Systematic Review

The neuroleptic malignant syndrome—a systematic case series analysis focusing on therapy regimes and outcome

Kuhlwilm L, Schönfeldt-Lecuona C, Gahr M, Connemann BJ, Keller F, Sartorius A. The neuroleptic malignant syndrome—a systematic case series analysis focusing on therapy regimes and outcome.

Introduction: Neuroleptic malignant syndrome (NMS) is a rare, potentially life-threatening antipsychotic-associated disorder that requires an efficient and timely therapy. The aim of the study was to compare the effectiveness of different NMS therapies and to analyze its outcome depending on NMS severity.

Method: Systematic search for NMS cases in biomedical databases. The focus of the analysis was on therapy with dantrolene, bromocriptine, and electroconvulsive therapy (ECT) when each was compared with symptomatic therapy. Primary outcomes were the survival rate and the duration of treatment.

Result: 405 case reports were included. Overall, no statistically significant differences regarding mortality rate or duration of treatment were found between dantrolene, bromocriptine, or ECT compared to supportive care. A subgroup analysis regarding NMS severity showed that the mortality under specific NMS pharmacotherapy (dantrolene, bromocriptine) and under ECT was significantly lower than under purely symptomatic therapy in severe NMS ($P = 0.018$). The difference was not significant in mild and moderate cases.

Discussion: An overall superiority of the specific NMS therapy (dantrolene, bromocriptine, and ECT) was not found in this study. When regarding severity classification, specific therapies were superior but only in severe cases, and ECT showed the lowest mortality rate. In previous case series, an effect on survival or the duration of the disease could only be observed in part for specific therapies, but the evidence available is inconsistent. The results of this study support our hypothesis that NMS treatment with dantrolene, bromocriptine, and ECT is advantageous over purely symptomatic therapy in severe NMS cases.

Summations
- In mild to moderate NMS, symptomatic therapy might be sufficient. Specific NMS therapy (dantrolene, bromocriptine, electroconvulsive therapy) should be applied in severe cases.
- No studies are currently available on the dose–response relationship of specific NMS medication.

Limitations
- Retrospective study design.
Introduction

Neuroleptic malignant syndrome (NMS) is a rare and potentially life-threatening syndrome that mostly occurs after administration of antipsychotics (formerly labeled as ‘neuroleptics’). It was first described as ‘fatal hyperpyrexia’ by Frank J. Ayd in 1956, shortly after the introduction of the first antipsychotic, chlorpromazine (1). It is characterized by fever and rigidity; further symptoms include impaired consciousness, autonomic dysfunction, increased creatine kinase (CK), and leukocytosis (2). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies NMS as a sub-form of drug-induced movement disorders. The published comprehensive diagnostic criteria are shown in Table 1 (3).

The syndrome is primarily triggered by antipsychotics, but in rare cases, other substances with dopamine (D2) receptor antagonism such as anticonvulsants, antidepressants, or metoclopramide can also be causative (4–6). The abrupt discontinuation of dopamine agonists during therapy of Parkinson’s disease may also trigger an NMS (7). Known risk factors include dehydration, malnutrition, agitation, first-generation antipsychotics (formerly called ‘typical antipsychotics’), parenteral antipsychotics, as well as co-medication with lithium, preexisting organic brain damage, alcohol and drug addiction, and a history of NMS (2, 8, 9). Although the syndrome is considered as idiosyncratic drug side-effect, high doses of antipsychotics and rapid dose escalation seem to increase the risk (8, 10, 11). NMS complications are common and include electrolyte imbalance, thrombosis, pulmonary artery embolism, pneumonia, seizures, rhabdomyolysis, acute renal failure, sepsis, and multi-organ failure (12–14). If left untreated, the syndrome has often a deleterious prognosis and can lead to permanent neurological sequelae or death (15). The incidence in antipsychotic treated patients is 0.01–0.04% (16, 17). The mortality is high and ranges between 5% and 22% (18, 19). The average age of onset is approximately 40 years, but all age groups can be affected (12, 18, 20). NMS usually manifests in the first one to two weeks after beginning of treatment, and however, it can occur any time during the use of antipsychotic drugs. The disease usually lasts 7–13 days, but depot preparations or complications can prolong the course (2, 12). The pathomechanism of NMS is not fully understood. An underlying blockade of striatal dopamine receptors, which leads to acute dopaminergic hypoactivity, is assumed as crucial pathophysiological factor (21). Some researchers consider NMS and malignant catatonia to be two disorders on a same spectrum since they feature an important number of overlapping symptoms (such as immobility, mutism, and rigidity), and furthermore, they also share a similar treatment response to benzodiazepines and ECT (22). However, malignant catatonia is a psychomotor syndrome, which can occur in many different medical or psychiatric illnesses, whereas NMS is mostly associated with antipsychotic medication.

