number of cases of NMS have also been reported with risperidone (Bonwick et al., 1996; Buckley, 1996; Dave, 1995; Levin et al., 1996; Murray and Haller 1995; Najara and Enikeev, 1995; Newman et al., 1997; Sharma et al., 1996; Singer et al., 1995; Tarsy, 1996; Webster and Wijeratne, 1994). The clinical picture of NMS induced by atypical antipsychotics is likely to be different in view of the different receptor profile of the atypical antipsychotic drugs (Newman et al., 1997; Sachdev et al., 1995). However, insufficient evidence currently exists to support the concept of 'atypical' NMS with novel antipsychotics (Hasan and Buckley, 1998). Approximately 3% of patients receiving clozapine develop benign hyperthermia and approx. 25% have autonomic instability during initial titration of clozapine or risperidone treatment (Buckley and Meltzer, 1995). The potential for diagnostic confusion is considerable because of overlap between features of NMS and adverse side-effects of atypical antipsychotics (Hasan and Buckley, 1998).

Theoretical and nosologic issues

There is some confusion in the literature about whether this represents an extrapyramidal disorder just like other motor side-effects of neuroleptics that are secondary to the blockade of dopaminergic receptors in the basal ganglia (nigrostriatal or A9 dopaminergic pathways). Besides blockade of striatal dopaminergic D2 receptors, NMS also involves clinical features, some of which are determined by blockade of hypothalamic dopaminergic D2 receptors. Hence, NMS represents something more than the usual neuroleptic-induced EPS. It is the concurrent and massive blockade of dopaminergic receptors not only in the striatum, but also in the hypothalamic region which gives rise to the NMS picture. Positron emission tomographic studies have shown that a critical striatal dopaminergic D2 receptor occupancy threshold is required for the side-effects of antipsychotic medications to manifest. Farde et al. (1992) suggest that this threshold is much higher (74–82%) for EPS to manifest. The striatal dopaminergic receptor occupancy may be as high as 100% along with the hypothalamic dopaminergic receptor blockade in the case of NMS. Functional neuroimaging of dopaminergic receptors using SPECT in a patient with NMS during acute and recovery phases corroborates this notion (Jauss et al., 1996).

Although in psychiatry there is a controversy as to how presentations should be classified, in case of NMS the debate is still often at a stage of uncertainty as to whether this particular syndrome actually exists. Levinson and Simpson (1986) challenged the unitary concept and nosological status of NMS and emphasized the heterogeneity. The authors reviewed 39 cases from the literature and divided them into three categories: (i) ill patients in which known medical factors appeared to satisfactorily explain the fever; (ii) possibly ill patients in which initial complicating medical factors led to dehydration, which subsequently might have caused the fever; and (iii) not ill patients in which fever was otherwise inexplicable. They considered the term NMS to be a misnomer and chose to label all such cases as 'neuroleptic-induced extrapyramidal symptoms with fever' (Levinson and Simpson, 1986). Their conclusions were restricted because their selection criteria of cases was rather biased and limited; they interpreted NMS only as a constellation of EPS and fever, disregarding the other clinical components of NMS. The authors blurred the distinction between complications of NMS and concurrent illness simulating NMS, and confused causes of NMS with causes of death in NMS patients (Caroff et al., 1987).

The concept of NMS as a specific syndrome

A clinical syndrome consists of a cluster of related symptoms with a characteristic time-course (Kendell, 1989). Therefore, the two elements to a syndrome are a group of correlated symptoms and a more or less distinctive temporal evolution. When structural pathology for a syndrome is discovered, it tends to be elevated to the status of a disease (Kraupl Taylor, 1983). Robins and Guze (1970) have suggested five criteria for the recognition and definition of a valid syndrome: (1) clinical description; (2) delimitation from other disorders; (3) laboratory studies; (4) follow-up studies; and (5) family studies. The usual process of validating a diagnostic category begins with description of a distinctive clinical

picture (face and descriptive validity) and proceeds with collection of further evidence supporting the hypothesis that the original grouping is homogeneous. Such evidence results from follow-up studies and studies of treatment response (predictive validity) or the demonstration of a familial pattern of the disorder (Spitzer and Williams, 1985).

