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Antipsychotic-associated neuroleptic malignant syndrome (NMS) in schizophrenia patients: a narrative review

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a neurological disorder with an high mortality rate among schizophrenia patients who receive antipsychotics as the primary long-term therapy. Appropriate selection of antipsychotics in NMS should be carefully considered to obtain maximal effectiveness with minimal side effects. An evaluation of the safety profile of the antipsychotics is important due to their different treatment patterns and rapid onset of symptoms. This review article aimed to compare the safety profile of antipsychotics in relation to NMS in schizophrenia patients. It was a narrative review using multiple search engines included PubMed, Google Scholar, and Springer to collect publications from 2007 to 2023. Of the total 14 articles reviewed, 7 articles explained the role of antipsychotics in NMS, 5 articles about the onset of NMS, and 7 articles about mortality rate. The incidence of NMS was less then 0.11%, typical antipsychotics were the most common cause of NMS, especially high-potency antipsychotics compared with atypical antipsychotics. Meanwhile, the onset of NMS consistently occured within 30 d of antipsychotic initiation with a symptom duration of 1 to 30 d, and the mortality rate was also higher for typical antipsychotics. In conclusion, the choice of antipsychotics must be carefully considered and its use must be monitored due to the rapid onset and high mortality. The use of antipsychotics is not free from the risk of NMS. The heterogeneous symptoms of NMS require earlier detection to reduce disease progression.

ABSTRAK

Sindrom neuroleptik maligna (SNM) merupakan kelainan neurologis dengan angka kematian tinggi pada pasien skizofrenia yang mendapat antipsikotik sebagai terapi utama jangka panjang. Pemilihan antipsikotik yang tepat pada SNM harus dipertimbangkan dengan cermat untuk memperoleh efektivitas maksimal dengan efek samping minimal. Evaluasi profil keamanan antipsikotik penting karena pola pengobatan yang berbeda dan timbulnya gejala yang cepat. Tinjauan pustaka ini bertujuan membandingkan profil keamanan antipsikotik berkaitan dengan kejadian SNM pada pasien skizofrenia. Tinjauan naratif ini menggunakan beberapa mesin pencari termasuk PubMed, Google Scholar, dan Springer untuk mengumpulkan publikasi dari tahun 2007 hingga 2023. Dari total 14 artikel yang dikaji, 7 artikel menjelaskan peran antipsikotik pada SNM, 5 artikel tentang timbulnya SNM, dan 7 artikel tentang angka kematian. Angka kejadian SNM kurang dari 0,11%, antipsikotik tipikal merupakan penyebab tersering SNM, terutama antipsikotik potensi tinggi dibandingkan dengan antipsikotik atipikal. Sementara itu, timbulnya SNM secara konsisten terjadi dalam waktu 30 hari setelah penggunaan antipsikotik dengan durasi gejala 1 hingga 30 hari, dan angka kematian juga lebih tinggi pada antipsikotik tipikal. Kesimpulannya, pemilihan antipsikotik harus dipertimbangkan secara hati-hati dan penggunaannya harus dipantau karena onsetnya yang cepat dan angka kematian yang tinggi. Penggunaan antipsikotik tidak lepas dari risiko NMS. Gejala NMS yang heterogen memerlukan deteksi dini untuk mengurangi perkembangan penyakit.

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a neurological emergency syndrome that can be caused by an adverse reaction to dopamine receptor blockade (antipsychotics) or rapid withdrawal of dopaminergic therapy. The incidence rate of NMS is quite low, ranging from about 0.02 to 3.2%.[1] However, it has a high mortality rate of 10 to 55%.[2] Neuroleptic malignant syndrome is more common in males than females, and most cases peak in the young adulthood age range of 20 to 25 yr.[3]

The onset of NMS occurs within a few hours or days of initial therapy, but most symptoms develop between 2 wk and 30 d after the intial treatment. The clinical symptoms of NMS are specific and include muscle rigidity, hyperthermia or elevated temperature possibly associated with antipsychotics, autonomic instability, and altered mental status. The underlying pathophysiology of NMS is complex and not well understood. However, it is likely that antipsychotic-induced dopamine blockade plays a crucial triggering role. Antipsychotics cause NMS by a mechanism of sudden reduction in central dopaminergic activity due to a D_2 receptor blockade or abrupt withdrawal of D_2 receptor stimulation.[4,5] The primary pharmacological risk factor for NMS is often associated with the use of antipsychotics, including high dosages, dose escalation during the initial phases of antipsychotic treatment, antipsychotic combinations or polypharmacy, and parenteral administration.[6]

