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Review article

Atypical neuroleptic malignant syndrome: A systematic review of case reports

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1. Introduction

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic and potentially fatal side effect of antipsychotic medications. The prevalence of NMS is found to be variable, ranging from 0.02 to 2.4%. [1] At least six sets of diagnostic criteria have been proposed for the same including Diagnostics and Statistical Manual of Mental Disorders-5 criteria, Diagnostics and Statistical Manual of Mental Disorders- IV-TR criteria, Caroff and Mann, Sachdeva, Levenson criteria and the 2011 international consensus criteria by Gurrera RJ, et al. (Table 1) [2–7] The latter criteria was developed by Delphi method involving experts from different fields. It provides critical values/cut offs for pertinent elements, focusing on their importance. Besides, this set of criteria also attempts to overcome the influence of certain theoretical biases. These factors help it in overcoming limitations of the previous criteria. Though there are subtle differences among these criteria, a general consensus of four principal symptoms is considered as the core of NMS: hyperthermia, rigidity, mental status changes, and autonomic dysfunction. [8]

A lesser discussed yet equally significant entity is that of atypical NMS. Atypical NMS refers to subthreshold presentations of NMS. Due to lack of well-defined validated criteria for atypical NMS, clinicians have been at risk of missing out on the diagnosis of NMS, often attributing the atypical presentations of NMS to other neurological and medical illnesses. Few case reports have defined atypical NMS as having at least three of the above four core criteria [9–11]. DSM-5 has laid emphasis on elevated creatine kinase as an important distinguishing criterion of NMS. Hence elevated creatine kinase might need to be considered as one of the core criteria. Thereby, it might be prudent to diagnosis atypical NMS if the subject has four of the following criteria: hyperthermia, rigidity, mental status changes, autonomic dysfunction and elevated creatine kinase.

The most important limitation with the existing literature is that it is largely limited to case reports. Apart from this, the literature landscape is confined to few commentaries, reviews and letters to editor. [10,12–16] Further, it is important to note that some of these reviews studied about NMS occurring with atypical antipsychotics rather than focusing on atypical NMS per se. An important issue to be addressed is the conflation and misrecognition of NMS caused by atypical antipsychotics as atypical NMS which could lead to overinflation of rates of atypical NMS. [17–19] Another flaw with the extant literature is misdiagnosis of cases of catatonia as NMS [20]. Hence, there is need for carefully reviewing cases labelled as atypical NMS if they actually fulfil criteria of atypical NMS. Though case reports are the lowest level of evidence they are the most important means currently to fill the literature gap and also to guide for further research. With this background, we present a systematic review of cases of atypical NMS. The PICOS format is as follows:

- Population: Patients with psychiatric illness
- Intervention: Receiving psychotropic medication
- Comparison: Not applicable
- Outcome: Atypical NMS was defined as presence of four out of following five criteria:
  - Hyperthermia: (> 100.4 °F/38 °C) [3]
  - Generalized rigidity
  - Autonomic disturbances (tachycardia, diaphoresis, elevated or fluctuations in blood pressure, urinary incontinence, pallor) [3]
  - Mental status changes (delirium, altered sensorium presenting on spectrum from stupor to coma) [3]
  - Elevated Creatine Kinase (atleast four times upper limit of normal) [3]
- Study type: Case reports, case series, letter to editor

2. Materials and methods

2.1. Search strategy and study selection

Electronic searches of PubMed and Google Scholar databases were carried out with the aim of identifying published case reports describing atypical neuroleptic malignant syndrome.

The search was done using combination of the following search terms, “Neuroleptic Malignant Syndrome” and “Atypical”; “Atypical” and “Neuroleptic malignant syndrome”. The search was carried out in April 2019 with the time period specified from inception till March 2019. This was independently performed by the two authors. The

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search filter of "case report" was not used as many case reports are increasingly being published as letters to the editor.

