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SYSTEMATIC REVIEW

Second-Generation Antipsychotics and Neuroleptic Malignant Syndrome: Systematic Review and Case Report Analysis

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Abstract

Background Neuroleptic malignant syndrome (NMS) is a rare, severe, idiosyncratic adverse reaction to antipsychotics. Second-generation antipsychotics (SGAs) were originally assumed to be free from the risk of causing NMS, however several cases of NMS induced by SGAs (SGA-NMS) have been reported.

Objectives The aim of this study was to systematically review available studies and case reports on SGA-NMS and compare the presentation of NMS induced by different SGAs.

Data Sources Citations were retrieved from PubMed up to November 2013, and from reference lists of relevant citations.

Study Eligibility Criteria Eligibility criteria included (a) primary studies reporting data on NMS, with at least 50 % of the sample receiving SGAs; or (b) case reports and case reviews reporting on NMS induced by SGA monotherapy, excluding those due to antipsychotic withdrawal.

Study Appraisal and Synthesis Methods A standardized method for data extraction and coding was developed for the analysis of eligible case reports.

Results Six primary studies and 186 individual cases of NMS induced by SGAs were included. Primary studies suggest that SGA-NMS is characterized by lower incidence, lower clinical severity, and less frequent lethal outcome than NMS induced by first-generation antipsychotics. Systematic analysis of case reports suggests that even the most recently marketed antipsychotics are not free from the risk of inducing NMS. Furthermore, clozapine-, aripiprazole- and amisulpride-induced NMS can present with atypical features more frequently than other SGA-NMS, i.e. displaying less intense extrapyramidal symptoms or high fever.

Limitations Case reports report non-systematic data, therefore analyses may be subject to bias.

Conclusions and Implications of Key Findings Clinicians should be aware that NMS is virtually associated with all antipsychotics, including those most recently marketed. Although apparently less severe than NMS induced by older antipsychotics, SGA-NMS still represent a relevant clinical issue.

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Key Points

Neuroleptic malignant syndrome (NMS) induced by second-generation antipsychotics is characterized by lower incidence, lower clinical severity, and less frequent lethal outcome than NMS induced by first-generation antipsychotics.

Even the most recently marketed antipsychotics are not free from the risk of inducing NMS.

Clozapine-, aripiprazole- and amisulpride-induced NMS can present with atypical features more frequently than other SGA-NMS, i.e. displaying less intense extrapyramidal symptoms or high fever.

1 Introduction

Neuroleptic malignant syndrome (NMS) is a rare, unpredictable adverse reaction associated with antipsychotic use. It is generally characterized by rigidity, tremor, fever, dysregulated sympathetic nervous system hyperactivity, alterations of mental status, leukocytosis, and creatine kinase (CK) elevation [1]. If not promptly recognized and treated, NMS can lead to patient death or permanent damages, such as neurological sequelae [2, 3]. Second-generation antipsychotics (SGAs) were initially assumed to be free from the risk of inducing NMS because of their more favorable pharmacodynamic profile [4]; however, after they had been marketed, cases of NMS induced by SGAs (SGA-NMS) began to be reported, with the first case implicating clozapine [5]. Notably, several cases of NMS induced by clozapine (CLZ-NMS) presented with different clinical features than those of NMS induced by first-generation antipsychotics (FGA-NMS), i.e. lacking cardinal signs or symptoms. These observations led to the hypothesis that 'atypical' antipsychotics might determine 'atypical' forms of NMS on the basis of different pharmacological properties [6]. Furthermore, newer SGAs such as aripiprazole [7] and amisulpride [8] possess peculiar pharmacodynamic profiles [9, 10] which might be associated with different NMS presentation. At present, while it is commonly accepted that no antipsychotic is free from the risk of inducing NMS, there is still uncertainty on the clinical profile of SGA-NMS [6, 11].

SGAs are the most commonly prescribed antipsychotics [12] but our knowledge on SGA-NMS continues to be very limited given the intrinsic difficulties of studying NMS under experimental conditions. Of note, case reports remain one of the main sources of information for clinicians. Hence, there is still great uncertainty regarding SGA-NMS epidemiology [13, 14], diagnostic definition [1], presentation, clinical course, and pathophysiology [15], and possible influence of concomitant drugs [16]. Considerable time has elapsed since this topic was examined in a systematic fashion [6], hence our aim was to review the available evidence on SGA-NMS, considering both primary studies and case reports. In order to minimize the risk of bias in the interpretation of available evidence, a standardized approach was used to analyze the available information.

2 Methods

2.1 Search Strategy

The Pubmed database was searched using the following search string: <Malignant AND ('Antipsychotic Agents' [Mesh] OR amisulpride OR aripiprazole OR asenapine OR clozapine OR olanzapine OR paliperidone OR quetiapine OR risperidone OR ziprasidone OR iloperidone OR zotepine OR sertindole OR lurasidone)>. Two independent researchers screened and systematically assessed all retrieved references to identify (1) primary studies on SGA-NMS, i.e. those conducted on clinical samples; and (3) case reports or case reviews of SGA-NMS. All works published prior to November 2013 as well as relevant citations obtained from bibliographies were screened. In addition to citations in English, those written in Italian, Spanish, and French were included as two researchers were fluent in these languages.

2.2 Inclusion and Exclusion Criteria

For the review of primary studies, any study that reported data on NMS developed during a treatment course with any SGA was included. If studies were conducted on samples where NMS was developed during treatment with both FGAs and SGAs, only those where at least 50 % of participants were treated with SGAs were included.

For the review of case reports, the aim was to obtain the maximum degree of clinical homogeneity; hence, cases (a) with an unclear diagnosis of NMS, meaning that the reporting clinician did not explicitly state this diagnosis, irrespective of the set of diagnostic criteria that were used [1]; (b) where an SGA was given in association with another antipsychotic (either FGA or SGA) in the week preceding the diagnosis of NMS; and (c) where the NMS was apparently induced by withdrawal of an antipsychotic [15, 17], were excluded.

2.3 Data Extraction

For the case review, researchers extracted, coded, and analyzed relevant data available from case reports using a standardized method (described in detail in the Methods section of the Online Resource). Briefly, two researchers (AG and MB), blinded to each other, coded for each case detailed information on subject sociodemographic and clinical features, treatment with SGAs and other psychotropic drugs, NMS clinical presentation, course and management. In order to provide a description of the time course of NMS, all available data relative to the temporal sequence of events were extracted. An adapted version of the Francis–Yacoub NMS Rating Scale [18] was used to improve the homogeneity for the ratings of NMS severity.

2.4 Statistical Analysis

For all cases of SGA-NMS, a summary of descriptive data was reported, including demographic and clinical characteristics. Furthermore, to explore the presence of potential intraclass differences between cases of NMS prompted by different SGAs, exploratory statistical analyses were conducted comparing the demographic and clinical characteristics of cases by means of the Chi-square test and analysis of variance (ANOVA). Since description of the case reports was not conducted in a systematic fashion, a significant amount of missing data was expected; to provide the reader with an estimation of the representativity of results, the percentage of cases with missing data for each comparison is reported. Also, Pearson's correlation index (R) and Student's *t* test were used to test whether sociodemographic and clinical features of NMS showed associations with the global severity of NMS (expressed as the total severity score for each case). Statistical analyses were conducted including only the SGA-NMS groups where a sufficient number of NMS cases were available (setting an arbitrary threshold of ten cases per subgroup), using the Statistical Package for Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Search Results

The search yielded 918 citations (see Fig. S1 in the Online Resource). Of these, six primary studies were included in the review [11, 14, 19–22], while 247 case reports were potentially eligible for inclusion. After full-text review, 105 more citations were excluded, leading to the inclusion of 142 citations (case reports or case series). These accounted for 186 individual case reports of SGA-NMS. References for included case reports are included in the References section of the Online Resource. Table 1 reports the description of the included primary studies.