The potent typical antipsychotic has been most frequently associated with NMS and is believed to confer the greatest risk more than atypical antipsychotic because it has a stronger effect on D_2 dopamine antagonist effects. Due to their different pharmacodynamic properties, atypical antipsychotics were initially thought to have a minimal risk of NMS. However, several atypical neuroleptics, including risperidone, clozapine, quetiapine, olanzapine, aripiprazole, and ziprasidone have been reported to cause NMS.[7] Various other risk factors have been associated with the development of NMS, such as decreased iron levels, feelings of restlessness, exposure to high temperatures, lack of hydration, physical fatigue, hyponatremia, abnormalities of CNS dopamine activity, as well as the presence of a structural or functional brain disorder.[8]

Antipsychotic therapy, which can be a cause of NMS, is mainly used in the treatment of schizophrenia. Antipsychotics have traditionally been classified as typical (first-generation antipsychotic or FGAs) and atypical (second-generation antipsychotic or SGAs). Antipsychotic therapy is effective in reducing acute symptoms, and long-term antipsychotic therapy is recommended to reduce the risk of relapse; however, its effectiveness is variable and its adverse effects can be significant. The adverse effects of antipsychotics are often serious, including sedation, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, cardiac arrhythmias, metabolic syndrome, sexual dysfunction, and neuroleptic malignant syndrome. Guidelines and experts generally recommend that the choice of antipsychotic medication should be based on side effects rather than efficacy.[9-11]

The use of antipsychotics in schizophrenia has increased every year with different patterns of antipsychotic therapy according to symptom targets; therefore, it has the risk of causing an increase in the occurrence of NMS and mortality rate. The aim of the article review was to compare the safety profile of antipsychotics associated with NMS in schizophrenia patients to reduce the risk of adverse effects and improve the quality of life of patients.

MATERIAL AND METHODS

The literature review approach involved the use of multiple search

engines, including PubMed, Cochrane, and ScienceDirect. The scope of the review included publications from 2007 to 2023 using the search terms "neuroleptic malignant syndrome", "schizophrenia", "typical antipsychotics ", "atypical antipsychotics or FGAs " and "typical antipsychotics or SGAs". The inclusion criteria for this narrative review included systematic reviews, randomized controlled trials (RCT), case-control studies, case series and cohort studies of neuroleptic malignant syndrome in patients with schizophrenia using antipsychotics. The selected primary literature adhered to specific criteria included 1) inclusion of subjects diagnosed with schizophrenia or NMS; 2) inclusion of subjects who received antipsychotic therapy; 3) publication of articles in English between 2007 and 2023. The exclusion criteria for articles included 1) irrelevant articles; 2) non-English studies; 3) duplicates; 4) narrative reviews; and 5) studies without a comparator antipsychotic.

The main focus of these studies is the safety profile of antipsychotics associated with NMS, including the risk factor and mortality. The review does not classify the findings based on disease severity and specific populations of schizophrenia or specific antipsychotics.

RESULTS

A literature search using multiple search engines yielded 130 articles, which were then evaluated according to inclusion and exclusion criteria. A total of 116 articles were excluded for duplication, narrative reviews, no comparison antipsychotic, irrelevant or non-English, while a total of 14 articles that met the inclusion criteria (TABLE 1). In summary, the reviewed articles consisted of 7 discussing the role of antipsychotics in the development of NMS, 5 on the incidence of NMS, and 7 on the mortality of NMS associated with antipsychotics.