The search results of the two authors were compared and after sorting out duplicate articles, a consolidated list of the case reports was drawn up. In addition, a supplemental Google search using random combinations of the above terms was done to further screen the available literature. Cross references of selected papers were also screened to identify relevant articles. The search was restricted to articles in the English language. We included case reports that described atypical NMS as per the criteria mentioned above. Any disagreement was sorted out through mutual discussion and consensus. We did not include unpublished material or those not available in peer reviewed journals (e.g., conference presentations) as they were not readily accessible. We contacted authors for full text of articles where ever required. Comprehensive hand searches of the physical library were not carried out as part of the present review. The study selection is enumerated in Fig. 1.

2.2. Data extraction

The full texts of the relevant articles were used to extract information about relevant demographic variables such as age, gender, and

Table 1.
Diagnostic criteria for Neuroleptic malignant syndrome

Sr no	Name of criteria	Criteria details
1.	Caroff and Mann [2]	* 1) Treatment with neuroleptics within seven days of onset (2 to 4 weeks for depot neuroleptics) 2) Hyperthermia (> 38 °C) 3) Muscle rigidity 4) Five of the following: Change in mental status, tachycardia, hypertension or hypotension, tachypnea or hypoxia, diaphoresis or sialorrhea, tremor, incontinence, creatine phosphokinase elevation or myoglobinuria, leucocytosis, metabolic acidosis 5) Exclusion of other drug-induced, systemic, or neuropsychiatric illnesses * All five items required concurrently.
2.	Diagnostics and Statistics Manual of Mental disorders- 5 [3]	Diagnostic features: - ● Exposure to dopamine antagonist within 72 h before symptoms development ● Hyperthermia (> 100.4 °F or > 38.0 °C on at least two occasions measured orally), associated with profuse diaphoresis. Mentioned as a distinguishing feature. ● Generalized rigidity ("lead pipe"). Mentioned as a cardinal feature. ● Creatine kinase elevation (at least four times the upper limit) ● Mental status changes (delirium or altered consciousness) ● Autonomic activation or instability (Tachycardia: -rate > 25% baseline, blood pressure elevation systolic or diastolic ≥25% baseline, blood pressure fluctuation ≥20 mmHg diastolic change or ≥ 25 mmHg systolic change within 24 h, diaphoresis, urinary incontinence, pallor) ● Tachypnea (rate > 50% above baseline) is common, and respiratory distress can occur. *There is no mention about the specific no. of features to be present for a certain diagnosis
3.	Diagnostics and Statistics Manual of Mental disorders- IV-TR [4]	A. Development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication. B. Two (or more) of the following: (1) Diaphoresis (2) Dysphagia (3) Tremor (4) Incontinence (5) Changes in the level of consciousness ranging from confusion to coma (6) Mutism (7) Tachycardia (8) Elevated or labile blood pressure (9) Leukocytosis (10) Laboratory evidence of muscle injury (e.g., elevated CPK*) C. The symptoms in criteria A and B are not due to another substance or a neurological or another general medical condition. D. The symptoms in criteria A and B are not better accounted for by a mental disorder.
4.	Levenson criteria [5]	*Creatinine phosphokinase Major manifestations Fever Rigidity Elevated creatine phosphokinase level Minor manifestations Tachycardia Abnormal blood pressure Tachypnea Altered consciousness Diaphoresis Leucocytosis The presence of all three major, or two major and four minor, manifestations indicates a high probability of the presence of neuroleptic malignant syndrome, if supported by clinical history (e.g., not indicative of malignant hyperthermia)

(*continued on next page*)

Table 1. (*continued*)