NMS can be subdivided into three degrees of severity shown in Table 2: mild, moderate, and severe (23). Atypical courses without a complete clinical picture also exist (11, 12).

Important differential diagnoses that must be taken into account include malignant catatonia, malignant hyperthermia, serotonin syndrome, anticholinergic syndrome, CNS infection, tetanus, and lithium intoxication (8, 24). Various treatment options are available for NMS therapy. The rapid identification of the syndrome and the immediate discontinuation of the offending agent, as well as the implementation of symptomatic therapy and

| Diagnostic criteria of NMS based on DSM-5 |
|-----------------------------------------|
| **Major symptoms**                      |
| 1. Rigidity                             |
| 2. Hyperthermia (>38.0°C, measured minimum 2 times orally) |
| 3. Diaphoresis                          |
| 4. Exposure to dopamine antagonist within 72 h prior to the beginning of symptoms |
| **Minor symptoms**                      |
| Autonomic nervous system: Tachycardia (rate > 25% above baseline), hypertonia (>25% above baseline or with fluctuation), sialorrhea, urinary incontinence, pallor, tachypnea (>50% above baseline), dyspnea |
| Mental status: Altered consciousness: qualitative (delirium); quantitative (stupor to coma) |
| Motor symptoms: Tremor, akinesia, dystonia, myoclonia, trismus, dysarthria, dysphagia |
| Laboratory findings: ↑Leukocytes, ↑CK, ↑Myoglobin, ↑Creatinine, ↓Fe, metabolic acidosis, hypoxia |
| **Exclusion criteria**                   |
| The above-named symptoms are not due to another substance or a neurological or other general medical condition |

| NMS, Neuroleptic malignant syndrome; DSM, Diagnostic and Statistical Manual of Mental Disorders.

| NMS stage | Mild | Moderate | Severe |
|-----------|------|----------|--------|
| Symptoms  | R rigidity, catatonia or confusion | R rigidity, catatonia or confusion | Severe rigidity, catatonia or confusion |
| Temperature | ≤50°C | 38–40°C | ≥40°C |
| Heart rate | ≤100 min⁻¹ | 100–120 min⁻¹ | ≥120 min⁻¹ |

NMS, Neuroleptic malignant syndrome.
close monitoring are considered important and uncontroversial steps (2, 25). Controlled hydration should be ensured in symptomatic therapy, since fever and diaphoresis often lead to dehydration (20, 26). Hydration is also necessary to treat CK elevation. Antipyretics are mostly ineffective because hyperthermia is presumably not prosta-glandin-mediated but is probably caused by anti- dopaminergic and anticholinergic effects of the antipsychotics (8). Other recommendations include mechanical cooling, nutritional supplementation, laboratory value controls, circulatory stabilization, prophylactic anticoagulation, cardiac rhythm control, and ventilation (25). Intensive medical treatment is often necessary (24). Due to the severity of the syndrome, symptomatic management is not always sufficient, and specific NMS therapies such as the application of muscle relaxants (e.g., dantrolene, benzodiazepines), dopamine agonists (bromocriptine), or electroconvulsive therapy (ECT) can be useful (27–29). The benefits of benzodi- azepines, for example, lorazepam, is controversial in the literature and is therefore recommended only in cases with mild symptoms or uncertain diagnosis (20, 23). There are also treatment recommendations for anti-Parkinson drugs such as amantadine, levodopa/carbidopa, and apomor- phine (28, 30, 31). International NMS treatment guidelines mostly recommend immediate discontinuation of antipsychotic medication, supportive therapy, and optional use of dopamine agonists, dantrolene, or ECT, although these guidelines are heterogeneous and inconsistent as shown in a recent review (32). They are based on single case reports and case series, which according to the Oxford Levels of Evidence represents one of the lowest levels (33). To the best of our knowledge, there is no study analyzing the advantages of a differentiated therapy regime of NMS considering the grade of severity. A randomized, controlled prospective study appears to be difficult to carry out in NMS due to its low incidence and because of the unpredictability of appearance (34). The aim of this study is to perform a systematic case report analysis using PICO (Patient-Intervention-Comparison-Outcome) schema to collect further evidence for the therapy of NMS. The focus was put on NMS therapy performed and the patient's outcome. Following questions were used for the analysis:

1. Does the specific NMS therapy with dantrolene, bromocriptine, or ECT have a better outcome than purely symptomatic therapy?
2. Does the outcome of the specific NMS therapies differ in comparison with the purely symptomatic therapy depending on NMS severity?

Material and Methods

The Ethics Committee of the University of Ulm previously approved the study design. We followed PRISMA guidelines for reporting systematic reviews (35). The aim of the research strategy was to identify NMS case reports in medical databases. With a systematic search, NMS cases were searched in the biomedical literature databases MEDLINE (PubMed Central (PMC) NCBI) and EMBASE for the truncated keyword 'neuroleptic malignant syndrome'. Publications available only online ('epubs ahead of print') were taken into account. The most recent search was on May 27, 2019. The results of the literature database search were screened using Covidence, a data extraction, and screening tool for systematic reviews of the Cochrane Collaboration® (www.covidence.org). Inclusion criteria were the presence of at least one NMS case report, patient age ≥14 years, NMS diagnosis according to DSM-IV or -5, antipsy- chotic exposure prior to NMS, the mention of NMS therapy and its outcome; reports in English, German, French, or Spanish Language. If the inclusion criteria were not met or if the information was incomplete or inadequate, the respective report was excluded. To avoid selection bias, multiple reports of the same patient (e.g., recurrences) were not included. Two authors (LK and CSL) performed the search independently and determined the inclusion or exclusion of each report; in case of conflict, a consensus was built conjointly. If available, the following data were extracted from the case reports: Publication date, age, and gender, diagnosis, offending antipsychotic (generation, pharmaceutical form, and number). Furthermore, the latency between antipsychotic treatment begin/dose increase and NMS onset, underlying psychiatric illness (ICD-10 F), somatic comorbidity, pre-existing brain damage, vital signs (blood pressure, heart rate, temperature, respiratory rate), labora- tory parameters (CK, leukocytes), syndrome severity, therapy, outcome (survival, treatment duration), total duration of illness, and reported complications. The syndrome severity was deter- mined based on the NMS severity classification by Woodbury and Woodbury (23). If there were several underlying mental illnesses at the same time, the one that was assigned to the deepest or most organic layer in the Jaspers shift model was taken into account (36). Brain damage included hypoxic, traumatic, inflammatory, toxic, or tumor-related damage. Since the focus was on NMS therapy, cases were divided into groups according to their received treatment: (i) symptomatic therapy (no specific NMS medication, no high-dose
benzodiazepines), (ii) dantrolene, (iii) bromocriptine, (iv) dantrolene plus bromocriptine, (v) ECT, and (vi) others (e.g., other anti-Parkinson drugs, high-dose benzodiazepines, or the combination of various specific NMS drugs). The treatment groups were compared in terms of age, gender, somatic comorbidity, and NMS severity. In order to evaluate the effectiveness of the therapies, the groups with specific NMS therapy were compared with the group with purely symptomatic therapy in terms of survival and duration of treatment. Statistical methods were applied and carried out with IBM © SPSS © Statistics 25.0. Absolute and relative frequencies as well as minimum, maximum, arithmetic mean, standard deviation, and median were calculated for descriptive data. The level of significance for the statistical tests was previously defined as \( \alpha = 0.05 \). T-test (continuous, normally distributed variables), one-factor analysis of variance (ANOVA; continuous variables), Pearson chi-square test, and Fisher’s exact test (categorical variables) were used. In order to evaluate several influencing factors in combination, a logistic regression analysis with ‘death’ as the dependent variable and ‘age’, ‘gender’, ‘NMS severity’, and ‘therapy’ as predictors was carried out.

Results

The search strategy in the literature databases provided 3,623 results. After the screening process, 405 NMS single cases from 357 scientific publications were included in the study (the flowchart is shown in Figure 1).