3.2 Case Report Analysis

Tables 2, 3 and 4 report data on cases of SGA-NMS that were considered for statistical analysis (n = 155): 42 cases of NMS were induced by olanzapine (OLA, mean dose 12 ± 5.8 mg), 44 by risperidone (RSP, mean dose 3.7 ± 3.2 mg), 19 by quetiapine (QUE, 335 ± 270 mg), 36 by clozapine (CLZ, 332 ± 263 mg), and 14 by aripiprazole (ARP, 18.9 ± 9.2 mg). Table 5 reports descriptive data of those cases of SGA-NMS for which only descriptive analyses are provided. These were induced by amisulpride (AMI, n = 7; mean dose 480 ± 179 mg), ziprasidone (ZPR, n = 6; 86.7 ± 46.8 mg), paliperidone (PAL, n = 4; 7.5 ± 1.7 mg), and zotepine (ZOT, n = 4; 325 ± 247 mg). Lastly, because of a low number of cases, ten cases of NMS induced by other antipsychotics (perospirone, clotiapine, tiapride, iloperidone, asenapine, remoxipride) were excluded from the review.

The majority of case reports did not specify which diagnostic criteria set was used for the diagnosis of NMS (n = 131, 70.1 %), whereas in the remainder of cases the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria were used most commonly (n = 35,18.7 %) [23], followed by the criteria of Levenson (n = 13, 7 %) [24], Sachdev (n = 3, 1.6 %) [25], Pope et al. (n = 2, 1.1 %) [26], and Caroff and Mann (n = 2, 1.1 %) [27].

3.3 Intraclass Comparison of Cases of Second-Generation Antipsychotic-Induced Neuroleptic Malignant Syndrome (SGA-NMS)

3.3.1 Sociodemographic, Clinical Features and Treatment with SGAs

Table 1 reports the comparison of subjects' sociodemographic and clinical features by each SGA-NMS. In the overall sample, the mean age was 41.5 ± 20.2. The majority were males (62.6 %), and the diagnoses were psychotic disorders (58.3 %), mood disorders (23.2 %), dementia (9.3 %), or other disorders (9.3 %). Half of the subjects receiving CLZ (50 %) and one-third of those treated with olanzapine (34.8 %) had already suffered from NMS in the past, whereas none of the subjects in the aripiprazole group (p = 0.04) had developed NMS.

Among those patients receiving risperidone and aripiprazole, more were antipsychotic-naïve than in the clozapine subgroup (41.2 and 38.5 vs. 4.0 %; p = 0.01). The mean reported doses of SGAs on the day of NMS insurgence were very similar between the five subgroups (p = 0.89).

Table 1 Studies on neuroleptic malignant syndrome induced by second-generation antipsychotics

References	Sample	Study design and data sources	Treatment	NMS criteria; no. of cases and estimate of incidence	Deaths [*n* (%)]	Main findings and limitations
Biswasl et al. [14]	1 Case of NMS; 8,858 subjects; 38 % F; mean age 43 ± 17 years; with SCZ, 39 %; PSY, 13 %; others 11 %; NS 33 %	Observational cohort study. Data on olanzapine prescriptions obtained from the NHS database through prescription-event monitoring method over a period of 2 years. Data on AEs collected through questionnaires sent to the GPs treating the subjects	OLA (100 %)	NS; 1/8.858 (0.056/ 1,000 × year)	None	Only one case of NMS reported, not lethal. EPS reported in 13 cases, more often among those aged 70 years and older than in younger subjects
Chen et al. [19]	50 Subjects with NMS; 44 % F; mean age 41 ± 14 years; with BD, 100 %. 800 controls without NMS matched for diagnosis, age, and date of BD insurgence	Case–control study. Data from medical claims database over a 5-year period. Cases with NMS identified from 154,474 subjects with BD, through spontaneous reports by treating physicians.	Cases: AP 34 %, of which 72 % were SGAs (OLA, 18 %; QUE, 28 %; RSP: 12 %; ZPR: 12 %; CLZ: 2 %); FGAs: 8 %; LIT: 10 %; BDZ: 16 %; APK: 8 %; AD: 30 %	ICD-9; 50/154.474 (0.064/ 1000*year))	None	NMS was associated with the use of AP (aOR 2.4), male gender (aOR 2.1), confusion (aOR 2.9), dehydration (aOR 4.0), delirium (aOR 4.9), and EPS (aOR 3.5). Notably, only 34 % of NMS cases had been classified as currently receiving AP; authors commented that most AP treatment likely had not been registered (paid out-of-pocket by patients)
Nakamura et al. [20]	210 Cases with SGA-NMS; INPT, 100 %; 42 % F; with psychiatric diagnoses and neurological diagnoses; 210 controls with FGA-NMS matched by AP exposure	Case–control study. Data from administrative claims database (Japanese Diagnosis Procedure Combination) registering admissions to general hospi-tals over a period of 4 years (n = 12 million). Cases and controls were selected from 1,585 admissions for NMS	Cases: SGAs, 100 % Controls: FGAs, 100 %	ICD-10; NA	SGAs: 7 (3.3) FGAs: 16 (7.6)	Compared with FGA-NMS, SGA-NMS were associated with fewer admissions to ICU (21 vs. 31 %; p = 0.02) and with lower mortality (aOR 0,44; p = 0.08) after adjusting for gender, age, and CVD CVD was associated with increased NMS-related mortality

Table 1 continued

References	Sample	Study design and data sources	Treatment	NMS criteria; no. of cases and estimate of incidence	Deaths [*n* (%)]	Main findings and limitations
Nielsen et al. [21]	83 Subjects with NMS; 48 % F; mean age 51 years; with PSY, 48 %; ORG, 31 %; MD, 16 %; NEUR, 5 % 415 Controls matched by sex, age, and diagnosis; PSY, 48 %; ORG, 31 %; MD, 16 %; NEUR, 5 %	Retrospective and case–control study. Data from the DPCRR over a period of 12 years (224,000 subjects) Cases and controls were followed for 3 months before and after NMS diagnosis	Cases: SGAs, 37 %; FGAs, 69 % (high potency, 17 %; medium potency, 23 %; low potency, 28 %; depot, 13 %); BDZ, 65 %; LIT, 12 % Controls: SGAs, 19 %; FGAs, 27 % (high potency, 4 %; medium potency, 10 %; low potency, 13 %; depot, 6 %); BDZ, 32 %; LIT, 4 %	ICD-10; 83/224.372 (0.031/ 1000*year)	7 (8.4)	In the general sample ($n = 83$), the risk of developing NMS was higher with lithium use (aOR 5.9; $p < 0.05$), depot (aOR 5.7; $p = 0.005$), SGAs (aOR 3.0; $p < 0.01$), benzodiazepine use (aOR 2.7; $p < 0.005$), and dose of AP (aOR 1.002; $p < 0.05$) In the group of patients treated with AP for 3 months before hospitalization ($n = 62$), the risk of developing NMS was higher with high-potency FGAs (aOR 23.4; $p < 0.001$), SGAs (aOR 4.7; $p = 0.001$), and depot AP (aOR 4.5; $p < 0.005$) Mortality within the first 30 days after NMS was higher among cases (HR 1.9; $p < 0.01$), especially females. Cases and controls were not matched by AP use, but for sex, age, and diagnosis
Trollor et al. [11]	165 Subjects with SGA-NMS; 27 % F; mean age 49 years; with PSY, 49 %; ORG, 2 %; MD, 3 %; ANX, 1 %; NS, 46 %. 43 controls with FGA-NMS; 30 % F; mean age 62 years; with PSY, 30 %; MD, 7 %; ORG, 2 %; other, 9 %; NS, 51 %	Retrospective study. Data from spontaneous NMS reporting in Australian ADRAC database over a period of 16 years Subjects in polytherapy were excluded ($n = 85$)	SGA-NMS: CLZ, 37 %; RSP, 16 %; OLA, 14 %; QUE, 7 %; AMI, 3 %; ARP, 2 %; PAL, 1 %	Delphi consensus; NA	SGAs: 3 %; FGAs: 16 %	Mortality rate in individuals with SGA-NMS was significantly lower than that of FGA-NMS, but the difference was reduced after adjusting for age. No other significant differences were found between the clinical presentation of SGA-NMS and that of FGA-NMS, except for clozapine-induced NMS that was characterized by a lower presence of rigidity and other EPS compared with other SGA-NMS