TABLE 1. Results of a search for studies on the safety profile of antipsychotics associated with NMS

Authors	Tittle of article	Incidence	Onset/duration/mortality	Conclusion
Langan *et al.*[12]	Antipsychotic dose escalation as a trigger for neuroleptic malignant syndrome (NMS): literature review and case series report	Antipsychotic rapid escalation in NMS occurred less than half as often (38.5%) as non-rapid escalation (61.5%).	Antipsychotic polypharmacy (53.8%) and parenteral antipsychotics (38.5%) received in the 30 d prior to NMS onset.	It is difficult to identify rapid dose escalation as the main cause of NMS, but cumulative antipsychotic dose is thought to be an important factor in the development of NMS. Polypharmacy and parenteral antipsychotics may also cause NMS.
Neuhut *et al.*[13]	Neuroleptic malignant syndrome in children and adolescents on atypical antipsychotic medication: a review	There were 23 episodes in 20 subjects, aged 11 to 18 yr, with the most common atypical antipsychotics being risperidone (n=7), olanzapine (n=7) and aripiprazole (n=3).	Onset of NMS ranged from immediately to 56 days (mean 8.7-16.2 d). Duration of NMS symptoms ranged from 1-31 days (mean 6.1-6.4 d).	In children and adolescents, risperidone, olanzapine and aripiprazole can cause NMS.
Nielsen *et al.*[14]	Neuroleptic malignant syndrome: an 11-year longitudinal case–control study	Incidence of NMS occurred in around 0.04% of the 224,372 patients. SGAs increased the risk of NMS (OR=4.66). High-potency FGAs (OR=23.41), middle-potency FGAs (OR=4.81) and depot antipsychotics (OR=4.53).	Mortality in patients (HR=1.88; 95%CI: 1.19 to 2.98).	The incidence of NMS is low and predicting NMS is difficult. Previous treatment with FGAs and SGAs has been identified as a risk factor for the development of NMS. NMS increases mortality within 30 d of NMS

TABLE 1. Results of a search for studies on the safety profile of antipsychotics associated with NMS (cont.)

Authors	Tittle of article	Incidence	Onset/duration/mortality	Conclusion
Trollor *et al.*[15]	Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics	-	The median time to NMS onset after antipsychotic initiation was 23.0 d, with no significant difference between those with 1G and 2G NMS. Mortality was significantly lower in 2G-NMS (3.0%) than 1G-NMS (16.3%).	The characteristics of NMS in the two groups were very similar, and mortality was higher in FGAs than in SGAs.
Kimura *et al.*[16]	Antipsychotics-associated serious adverse events in children: an analysis of the FAERS database	Haloperidol, olanzapine, quetiapine, risperidone and aripiprazole were found to signal NMS, with haloperidol and aripiprazole scoring higher than other antipsychotics.	-	Signal scores were higher for haloperidol and aripiprazole than for the other antipsychotics, suggesting that SGAs show lower susceptibility to NMS.
Murri *et al.*[17]	Second generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis	Global severity from six primary studies and 186 individuals was significantly lower for clozapine than risperidone [p = 0.02] or olanzapine [p = 0.03]	-	Second-generation antipsychotics have a risk of NMS induction. NMS is induced more frequently by clozapine, aripiprazole and amisulpride than by other SGAs with less severe extrapyramidal symptoms or high fever.
Sahin *et al.*[18]	A retrospective analysis of cases with neuroleptic malignant syndrome and an evaluation of risk factors for mortality	The prevalence of NMS in patients presenting in the last 10 yr is 0.004%. The most common cause of NMS was atypical antipsychotics (78.6%).	-	The most common agent that cause NMS was atypical antipsychotics
Amenero *et al.*[19]	Neuroleptic malignant syndrome in children and adolescents: systematic review of case reports	-	The onset of NMS occurred at 11.25 ± 20.27 d with typical antipsychotics and at 13.69 ± 22.43 d with atypical antipsychotics.	The onset of NMS in 54 patients was more rapid with typical antipsychotics than with atypical antipsychotics.
Guinart *et al.*[20]	Outcomes of neuroleptic malignant syndrome with depot versus oral antipsychotics: a systematic review and pooled, patient-level analysis of 662 case reports	-	Duration of hospitalization LAIs = 5.0 wk vs OAPs= 3.8 wk, (p= 0.8322),	Antipsychotic formulations have not been shown to significantly increase NMS, but should reduce safety concerns in use with LAIs.
Lao *et al.*[21]	Antipsychotics and risk of neuroleptic malignant syndrome: a population-based cohort and case-crossover study	The risk of developing NMS was 0.11% in 297,647 patients.	Of the 336 cases, 20 (6%) died within 30 d of the index date, and only one case was NMS recorded as the primary cause of death.	The risk of developing NMS with antipsychotic use was 0.11%, with frequent mortality within 30 d.

TABLE 1. Results of a search for studies on the safety profile of antipsychotics associated with NMS (cont.)

