# Treatment of the Neuroleptic Malignant Syndrome in International Therapy Guidelines: A Comparative Analysis

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## ABSTRACT

**Introduction** The neuroleptic malignant syndrome (NMS) is a potentially life-threatening condition associated to the use of antipsychotics. Since it requires rapid and efficient medical care, high-quality treatment guidelines should be available. In this article, we analyzed and compared different international therapy guidelines for the treatment of schizophrenia, in which NMS treatment recommendations might be contained.

**Methods** We performed an Internet-based search for schizophrenia guidelines via the website of the respective medical society. Guidelines in English, French, Italian, and German from countries whose medical care meets high standards were selected for further analysis and comparison of the NMS treatment recommendations (if present), and their underlying evidence.

**Results** The NMS is mentioned in 12 of 14 guidelines. Only 9 report concrete therapy recommendations (benzodiazepines/dantrolene/bromocriptine/amantadine/intensive care and/or electroconvulsive therapy (ECT)), however, with high heterogeneity. Only 5 guidelines included all possible drug therapy options and ECT, but with differing combination strategies, dosages, application forms, and combinability of options. The level of evidence of the different recommendations was estimated as low.

**Discussion** One-third of the selected guidelines do not report any NMS therapy recommendations. Most guidelines mentioning the NMS do not provide therapy recommendations that include all relevant treatment options. The results show a very high heterogeneity, and the recommendations and statements are of low-evidence levels. The lack of knowledge about the NMS and its treatment may delay the onset of therapy, impair the quality of treatment, and lead to a worse outcome or death.



## Introduction

The neuroleptic malignant syndrome (NMS) is a neuropsychiatric condition, which represents a clearly defined, independent diagnostic entity according to DSM-5. It is a life-threatening, antipsychotic-associated side effect characterized by rigor, fever, diaphoresis, impaired consciousness, and autonomic dysfunction (▶ **Table 1**). Thus, every NMS should be considered as a medical emergency requiring timely intensive care [1]. In 1956, Frank J. Ayd first described the syndrome, shortly after the discovery of the first antipsychotic [2]. In the ICD-10 and the DSM-5, NMS is classified as a subset of drug-induced movement disorders [3, 4]. The underlying pathophysiological mechanisms are not fully understood yet, but it may

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▶ **Table 1** Diagnostic criteria and complications of the NMS based on DSM-5 [4].

| **Major criteria** | |
|---|---|
| Fever | > 38 ° (oral), measured minimum 2 times, no signs of infection |
| Profuse diaphoresis | Doesn't occur in any other neuroleptic-induced side effect; differential diagnosis: malignant catatonia |
| Generalized rigidity | Usually unresponsive to antiparkinsonian agents |
| **Minor criteria** | |
| Motor symptoms | Tremor, akinesia, dystonia, myoclonia, trismus, dysarthria, dysphagia |
| Mental status | Altered consciousness: qualitative = delirium; quantitative = from stupor to coma |
| Autonomic nervous system | Tachycardia: rate > 25 % above baseline; hypertonia: systolic or diastolic > 25 % above baseline or with fluctuation; tachypnea: rate > 25 % of baseline, urinary incontinence and pallor |
| Laboratory findings | ↑ Leukocytes, ↑ CK, ↑ myoglobine, ↑ catecholamines, ↑ creatinine, ↓ Fe |
| **Complications** | |
| Muscle | Rhabdomyolysis with CK 4 times upper limit of normal, myoglobinemia, acute renal failure, multi organ failure |
| Metabolic system | Metabolic acidosis, dyspnea, tachypnea |
| Respiratory system | Aspiration pneumonia, pulmonal embolism |
| **Exclusion criteria** | |
| Exclusion criterion 1 | The above-named symptoms are not due to another substance or a neurological or other general medical condition (e. g. viral infection). |
| Exclusion criterion 2 | The above-named symptoms are not better accounted for by a mental disorder. |