The case reports examined range from 1982 to 2019. 61.2% of cases were male, and the age yielded between 14 and 95 years (mean 39.0 ± 17.6 years, median 36.0 years); on average, men were approximately four years younger than women (37.4 ± 17.8 years vs. 41.6 ± 17.1 years; \( P = 0.018 \)). The most frequent underlying psychological disorders came from the group of the schizophrenia spectrum, schizotypic, and delusional disorders (52.6%), followed by affective disorders (21.0%). Other diagnoses were mental retardation (9.6%), organic mental disorder (4.7%), and psychological and behavioral disorders caused by psychotropic substances (4.0%). In 4.4% of the cases, there was no diagnosed mental disorder; in 3.7%, there were other mental disorders, or the information was missing. If there was no mental disorder, the antipsychotics were prescribed due to agitation or nausea. Somatic comorbidity or trauma was present in 19.3% of the patients, and in this group, the mortality rate was significantly higher (16.7%) than in patients without comorbidities (6.4%; \( P = 0.003 \)). Brain damage was reported in 6.2%; this had no significant impact on survival (96.0% with brain damage vs. 91.3%; \( P = 0.71 \)). Of the triggering antipsychotics, 53.3% were typical, 33.8% were atypical, and in 12.6% of the cases, substances from both generations were administered simultaneously. The mortality rate was significantly higher when typical medication was part of the medication (9.8–12.0%) than with atypical antipsychotics alone (2.2%; \( P = 0.002 \)). The dosage form was enteral in 60.9% of the cases (7.1% mortality), parenteral in 19.0% (5.7% mortality), and mixed in 20.1% (9.5% mortality). The type of antipsychotic application had no significant influence on the outcome (\( P = 0.100 \)). Most patients received exactly one antipsychotic drug (66.4%), 26.4% received two, 5.2% three, and 1.7% four antipsychotics at the same time. The number did not affect survival (\( P = 0.974 \)). The median of 4 days elapsed between the start of antipsychotic therapy or dose increase and NMS manifestation (less than 24 h up to 1 year; mean 18.8 days). The duration of the disease averaged 13.5 days (less than 24 h – 150 days; median 9 days).

NMS manifested with a variety of different symptoms. As being part of this review’s inclusion criteria, fever and rigidity were present in 100% of the cases, other symptoms were tachycardia ≥100 min⁻¹ (70.6%), impaired consciousness (69.9%), diaphoresis (50.4%), hypertension ≥140/90 mmHg (35, 3%), hypotension <100/60 mmHg (7.2%), tremor (32.3%), tachypnea >20 min⁻¹ (30.6%), mutism (25.2%), urinary incontinence (14, 8%), hypersalivation (11.9%), and agitation (10.6%). The average temperature was 39.2°C. An increase in CK >300 IU/L was found in 93.5% of the cases reported, and leukocytosis was observed in 85.8%. 11.1% of the patients suffered from mild NMS, 56.3% were moderately ill, and 32.6% severely ill. With increasing severity grade, the survival rates dropped down (from 95.6% in mild to 94.7% in moderate, and to 84.8% in severe cases (\( P = 0.004 \)). The total complication rate was 29.1%. The most common complications included pneumonia (11.4%), acute kidney failure (9.1%), and thromboembolic event (3.5%). Without occurrence of complications, 98.3% survived, with complications it was only 75.4% (\( P = 0.0001 \)). The overall mortality rate was 8.4%, and the mean duration of treatment was 11.3 days (1–121 days; median 7.0 days). The different therapy groups were compared in terms of gender, age, NMS severity, somatic comorbidity, and complications (Table 3). The differences between these groups were significant for the variables gender (\( P = 0.019 \), age

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P = 0.001,\text{ and complication rate } (P = 0.008), \text{ but not for the level of severity } (P = 0.08). \text{ The influence of NMS therapies on mortality was then considered, as can be seen in Table 3, which was not statistically significant } (P = 0.688).
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Table 4 illustrates the survival rates of symptomatic therapy, specific NMS pharmacotherapy (dantrolene and bromocriptine in mono- and combination therapy) and ECT. Relatively more cases survived in the ECT group than in the pharmacologic and symptomatic therapy group in which the outcome was similar.