Sr no	Name of criteria	Criteria details
5.	Sachdev criteria [6]	1.Oral temperature: Presence of fever in the past 24 h 2. Extrapyramidal symptoms: • rigidity, • dysphagia, • resting tremor 3. Autonomic symptoms: • Systolic blood pressure rise = 30 mm above baseline for the subject (or = 150 mm if no baseline reading available). • Diastolic blood pressure = 20 mm above baseline (or = 100 mm if no baseline reading available). • Tachycardia: heart rate = 30/min above baseline (or = 100 if no baseline reading available). • Diaphoresis: Profuse sweating not accounted for by ambient temperature or analgesic use to lower temperature. • Incontinence: Fecal or urinary incontinence not accounted for by altered consciousness or catatonic state • Tachypnea: Respiratory rate = 15/min above baseline (or = 40/min if baseline not available). 4. Altered mental status 5. Catatonia/movement disorder 6. Laboratory investigations Elevated creatine kinase level * Symptoms to be present in 3 or more categories for a definitive diagnosis
6.	Gurrera et al. [7]	1. Recent dopamine antagonist exposure, or dopamine agonist withdrawal 2. Hyperthermia 3. Rigidity 4. Mental status alteration 5. Creatine kinase elevation 6. Sympathetic nervous system lability; tachycardia plus tachypnea 7. A negative workup for other causes. The following critical values for quantitative criteria: hyperthermia, > 100.4 °F or > 38.0 °C on at least 2 occasions; creatine kinase elevation, at least 4 times the upper limit of normal; blood pressure elevation, ≥25% above baseline; blood pressure fluctuation, ≥20 mmHg (diastolic) or ≥25 mmHg (systolic) change within 24 h; tachycardia, ≥25% above baseline; and tachypnea, ≥50% above baseline.

country of residence. Clinical information such as psychiatric diagnosis, medical or surgical issues, possible offending agent and dose, time to initiation of NMS after initiation or change in dose of the drug, clinching features of NMS, features suggestive of atypical NMS and the diagnostic criteria used were also gathered.

2.3. Data analysis

Descriptive analysis was used to analyse the data collected. Demographic and clinical variables were expressed as simple frequencies and percentages. Inferential statistics were not required. As the review included only individual case reports, we could not calculate effect sizes.

3. Results

A total of 20 cases had met the criteria for atypical NMS [21–41]. Profile of cases and details of each case are mentioned in Tables 2 and 3 respectively. The mean age of the cases reported was 43.5 years (SD = 18.34). The highest prevalence of atypical NMS was found to be in subjects aged 50 years or more (n = 9). Majority of patients were males (n = 14, 70%). 50% cases (n = 10) had medical or surgical issues associated with them. Hypertension (n = 3 each, 15%) and Diabetes Mellitus (n = 2, 10%) were the most common co-morbid medical illnesses. In 1 case (5%), there was a recent history of an operative procedure.

All cases except one had absence of severe rigidity or absence of hyperthermia. Absence of rigidity (65%) was the most common atypical feature followed by absence of hyperthermia/fever (30%) and lastly, absence of autonomic instability (5%).

Talking about the offending neuroleptics, a significant majority (n = 18, 90%) of cases were exclusively attributable to atypical antipsychotics, with Clozapine being the most commonly involved exclusive offending agent (n = 7,35%) followed by Olanzapine (n = 4,25%). The other offending neuroleptics among cases exclusively on atypical antipsychotics were Quetiapine, Risperidone, Paliperidone, Iloperidone and Asenapine. Only 2 (10%) cases were exclusively attributable to be caused by typical antipsychotics. In one case, a combination of typical and atypical antipsychotics was responsible for the atypical NMS episode. NMS is found to occur during abrupt change of antipsychotics without dose titration. [10,12]

The duration of NMS to develop varied from the same day to about ten years from the initiation of offending agent. About half (n = 10, 50%) the cases in this review had the onset of illness within one week of initiation, dose change or withdrawal of the respective offending drug. In 15% cases (n = 3) time to induction was in the 2nd week.

In some cases (n = 2, 10%) time to induction varied from two weeks to one month. One case had time to onset between 30 and 90 days. In two cases, patient was on antipsychotic for about ten years and in another case for five years. In these three cases, it is not mentioned if there was any increase or skipping or change of dosage of medication [23,29,40].

4. Discussion

4.1. Similarities and differences in profile of patients between NMS and atypical NMS

The patient profile of patients with atypical NMS is similar to those with NMS in certain aspects. Atypical NMS was found to be more common in males in our review (Males = 70%). This is in concordance with existing literature that NMS is more common in males. However, characteristics such as age, comorbidity profile, offending agent were found to vary between cases of NMS and atypical NMS. The incidence of NMS peaked at age 20–25 years as per a recent systematic review. [42] This is in contrast to our finding of NMS being more common after 50 years of age.