Table 1 continued

References	Sample	Study design and data sources	Treatment	NMS criteria; no. of cases and estimate of incidence	Deaths [*n* (%)]	Main findings and limitations
Su et al. [22]	67 Subjects with NMS; 36 % F; mean age 43 ± 18 years; with PSY, 46 %; BD, 27 %; SCZAFF,12 %; DEP, 4 %; others, 10 %; 254 controls matched (1:4) by age, gender, and diagnosis: PSY, 46 %; BD, 27 %; SCZAFF, 13; DEP, 5 %; others, 9 %	Case–control study. Data from the South London and Maudsley NHS Foundation Trust Case Register over a period of 9 years. At least one criteria for NMS diagnosis. Drugs were administered 5 (oral AP) or 15 (depot AP) days before the index date	48 % SGAs only, 18 % FGAs only, 4 % ARP only, 45 % polytherapy, 10 % depot only	Levenson, Addonizio, Pope (definite or probable), Caroff, Adityanjee, DSM-IV	Deaths: NA	In univariate analyses, FGAs were associated with an OR of NMS of 3.9 ($p < 0.001$), whereas SGAs were not associated with significantly higher risk of NMS, with the exception of ARP (OR 2.5; $p = 0.04$). In multivariate analyses, compared with SGAs, the OR for NMS was significant for FGAs (2.81; $p = 0.01$), SGA/FGA associated (5.52; $p < 0.001$), but not for ARP ($p = 2.43$). Fluctuant doses and non-White ethnicity were also significant risk factors for NMS NMS case definition was based on fulfilling at least one of the six criteria set, resulting in a high degree of diagnostic heterogeneity. Only one case fulfilled all six criteria

AEs adverse events, *AD* antidepressants, *ADRAC* Adverse Drug Reaction Advisory Commitee, *AMI* amisulpride, *ANX* Anxiety Disorders, *aOR* adjusted odds ratio, *AP* antipsychotic, *APK* antiparkinson agents, *ARP* aripiprazole, *BD* bipolar disorder, *BDZ* benzodiazepines, *CLZ* clozapine, *CVD* cardiovascular disease, *DEP* unipolar depression, *DPCRR* Danish Psychiatric Central Research Register, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition, *EPS* extrapyramidal symptoms, *F* female, *FGA* first-generation antipsychotic, *FGA-NMS* FGA-induced NMS, *GPs* general practitioners, *HR* hazard ratio, *ICD-9* International Classification of Diseases, 9th revision, *ICD-10* International Classification of Diseases, 10th revision, *ICU* intensive care unit, *INPT* inpatients, *LIT* lithium, *MD* mood disorder, *NA* not applicable, *NEUR* neurotic disorders, *NHS* National Health Service, *NMS* neuroleptic malignant syndrome, *NS* not specified, *OLA* olanzapine, *OR* odds ratio, *ORG* organic disorders, *PAL* paliperidone, *PSY* psychotic disorders, *QUE* quetiapine, *RSP* risperidone, *SCZAFF* schizoaffective disorder, *SCZ* schizophrenia, *SGA* second-generation antipsychotic, *SGA-NMS* SGA-induced NMS, *ZPR* ziprasidone

Table 2 Cases of neuroleptic malignant syndrome induced by olanzapine, quetiapine, risperidone, aripiprazole, and clozapine

	OLA (n = 42)	QUE (n = 19)	RSP (n = 44)	ARP (n = 14)	CLZ (n = 36)	Missing [n (%)]	Statistics
Gender [female; %]	33.3	42.1	50	42.9	22.2	–	$\chi^2 = 7.18$, $df = 4$, $p = 0.13$
Age [years; mean ± SD]	46.2 ± 22.4	45.3 ± 18.8	39.6 ± 21.2	32.1 ± 18.2	39.9 ± 16.3	–	$F = 1.68$, $df = 4$, $p = 0.16$
Ethnicity [Caucasian; %]	41.2	42.9	55	60	87.5	93 (60)	$\chi^2 = 9.74$, $df = 12$, $p = 0.64$[c]
Diagnosis [%]						4 (2.6)	$\chi^2 = 13.99$, $df = 12$, $p = 0.3$
Psychotic disorders	52.5	44.4	50	71.4	77.1		
Mood disorders	25	27.8	25	21.4	17.1		
Dementia	15	15	9.1	–	2.9		
Other	7.5	7.5	15.9	7.1	2.9		
Previous NMS [%]	34.8	12.5	12.5	0	50	119 (76)	$\chi^2 = 9.74$, $df = 4$, $p = 0.04$*[c]
AP naive [%]	26.7	15.4	41.2	38.5	4.0	40 (26)	$\chi^2 = 12.15$, $df = 4$, $p = 0.02$*,[c]
Dose [mg; mean ± SD]	12.1 ± 5.9	335 ± 270	3.7 ± 3.2	18.9 ± 9.2	332 ± 263	23 (15)	–
CPZ eq [mean ± SD]	253 ± 124	236 ± 190	279 ± 240	295 ± 144	308 ± 243	23 (15)	$F = 0.48$, $df = 4$, $p = 0.75$
Dose increase [%][a]	33.3	15.8	25	50	36.1	–	$\chi^2 = 5.71$, $df = 4$, $p = 0.22$
Dose increase ≥50 [%][b]	30.0	10.5	25	50	33.3	–	$\chi^2 = 6.87$, $df = 4$, $p = 0.14$
Other treatments [%]							
SSRI	11.9	10.5	11.4	7.1	2.8	31 (20)	$\chi^2 = 2.54$, $df = 4$, $p = 0.64$
Other AD	4.8	5.3	6.8	0	2.8	31 (20)	$\chi^2 = 1.49$, $df = 4$, $p = 0.83$
LIT	11.9	5.3	13.6	7.1	13.9	31 (20)	$\chi^2 = 1.38$, $df = 4$, $p = 0.85$
Other MS	21.4	10.5	13.6	7.1	8.3	31 (20)	$\chi^2 = 3.7$, $df = 4$, $p = 0.45$

AD antidepressant, *AP* antipsychotic, *ARP* aripiprazole, *CLZ* clozapine, *CPZ eq* chlorpromazine equivalents, *df* degrees of freedom, *LIT* lithium, *NMS* neuroleptic malignant syndrome, *OLA* olanzapine, *QUE* quetiapine, *RSP* risperidone, *SSRI* selective serotonin reuptake inhibitor, *MS* mood stabilizers, *SD* standard deviation

* $p < 0.05$

[a] Any dose increase of AP in the 5 days preceding NMS onset

[b] Percentage of dose increase was calculated as 100 % when the APs were newly introduced in the 5 days before NMS diagnosis

[c] Missing values over 25 %

Instead, a steep dose titration before NMS was found more frequently in the aripiprazole group than in the quetiapine group (50 vs. 10.5 %; $p = 0.04$). Olanzapine, quetiapine, and risperidone were more often associated with antidepressant use than clozapine and aripiprazole. Lithium was prescribed to 5.3 % of participants using quetiapine and up to 13.9 % of those taking clozapine.