Currently, there is ample evidence to support both the face and descriptive validity of NMS. Attempts have been made to tease out the spectrum concept of NMS. On the basis of longitudinal history and treatment response, Adityanjee et al. (1988) separated the neuroleptic-induced extrapyramidal side-effects from NMS. Others have highlighted the role of specific treatment in decreasing the mortality and the duration of an episode (Rosenberg and Green, 1989; Sakkas et al., 1991). This is an attempt to establish predicative validity of NMS. There is a lack of robust evidence on the construct validity of NMS. Deuschl et al. (1987) reported cases of twin patients with schizophrenia who experienced the NMS. Otani et al. (1991) reported familial cases of NMS. Familial NMS in siblings with GM2 gangliosidosis indicates a possible association between this genetic neurological disease and predilection for NMS (Manor et al., 1997). It has been reported in a patient with mutation in the dopamine D2 receptor gene (Ram et al., 1995). CYP2D6 genotype has been associated with susceptibility to the NMS (Iwahashi, 1994). A more recent study failed to find association between NMS and polymorphisms in the 5-HT-1A and 5-HT-2A receptor genes (Kawanishi et al., 1998). It is important to distinguish between one syndrome and another as accurately as possible because such a distinction makes it possible to predict as to who will respond to a particular treatment modality and who will not (Kendell, 1989). It also helps to discover aetiology. On the basis of signs and symptoms alone, it is difficult to distinguish NMS from conditions like catatonia (Blumer, 1997; Buckley and Hutchinson, 1995; Caroff et al., 1998; Fink, 1995, 1996a; Hynes and Vickar, 1996; Raja et al., 1994); lithium neurotoxicity (Adityanjee, 1987a); central anticholinergic toxicity (Catterson and Martin, 1994; Howells, 1994); organophosphate poisoning (Ochi et al., 1995); hyponatraemia (Looi et al., 1995) and serotonin syndrome (Fink, 1996b; Miyaoka and Kamijima, 1995). The NMS-like encephalopathy that develops in association with the use of antidepressants indicates that NMS and serotonin syndrome are spectrum disorders induced by drugs with both antidopaminergic and serotoninergic effects (Miyaoka and Kamijima, 1995). It has been suggested that NMS and toxic serotonin syndrome (TSS), instead of being specific syndromes, are examples of a non-specific generalized neurotoxic syndrome and may represent variants of catatonia (Fink, 1996a,b).

The spectrum concept of NMS

The concept that NMS is one end of a spectrum starting from neuroleptic-induced parkinsonism (EPS) has been put forward by several authors. Fogel and Goldberg (1985) were first to enunciate the concept of a spectrum of severe neuroleptic-related toxicity, with various combinations of extrapyramidal, cortical and autonomic dysfunction. Supporting this concept, Guze and Baxter (1985) maintained that NMS is not a single entity with a uniform presentation. It has been suggested that it may represent an exaggerated form of neuroleptic-induced parkinsonism (Cohen et al., 1985). Conlon (1986) described a single case report lending credence to the spectrum concept of neuroleptic-related toxic reactions and argued that NMS represents an extreme end of the spectrum. A similar stance was adopted by Addonizio et al. (1986, 1987) who state that NMS represents a continuous spectrum of pathophysiological reactions to neuroleptics and that in some patients, it takes a severe and potentially lethal form. Lazarus and Lipschutz (1991) perceive it to be a spectrum disorder depending on the degree and the central sites of dopamine blockade. Others consider NMS to have a wide spectrum of clinical severity and caution that any criteria might be subject to unnecessary exclusion or over-inclusion (Friedman et al., 1988; Gurrera et al., 1992; Nierenberg et al., 1991; Walker, 1988; Wong, 1996). Clinicians have argued that atypical or incomplete forms are possible and that their recognition and treatment are compromised by adhering to rigid 'classic' diagnostic criteria (Nierenberg et al., 1991). A spectrum of symptoms needs to be distinguished from a dimension of increasing clinical severity (Pelonero et al., 1998). The proponents of the spectrum approach tend to confuse among the following issues that are conceptually different:

(1) a spectrum of different symptoms under the broad rubric of a single syndrome, e.g. muscular rigidity or hyperthermia being an essential requirement for the diagnosis;
(2) a spectrum of different syndromes with merging boundaries, e.g. EPS, NMS, central anticholinergic toxicity and serotonin syndrome;
(3) a dimension of increasing clinical severity within the same discrete syndrome, i.e. mild, moderate or severe;
(4) mode of onset (acute, subacute and insidious), prodromal/incipient phase vs. complete syndrome and progression of symptoms as part of the natural history of the syndrome.