probably be caused by blockade of striatal dopamine receptors leading to striatal dopaminergic hypofunction [5]. The NMS is mainly triggered by high-potent antipsychotics, and it occurs more frequently among the first generation antipsychotics, which mostly cause a stronger D2-antagonistic effect than second and third generation antipsychotics [6, 7]. Other centrally acting drugs with D2-antagonism, such as the antiemetic metoclopramide, may in rarer cases also trigger an NMS [6]. Moreover, it can also occur due to withdrawal of dopaminergic therapy in Parkinson's disease [8]. The estimated incidence in patients under antipsychotic medication is 0.01–3.23 % [6, 7]. Generally, NMS occurs at the beginning of treatment (mostly within 24 h to 1 week); in rare cases, it takes more than 30 days. It occurs among all age groups; men are more frequently affected [9, 10]. Risk factors include a pre-existing organic brain damage, dehydration, agitation, severe fatigue, psychiatric disorders such as bipolar disorder, and the rapid uptake or parenteral administration of antipsychotics [11]. The median recovery time after stopping the antipsychotics is 7–10 days with most remissions occurring within 30 days [6]. The mortality rate is 10–20 %, especially when initially misdiagnosed [12].

Important differential diagnoses include malignant catatonia (this specific differential diagnostic situation is known as "catatonic dilemma"), malignant hyperthermia, serotonin syndrome, anticholinergic syndrome, infectious diseases of the CNS, tetanus infection, and severe lithium intoxication [11, 13].

There is no gold standard for treating the NMS. The most common procedure is as follows: 1) immediate discontinuation of the antipsychotic(s); 2) symptomatic treatment in order to avoid potentially lethal complications such as electrolyte derangement, dehydration, rhabdomyolysis and acute renal failure, aspiration pneumonia, deep vein thrombosis, seizure, sepsis, or cardiac arrest [14]; 3) pharmacotherapy with centrally acting (benzodiazepines) and peripherally acting (dantrolene) muscle relaxants and dopamine agonists (bromocriptine, amantadine) [15, 16]; and 4) electroconvulsive therapy (ECT)[17]. NMS patients usually require continuous monitoring and intensive care, which cannot be secured in the standard psychiatric facility; therefore, patients need to be transferred to the intensive care unit (ICU) for further treatment. A diagnostic failure, treatment in an insufficient setting, or delayed treatment may result in permanent damage or death [10]. Due to its low incidence, only case reports and case series that illustrate practical therapeutic approaches on this condition exist in the scientific literature. Data from randomized controlled trials (RCTs) are missing. The aim of the present study is to read out and compare available internationally relevant treatment guidelines regarding the therapeutic recommendations of the NMS.

## Methods

The search for relevant treatment guidelines was carried out via the websites of the respective medical societies and a free online search using the Google search engine (www.google.de). Because the NMS is associated to antipsychotic medication, which is commonly used for the treatment of schizophrenia, we focused on reviewing guidelines for the treatment of schizophrenia. We included the guidelines edited by a nationwide active psychiatry association or by renowned and recognized expert groups ("research teams"). Based on the authors' language resources, we analyzed guidelines written in English, French, Italian, or German from countries with high standards of medical care. We searched for guidelines from Germany, Austria, Switzerland, France, Great Britain, and Italy, as well as guidelines from Australia and New Zealand, Canada, India, Japan, and the United States of America. Consensus-based as well as evidence-based guidelines were included. We excluded regional guidelines, guidelines subsidized by pharmaceutical companies, and duplicates (guidelines that were transcripts of an already included guideline). The search terms consisted of the name of the professional association (society) or the country and "guidelines

schizophrenia." For the German-speaking countries, we used the name of the society and the key words: "Leitlinie Schizophrenie" AND "malignes neuroleptisches Syndrom" AND "MNS"; for Italian: "raccomandazione sul trattamento della schizophrenia" AND "sindrome neurolettica maligna" AND "SNM"; for guidelines in English: "guideline schizophrenia" AND "neuroleptic malignant syndrome" AND "NMS"; for French: "recommandation de traitement schizophrénie" AND "syndrome malin des neuroleptiques" AND "SMN." In addition, we examined the emergency medicine and intensive care medicine guidelines existing in the German-speaking countries for treatment recommendations for the NMS, since affected patients need to be treated with intensive care in an appropriate setting (mostly in an ICU) by anesthesiologists and intensive care specialists. The search's deadline was set for the 31 January 2019. The treatment guidelines were evaluated with the help of the following 4 questions:

1. Is the NMS mentioned in the guideline?
2. Are there concrete therapy recommendations?
3. How extensive are these?
4. What evidence is the guideline based on?