3.3.2 NMS Clinical Features

The comparisons of the prevalence, duration, and severity of NMS symptoms are reported in Table 3. The clinical presentation of NMS showed significant differences according to the SGA used; rigidity and tremor were less frequent in CLZ-NMS than in other subgroups ($p < 0.01$ and $p = 0.03$, respectively). While a degree of hyperpyrexia was almost ubiquitary, higher temperatures were less commonly observed for aripiprazole (58.3 %) than other SGAs, but this difference did not reach statistical significance ($p = 0.10$). Diaphoresis was constant or very frequent in olanzapine, quetiapine, and clozapine (100, 100, and 94 %, respectively), less frequent in risperidone (75 %), and in cases of aripiprazole-induced NMS (ARP-NMS) [42.9 %; $p = 0.001$]. Considering laboratory tests, both CK elevation and leukocytosis were very frequent without showing intra-class differences.

Global severity was significantly lower for CLZ–NMS than risperidone-induced NMS (RSP-NMS) [$p = 0.02$] or olanzapine-induced NMS (OLA-NMS) [$p = 0.03$]. There was no significant association between global severity and age ($r = 0.07$, $p = 0.48$), gender ($t = 1.37$, $p = 0.17$), diagnoses ($F = 0.18$, $p = 0.91$), antipsychotic dose ($r = 0.08$, $p = 0.44$) or percentage of dose increase in the preceding week ($r = 0.13$, $p = 0.48$), use of mood stabilizers ($t = 0.49$, $p = 0.69$) or benzodiazepines ($t = 0.76$, $p = 0.45$) in the preceding week. There was a statistical trend for an association between antidepressant use in the past week and a higher global severity (37.0 ± 9.6 vs. 32.4 ± 8.7; $p = 0.08$) but this disappeared after adjusting for the type of antipsychotic.

There were differences in the timing of the onset of some symptoms between the SGA-NMS subgroups (see Table 5), although no comparison reached statistical

Table 3 Clinical features of neuroleptic malignant syndrome induced by olanzapine, quetiapine, risperidone, aripiprazole, and clozapine

	OLA (n = 42)	QUE (n = 19)	RSP (n = 44)	ARP (n = 14)	CLZ (n = 36)	Missing [n (%)]	Statistics
Symptoms [%]							
Mental status change	100	85.7	88.2	100	96.6	33 (21)	$\chi^2 = 7.195$, $df = 4$, $p = 0.13$
Rigidity	91.4	92.3	94.1	100	67.6	27 (17)	$\chi^2 = 15.472$, $df = 4$, $p < 0.01$*
Tremor	92.3	100	91.7	81.8	44.4	107 (69)	$\chi^2 = 10.596$, $df = 4$, $p = 0.03$*[d]
Other EPS	84.6	71.4	66.7	83.3	58.3	105 (68)	$\chi^2 = 2.691$, $df = 4$, $p = 0.61$[d]
Hyperpyrexia	88.9	92.3	97.3	84.6	91.4	21 (14)	$\chi^2 = 2.79$, $df = 4$, $p = 0.59$
Temperature ≥38 °C	79.4	78.9	94.3	58.3	79.2	31 (20)	$\chi^2 = 13.386$, $df = 8$, $p = 0.10$
Diaphoresis	100	100	75	42.9	95	90 (58)	$\chi^2 = 19.467$, $df = 4$, $p = 0.001$*[d]
BP alteration	88.2	90	73.7	76.9	81	58 (37)	$\chi^2 = 2.499$, $df = 4$, $p = 0.64$[d]
Tachycardia	100	100	95.7	91.7	100	45 (29)	$\chi^2 = 5.067$, $df = 4$, $p = 0.28$[d]
Tachypnea	70	100	70	60	100	113 (73)	$\chi^2 = 5.163$, $df = 4$, $p = 0.27$[d]
Dysphagia	13.2	8.7	17.6	15.4	11.1	51 (27)	$\chi^2 = 1.139$, $df = 4$, $p = 0.89$[d]
Other autonomic symptoms	14.3	15.8	25	35.7	25	–	$\chi^2 = 3.845$, $df = 4$, $p = 0.43$
Laboratory tests							
CK elevation [%]	97.4	91.7	97.1	92.3	85.2	18 (11)	$\chi^2 = 4.885$, $df = 4$, $p = 0.30$
CK [100 UI/l; mean ± SD]	22.8 ± 55.0	29.1 ± 47.8	57.3 ± 15.5	24.8 ± 63.6	11.2 ± 41.9	33 (21)	$F = 1.347$, $df = 4$, $p = 0.33$
CK peak [100 UI/l; mean ± SD]	48.1 ± 65.5	54.8 ± 57.1	85.0 ± 178.9	35.9 ± 65.6	54.6 ± 121.7	33 (21)	$F = 0.569$, $df = 4$, $p = 0.69$
Leukocytosis [%][a]	80.0	80	70.8	70.0	75	54 (35)	$\chi^2 = 0.824$, $df = 4$, $p = 0.94$[d]
WBC [1,000 U/l; mean ± SD]	14.3 ± 7.6	11.9 ± 4.8	15.3 ± 5.2	15.5 ± 5.4	13.9 ± 6.0	78 (50)	$F = 0.443$, $df = 4$, $p = 0.78$[d]
Symptom duration [days; mean ± SD]	8 ± 5.4	13.7 ± 8.4	9.7 ± 9.8	7.5 ± 3.0	10.4 ± 9.9	65 (42)	$F = 1.174$, df = 4, $p = 0.33$[d]
NMS severity [points; mean ± SD][b]	35.3 ± 8.3	31.1 ± 8	36.3 ± 8.3	31.6 ± 10.1	28.8 ± 8.3	57 (36)	$F = 3.3$, $df = 4$, $p = 0.01$*[d]
Timing of NMS symptoms[c]							
Mental status change	1.0	0.5	1.5	0.8	1.0	57 (36)	$F = 0.319$, $df = 4$, $p = 0.86$[d]
Rigidity	1.2	0.3	1.5	1.1	−1.2	48 (30)	$F = 1.163$, $df = 4$, $p = 0.33$[d]
Tremor	1	0.7	1.7	1.1	0.0	115 (74)	$F = 0.183$, $df = 4$, $p = 0.94$[d]
Other EPS	1.9	0.3	3.4	1.6	2.0	–	$F = 0.040$, $df = 4$, $p = 0.99$
Diaphoresis	0.7	0.8	−0.1	0.0	1.4	103 (66)	$F = 0.212$, $df = 4$, $p = 0.93$[d]
Hyperpyrexia	0.7	0.1	0.7	−2.2	2.2	43 (27)	$F = 1.363$, $df = 4$, $p = 0.25$[d]
Tachycardia	−0.4	0.3	−0.2	−3.3	1.4	61 (39)	$F = 1.992$, $df = 4$, $p = 0.10$[d]
Tachypnea	−1.1	0.2	−0.5	0.0	−0.5	113 (72)	$F = 0.373$, $df = 4$, $p = 0.83$[d]
BP alteration	−0.1	0.1	−0.1	0.2	0.4	74 (47)	$F = 0.282$, $df = 4$, $p = 0.89$[d]
Other autonomic disorders	5.3	0.0	2.7	0.0	3.0	–	$F = 0.539$, $df = 4$, $p = 0.71$
CK	−0.7	0.0	0.0	−3.6	−0.4	42 (27)	$F = 1.939$, $df = 4$, $p = 0.11$[d]

Table 3 continued

	OLA (n = 42)	QUE (n = 19)	RSP (n = 44)	ARP (n = 14)	CLZ (n = 36)	Missing [n (%)]	Statistics
Leukocytosis	0.5	−0.1	0.0	0.0	−0.6	69 (44)	$F = 0.861$, $df = 4$, $p = 0.49$[d]

ARP aripiprazole, *BP* blood pressure, *CK* creatine kinase, *CLZ* clozapine, *df* degrees of freedom, *EPS* extrapyramidal symptoms, *NMS* neuroleptic malignant syndrome, *OLA* olanzapine, *QUE* quetiapine, *RSP* risperidone, *SD* standard deviation, *WBC* white blood cells

* $p < 0.05$

[a] White blood cell count >1,000 U/l

[b] Estimated with our adaptation of the Francis–Yacoub NMS rating scale

[c] Mean distance in days between each symptom onset and the day of NMS onset. Positive values represent symptoms that started before NMS diagnosis, while negative values represent symptoms that were shown after NMS diagnosis

[d] Missing values over 25 %

significance. For olanzapine and clozapine, the first symptoms to appear were autonomic disorders (nausea, vomiting, and fecal and urinary incontinence), while for risperidone and aripiprazole, the first symptoms to appear were extrapyramidal symptoms (EPS; akathisia, diskinesia, bradikinesia, myoclonus, hyperreflexia, hyporeflexia). Quetiapine-induced NMS (QUE-NMS) seemed to appear suddenly, showing most symptoms on the same day, with the exception of diaphoresis and tremor. In most cases, rigidity and tremor appeared rapidly, particularly in RSP-NMS (mean 1.5 and 1.7 days before NMS diagnosis, respectively), while in CLZ-NMS, hyperpyrexia and tachycardia were early symptoms (2.2 and 1.4 days before NMS diagnosis, respectively). Finally, CK elevation always followed the NMS date, particularly in the aripiprazole subgroup.