Unfortunately, the adherents of spectrum concept, in different publications, have lumped all four conceptually different issues under the same concept. Others argued against this broad approach and stress the advantages of

strict diagnostic criteria (Adityanjee et al., 1988; Buckley and Hutchinson, 1996; Hasan and Buckley, 1998; Modestein et al., 1992).

Stringent vs. broad criteria for NMS

In an effort to compare the different diagnostic criteria for NMS Gurrera et al. (1992) examined the charts of 64 patients who were referred over a 6 yr period, suspected of having NMS. Clinical data from each possible NMS episode were assessed by three sets of diagnostic criteria: Levenson (1985), Pope et al. (1986a) and Addonizio et al. (1986). Agreement among these criteria was quantified statistically by means of the kappa and intra-class correlation coefficients. Pope et al.'s definite criteria identified the fewest episodes whereas Levenson's criteria identified the maximum number of episodes. Approximately 65% of the episodes met at least 1 of the 3 sets of published criteria studied but only one-third of these met all three sets of published criteria (Gurrera et al., 1992). Agreement was best among these criteria when the 'probable' category was employed. The authors found it difficult to compare some individual criteria because of: (*a*) differences in their composition structure, (*b*) uniqueness of some criteria, (*c*) complex structure of some criteria (Gurrera et al., 1992). Some frequency differences among comparable criteria were attributed to different thresholds. They concluded that the three sets of diagnostic criteria they studied do not consistently identify NMS episodes and demonstrate different thresholds for assigning this diagnosis. They also implicated choice of diagnostic criteria as a factor in wide-ranging estimates of incidence (Gurrera et al., 1992). Such a view has been expressed earlier (Adityanjee, 1987b; Adityanjee et al., 1988; Kellam, 1990; Modestein et al., 1992). All the three sets of diagnostic criteria compared in this study were enunciated by the proponents of the spectrum approach to the diagnosis of NMS. Gurrera et al. (1992) concluded that their study lends indirect support to the spectrum concept of NMS and provides evidence for the assertion that some cases of NMS go unrecognized. Their results would have been more interesting if they had compared diagnostic criteria adhering to the spectrum approach with those not adhering to such an approach. The only such epidemiological study failed to support the spectrum concept (Modestein et al., 1992).

Official classifications

The section on mental and behaviourial disorders (chapter V) of the ICD-10 does not include NMS, however, it has a four-character code of G-21.0 under secondary parkinsonism (see WHO, 1992, ch. VI). The DSM-IV gives very broad criteria for diagnosis of NMS that are essentially a modified version of criteria given by Caroff's group and suffer from the same deficiencies (APA, 1994; Lazarus et al., 1989). It is important to compare the diagnostic validity of the DSM-IV criteria against other established criteria (Buckley and Hutchinson, 1995). The DSM-IV criteria have limited use in research and epidemiological studies because the extent of fever is not defined.

Discussion

Estimates of the incidence of this particular disorder are influenced by the criteria used to define it (Adityanjee, 1987b, 1988; Adityanjee et al., 1988, In Press; Friedman et al., 1988; Gurrera et al., 1992; Kellam, 1990; Modestein et al., 1992). The existence of a spectrum of clinical severity and the relative importance of specific signs and symptoms for the diagnosis of NMS are two issues that still await resolution (Adityanjee, 1988; Adityanjee et al., 1988; Buckley and Hutchinson, 1995; Gurrera et al., 1992; Levinson and Simpson, 1986). Given poor specificity, claims for the use of CK values as a marker for the diagnosis and course of the NMS appear injudicious (Adityanjee, 1991; Buckley and Hutchinson, 1995; Goldwasser et al., 1989; O'Dwyer and Sheppard, 1993). The over-representation of single or brief series of case studies and the application of variable diagnostic criteria for NMS have hampered rigorous scientific enquiry into the nature of this condition (Buckley and Hutchinson 1995). All the ambiguity in research and the difficulty in comparing the results across the studies will be eliminated if we have a set of universally agreed research diagnostic criteria. A similar situation prevailed in tardive dyskinesia research until a provisional set of research diagnostic criteria were proposed (Schooler and Kane, 1983).

It is important to propose a set of stringent research criteria and take into consideration the impact of atypical antipsychotics. The research diagnostic criteria should be more stringent than broader clinical diagnostic criteria because clinical situations call for more flexibility.

Proposed research diagnostic criteria

In order to reduce confusion and have a common vocabulary for research communications, we propose the following definitions.