The logistic regression was calculated with 386 cases. The following values were determined for the effects of the influencing variables on predicting ‘death’:

- **Age**: \( P = 0.018 \)/OR: 1.03 (95% CI 1.004–1.048)
- **NMS severity grade**: \( P = 0.003 \)
  - Ratio ‘severe’ to ‘moderate’ OR: 4.13 (95% CI 1.79–10.04)
  - Ratio ‘severe’ to ‘mild’ OR: 3.32 (95% CI 0.72–15.38)
- **There was no influence of therapy** \( (P = 0.99) \) and gender \( (P = 0.71) \)

With every year of one’s life, the estimated risk of succumbing to NMS increases by 3%. Severe

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**Table 3. Properties and mortality in the different NMS treatment groups**

|                          | Symptomatic therapy \((n = 108)\) | Dantrolene \((n = 59)\) | Bromocriptine \((n = 75)\) | Dantrolene + Bromocriptine \((n = 42)\) | ECT \((n = 41)\) |
|---------------------|---------------------------------|-----------------|-------------------|-----------------------------|-----------------|
| **Gender**          |                                 |                 |                   |                             |                 |
| Male                | 64.8%                           | 67.8%           | 50.7%             | 73.8%                       | 46.3%           |
| Female              | 35.2%                           | 32.2%           | 49.3%             | 26.2%                       | 53.7%           |
| **Age (mean)**      | 43.7 years                      | 41.0 years      | 37.3 years        | 35.4 years                  | 32.3 years      |
| **NMS severity grade** |                               |                 |                   |                             |                 |
| Mild                | 11.1%                           | 6.8%            | 13.3%             | 4.8%                        | 17.1%           |
| Moderate            | 61.1%                           | 42.4%           | 56.0%             | 54.8%                       | 56.1%           |
| Severe              | 27.8%                           | 50.8%           | 30.7%             | 40.5%                       | 26.8%           |
| **Somatic comorbidity** |                               |                 |                   |                             |                 |
| Mild                | 15.7%                           | 27.1%           | 17.3%             | 26.2%                       | 12.2%           |
| Moderate            | 26.9%                           | 42.4%           | 28.0%             | 45.2%                       | 14.6%           |
| Severe              | 10.2%                           | 10.2%           | 8.0%              | 7.1%                        | 0%              |

ECT, Electroconvulsive therapy; NMS, neuroleptic malignant syndrome.
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Table 4. Survival of NMS treatment groups independent from NMS severity \(P = 0.078\)

| All NMS severity grades | Survival % - \(n\) | Death % - \(n\) | Total |
|-------------------------|---------------------|-----------------|-------|
| Symptomatic therapy     | 89.8% (97)          | 10.2% (11)      | 100% (108) |
| NMS-Pharmaco-therapy    | 91.5% (161)         | 8.5% (15)       | 100% (176) |
| ECT                     | 100% (41)           | 0% (0)          | 100% (41) |
| Total                   | 92.0% (299)         | 8.0% (26)       | 100% (325) |

NMS, Neuroleptic malignant syndrome; ECT, Electroconvulsive therapy.

Considering the severity levels, the mortality rates under ECT and specific NMS pharmacotherapy were lower or the same (on a descriptive level) as under purely symptomatic treatment. These differences were not statistically significant; likewise, no shortening of the duration of the illness could be determined by the specific NMS therapies. In the subgroup analysis on NMS severity levels, it was noted that the influence on mortality rates differed between severity levels: Only in cases of severe NMS the mortality rate was significantly lower under specific NMS therapies compared with purely symptomatic therapy. Thus, symptomatic therapy could be sufficient for the treatment of mild to moderate NMS, while specific therapy should be applied in severe cases.