3.3.3 NMS Management and Clinical Outcomes

Table 4 reports the comparison of clinical management between the subgroups of SGA-NMS. Only one-third of patients required intubation and transfer to the intensive care unit (ICU), with no intraclass differences. Antiparkinsonian drugs were used in approximately half of the cases in the risperidone and aripiprazole subgroups, and in one third of those in the olanzapine and clozapine groups ($p = 0.07$).

Complete recovery was the most frequent outcome, with highest rates in the risperidone groups (87.9 %) and the lowest in the quetiapine groups (61.5 %; $p = 0.37$). Overall, a fatal outcome was reported in less than 10 % of cases—from no reported cases for aripiprazole to 7.1 % for clozapine, and 7.7 % for those receiving quetiapine ($p = 0.81$). Exploratory analyses showed that lethal cases were older in age than non-lethal cases (59.5 ± 14 vs. 40.0 ± 20.5; $t = 2.64$; $p = 0.009$), while they did not differ significantly in terms of gender ($p = 0.47$) or previous use of antipsychotic ($p = 0.81$). The dose of antipsychotic in chlorpromazine equivalents was even lower, although not significantly (295 ± 209 vs. 141 ± 102; $t = 1.63$; $p = 0.11$). Use of mood stabilizers was not associated with death ($p = 0.62$), while the use of an antidepressant in the preceding week showed a more frequent trend in lethal cases than in non-lethal cases (37.5. vs. 12.4 %; $\chi^2 = 4.00$; $p = 0.08$), that persisted after adjusting for age ($p = 0.07$).

4 Discussion

The aim of this review was to systematically examine the available evidence on NMS induced by SGAs. Primary studies suggest that SGA-NMS differs from FGA-NMS in

Table 4 Clinical management of neuroleptic malignant syndrome induced by olanzapine, quetiapine, risperidone, aripiprazole, and clozapine

	OLA (n = 42)	QUE (n = 19)	RSP (n = 44)	ARP (n = 14)	CLZ (n = 36)	Missing [n (%)]	Statistics
NMS treatment [%]							
ICU and intubation	35.7	30.0	24.2	38.5	29.2	47 (30)	$\chi^2 = 1.38$, $df = 4$, $p = 0.85$[a]
Any antiparkinsonian	34.4	40	59.0	53.8	27.6	27 (17)	$\chi^2 = 8.52$, $df = 4$, $p = 0.07$
Dopaminergic	30.3	40	53.8	38.5	27.6	26 (17)	$\chi^2 = 6.27$, $df = 4$, $p = 0.18$
Anticholinergic	3.1	6.7	10.3	23.1	3.4	27 (17)	$\chi^2 = 6.30$, $df = 4$, $p = 0.18$
Myorelaxants	51.5	86.7	48.7	61.5	51.3	26 (17)	$\chi^2 = 7.21$, $df = 4$, $p = 0.13$
Outcome [%]							
Complete recovery	75	61.5	87.9	81.8	80	50 (32)	$\chi^2 = 4.32$, $df = 4$, $p = 0.37$[a]
Death	6.5	7.7	2.9	0	7.1	36 (23)	$\chi^2 = 1.64$, $df = 4$, $p = 0.81$

ARP aripiprazole, *CLZ* clozapine, *df* degrees of freedom, *ICU* intensive care unit, *NMS* neuroleptic malignant syndrome, *OLA* olanzapine, *QUE* quetiapine, *RSP* risperidone

[a] Missing values over 25 %

regard to its epidemiology, clinical features, and outcomes. Furthermore, the analysis of case reports of SGA-NMS highlighted the presence of clinical heterogeneity among NMS induced by different SGAs, particularly for clozapine, aripiprazole, and amisulpride.

4.1 Comparison Between SGA-NMS and First-Generation NMS

Almost 30 years have elapsed since Pope and colleagues reported the first case of NMS induced by an atypical antipsychotic [5]. Despite this, the knowledge on SGA-NMS is still quite limited and few studies have been conducted with a systematic methodology. Available evidence suggests that NMS is less frequent during treatment with SGAs than with FGAs. Two studies collected spontaneous reporting from pharmacovigilance databases and estimated an annual incidence of SGA-NMS at 0.056/(1,000 × year) in patients receiving olanzapine [14] and 0.064/(1,000 × year) among patients receiving various SGAs [19], whereas a recent meta-analysis indicated that SMN occurred in 0.17–32 persons for every 1,000 receiving FGAs [13]. However, both figures relative to FGAs and SGAs should be considered only indicative given that epidemiological data on SMN are affected by significant methodological bias. Furthermore, the meta-analysis reporting data on FGA-NMS is more likely to have overestimated its prevalence since it included studies that were mostly conducted on inpatients, among whom NMS tends to occur more frequently. However, in a direct comparison, SGAs were still associated with an almost threefold higher probability of incident NMS than FGAs [22].

A few significant risk factors for SGA-NMS could be identified, i.e. male gender, confusion, dehydration, delirium, and EPS in one study [19], and non-White ethnicity, number of antipsychotics, use of aripiprazole, and increasing/fluctuant dosing patterns in another [22]. This is broadly similar to findings on FGA-NMS, although data are still too limited to draw meaningful comparisons [28, 29].

Only one study directly compared the clinical features of SGA-NMS and FGA-NMS, and did not find overall between-class differences. However, it is noteworthy that CLZ-NMS alone was characterized by less rigidity and EPS than other SGAs [11]. Other studies also suggested that SGA-NMS was associated with a less severe clinical picture than FGA-NMS, since the authors found lower rates of admissions to the ICU [20], and lower mortality rates than for FGA-NMS [11, 20]. In our case review, eight cases of SGA-NMS were lethal, from a total of 145 cases that reported this information (5.5 %). Therefore, the mortality rate seems to be much lower for SGA-NMS than previous estimates of 10–20 % among cases of FGA-NMS [30, 31]. Consistent with other reports, in our analysis lethal cases tended to occur in older individuals [11, 31].

4.2 NMS Induced by SGAs

Newer antipsychotics are commonly grouped under the umbrella term of ‘atypical’ or ‘second-generation’ compounds, given their relative freedom from risks of adverse extrapyramidal effects [4, 11]. However, it was well established that each SGA possesses specific pharmacokinetic and pharmacodynamic properties, as well as different profiles of clinical effects and toxicity [9, 10]. Pharmacological properties might constitute the basis of intraclass differences in the expression of SGA-NMS.