(1) *Type I NMS (classical neuroleptic malignant syndrome)*

This refers to a classical NMS picture induced by exposure to typical neuroleptics or other non-neuroleptic dopamine

blockers like metoclopramide. The type I syndrome is a complete NMS picture with all the essential criteria and is not caused by antidepressants, MAO inhibitors, lithium or serotoninergic agents. We suggest that the criteria enumerated in Appendix 6 (based on the diagnostic criteria of Adityanjee et al., 1988) be utilized for NMS research diagnostic purposes. These proposed criteria are very stringent and based on a narrow concept so as to minimize the false-positive rates.

(2) *Type II NMS (atypical neuroleptic malignant syndrome)*

Type II NMS refers to a NMS-like picture, either complete or incomplete following exposure to atypical antipsychotics like clozapine, risperidone, olanzapine, quetiapine, etc. The type II NMS differs from the classical NMS by exposure to atypical antipsychotic agents and possible absence of muscular rigidity (Appendix 6). A number of such cases have been reported (Hasan and Buckley, 1998; Newman et al., 1997; Sachdev et al., 1995).

(3) *Type III NMS (impending/threatened/incipient/aborted neuroleptic malignant syndrome)*

Type III NMS refers to episodes caused by either typical or atypical antipsychotics which do not fulfill criteria for type I or type II NMS, yet there is a strong clinical suspicion for the diagnosis. This includes cases in which patients do not show full expression, e.g. when a partial syndrome and/or prodromal symptoms lead to a clinical suspicion followed by intervention. Some of these episodes may metamorphose into a full-blown picture if intervention is not made. For research purposes such episodes cannot be considered complete. No diagnostic criteria are being proposed for this subtype.

(4) *Type IV NMS (miscellaneous conditions as neuroleptic malignant syndrome)*

This subtype refers to those miscellaneous conditions that result from withdrawal of anti-parkinsonian agents (Bower et al., 1994; Simpson and Davis, 1984; Toru et al., 1977), exposure to cocaine or other psychostimulants (Darras et al., 1995; Wetli et al., 1996), exposure to dopamine depleters like tetrabenazine (Ossemann et al., 1996). Cocaine-associated agitated delirium appears to have increased drastically in recent years (Wetli et al., 1996). There is a superficial resemblance with the typical NMS picture despite lack of exposure to neuroleptics. Since chronic cocaine use may alter the availability of dopamine either through transmitter depletion or a decrease in the number of dopamine receptors, a common pathogenetic mechanism is possible (Darras et al., 1995).

Conclusion

We propose that NMS be conceptualized as a drug-induced hyperthermia with other concomitant catatonic features. Since drug-associated hyperthermia is defined as a temperature $\geqslant 40.5$ °C for at least 1 h in relation to exposure to a recreational, therapeutic or excessive doses of a drug or drug combinations (Rosenberg et al., 1986), we advocate using very stringent research diagnostic criteria. Theoretically, types III and IV cannot be conceptualized as variants of NMS but may be useful constructs in clinical practice. One may even object to use the term NMS for them. It is proposed that type I and type II entities are true (definitive) NMS whereas type III and type IV represent, at best, probable NMS. The difference between type I and type II syndromes is not that of clinical severity but a qualitative one based on syndrome definition. Type II is not necessarily a milder version of type I, clinically it may also be severe. Nor do we conceptualize type II being a stage in the evolution of type I syndrome. Type I syndrome though complete may be of mild or moderate clinical severity. The key distinction here, defined arbitrarily, is the exposure to atypical antipsychotics in type II syndrome. The essential difference in the clinical picture is based on possible/allowable absence of muscular rigidity for diagnosis to be made. Type I has all four classical clinical components, type II has three or more. This distinction in systematic research studies will eventually help to see if typical and atypical antipsychotics produce the same or a different syndrome clinically. While the type I picture could be caused by typical antipsychotics and other dopamine blockers, we would not classify a type II picture as being caused by classical (typical) neuroleptics. Type II syndrome can be caused by atypical agents alone; it cannot be caused by typical neuroleptics. If a patient is on both typical and atypical agents, as happens when converting from one to the other, potentially either type I or type II could occur.