The grading of the evidence classes and the grade of recommendation (▶ **Table 2**) was based on the SIGN Levels of Evidence, which are standard in evidence-based medicine (EBM) [18]. If the level of evidence and the recommendation grade were mentioned in the guidelines, they were directly extracted. Information and evidence classes that could not be gained from the guideline were extracted from the primary sources quoted using the mentioned EBM standards and were then extrapolated and marked with an asterisk ( * ), (▶ **Table 3**). We performed a narrative description of the guideline's content. Two authors (LK, MC) operated the search and review of the guidelines independently. A third party (CS-L) was involved in case of uncertainty regarding the inclusion and evaluation of a guideline.

## Results

The Web-search identified 14 guidelines that were thematically related to the NMS or its treatment: 8 in English, 6 in German, and 1 in French. No guidelines were identified for Italy or Japan (▶ **Table 3**).

In German-speaking countries, the S3 Schizophrenia Treatment Guideline (2006) by the German Society for Psychiatry, Psychotherapy, and Psychosomatics (DGPPN) is chronologically the first to address the NMS and its treatment [19]. It contains only basic definitions and treatment recommendations; for the latter only with a low recommendation grade (0). The update of the DGPPN S3 Schizophrenia Treatment Guideline (2019) [20] is significantly differentiated. It classifies the NMS into 5 severity levels, with grade 3–5 being termed "early/moderate/severe NMS" that is based on the classification by Strawn et al. [21] and Woodbury and Woodbury [22] (▶ **Table 4**). The respective therapy is adapted to the degree of severity. While bromocriptine and amantadine are recommended in moderate and severe NMS, dantrolene is recommended only in case of hyperthermia and proven hypermetabolism (severe NMS). Benzodiazepines are recommended as the treatment of choice in case of diagnostic uncertainty. The recommendations are based on clinical consensus statement (CCS) and data from case reports and case-series analyses.

The S2k guideline ("emergency psychiatry treatment guideline") by the Emergency Psychiatry Panel of the DGPPN (2019) distinguishes between "mild NMS" (with a slight increase in temperature and vegetative symptoms) and "severe NMS" (not specified) [23]. The treatment recommendations are extracted directly from the review article by Strawn et al. [21], whose recommendations

▶ **Table 2** Levels of evidence and grades of recommendation according to the Scottish Intercollegiate Guidelines Network (SIGN) [18].

| **Levels of evidence** | |
|---|---|
| **Ia** | Evidence from a meta-analysis of at least 3 RCTs * |
| **Ib** | Evidence from at least one RCT * or a meta-analysis of less than 3 RCTs * |
| **IIa** | Evidence from at least one well-designed controlled trial without randomisation |
| **IIb** | Evidence from at least one well-designed, quasi experimental descriptive study |
| **III** | Evidence from well-designed, non-experimental observational studies e. g. comparative trials, correlational studies and case studies |
| **IV** | Evidence from expert committees' reports or opinions and/or clinical experience of respected authorities |
| **Category of recommendation** | |
| **A** | At least one RCT * of overall good quality and consistency, directly related to the recommendation and not extrapolated (evidence levels Ia and Ib) |
| **B** | Well-conducted clinical studies, but no RCTs * , directly related to the recommendation (evidence levels II or III) or extrapolation from evidence level I if the relation to the specific question is missing |
| **C/0** | Reports from expert circles or expert opinion and / or clinical experience of recognized authorities (evidence category IV) or extrapolation from evidence levels IIa, IIb, or III. This classification indicates that directly applicable clinical trials of good quality were absent or unavailable |
| **CCS (clinical consensus statement)** | Recommended as a good clinical practice point by consensus and based on the clinical experience of members of the guideline group as a standard of care for which experimental scientific research is not possible or desired |
| **Statement** | Statements were used when there was no evidence for practical procedures and treatment advice, although these were plausible from the expert's point of view of the consensus round or should be pointed out to lack of evidence and corresponding research needs |

* RCTs = randomized controlled trials.