Authors	Tittle of article	Incidence	Onset/duration/mortality	Conclusion
Guinart *et al.*[22]	A systematic review and pooled, patient-level analysis of predictors of mortality in neuroleptic malignant syndrome		NMS mortality was associated with antipsychotic discontinuation (OR=4.39; p< 0.0001), respiratory distress (OR=3.54; p < 0.0001), hyperthermia severity (OR=1.30; p= 0.0014) and older age (unit OR=1.05; p=0.0014).	Mortality in NMS was not related to antipsychotic generation. Predictors of NMS mortality were lack of antipsychotic discontinuation, respiratory problems, severity of hyperthermia and older age.
Misawa *et al.*[23]	Neuroleptic malignant syndrome associated with long-acting injectable versus oral second-generation antipsychotics: analyses based on a spontaneous reporting system database in Japan	The NMS incidence caused by LAI-SGAs or equivalent oral SGAs was 13%.	Mortality rates for oral aripiprazole, oral risperidone/paliperidone, LAI risperidone, and LAI paliperidone were 13.1%, 8.8%, 4.2%, and 3.4%, respectively.	The NMS incidence with LAI and oral SGAs are comparable and the use of oral aripiprazole is associated with higher mortality.
Oneib *et al.*[24]	Neuroleptic malignant syndrome: clinical expression, complication, course, and atypical clinical picture	The patients were 16 men and 9 women with a mean age of 40.45±9.772 yr, ranging from 22 to 57 yr. 92% of patients received FGAs. Half of these were injectable.	-	The NMS prevalence is highest in men, with conventional antipsychotics (FGAs) as the main cause.
Touzani *et al.*[24]	Neuroleptic malignant syndrome cases in a Moroccan intensive care unit: a retrospective analysis and literature review	The male to female ratio was 1:4 and the average age was 36.6 yr. The most commonly prescribed drugs (80%) were FGAs.	Onset of symptoms was 7.6 d and mortality was 10%, mainly due to renal failure.	The NMS is more common in patients using FGA than SGA, with a mortality rate of 10%, and mostly affects women.

Two key findings were obtained in this review. The first one concerns the association between antipsychotics use and NMS incidence. The risk of NMS incidence is most common with first-generation antipsychotics or typical antipsychotics (FGAs) due to their higher dopamine D_2 blocking potential. However, second-generation antipsychotics or atypical antipsychotics (SGAs) may also have a risk for NMS incidence. The second one concerns antipsychotic use and NMS onset and mortality. The onset of antipsychotic-induced NMS occurred within 30 d after antipsychotics administration, with symptom duration ranging from 1 to 30 d. The NMS incidence up to 0.04% with mortality rate is higher in the FGAs (up to 16.3%) use than in the SGAs use.

DISCUSSION

Antipsychotic induced NMS

Although NMS incidence is rare, it is a potentially fatal adverse drug reaction of antipsychotics which can range in

severity from mild to life-threatening.[25] Antipsychotics are the main therapy for schizophrenia. The common property of effective antipsychotics is D_2 receptor blockade. Antipsychotics are useful for maintaining the stability of the disease in remission, improving the social functioning of patients, achieving recovery goals and return to society. The maximum clinical response to antipsychotics is achieved when there is ~65-75% inhibition of the dopamine D_2 receptors.[26]

An adverse drug reaction or side effect is a harmful and unintended response to a drug that occurs at a dose normally used in patients for the prophylaxis, diagnosis, or treatment of disease or for the modification of physiological function. The side effects of antipsychotics have been reported to interfere with medication adherence, worsen illness, and even increase the risk of certain medical conditions. This is due to the fact that each drug has a different affinity for different synaptic receptors, which may result in a different efficacy and safety profile.[27]

Pharmacodynamic differences exist between the 2 groups of antipsychotics (TABLE 2). In general, the SGAs have a lower affinity for the D_2 dopamine receptor, while they are potent antagonists at the 5-HT_{2A} serotonin receptor. The high ratio of 5-HT_{2A} receptor occupancy is thought to confer the reduced likelihood of extrapyramidal side effects. The high level of D_2 affinity of FGAs leads to an increased inhibition of D_2 blockade, resulting in a sudden decrease of central D_2 dopamine through the nigrostriatal, hypothalamic, and mesolimbic/cortical pathways. A low level of D_2 receptor binding in the acute phase and a low level of dopamine homovanillic acid metabolites in the cerebrospinal fluid of patients also increase the incidence of NMS.[2] Antipsychotic dopamine blockade can occur in several pathways, responsible for different clinical symptoms. Blockade of the nigrostriatal pathway causes rigidity, whereas the hypothalamic pathway is associated with impaired central thermoregulatory and autonomic regulation. Altered dopamine neurotransmission in the brainstem reticular activation system is responsible for altered consciousness.[29]