4.2.1 Olanzapine

Cardinal signs of NMS were present in the vast majority of cases of OLA-NMS, while 10–20 % did not display EPS or

Table 5 Neuroleptic malignant syndrome induced by amisulpride, paliperidone, ziprasidone, and zotepine

	AMI (n = 7)	PAL (n = 4)	ZPR (n = 6)	ZOT (n = 4)	Missing [n (%)]
Gender, female	28.6	50	66.7	25	–
Age [years; mean ± SD]	47.6 ± 18.9	39.5 ± 24.7	35 ± 16.1	52.5 ± 13.6	–
Ethnicity [Caucasian; %]	33.3	100	–	40	18 (60)
Diagnosis [%]					
Psychotic disorders	42.9	75	66.7	100	
Mood disorders	28.6	–	33.3	–	
Dementia	28.6	–	–	–	
Other	–	25	–	–	
Mean dose [mean ± SD][a]	480 ± 179	7.5 ± 1.7	86.7 ± 46.8	325 ± 247	8 (26.7)
Symptoms [%]					
Mental status change	100	100	100	100	2 (6.7)
Rigidity	83.3	100	80	100	5 (16.7)
Diaphoresis	75	100	100	100	12 (38.7)
Hyperpyrexia	71.4	100	100	100	3 (10)
Temperature ≥38 °C	50	50	50	66.7	4 (13.3)
Tachycardia	80	100	100	100	10 (33.3)
Tachypnea	–	–	33	–	24 (80)
BP alteration	83.3	75	83.3	–	7 (23.3)
Other autonomic symptoms	100	25	33.3	–	–
Tremor	–	100	100	50	17 (56.7)
Other EPS	–	100	100	–	23 (76.7)
Laboratory tests					
CK [100 UI/l; mean ± SD]	77.9 ± 62.9	74.2 ± 129	319 ± 437	21.3 ± 37.3	–
CK peak [100 UI/l; mean ± SD]	79.5 ± 61.5	76.7 ± 128	382 ± 475	392 ± 392	3 (10)
Leukocytosis [%]	80	50	80	100	10 (33.3)
WBC [1,000 U/l; mean ± SD]	16.6 ± 4.8	16.2	20 ± 9.4	15.3 ± 2.9	15 (50)
Symptom duration [days; mean ± SD]	10.5 ± 5.8	14.2 ± 5.7	10.4 ± 1.5	15.0 ± 1.5	12 (40)
Outcome [%]					
Complete recovery	80	100	75	100	10 (33.3)
Death	20	–	–	–	7 (23.3)

AMI amisulpride, *BP* blood pressure, *CK* creatine kinase, *EPS* extrapyramidal symptoms, *PAL* paliperidone, *SD* standard deviation, *WBC* white blood cells, *ZPR* ziprasidone, *ZOT* zotepine

[a] Mean dose on the day of NMS onset

high fever. On average, symptoms of autonomic imbalances were only slightly more frequent in OLA-NMS than in other SGA-NMS, but were often the first signs to appear (up to 5 days prior to NMS diagnosis), followed by EPS and mental status change, and then diaphoresis and fever. Nausea was rare, consistent with established olanzapine antiemetic properties [32], except when it was administered together with sertraline [33] or valproate [34]. Among the most peculiar clinical cases that were reported, OLA-NMS displayed severe neurological symptoms, such as coma [35], hemiplegia [36], ataxia [37], and seizures [38]. Overall, OLA-NMS was reported to be quite rare [14], but several cases have been described in patients taking psychoactive drugs other than antipsychotics, such as antidepressants or mood stabilizers. In these cases, the resulting clinical picture was often characterized by a higher global severity, and resulted in substantial mortality rates. In general, despite the fact that OLA-NMS might present with a different clinical picture than those of typical FGA-NMS, these findings do not seem sufficient to justify the definition of an atypical presentation, as was also noted by previous authors [6, 39, 40].

4.2.2 *Quetiapine*

The average age of cases suffering from QUE-NMS was high, although one case was reported in a 4-year-old patient [41]. Clinically, QUE-NMS was characterized by the constant presence of EPS and pronounced autonomic symptoms, such as diaphoresis, tachycardia, tachypnea,

and blood pressure alterations. In particular, the latter symptoms might be related to its inhibition of noradrenaline reuptake, α-adrenergic and histaminergic antagonism, and also to serotonin-related toxicity [10]. Of note, this clinical picture was observed in spite of similar patterns in the prescription of other psychotropic drugs, such as antidepressants or mood stabilizers. Symptoms of QUE-NMS seemed to have their onset synchronously, on average a day before the diagnosis of NMS was made. Furthermore, QUE-NMS had the longest duration among SGA-NMS. Together, these elements suggest that an abrupt onset prompted an early diagnosis of NMS by the reporting clinicians, thus prolonging the observation period. The mean severity index was in the low range, but the observed outcomes were overall poor, despite patients received similar supportive treatments as in other SGA-NMS. This is in apparent contrast with previous case reports [6, 42], but might be explained by the higher age of the subjects, which is a significant predictor of negative outcomes [11, 43]. In addition, symptoms of autonomic dysfunction were given a smaller weight than other dimensions of NMS in the rating of clinical severity [18], and this might have led to a relative underestimation of the severity of QUE-NMS. Overall, the clinical picture of QUE-NMS seems similar to that of OLA-NMS, which is consistent with several commonalities in their pharmacological profiles [10]; this suggests caution in the definition of an 'atypical' presentation.

4.2.3 Risperidone

Since publication of the review by Trollor and colleagues [6], ten cases of RSP-NMS have been published. Overall, RSP-NMS was frequently observed among younger patients, more often neuroleptic-naïve, who mostly developed full-blown, severe clinical presentations. Notably, the presentation of RSP-NMS was characterized by marked EPS, high temperatures, and great elevations of the indexes of rhabdomyolysis. Among autonomic signs, tachycardia was more common than diaphoresis (96 vs. 75 %). On average, most cardinal signs of NMS had already appeared 1–3 days prior to the formal diagnosis of NMS, while the onset of fever was recorded only 0.7 days earlier. It seems likely that fever could have been the sign that led clinicians to perform further laboratory tests, often carried out on the same day of the diagnosis. One-third of cases of RSP-NMS also showed other autonomic gastrointestinal symptoms, such as vomiting, diarrhea, or sialorrhea, which generally appeared early in its course. Furthermore, 17 % of cases of RSP-NMS presented with dysphagia; notably, this symptom has also been described as a dose-dependent, reversible side effect of risperidone, closely related to EPS [44]. After the onset of full-blown NMS, signs of cardiorespiratory dysregulation appeared in most cases. In anecdotal cases, RSP-NMS was even accompanied by acute pancreatitis [45] or dermatologic lesions [46]. RSP-NMS was treated promptly with high doses of antiparkinsonian drugs and, despite it being significantly more severe than other SGA-NMS, it often led to complete recovery. Overall, the descriptions provided by available clinical cases are largely compatible with a 'typical' presentation [42, 47].

4.2.4 Aripiprazole

Since last review on this topic [6], five more cases of ARP-NMS have been published, with similar characteristics to those that were already available. Although aripiprazole was given at standard doses, half of the cases of NMS seemed to be triggered by a relatively fast titration scheme. Clinical presentation of ARP-NMS was characterized by the constant presence of rigidity and mental status changes, the highest rates of nausea and vomiting, and by a lower frequency of hyperpyrexia, diaphoresis, and tachypnea than other SGA-NMS. Despite all cases suffering rigidity and frequent EPS of other types, rhabdomyolysis seemed to be associated with lower peaks of CK. All the main symptoms appeared earlier or on the same day of NMS diagnosis, with the exception of hyperpyrexia (mean 2.2 days later than the diagnosis). Fever was also less severe than for other SGA-NMS. The severity and duration of NMS was lower than for other SGA-NMS, possibly related to the peculiar pharmacodynamic profile of aripiprazole. In fact this compound not only exerts partial agonist activity on the D_2 receptor but also on the D_3 D_4 and 5-HT_{1A} receptors [10]. A wide proportion of cases with ARP-NMS were younger in age and were promptly admitted to the ICU, which might be the reason for the absence of mortality. Overall, the clinical picture of ARP-NMS might be considered, at least in part, 'atypical' due to a lower incidence of high fever and diaphoresis.