▶ **Table 3** NMS treatment recommendations in the international Schizophrenia guidelines .

| Country (language), medical society | Guideline title (year) | NMS therapy recommendation | | | | | | Evidence Level | Grade of recommendation |
|---|---|---|---|---|---|---|---|---|---|
| | | AP Stop | Symptomatic therapy | Pharmacotherapy | ECT | Resumption of AP-therapy | Other | | |
| **Germany (dt)** DGPPN | S3-Praxisleitlinie in Psychiatrie und Psychotherapie zur Behandlung von Schizophrenie (2006) [19] | Yes | Yes, intensive care therapy, if needed | Dantrolene, bromocriptine, amantadine and benzodiazepines, if needed | As second line therapy | / | / | IV, II | CCS, 0 |
| | S3-Behandlungsleitlinie Schizophrenie update (2019) [20] | Yes | Stabilization of the vital signs and fever reduction, monitoring, intensive care therapy | – Early NMS: Lorazepam up to 8 mg/day<br>– Moderate NMS: Lorazepam up to 8 mg/day, bromocriptine up to 15 mg/day, amantadine up to 300 mg/day.<br>– Severe NMS: Dantrolene (up to 10 mg/day), bromocriptine up to 15 mg/day, amantadine up to 300 mg/day.<br>– Regardless of the stage: Anticholinergics, Clonidin | As second line therapy | >14 days after MNS | / | III * IV * | 0 * |
| | S2k-guideline emergency psychiatry (2019) [23] | Yes | Volume therapy with full electrolyte solution, monitoring, intensive care therapy | – Mild NMS: Benzodiazepines<br>– Severest NMS: Lorazepam i. v./i.m. (up to 7.5 mg/d), dantrolene i. v. (initially 2.5 mg/kg BW, 10 mg/kg BW/day as continous infusion, then 2.5 mg/kg BW/day), alternatively bromocriptine (10–60 mg/day) or amantadine i. v. (200–400 mg/day) | As "Ultima Ratio" | >14 days after MNS | Embolism and pneumonia prophylaxis | III * | 0 * |
| **Austria (dt)** ÖGBP | Schizophrenie – Medikamentöse Therapie (2016) [26] | Only typicals | / | / | As second line therapy | / | / | IV * | CCS * |
| **Swiss (dt)** SGPP | Behandlungsempfehlungen Schizophrenie (2016) [27] | / | Intensive care therapy | / | As second line therapy | / | / | IV * | CCS * |
| **USA (eng)** APA | Practice Guideline for the Treatment of Patients with Schizophrenia (2004) [28] | Yes | Hydration and fever reduction | Dantrolene, bromocriptine, amantadine and benzodiazepines | As second line therapy | / | / | III IV | 0 |
| **USA (eng)** PORT | Translating Research Into Practice: The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (2009) [29] | No therapy recommendations available | | | | | | | |

▶ **Table 3** Continued

| Country (language), medical society | Guideline title (year) | NMS therapy recommendation | | | | | | Evidence Level | Grade of recommendation |
|---|---|---|---|---|---|---|---|---|---|
| | | AP Stop | Symptomatic therapy | Pharmacotherapy | ECT | Resumption of AP-therapy | Other | | |
| **UK (eng)** NICE | Psychosis and Schizophrenia in Adults – The NICE Guideline on Treatment and Management (2014) [30] | No therapy recommendations available | | | | | | | |
| | Psychosis and Schizophrenia in Children and Young People – Recognition and Management (2016) [31] | No therapy recommendations available | | | | | | | |
| **International association (eng)** WFSBP | Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects (2013) [32] | Yes | Intensive care therapy with stabilization of the vital signs and fever reduction | Dantrolene (2.5–10 mg/kg BW) only when presence of extremely high temperature, rigor and hypermetabolism | 6–10 Session | / | / | III | 0 |
| **Canada (eng)** CPA | Clinical Practice Guidelines – Treatment of Schizophrenia (2005) [33] | Yes | Yes | Dantrolene, bromocriptine or amantadine | / | / | / | III * | 0 * |
| **Australia (eng)** RANZCP | Clinical Practice Guidelines for the Management of Schizophrenia and related disorders (2016) [35] | No therapy recommendations available | | | | | | | |
| **India (eng)** IPS | Clinical Practice Guidelines for Management of Schizophrenia (2017) [36] | Yes | Yes | Dantrolene, bromocriptine, amantadine or lorazepam | As second line therapy | / | / | III | 0 |
| **France (fr)** HAS | Guide médecin sur les schizophrénies (2007) [37] | No therapy recommendations available | | | | | | | |