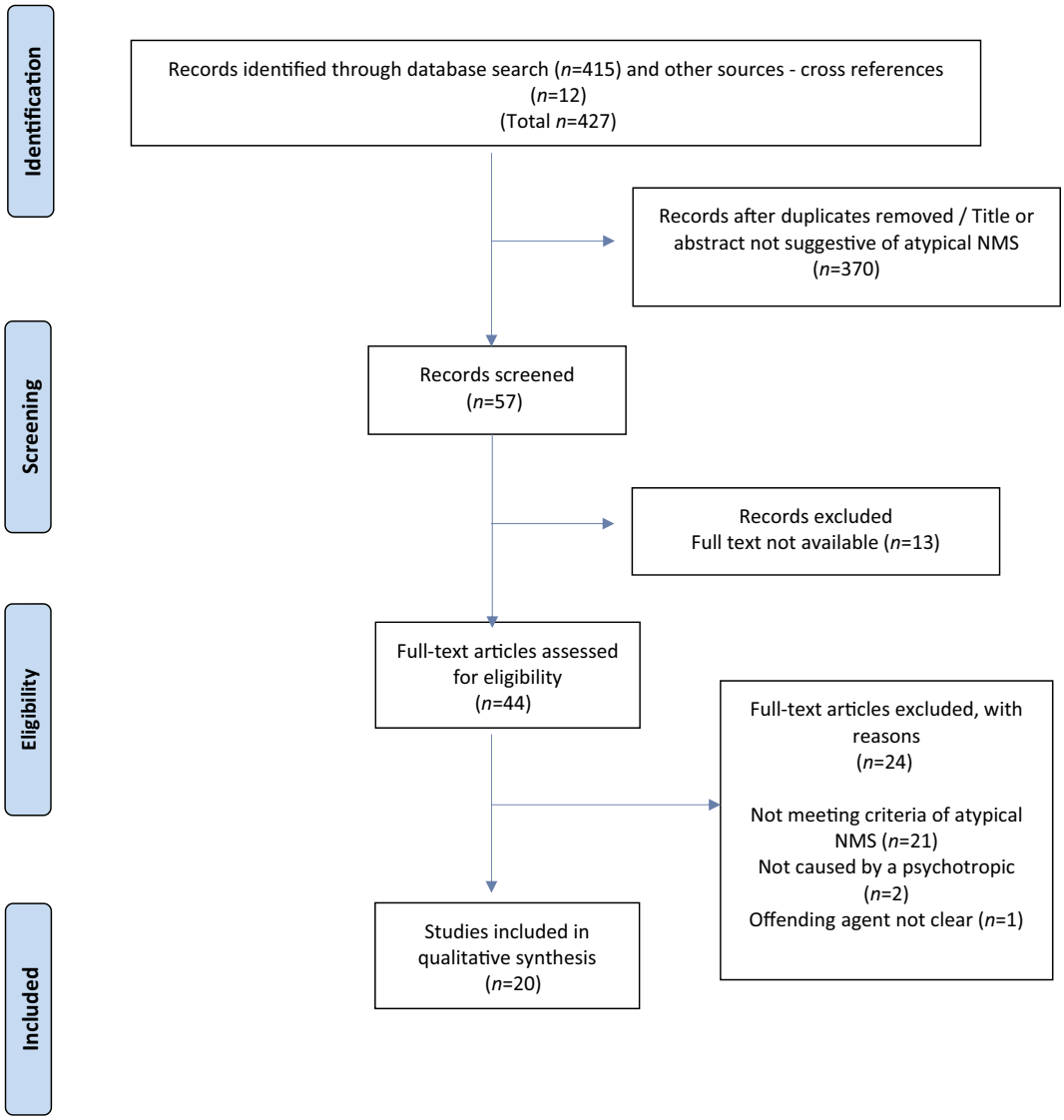

Fig. 1. PRISMA flow diagram (flow chart of selection of studies).