4.2.5 Clozapine

Since the publication of the review by Trollor and colleagues [6], five more reports of CLZ-NMS have been published. Cases of CLZ-NMS were characterized by rapid dose increases, limited concurrent use of antidepressants or mood stabilizers, and high rates of previous treatments with other antipsychotics. Furthermore, patients suffering CLZ-NMS had a more frequent clinical history of previous NMS. Tachycardia, tachypnea, blood pressure lability, and other autonomic symptoms were very frequent and severe, possibly related to the high affinity of clozapine for adrenergic and muscarinic receptors [48]. Fever was often one of the first symptoms to appear, together with

autonomic dysfunction, and this clinical picture often made it necessary to rule out clozapine-related agranulocytosis [49]. In fact, increases of CK were lower and delayed [50] and EPS were generally more rare, consistent with the lower affinity of clozapine for D_2 receptors [51]. EPS appeared at various stages along the course of CLZ-NMS, often as mild early signs which were followed by tremor and, only after a mean of 1.2 days from the diagnosis of NMS, rigidity. Overall, the duration of CLZ-NMS was longer than other SGA-NMS but was associated with lower clinical severity. Consistently, cases of CLZ-NMS received, less frequently, antiparkinsonian agents and admission to the ICU; high mortality rates could have derived from possible underestimation of its severity. The rarity of EPS in the context of CLZ-NMS has been previously noted [11, 52, 53], and underlines the need for taking NMS in consideration even when a full-blown clinical picture is absent. On the other side, some authors have argued that some of these cases would fall outside the boundaries of stringent diagnostic classifications, therefore they should not diagnosed as NMS in the first place [53]. However, there is little doubt that the presentation of CLZ-NMS can be considered as the most atypical among SGA-NMS [6, 11].

4.2.6 *Amisulpride*

Despite several decades of amisulpride use, only seven cases of amisulpride-induced NMS (AMI-NMS) have been described [8, 54–59]. Most cases occurred in older males. Among the cases of AMI-NMS, four occurred following an increase in the dose of the drug, and one led to the death of the patient. The clinical picture was characterized by the constant presence of mental status alterations, frequent rigidity (83 %), and high levels of CK. Instead, high fever, other EPS, and other autonomic symptoms were less frequently reported than in other SGA-NMS. Based on these findings some authors, but not all [11], have advocated for an 'atypical' presentation of AMI-NMS [57, 58]. Furthermore, similar to CLZ-NMS, the duration of symptoms appeared to be slightly longer than for other SGA-NMS; this could reflect the fact that patients received less prompt or intensive clinical management. Considering its pharmacologic properties, amisulpride has a peculiar mechanism of action that relies on a delayed pattern of D_2/D_3 receptor occupancy, involving also presynaptic mechanisms with an apparent specificity for mesolimbic pathways. These features are thought to be related to its low capacity to induce EPS, and might also explain the low occurrence of NMS with this drug [60]. Furthermore, amisulpride has a low affinity for muscarinic, α-adrenergic, serotonergic, and histamine receptors, which could explain the lower induction of autonomic dysfunction [61].

4.2.7 *Paliperidone*

PAL is the main active metabolite of RSP and has a similar receptor profile, being a D_2 receptor antagonist—although with lower affinity than RSP- and a 5-HT_{2A} antagonist [62]. Only four cases of NMS were induced by paliperidone [63–66], three of which emerged in patients suffering from schizophrenia, and appeared when subjects were treated at doses of 6–9 mg. Most cases had been previously treated with other SGAs, with recent cross-titration schemes or dose increases. Paliperidone-induced NMS (PAL-NMS) was characterized by a typical presentation, with nearly all cases presenting with mental status alteration, rigidity, diaphoresis, hyperpyrexia (even if only half of the cases reached a temperature higher than 38 °C), tremor, and other EPS. All cases had a favorable evolution, with complete recovery of patients.

4.2.8 *Ziprasidone*

Six cases of ziprasidone-induced NMS (ZPR-NMS) were included [67–72], whereas a previous review examined five cases [6]. The mean age of patients was 35 years; two-thirds of patients were females and the same proportion was diagnosed with a psychotic disorder. The onset of NMS was generally abrupt, with most cases displaying typical symptoms such as alterations of mental status, diaphoresis, hyperpyrexia, tachycardia, blood pressure alterations, leukocytosis, tremor, and other EPS. Levels of CK were very high and became evident soon after the onset of the syndrome; however, only half of the cases reached a temperature higher than 38 °C. Notably, in two cases rigidity was absent [67, 72], while in one case it superimposed on pre-existing Parkinson's disease [68]. Hence, the effective presence of rigidity might be lower for ZPR-NMS than for other SGA-NMS, consistent with a lower affinity for D2 receptors [73]. The overall outcome of ZPR-NMS was generally favorable; no case was lethal and most patients underwent complete recovery within 10 days of diagnosis.

4.2.9 *Zotepine*

Zotepine is an atypical antipsychotic antagonizing serotonin (5-HT_{2A},5-HT_{2C}, 5-HT_6, and 5-HT_7) and dopamine (D_1 and D_2) receptor. Furthermore, it also has noradrenaline reuptake inhibition properties [74]. Four cases of ZOT-NMS were found [75–78]. Only one case occurred in a woman, and the mean age of patients was higher than among other cases of SGA-NMS (52.5 years). Rapid dose escalation was reported in only one case prior to zotepine-induced NMS (ZOT-NMS) onset, but the mean dose was in the high range (325 mg). ZOT-NMS was characterized by

most cardinal symptoms and by a slightly longer duration than other SGA-NMS (15 days). All cases were reported to present with alterations of mental status, rigidity, diaphoresis, hyperpyrexia, tachycardia, and leukocytosis. However, a lower proportion displayed high fever, tremor, tachypnea, alterations in pressure or other symptoms of autonomic imbalance. On average, mean CK values showed a large increase in the days following NMS diagnosis (from 2,130 to a peak value of 39,190 UI/l), similar to what was observed in CLZ-NMS. All cases underwent complete recovery.

4.3 Diagnostic Issues

Considering the case reports of SGA-NMS that were reviewed, it is surprising that very few authors stated which set of diagnostic criteria they relied on. In the past years more than 12 sets of criteria were proposed to operationalize NMS, each characterized by different type, number of symptoms, and by differences in the weight they are given to establish the diagnosis [1, 79]. There is still ongoing debate regarding which clinical features should be used to diagnose NMS; disagreement between diagnostic criteria appears to be high, and most criteria sets do not correspond to the empirical diagnoses that are adopted in clinical practice [80].

In our review, the DSM-IV-TR criteria were the most frequently used and could be considered as fairly stringent; they require the presence of both elevated temperature (without defining a specific threshold) and severe muscle rigidity, plus two other minor criteria such as autonomic disorders, other EPS, mental status changes, and laboratory alterations [23]. The criteria set by Adityanjee and Aderibigbe are among the most stringent, and require both fever over 39 °C and rigidity as necessary conditions to diagnose NMS; by admission of the authors themselves, several cases of SGA-NMS would not reach the diagnostic threshold [79].

On the contrary, Levenson proposed that NMS could be diagnosed even in the absence of rigidity, if CK alterations were observed [24]. This would allow an easier inclusion of atypical forms, although the diagnostic boundaries of NMS would lose specificity [16, 42]. Similarly, other criteria set allow the possibility of diagnosing probable, as opposed to definite, cases of NMS by including those cases without cardinal signs, such as rigidity or fever [26, 81]. Several authors have in fact advocated for the adoption of a spectrum-conceptualization of NMS (i.e. using a dimensional model rather than a dichotomous approach), which might help in clarifying the pathogenetic mechanisms of this syndrome [16]. Indeed, it was argued that the rise of clinical awareness towards NMS and the more widespread availability of treatments makes the natural course of the syndrome more likely to be influenced by early treatments and/or antipsychotic discontinuation, possibly leading to frequent observations of prodromal or abortive stages [6, 16, 82]. On a similar note, other authors proposed to add diagnostic specifiers for the clinical stage of NMS [83, 84].