DGPPN = Deutsche Gesellschaft für Psychiatrie, Psychotherapie, Psychosomatik und Nervenheilkunde; AWMF = Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; DIVI = Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin; APA = American Psychiatric Association; PORT = Schizophrenia Patient Outcomes Research Team; NICE = National Institute for Health and Care Excellence; WFSBP = World Federation of Societies of Biological Psychiatry; CPA = Canadian Psychiatric Association; RANZCP = Royal Australian and New Zeland College of Psychiatrists; IPS = Indian Psychiatry Society; HAS = Haute Autorité de Santé; ÖGPB = Österreichische Gesellschaft für Neuropsychopharmakologie und Biologische Psychiatrie; SGPP = Schweizerischen Gesellschaft für Psychiatrie und Psychotherapie; eng = English; dt = German; fr = French; AP = Antipsychotic; KG = weight in kilogramm; ECT = Elektroconvulsion-Therapy; extrapolated levels and grades of recommendation by the authors were marked by an asterisk ( * ).

▶ **Table 4** NMS stages and treatment recommendations in the current version of the update of the DGPPN S3-schizophrenia guideline [20].

| MNS Stage | Clinical presentation | Proposed treatment |
|---|---|---|
| I: Drug-induced parkinsonism | Rigidity, tremor | Reduce or switch antipsychotics Anticholinergic agents |
| II: Drug-induced catatonia | Rigidity; mutism; stupor | Discontinue, reduce, or switch antipsychotics Lorazepam (up to 8 mg/day) |
| III: Mild, early NMS | Mild rigidity; catatonia or confusion; temperature ≤ 38 °C (100.4 °F); heart rate ≤ 100 bpm | Discontinue antipsychotics Lorazepam (up to 8 mg/day) |
| IV: Moderate NMS | Moderate rigidity; catatonia or confusion; temperature 38–40 °C (100.4–104 °F); heart rate 100–120 bpm | Discontinue antipsychotics Intensive care Lorazepam (up to 8 mg/day), bromocriptine (up to 15 mg/day), or amantadine (up to 300 mg/day) ECT as second line therapy |
| V: Severe NMS | Severe rigidity; catatonia or coma; temperature ≥ 40 °C (104 °F); heart rate ≥ 120 bpm | Discontinue antipsychotics Intensive care Dantrolene (up to 10 mg/day), bromocriptine (up to 15 mg/day), or amantadine (up to 300 mg/day) ECT as second line therapy |

for ECT in turn are based on a series of 45 cases [24]. The pharmacotherapy recommendations stem from 2 other publications (a case series with 64 cases [15] and a case-control study with 734 cases [16]), and a textbook chapter on the NMS [25].

The Austrian Society for Neuropsychopharmacology and Biological Psychiatry published a consensus statement on schizophrenia treatment by an expert committee in 2016. It recommends pausing all neuroleptics and the use of ECT (without further specification) [26].

The treatment guidelines for schizophrenia issued by the Swiss Society of Psychiatry and Psychotherapy in 2016 generally recommend intensive care for patients with NMS and ECT in case of failure of pharmacological therapy, without specification of medication [27]. The recommendations are made by a national expert committee.