TABLE 2. Receptor binding of antipsychotic[28]

Antipsychotic	Receptor					
	D_2	$5HT_{2A}$	$5HT_{2C}$	H_1	M_3	α_1
Chlorpromazine	+++	+++	++	+++	++	+++
Haloperidol	+++	+	-	-	-	++
Clozapine	+	+++	++	+++	++	+++
Olanzapine	++	+++	++	+++	++	++
Risperidone	+++	++++	++	+++	-	+++
Quetiapine	+	++	+	+++	+	++
Aripripazole	+++	++	++	++	-	++

Note. +: weak association; ++: moderate association; +++: strong association; ++++: very strong association

TABLE 3. Comparative NMS risk of antipsychotics.[32]

Antipsychotic	NMS
Typical	
• Chlorpromazine *	+
• Haloperidol **	++
Atypical	
• Aripripazole	+
• Clozapine	+
• Olanzapine	+
• Quetiapine	+
• Risperidone	+

Note: *=low potency; **= high potency; 0=rare; += lower risk; ++= medium risk; +++=higher risk

The NMS incidence is generally quite low and difficult to predict. Neilsen *et al.*[13] reported NMS events occurred in only 0.04% of 224,372 patients. Sahin *et al.*[18] also reported only 0.004 of patients developed NMS in 10 last year retrospective analysis, whereas Lao *et al.*[21] reported 0.11% of 297,647 patients developed NMS.

Both FGAs and SGAs can cause NMS with varied different potency and risk.[16,24,30] However, the FGAs generally have higher NMS risk than SGAs. A study conducted by Neuhut *et al.*[13] concerning the relationship between SGAs use and NMS risk in children and adolescents showed that risperidone and olanzapine have a higher NMS risk than clozapine. Furthermore, Nielsen *et al.*[14] reported that the increase of NMS risk is higher after high-potency FGA treatment (OR=23.41) compared to mid-potency FGA (OR=4.81) and SGA (OR=4.66). Although SGAs have low D_2 dopamine receptor binding, SGAs can stimulate 5-hydroxytryptamine receptors leading to γ-amino butyric acid in the nucleus accumbens resulting in D2 dopamine receptor inhibition.[31]

As above demonstrated the type of antipsychotic is one of the risk factors for the developing of NMS. Other risk factors for developing NMS including escalation of antipsychotic dose, treatment formulation, and polypharmacy of antipsychotics were discussed in this review. Langan *et al.*[12] reported antipsychotic escalation dose was reported as important risk factors for the developing of NMS. Although the non-rapid escalation has a much higher daily cumulative antipsychotic dose compared to the rapid excalation, it is possible that cumulative antipsychotic dose may also play a role in developing NMS.

Treatment formulation was also reported as risk factors for developing of NMS.[6,14] However, recent studies reported no association between treatment formulation and NMS incidence. The incidence of NMS was not different between long-acting injectable antipsychotics (LAIs) and oral antipsychotic (OAP) treatment.[22,23]

Polypharmacy of antipsychotics is a general strategy for the treatment of disturbed behavior, poor response to antipsychotic monotherapy, or acute exacerbation of positive symptoms.[33] It was estimated that 19.6% of patients with schizophrenia worldwide receive polypharmacy or combination antipsychotic therapy.[34] Polypharmacy was reported as risk factors for the

developing NMS. About 58.3% patients with NMS received polypharmacy.[12]

Onset, duration and mortality of NMS

Neuroleptic malignant syndrome has an onset of symptoms within a few h or d of initiation of antipsychotic therapy. However, most symptoms occur within 2 wk to 30 d of initiation. It was reported that 16% of cases of NMS develop within 24 h, 66% develop within the first wk, and nearly all cases occur within 30 d of initiation of antipsychotic therapy.[4,12,15,19,21] Neuhut *et al.*[13] reported that NMS symptoms appear immediately after initiation, and have a longer range of onset up to 56 d after antipsychotic initiation.[13]