We suggest that all patients with suspected NMS and those with a similar superficial clinical picture be studied in depth prospectively. Besides clinical work, such patients should have their clinical symptoms assessed in a standardized method on the following scales: Glasgow Coma Scale (Teasdale and Jennett, 1974); Bush–Francis Catatonia Rating Scale (Bush et al., 1996); and Simpson–Angus EPS Rating Scale (Simpson and Angus, 1970). This is important because verbal descriptions of the level of

consciousness lead to ambiguities and misinterpretations when patient information is exchanged between medical personnel, when different treatment methods are compared or when comparisons are made among different centres or studies (Sacco et al., 1990). Glasgow Coma Scale (GCS) scores have been found to be of predictive value in non-traumatic comas as well (Sacco et al., 1990). A standardized assessment of clinical symptoms will avoid unnecessary confusion, improve inter-rater reliability, and provide a common language for psychiatrists, neurologists, internists and intensive care physicians. It will also avoid idiosyncratic use of certain clinical terms because the items on these scales have standardized operational definitions.

We also believe that NMS is a misnomer as a descriptive term. Despite several alternative names, widespread use of the term NMS has persisted in the literature. In order to avoid premature aetiological closure, Peele et al. (1988) proposed the name hyperthermic catatonia. We do not attempt to propose yet another name for this syndrome but believe the descriptive name *drug-induced hyperthermic catatonia* (DIHC) allows greater research flexibility and clinical options (Peele et al., 1988). This will avoid repetitive, sterile and unnecessary debate about whether NMS is a separate syndrome or a drug-induced variant of lethal catatonia.

The proposed classificatory approach and descriptive name may represent a pragmatic way of avoiding unnecessary and unproductive nosologic and diagnostic controversy while fostering clinical research. We hope that future studies will use these research diagnostic criteria for NMS while studying its epidemiology, diagnosis, aetiology, pathophysiology and treatment response. With future advances in psychopharmacology, the syndrome may become an entity of historical interest only.

Appendix 1. NMS: Diagnostic criteria (Levenson, 1985)

(A) Major manifestations
- (1) Fever
- (2) Rigidity
- (3) Elevated CPK levels

(B) Minor manifestations
- (1) Tachycardia
- (2) Abnormal blood pressure
- (3) Tachypnoea
- (4) Altered consciousness
- (5) Diaphoresis
- (6) Leucocytosis

The presence of all 3 major or 2 major and 4 minor manifestations indicates a high probability of the presence of NMS, if supported by clinical history (e.g. not indicative of malignant hyperthermia).

Appendix 2. NMS: Diagnostic criteria (Addonizio et al., 1986)

(1) Elevated temperature: at least 37.5 °C in the absence of other systemic illness
(2) Rigidity
(3) Tremor
(4) Tachycardia (at least 100 beats/min)
(5) Elevated blood pressure (at least 150/100 mmHg)
(6) Diaphoresis
(7) Incontinence
(8) Leucocytosis (greater than 10800 cells/cmm)
(9) Confusion
(10) Elevated CPK levels (greater than 83 U/l)

The occurrence of 5 out of 10 symptoms in the same 48 h period is used to identify an episode. The absence of fever and extrapyramidal symptoms preclude the diagnosis of NMS.

Appendix 3. NMS: Diagnostic criteria (Pope et al., 1986a; modified by Keck et al., 1989)

(1) Hyperthermia
Oral temperature of at least 38 °C* in absence of other aetiology

(2) Extrapyramidal symptoms (at least 2 of the following)

Leadpipe rigidity	Trismus
Cogwheel rigidity	Dysphagia
Sialorrhoea	Chorea
Oclogyric crisis	Dyskinetic movements
Retrocollis	Festinating gate
Opisthotonos	Flexor/extensor posturing

(3) Autonomic dysfunction (at least 2 of the following)
Hypertension (at least 20 mmHg diastolic above the baseline)
Tachycardia (at least 30 beats above baseline)
Tachypnoea (at least 25/min)
Profuse sweating
Incontinence

(4) For retrospective diagnosis
If documentation of one of the above criteria is inadequate, diagnosis of probable NMS is permissible if the remaining two are met plus one of the following: clouded consciousness; delirium; mutism; stupor or coma; leucocytosis (WBC greater than 15 000/cmm); serum CK level greater than 1000 U/l.

* The original criteria of Pope et al. (1986a) permitted a diagnosis of NMS with oral hyperthermia of only 37.5 °C.

Appendix 4. NMS: Diagnostic criteria (Adityanjee et al., 1988)

Essential clinical criteria (all 4 of the following must be present)

(1) Altered sensorium (any of the following)
Confusion
Clouding of consciousness
Disorientation
Mutism
Stupor
Coma

Should be documented by at least two independent observers on at least two consecutive days. Non-specific changes in mental state, e.g. restlessness or agitation should not be equated with altered sensorium.