Table 2
Profile of patients developing atypical NMS (N = 20 cases).

Mean age in years	43.5 (SD=)
Male gender	70%
Primary psychiatric diagnosis	Frequency (n)
Schizophrenia	10
Other psychosis	1
Schizoaffective disorder	2
Bipolar disorder	4
Mania	1
Depression	1
Not specified/final	1
Other diagnoses	Frequency (n)
Medical/surgical comorbidity (n)	10
Post-operative status (n)	1

4.2. What makes atypical NMS atypical: pathophysiology, drugs and doses

Severe rigidity as well as hyperthermia were equally absent in the cases reviewed in our study. Some of the cases had late appearance of fever. Rather, prominent autonomic dysfunction and diaphoresis has been noted among many of the cases. [13] Further, second generation antipsychotics were the offending agent in majority of cases. These findings are in stark contrast to the reported cases of typical NMS, which are known to be more commonly caused by the typical antipsychotics.

There are various hypotheses put forward by the researchers about the pathogenesis of atypical NMS. The most widely held hypothesis is that atypical antipsychotics by virtue of their action on the serotonergic system as well as lesser degree of dopaminergic blockade could lead to lesser motor symptoms. Action on adrenergic and muscarinic receptors could lead to autonomic dysfunction. [13]

Among the atypical antipsychotics, it is important to note that NMS caused by Quetiapine was found to have poor outcome and NMS caused by Clozapine was found to have less severe presentations [13]. Most of the cases were prescribed dosing regimens as per the standard treatment guidelines. [42]

Another hypothesis is that these atypical presentations could actually be cases which were picked up early in the prodromal phase or before a syndromal presentation could occur. This highlights the need for adopting the spectrum concept of understanding NMS to account for the atypical presentations of NMS. [43]

4.3. Challenges in diagnosing atypical NMS

Since there is paucity of well-defined validated criteria for atypical

Table 3
Studies reporting atypical NMS.