The clinical presentation of NMS symptom is generally heterogeneous leading to difficult to diagnose, especially in the early stages. It usually begins as an unexplained cluster of symptoms including tremors and muscle spasms, unstable blood pressure, and mental status changes.[35] It was reported 70% of NMS cases demonstrated the following sequences of events ending in coma at the terminal phase; mental status changes appear first, followed by rigidity, then hyperpyrexia, and finally autonomic dysfunction (dysautonomia).[29] A cohort study by Langan *et al.*[12] supported the heterogeneous symptoms of NMS. The most frequently documented features is elevated CK, altered GCS and tachycardia and only 38.5% of patients presented with the classic triad of rigidity, hyperthermia and altered level of consciousness. Increased creatine phosphokinase (CPK) was the most common finding (100%), followed by fever (78%), tachycardia (74%), rigidity (70%), and altered mental status (61%), which were also seen with atypical antipsychotics inducing NMS.[17] However, clozapine-induced NMS have less rigidity and tremor, and higher temperatures were observed less frequently with aripiprazole (58.3%) than with other SGAs.[13]

Mortality due to NMS was 10%, with atypicals having a significantly lower mortality rate (3.0%) than typicals (16.3%). However, other studies reported that aripripazole has a higher SGA mortality rate (13.8%).[15,23,30] In contrast, Guinart *et al.*[22] reported that mortality due to NMS is not related to the antipsychotics use. Predictors of NMS mortality were lack of antipsychotic discontinuation, respiratory problems, severity of hyperthermia, and older age.[22]

To prevent NMS, it is important to limit antipsychotic use except when clearly indicated for psychiatric problems. It is known that the prescription of low-dose antipsychotics still increases the risk of developing NMS. Therefore, minimizing unnecessary prescriptions can help reduce the NMS incidence. In several cases, optimization of antidepressant, anxiolytic, and mood-stabilizing treatments can also help avoid augmentation with antipsychotics. Antipsychotics with lower D_2 blocking effects, such as atypical antipsychotics, should be selected whenever possible for clinical use. These antipsuchotics are less frequently associated with NMS, less severe and less potential fatal condition.[25]

Clinicians should avoid parenteral administration, rapid titration, and high doses of antipsychotics due to their association with a higher risk for developing NMS. It is recommended to consider the use of antipsychotics with caution. In addition, it should be noted that antipsychotic polypharmacy not only increases the NMS risk but also leads to higher morbidity and mortality rates. If necessary, patients who have experienced NMS can get antipsychotics as rechallenge. It is recommended to begin with a low dose and gradually increase towards the target dose. Patients should be monitored closely for fever, autonomic instability, changes in mental status, extrapyramidal symptoms, and dehydration. The antipsychotic should be stopped immediately if fever, rigidity, or labile blood pressure occur.[25]

Studies concerning the association

between antipsychotics and NMS incidence are limited due to the rare NMS incidence. In addition, antipsychotics have a NMS risk causing difficulties in comparing the specific types of antipsychotics that may cause the NMS. This narrative review has several limitations, including 1) the limited amount of new research comparing antipsychotics causing NMS; 2) not all of the previous studies discussed in detail about the onset, duration, or mortality of each antipsychotic medications. It is well known that typical antipsychotics have a higher NMS incidence compared to atypical antipsychotics. Therefore, the prescription of antipsychotics must be carefully and appropriately considered. In addition, since the use of atypical antipsychotics is more recommended due to fewer side effects, further studies to compare more atypical antipsychotics causing NMS are needed.

CONCLUSION

The choice of antipsychotics must be considered carefully and need to be monitored due to the rapid onset and high mortality. The use of typical antipsychotics tends to cause NMS at a higher rate, but the use of atypical antipsychotics is also associated with a risk of NMS, especially when used at high doses both orally and parenterally and in polypharmacy. Diagnostic symptoms were heterogeneous across antipsychotic groups, but the most specific symptoms of clozapine-induced NMS were less rigidity and tremor. Thus, accuracy in early diagnostic may help reduce patient mortality. Further studies are needed to specifically identify the atypical antipsychotic that causes NMS the most, considering that the typical antipsychotics still have a risk of NMS.

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