In English-speaking countries, the guideline for the treatment of schizophrenia published by the American Psychiatric Association (APA) in 2004 is the first to address the NMS [28]. It also contains the most detailed definitions and treatment recommendations: symptomatic therapy, drug treatment with bromocriptine, amantadine, dantrolene, or benzodiazepines (not specified); in refractory or severe NMS, ECT is recommended.

The US Schizophrenia Patient Outcomes Research Team, founded by the Agency for Health Care Policy and Research and the National Institute of Mental Health, adopted a treatment guideline on schizophrenia in 2009 [29]. The authors recommend only prescribing clozapine after regression of the NMS. For acute therapy, no recommendations are given.

For the United Kingdom, we identified 2 national guidelines for the treatment of schizophrenia from the National Institute for Health and Care Excellence (NICE): "The NICE Guideline on Treatment and Management of Psychosis and Schizophrenia in Adults" [30] and the treatment guidelines for schizophrenia in children and adolescents [31]. The NMS is only mentioned as a possible side effect in the guidelines for adult patients. None of the 2 guidelines contains a therapy recommendation.

The World Federation of Societies of Biological Psychiatry (WFSBP) guideline on schizophrenia published in 2013 recommends symptomatic treatment in the case of NMS and the use of dantrolene in the presence of extreme temperature elevation, rigor, or proven hypermetabolism [32].

The Canadian Psychiatric Association Guideline on Schizophrenic Treatment recommends symptomatic therapy and possibly the administration of dantrolene, bromocriptine, or amantadine for the NMS; ECT is not mentioned here [33]. The recommendations are based on a case series with 68 cases [34].

The Royal Australian and New Zealand College of Psychiatry treatment guidelines for schizophrenia [35] recommended an unspecified "prompt treatment with hospitalization" with no further specification.

The Indian Psychiatry Society Schizophrenia Treatment Guideline for adults (2017) [36] recommends symptomatic therapy and the application of dantrolene, bromocriptine, amantadine, or lorazepam (not specified), and ECT as second-line therapy. Those are based on case reports and case series.

Neither the French guideline on the treatment of schizophrenia of the Haute Autorité de Santé [37] nor the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI) [38] mention the treatment of the NMS, the later, in any of the consulted guidelines at the website of the respective national society.

## Discussion

A total of 14 relevant guidelines have been identified and compared. The NMS is mentioned in 12 of 14 guidelines (86 %). Only 9 of 14 guidelines (64 %) contain concrete therapy recommendations, 5 of 14 guidelines (36 %: the 3 DGPPN guidelines [19, 20, 23], the APA guideline [28], and the IPS guideline [36]) include all drug therapy options as well as ECT. Dosage recommendations for pharmacological treatment of the NMS are included in only 4 of 14 (28.5 %) guidelines [20, 23, 32, 39], however, they differ significantly. All treatment recommendations included in the guidelines are based on weak to very weak evidence levels and referral strengths (▶**Table 3**), as there is a lack of randomized, controlled trials on the treatment of the NMS. This is due to its rarity and the acute nature of its occurrence.

With the update of the German DGPPN S3 Schizophrenia Treatment Guideline [20], defined severity classifications are given for the first time, which is helpful for the practical handling. Here, doses for certain drugs are recommended (▶**Table 4**), but they raise new questions: i) The recommended daily maximum dose of dantrolene (10 mg per day) is well below the manufacturer's recommendation of 2.5 mg per kilogram of body weight per day in the available pre-

scribing information [40]. ii) The stated maximum dose of lorazepam (4–8 mg per day) is significantly lower than e. g., for the treatment of a status epilepticus (8 mg every 8 h) [41]; in a comparable life-threatening condition, an identical dose recommendation would be expected. iii) The bromocriptine dose recommendation (up to 15 mg per day) seems too low; in idiopathic Parkinson's syndrome, up to 30 mg per day is recommended [42]. The DGPPN Emergency Psychiatry Panel S2k guideline also includes a differentiation between 2 NMS severity levels and precise pharmacotherapy recommendations. It is the only guideline to contain the very relevant recommendation for prevention of pneumonia and thrombosis in order to avoid complications.