(2) Muscular rigidity

(3) Hyperpyrexia of unknown origin
Should be greater than 30 °C per ora (p.o.)
Should be more than 24 h in duration
No concurrent physical cause for hyperpyrexia

(4) Autonomic dysfunction (at least 2 of the following)
Rapid pulse (more than 90/min)
Rapid respiration (more than 25/min)
Blood pressure fluctuations (at least a change of 30 mmHg in systolic pressure or 15 mmHg in diastolic pressure)
Excessive sweating
Incontinence

Supportive features
(i) Elevations in serum CPK levels
(ii) Leucocytosis

These should be considered as inessential features only as they are fairly non-specific and not of much diagnostic value.

Appendix 5. NMS: Diagnostic criteria (Caroff et al., 1991; Caroff and Mann, 1993; Lazarus et al., 1989)

All 5 items required concurrently

(1) Treatment with neuroleptics within 7 d of onset (2–4 wk for depot neuroleptics)

(2) Hyperthermia (38 °C or more)

(3) Muscle rigidity

(4) Five of the following

Change in mental status	Tremor
Tachycardia	Incontinence
Hypotension or hypertension	CPK elevation or myoglobinuria
Tachypnoea or hypoxia	Leucocytosis
Diaphoresis or sialorrhoea	Metabolic acidosis
Dysarthria or dysphagia	

(5) Exclusion of other drug-induced, systemic or neuropsychiatric illness

Appendix 6. Research diagnostic criteria for NMS (Adityanjee et al., 1999)

(1) Altered sensorium (any one of the following)
- Confusion
- Clouding of consciousness
- Mutism
- Stupor
- Coma

Rating of severity should be done by at least two independent observers on Glasgow Coma Scale on at least two consecutive days. Non-specific changes in mental state, e.g. restlessness or agitation should not be equated with altered sensorium.

(2) Extrapyramidal motor symptoms (any one of the following)
- Muscular rigidity
- Dysphagia
- Dystonia

Motor symptoms should be rated on the Simpson–Angus EPS Rating Scale.

(3) Hyperpyrexia of unknown origin
- Should be greater than 38.5 °C per ora (p.o.)
- Should be sustained for at least 48 h in duration
- No concurrent physical/medical cause for hyperpyrexia

(4) Autonomic dysfunction (at least 2 of the following)
- (i) Tachycardia (pulse more than 100/min)
- (ii) Tachypnoea (respiration more than 25/min)
- (iii) Blood pressure fluctuations (at least a change of 30 mmHg in systolic pressure or 15 mmHg in diastolic pressure)
- (iv) Excessive sweating (diaphoresis)
- (v) New onset incontinence

(5) Relationship of onset of symptoms with exposure event defined by any one of the following
- (i) p.o. ingestion or parenteral administration (dose increase, dose decrease, discontinuation) of an antipsychotic drug (typical or atypical), a dopamine depleter (e.g. tetrabenazine) dopamine blocker (e.g. metoclopramide) or a psychostimulant drug (e.g. cocaine) during the previous 2 wk
- (ii) Withdrawal of antiparkinsonian (e.g. amantidine) or anticholinergic drug during previous 1 wk
- (iii) I.m. administration of a long-acting depot antipsychotic medication during the previous 8 wk

(6) Exclusion criteria

Symptoms not due to any other existing or new general medical (secondary to substance abuse, infectious illnesses, metabolic, delirium, etc.), neurologic (encephalitis, epilepsy, brain tumours, etc.) or psychiatric disorder (e.g. catatonic schizophrenia, mood disorder with catatonic features).

[*continued overleaf*

Appendix 6 (*cont.*)

(7) Supportive features (any two of the following)
  (i) Elevations in serum CPK levels
  (ii) Leucocytosis
  (iii) Low serum iron levels
  (iv) Elevation of liver enzymes
  (v) Myoglobinuria

Type I NMS
Criteria (1)–(6) must be present for making a research diagnosis.

Type II NMS
Criteria numbers (1), (3) and (4), (5), (6) and any one item from criteria number (7) must be present for the diagnosis. Criteria number (2) is not necessary for making diagnosis.

Standardized assessment
All the patients with a suspected diagnosis should be rated on the following: Glasgow Coma Scale, Simpson–Angus EPS Rating Scale and Bush–Francis Catatonia Rating Scale.

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