SN	Authors & place of report	AgeSex	Diagnosis	Medical/surgical issues	Possible culprit drug	Duration after medication initiation/change	Clinching features of atypical NMS	Atypical feature	Criteria used
1	Teo et al., 2018 [21] Singapore	43 M	Treatment-Resistant Schizophrenia	DM Hypertension	Clozapine Quetiapine overdose Dose not mentioned	The same day of the overdose	Hyperthermia, altered mental status, autonomic instability, elevated serum CK (30,764 IU/L), elevated transaminases	Absence of rigidity	None
2	Leonardo et al., 2017 [22] Columbia	55 M	Schizophrenia	–	Clozapine 500 mg	Ten years	Rigidity, altered mental status, autonomic instability, elevated CK (12,446 IU/L)	Absence of hyperthermia	None
3	Collins et al., 2016 [23] UK	57 M	Schizophrenia with alcohol abuse	Pyelonephritis with ARF	Reduction of 100 mg depot Haloperidol from fortnightly administration to once every three weeks	One day after reduction	Altered mental status, autonomic instability, muscle rigidity and elevated CK (12,069 IU/L)	Absence of hyperthermia	None
4	Cherry et al., 2016 [24] Australia	67 M	Treatment-Resistant Schizophrenia	ARF, Hypertension, IHD, DM, Gout BPH	Concomitant Clozapine 200 mg with Risperidal Consta 50 mg depot fortnightly	20 days after initiation of Clozapine	Altered mental status, hyperthermia, incontinence, autonomic instability, elevated CK (8145 IU/L), upper limb tremor	Absence of rigidity	None
5	Zhao et al., 2015 [25] China	63 M	Schizophrenia	POD 3 of lung resection for a nodule in the right lung	Sudden discontinuation (day of operation) and reinstitution of Olanzapine 20 mg on POD 1	One day after reinstitution (POD 2)	Altered mental status, autonomic instability, muscle rigidity, elevated CK (2250 IU/L)	Absence of hyperthermia	None
6	Tseng et al., 2015 [26] Taiwan	41 F	Schizoaffective disorder		Cross titration of Clozapine 150 mg with Aripiprazole 30 mg Olanzapine 10 mg injection on day 10 of titration	Day 11 of titration	Muscular rigidity, autonomic instability, diaphoresis, altered mental status, incontinence, acute dystonia, leukocytosis, elevated CPK (45,824 IU/L), elevated liver enzymes	Absence of hyperthermia	Sachdeva criteria
7	Kamis et al., 2014 [27] Turkey	53 F	Schizophrenia	Hyperlipidemia, COPD	Clozapine intoxication Plasma clozapine = 1439 ng/mL	Not mentioned	Hyperthermia, altered mental status, autonomic changes (blood pressure abnormalities, diaphoresis, urinary incontinence) elevated CK (2158 IU/L), Leucocytosis	Absence of rigidity	None
8	Saritas et al., 2014 [28] Turkey	42 F	Bipolar Disorder	Subacute antero-posterior myocardial infarction	Olanzapine 10 mg	Five years	Hyperthermia, altered mental status, autonomic changes (hypotension, tachycardia urinary incontinence) elevated CK (4560 IU/L), leucocytosis	Absence of rigidity	None
9	Paul et al. 2010 [29] U.S	36 F	Bipolar disorder	Presumed Urinary Tract Infection, Acetaminophen toxicity	?Loxapine recently added to Lithium, Sertraline, Venlafaxine, Bupropion, Lamotrigine, and Trazodone	Not mentioned	Hyperthermia, altered mental status, autonomic instability, elevated CK (354,160 IU/L)	Absence of rigidity	None
10	Nopoulous et al., 2011 [30] USA	31 M	Schizophrenia	Left-sided high output cardiac failure	Clozapine 400 mg/day	Day 11 of Clozapine (Day 3 at 400 mg/day)	Hyperthermia, altered mental status, autonomic instability, elevated serum CK (955 IU/L)	Absence of rigidity	Levenson
11	Hall et al., 2004 [31] USA	79 M	Not established	Transient ischemic attacks, Seizures, Alzheimer dementia, fever of unknown origin	Olanzapine 10 mg/day plus 4 mg every 4 h as required	Not mentioned	Hyperthermia, altered mental status, autonomic instability, elevated serum CK (3822 IU/L)	Absence of rigidity	Caroff and Mann
12	Amore et al., 1997 [32] Italy	67 F	Bipolar disorder	–	Clozapine 300 mg/day	Day 38 of Clozapine at 300 mg/day	Hyperthermia, altered mental status, autonomic instability, elevated serum CK (1989 IU/L), Leucocytosis, elevated SGOT, SGPT, and LDH	Absence of rigidity	Not mentioned

(*continued on next page*)

Table 3 (*continued*)