The previous evidence on the treatment of NMS is weak and exclusively based on predominantly small case series and single case reports (32). From literature, there is few comparative data on NMS therapy with dantrolene; in the majority of these studies, the mortality among dantrolene was slightly lower than in the present study (10.2%): 0% (12, 29, 37, 38), 5.3% (Silva et al., 1999), and 8.6% (28). Sakkas et al. were the only ones to observe a statistically significant reduction in mortality with dantrolene (28). Reulbach et al., however, reported a higher (16.2%) mortality rate (40). Regarding the dopamine agonist bromocriptine, some NMS case series report a zero percent mortality rate, but these case series are of low case numbers \(n \leq 18\) (12, 19, 37–39). In other, larger case series, the results for bromocriptine were comparable to those of our study (28, 41) which yielded 8.0%. Overall, the results of previous NMS case series analyses are only of limited comparability since the methodology of the individual studies differs greatly. For example, only children and adolescents were analyzed by Neuhaust and Silva (37, 39). Other studies used different NMS diagnostic criteria or included atypical and potentially milder syndromes which potentially impacted the outcome (29, 40). In Rosebush et al., dantrolene and bromocriptine were not administered exclusively in monotherapy (38); Neuhaust et al. analyzed only NMS cases triggered by atypical antipsychotics (SGA), which are often less life-threatening (37, 42). So far, a statistically significant reduction in the duration of treatment has been observed only for dantrolene (19). For the ECT, there are also reports with zero percent mortality in literature (12, 43). In other authors, the death rate was at 6.5–10.3% (44–46); in Davis et al., it was nevertheless half as high as in the symptomatically treated comparison group. ECT is generally considered a safe and effective therapy even for emergency

Table 5. Survival of NMS treatment groups only for severe NMS cases \(P = 0.018\)

| Severe NMS       | Survival % - \(n\) | Death % - \(n\) | Total |
|------------------|---------------------|-----------------|-------|
| Symptomatic therapy | 70.0% (21)          | 30.0% (9)       | 100% (30) |
| NMS-Pharmaco-therapy | 90.0% (65)         | 10.0% (7)       | 100% (70) |
| ECT              | 100% (11)           | 0% (0)          | 100% (11) |
| Total            | 85.6% (95)          | 14.4% (16)      | 100% (111) |

NMS, Neuroleptic malignant syndrome; ECT, Electroconvulsive therapy.
indications (47). Pregnancy and seniority are no contraindications; if it is not clearly differentiated from the differential diagnosis of malignant catatonia, ECT is advantageous because it has indications for both disorders (43, 48). For treatment of NMS, no exclusive recommendations can be found regarding parameters and application form of ECT; some authors recommend three weekly sessions; some others recommend a higher frequency up to once a day in severe cases (47) and bilateral electrode placement.

The distribution of characteristics such as average age, gender ratio, disease severity, comorbidity, and complication frequency was not homogeneous in the different treatment groups. The rate of comorbidities and severe NMS cases was higher in the group with specific NMS drugs than in the group with symptomatic therapy. It is possible that the effects of dantrolene and bromocriptine were less pronounced due to the more morbid patients. Conversely, the ECT group was about ten years younger than the symptomatic therapy group, which might have had an impact on the better outcome in this group. Considering that age is a well-established positive predictor of ECT response, it could also be vice versa. Finally, it can be discussed to what extent the various influencing variables such as gender and age and the therapy have had an impact on the outcome.

One of the strengths of the study is the large number of analyzed NMS cases in the individual therapy groups. Our work is primarily limited by the retrospective study design, collected from single cases or case series including their own biases and confounders. Especially the mortality rate might be inflated in the literature due to mild and moderate cases being unrecognized and underreported. Another possibility is certainly that cases with a lethal outcome are less likely to be published which would lead to an underestimated mortality rate. However, we do not assume the mortality rate in the different treatment subgroups to have different publication biases. Some of the case reports did not contain the complete data for extraction, so the total number of cases for each variable analyzed differed from the total number of cases included into the study. A subcategorization according to drug dose and depot preparation was dispensed in favor of the number of cases. No studies are currently available on the dose–response relationship of specific NMS drugs. Also, differences in therapeutic effectiveness found post hoc in subgroup analyses should be replicated (49).

This review article clearly demonstrates that the optimal treatment of NMS is not yet ensured. The optimal treatment should be driven by the clinical severity of the syndrome. For the first time, available NMS cases from the literature were analyzed regarding their severity level as defined by Woodbury & Woodbury (22). We showed that the influence on mortality of the various therapies differs depending on the severity of NMS. For severe cases, specific NMS therapy (with dantrolene, bromocriptine or ECT) is superior to purely symptomatic therapy. Within the ECT treatment groups, mortality rate was lowest, which could be an argument to upgrade ECT from a second-line therapy to a first-line therapy for severe cases. Further studies on the pathophysiology and causal treatment of NMS are necessary.

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Data availability statement
A complete list of the case reports and authors are available upon request by the authors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Reference list of all included case reports/case series in alphabetical order.