Although pharmacotherapy is recommended in 7 of 14 guidelines, the consultation of the prescribing information showed that only dantrolene (Dantamacrin) [40] as the originator is approved for the treatment of the NMS. Generics of this drug are not approved [43, 44]. Amantadine [45–47], bromocriptine [42, 48, 49], and lorazepam [41, 50, 51] are not approved for the treatment of the NMS either. Thus, the use of these drugs is off-label. Patients with NMS are often unable to consent to an off-label treatment. In case of emergency, however, the presumed will of the patient counts, so the consent can be assumed. The same legal basis is applicable for ECT.

None of the guidelines defines the duration time of drug administration. It remains unclear when a therapy must be considered unsuccessful and the medication changed or ECT initiated. Eight out of 14 guidelines recommend ECT as a therapeutic alternative. Regarding the practicability of ECT, the applicability of the guidelines' recommendations is problematic. In Germany, for example, ECT is only available in about 50 % of all psychiatric hospitals [52]. Furthermore, the ECT devices are commonly available on psychiatric wards and must be explicitly transported to the target unit. Furthermore, specially trained staff is necessary when applying ECT. Thus, ECT is often not practicable or can only be carried out with considerable delay. None of the guidelines describes concrete recommendations for ECT performance (e. g., for electrode placement, stimulation intensity, frequency, or duration). Only the WFSBP's treatment guideline indicates a number of sessions (6–10 ECTs) [32].

Since the NMS is usually treated in the ICU either from the beginning or later in the course, anesthesiologists and emergency physicians should address the NMS in their guidelines. The research for emergency medical and anesthesiological guidelines regarding treatment recommendations in the German-speaking countries showed negative results. The DIVI guidelines do neither mention the syndrome nor refer to other guidelines. This could be due to the nature of the patient's underlying disease (i. e., schizophrenia), which does not primarily belong in the area of responsibility in intensive care and emergency medicine. In addition, it is likely that the NMS is little discussed in these disciplines because of its rareness, or it's simply not well-known enough.

The strength of our work lies in the fact that, for the first time, an overview of therapy recommendations for the NMS was derived from international guidelines and several independent researchers performed the research. Another strength is the linguistic extent of the guideline research, which was performed in 4 languages.

Our research shows that the NMS therapy recommendations in international guidelines are (if any are reported) very heterogeneous, partly inconsistent, and of poor evidence, a fact that is not uncommon in the field of rare diseases [53]. This peculiarity makes it difficult to deduce the best possible treatment strategy from the analyzed guidelines. Occasionally, systematic reviews are of much higher value than current guidelines from a clinical point of view. That is the case when looking at the recommendations stated in a recent work (2019) based on a systematic literature review, which are consistent with our modest scientific opinion. These recommendations can be summarized as follows: In addition to discontinuing antipsychotics and regulating water and electrolyte balance, the use of lorazepam (1–2 mg every 4–6 h); bromocriptine (2.5–5 mg orally every 8 h), dantrolene (1–2.5 mg/kg i. v. every 6 h for 48 h); or amantadine (100 mg every 8h h orally) is advised [54]. In case of not responding to medication, ECT is recommended as a "first-choice and often life-saving" therapy. For bridging, a propofol intra-venous perfusor can be used. Depending on the severity of the NMS, intensive care treatment should be taken into consideration. However, it remains unclear when a therapy should be considered as unsuccessful and be changed, and when ECT should be initiated and in which way performed.

## Conclusion

The optimal treatment of this potentially life-threatening disorder is not assured yet, and current guidelines do not represent an adequate help offering a practicable therapy concept with a high evidence level. Favorable effects have been attributed to benzodiazepines, dantrolene, bromocriptine, and amantadine. In the case of treatment failure, ECT is a particularly important therapeutic option. The lack of knowledge about the NMS can delay the initiation of therapy, impair the quality of treatment, and thus lead to a worse outcome or death. A thorough revision of the current treatment guidelines seems essential to achieve a better clinical outcome for the NMS.

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### Conflict of Interest

The authors state that there are no conflicts of interest. This post does not include studies on humans or animals.

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