More recently, a new set of criteria was developed and validated by a panel of experts using a Delphi consensus method [1, 85], and was incorporated into the DSM-5 [86]. Interestingly, these criteria do not imply the need for a specific number of 'major' or 'minor' symptoms, but provide specific quantitative criteria for the severity of symptoms, with a pre-defined threshold score used to define the 'caseness' of NMS. This approach might be more suitable to inform future research on NMS, taking into account the existing clinical variants.

4.4 Pathogenesis

NMS can be described as a complex cascade of dysregulation in multiple neurochemical and neuroendocrine systems, potentially culminating in an end-stage hypermetabolic syndrome [84]. It has been generally regarded as an idiosyncratic drug reaction, implying that it is unpredictable and dose-independent, although this view has been recently challenged in consideration of cases of NMS induced by antipsychotic withdrawal [15, 17]. However, individual vulnerability for the development of NMS might exist, related to variations in the genes for neurotransmitter receptors or metabolic activity, although evidence in this regard is still preliminary [87, 88].

The exact pathogenetic mechanism that underlies NMS is still partly unknown. The fundamental triggering element seems to be a reduction in CNS dopaminergic tone, along with the dysregulation of autonomic nervous system activity, characterized by a loss of hierarchical integration and control. The functional imbalances seen during NMS are maintained by different feed-forward cycles that involve an increasing number of systems, leading to progressive damage of the muscular tissue and multi-organ failure [84, 89]. The hypothesis of hypodopaminergic tone was mainly based on the notion that the risk of developing NMS seemed to parallel the ability of the antipsychotic to induce EPS and the degree of inhibition of dopamine receptor activity, particularly the D_2 subtype in the nigrostriatal pathways [16, 84]. Reductions in the dopaminergic tone are also deemed responsible for the abrupt shifts that occur in the activity of the hypothalamic thermoregulatory system, which would in turn induce further dysregulation of the autonomic response [4, 84]. However, the report of NMS induced by withdrawal of antipsychotic [15] or induced by the use of SGAs such as clozapine, aripiprazole and amisulpride have cast doubt on the primary role of D_2 receptors, at least on the notion that D_2 receptors play a predominant role in all cases of NMS [16, 53, 89]. In fact,

these SGAs possess only weak activity at this level, with aripiprazole even acting as a partial agonist [10]. Not coincidentally, our case review showed that the same SGAs are associated with the highest rates of NMS with atypical features, i.e. lacking severe EPS/rigidity, high fever, or grossly elevated CK. Thus, it is now widely acknowledged, although awaiting further confirmation, that receptors other than dopaminergic (i.e. serotonergic, adrenergic, and cholinergic) might play an important role in the pathophysiology of NMS since they are known to take substantial part in extrapyramidal motor functions [90], thermoregulation, muscle metabolism [89], and mental status [16].

The serotonergic receptors, in particular, have gained increasing attention in recent years as possible contributors to the pathophysiology of NMS, especially that induced by SGAs. In part, this hypotheses spawned from the observation that important similarities exist between NMS and serotonin syndrome at the clinical level. According to this line of research, serotonin-related toxicity would be responsible for the pathogenesis of at least some symptoms of NMS, and this would be particularly evident among atypical SGA-NMS [91–93]. In apparent contrast with this hypothesis, most SGAs antagonize 5-HT_{2A} receptors, and were even suggested for use in the treatment of serotonin syndrome. However, it is noteworthy that quetiapine, aripiprazole, clozapine, and ziprasidone share agonistic actions at 5-HT_{1A} receptors; their stimulation was thus proposed to contribute to lower degrees of hyperthermia or EPS that are observed in some cases of SGA-NMS [16, 90]. Moreover, it was recently hypothesized that long-term treatment with SGAs might determine unbalances in serotonergic neurotransmission, leading to sensitization towards SGAs and other psychotropic agents [94, 95]. Lastly, the observation of cases of NMS apparently precipitated by antidepressants, lithium, or other mood stabilizers have further highlighted a possible pathogenetic role for serotonin, although these drugs are unlikely to trigger NMS alone, in the absence of previous antipsychotic use. However, it was postulated that an excess of central serotonin due to antidepressant use could determine a 'relative hypodopaminergic state', which might increase the risk of developing NMS [96, 97]. In our case review, only statistical trends were found for an association between antidepressants and worse clinical picture of NMS, and further studies based on larger samples are warranted before any clear role of these drugs can be confirmed. Overall, further evidence is also needed to elucidate the role of serotonergic neurotransmission in the pathophysiology of NMS.

4.5 Limitations

Our review needs to be evaluated in the light of its limitations, particularly related to the case review.

A dataset based on published case reports is only partially representative of the clinical reality because of its intrinsic nature. It can be affected by reporting biases related both to the reporting clinicians (e.g. authors might have tended to more frequently report cases of NMS with more peculiar presentations; some symptoms could be omitted from the report because they were not considered to depend on NMS, and in some cases serotonin syndrome might have been misdiagnosed for NMS) and to peer reviewers (e.g. possible lower acceptance rates for cases of SGA-NMS for which a wider literature already exists). However, since SGA-NMS is a rare condition, case reports are, by necessity, one of the few available sources of information.

We also included those cases where the authors did not report validating the diagnosis against standardized criteria; it is possible that if such criteria were applied, some cases would not have reached a formal diagnosis of NMS, possibly because patients received early treatment and underwent a partial resolution of symptoms [15]. Hence, the interpretation of findings needs to take into account a possible overrepresentation of atypical cases. However, it needs to be considered that, even when standardized criteria for NMS are used, agreement between different sets is still limited [15, 80], while the process of peer review of reports might contribute to filter out the more ambiguous cases [6]. Lastly, this inclusive approach is in line with the conceptualization of NMS as a spectrum proposed by several authors [16, 80].

The method for the extraction and coding of data was designed to be as conservative as possible, e.g. abstaining from labeling as absent those symptoms that were not mentioned in the reports. Nonetheless, this method might have introduced bias in the frequency of some symptoms, particularly towards overestimation. However, data on missing values were provided to aid in the interpretation of results.

Given the subgroup size, the statistical power was inadequate to detect some meaningful differences; therefore, statistical analyses should be considered only as exploratory and hypothesis generating.

5 Conclusions and Directions for Future Research

Clinicians should be aware that NMS is virtually associated with all antipsychotics, including the most recently marketed antipsychotics. SGA-NMS seems characterized by lower incidence, lower clinical severity, and more rare lethal outcomes than FGA-NMS. The clinical presentation of NMS induced by olanzapine, risperidone, quetiapine, paliperidone, and ziprasidone seems to be widely similar to that of 'typical' NMS, whereas 'atypical' presentations

might be observed more frequently during NMS triggered by clozapine (less severe EPS), aripiprazole (less severe fever and autonomic symptoms), and amisulpride (less severe EPS and fever). The clinician should pay particular attention to cases developing in older individuals and those receiving antidepressant drugs as these factors might increase the risk of mortality.

Further research is greatly needed to increase our knowledge on NMS and its pathophysiology in order to inform the clinical management of this severe condition. In particular, since case reports or pharmacovigilance systems are the main current sources of information, it would be desirable to develop standardized and systematic reporting methods to include detailed, relevant information on the course and severity of symptoms. Research would also likely benefit from the adoption of a spectrum conceptualization of NMS, with heightened vigilance on symptoms of autonomic dysregulation and serotonin toxicity. Moreover, further studies are needed to understand the role of individual liability for NMS (both genetic and related to individual features, such as physical comorbidities), the role of concomitant use of antidepressants, and other psychotropic medication. The recent development of novel, validated diagnostic criteria seems a promising step in this direction [1].

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