SN	Authors & place of report	AgeSex	Diagnosis	Medical/surgical issues	Possible culprit drug	Duration after medication initiation/change	Clinching features of atypical NMS	Atypical feature	Criteria used
13	El-Gaaly et al., 2009 [33] Canada	57 M	Major depressive disorder	–	Quetiapine 100 mg/day	Day 8 of Quetiapine	Rigidity, altered mental status, autonomic fluctuation, elevated CK (3781 IU/L)	Absence of hyperthermia	DSM-IV-TR
14	Rais et al., 2008 [34] USA	13 F	Brief Psychotic disorder	History of asthma	Quetiapine 200 mg/day -Olanzapine 5 mg single dose -Chlorpromazine 25 mg i.m single dose	Not mentioned	Hyperthermia, altered mental status, autonomic instability, elevated CK (1102 IU/L), transaminases, leucocytosis	Absence of rigidity	DSM-4
15	Ferioli et al., 2004 [35] Italy	19 M	Schizoaffective disorder	–	Clozapine 1000 mg and Venlafaxine 900 mg	On the day of consumption	Fever, altered mental status, autonomic fluctuation, elevated CK (3702 IU/L), leucocytosis	Absence of rigidity	Not mentioned
16	Spivak, Adams and Crockford., 2003 [36] Canada	22 M	Schizophrenia	–	Two episodes of atypical NMS One at Clozapine 325 mg/day and other at Haloperidol 5 mg/day	On day 17 of Clozapine drug declined by the patient, and on day 18 he developed signs of NMS The 2nd episode on day 5 of Haloperidol	Fever, altered mental status, autonomic fluctuation, raised CK (1442 IU/L with Clozapine and 598 IU/L with Haloperidol)	Absence of rigidity	Not mentioned
17	Spalding et al., 2004 [37] USA	17 M	Schizophrenia		Aripiprazole 15 mg/day	Within three days of initiation	Rigidity, altered mental status, autonomic instability, elevated levels of CK (762 IU/L), aspartate aminotransferase (47 IU/L), alanine aminotransferase (49 IU/L), and blood urea nitrogen (22 mg/dL).	Absence of fever	Caroff and Mann
18	Misiaszek and Potter., 1985 [38] USA	26 M	Manic episode	–	Haloperidol 45 mg/day	2nd day of the hike of dose	Fever, altered mental status, autonomic instability, elevated CK (1683 IU/L)	Absence of rigidity	Not mentioned
19	Corallo et al., 2008 [39] Australia	50 M	Chronic Paranoid Schizophrenia	–	Clozapine 600 mg/day	Ten years	Fever, altered mental status, autonomic dysfunction, elevated CK (63,328 IU/L), hyponatremia, leukocytosis	Absence of rigidity	DSM-4-TR
20	Das et al., 2017 [40] India	32 M	Bipolar disorder		Asenapine 50 mg	Three days after intake	Fever, rigidity, altered mental status, elevated CK (3560 IU/L)	Absence of autonomic disturbances	Not mentioned

CK = Creatine Kinase; DSM = Diagnostic and Statistical Manual; F = Female; M = Male; USA = United States of America.
DM = Diabetes Mellitus, COPD = Chronic obstructive pulmonary disease, IHD = Ischaemic heart disease, BPH = Benign prostatic hyperplasia.
ARF = Acute renal failure, CVA = Cerebrovascular accident, POD = Post-op day.

NMS, the issues of overdiagnosis, as well as underdiagnosis of this entity are a wide area of concern. Many cases may not fulfil the criteria for the classical form of NMS and yet qualify for atypical NMS. However, due to lack of a well-defined criteria, such cases maybe given another diagnostic label. Along similar lines, many other entities such as benign extrapyramidal symptoms, serotonin syndrome, catatonia, malignant hyperthermia, infections of the central nervous system, delirium may mimic the presentation of atypical NMS and hence face the danger of being labelled the same. [11,20] These diagnostic errors may lead to the danger of the patient not being properly treated, hence, increasing the morbidity and mortality.

4.4. Limitations

Our review is bound by certain limitations. Firstly, the search was limited to articles published in English language only. Secondly, the search was done on PubMed and Google Scholar due to accessibility issues. Thirdly, thirteen articles were excluded from the review due to unavailability of full text articles. Finally, due to the nature of included literature, quantitative synthesis of data could not be carried out.

4.5. Implication of recognizing atypical NMS

The single most important implication is early identification and management of atypical presentations of NMS due to higher rates of morbidity and mortality associated with NMS. [44,45] Also, there are no reliable figures available on the prevalence of atypical NMS. Further, as seen in our review, many of the cases had medical comorbidities which could further complicate the diagnosis. Hence, there is need for developing criteria which are sensitive to diagnose atypical forms of NMS as well as for generating epidemiological data about atypical NMS.

5. Conclusion

Atypical NMS is characterized by absence of severe rigidity or hyperthermia/late appearance of fever in the presence of other symptoms of NMS in majority of cases. Atypical NMS is found to be similar to classical NMS in terms of male predilection. In contrast, it is more common in the age group of > 50 years of age. Atypical antipsychotics are more commonly associated with atypical NMS than typical antipsychotics. There is a need for development of criteria which are sensitive to diagnose atypical forms of NMS.

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