Outcomes of Neuroleptic Malignant Syndrome With Depot Versus Oral Antipsychotics: A Systematic Review and Pooled, Patient-Level Analysis of 662 Case Reports

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ABSTRACT

Objective: This systematic review and pooled, patient-level analysis of neuroleptic malignant syndrome (NMS) case reports and series compared NMS characteristics and outcomes during long-acting injectable antipsychotic (LAI) versus oral antipsychotic (OAP) treatment.

Data Sources: Two authors independently searched MEDLINE, Embase, Cochrane, CINAHL, and PsycINFO databases for articles in English from database inception until October 9, 2018.

Study Selection: Case reports with author-defined NMS during ongoing antipsychotic treatment or within 1 injection interval of LAIs in adults aged 18–65 years.

Data Extraction: Demographic, clinical, treatment and outcome data were independently extracted following PRISMA guidelines. NMS severity was rated using the Francis-Yacoub scale. Characteristics and outcomes of NMS were compared when occurring during LAI versus OAP treatment, adjusting for significant between-group differences.

Results: Of 662 reported cases (median age = 36 years, male = 61.2%), 122 (18.4%) involved LAIs (second-generation antipsychotic [SGA] LAIs [SGA-LAIs] = 10, 1.5%), whereas 540 (81.6%) involved OAPs (SGA-OAPs = 159, 24.0%). The 2 groups did not differ in age, illness duration, comorbidities, or presence or severity of NMS symptoms (median Francis-Yacoub score: LAIs = 26 vs OAPs = 23, $P = .8276$). Antipsychotic formulation was not significantly associated with longer duration of hospitalization (LAIs = 5.0 weeks vs OAPs = 3.8 weeks, $P = .8322$), post-NMS sequelae (LAIs = 8.8% vs OAPs = 7.0%, $P = .7489$), or death (LAIs = 10.7% vs OAPs = 6.7%, $P = .0861$). When different, post hoc confounder-adjusted models were used, duration of NMS (but not hospitalization for NMS) was longer with LAIs than with OAPs (median = 2.6 vs 1.8 weeks, $P = .0339$), driven by FGAs rather than SGAs.

Conclusions: These data, plus the fact that only 10 published NMS cases exist with SGA-LAIs, should mitigate safety concerns regarding LAIs, but results should be interpreted cautiously since they are based on case reports.

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Neuroleptic malignant syndrome (NMS) is a rare, potentially fatal condition associated with dopamine-blocking agents, especially antipsychotics.[1–3] The reported incidence of NMS varies widely, with values ranging between 0.02% and 3.23%,[4–7] partly due to its idiosyncratic nature, making it difficult to study prospectively, and partly due to methodological differences in the definition and incidence estimation of NMS across different studies.[4] NMS is characterized by muscle rigidity, altered mental status, hyperthermia, autonomic dysfunction, leukocytosis, and increased creatinine kinase (CK).[3,8] The pathophysiology of NMS remains unclear, but dopamine antagonism seems to be required[9,10] and the differential diagnosis includes malignant hyperthermia, malignant catatonia, or serotonin syndrome.[11,12]

Management of NMS is supportive and involves stopping dopamine antagonists, hydration, and other supportive measures.[3] However, antipsychotic treatment cannot be stopped immediately in patients treated with long-acting injectable antipsychotics (LAIs) due to their prolonged medication release.[13] LAIs provide therapeutic blood antipsychotic levels during an injection interval that can last 2–12 weeks, depending on the LAI.[13] This feature is desirable to simplify the medication regimen and address/signal non-adherence.[14–16] Furthermore, LAIs have shown superiority versus oral antipsychotics (OAPs) for all-cause discontinuation, relapse, hospitalization, and mortality.[13,15,17–20]

However, although the safety of LAIs is generally not worse than that of OAPs,[21] it takes 5 half-lives until blood antipsychotic levels return to zero, and half-lives of LAIs range from 10 to 60 days.[13,22] Conversely, half-lives of most OAPs range from 8 to 30 hours,[23] enabling antipsychotic washout generally within a week and not within months as with LAIs. Nevertheless, it is unknown whether the advantage of longer-term medication

Clinical Points

- A systematic review and pooled, patient-level analysis of case reports and series of neuroleptic malignant syndrome (NMS) were conducted to determine whether NMS occurring with oral antipsychotics differs from that occurring with long-acting injectable antipsychotics (LAIs).
- No differences in severity, need for intensive care, length of hospital stay, recovery, sequelae, and mortality were found. Duration of NMS was slightly longer with LAIs, although not with second-generation LAIs.

release with LAIs may be offset by an increased risk of more prolonged, severe, and dangerous NMS, including mortality. Since prospective long-term studies targeting NMS are missing, only a systematic assessment of published case reports can address the question of whether LAIs are associated with worse outcomes of NMS than OAPs. In 1992, a limited, non-systematic review[24] of cases suggested no increased risk of various neuromotor adverse effects with LAIs versus OAPs, but the focus was not NMS. Moreover, this review predated second-generation antipsychotic (SGA) LAIs. Since the inability to stop LAIs immediately in case of a serious adverse event has been cited as an argument against LAI use,[13,25] we systematically reviewed all published case reports of NMS and compared clinical characteristics and outcomes of NMS in patients who developed NMS during LAI versus OAP treatment. We hypothesized that, despite the inability to abruptly discontinue LAIs as can be done with OAPs, outcomes would be similar.

METHODS

We performed a systematic literature review and pooled, patient-level analysis of NMS case reports and series reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.[26] A PRISMA checklist can be found in Supplementary Table 1.

Literature Search and Case Selection

Two authors (D.G., F.M.) independently searched MEDLINE, Embase, Cochrane, CINAHL, and PsycINFO databases from inception until October 9, 2018, for articles in English, using the following search terms: (antipsychotic* OR neuroleptic* OR antidopaminergic* OR "dopamine blocker") AND ("neuroleptic malignant syndrome" OR NMS). The electronic search was supplemented by a manual review of reference lists from eligible publications and relevant reviews. Whenever data were missing, or available data needed clarification, authors were contacted for additional information.

Case Screening and Selection

After the initial search and removal of duplicates, each study was independently screened by abstract and title. This initial selection was then double-checked by at least one other author. Inconsistencies were resolved by consensus or involvement of an additional reviewer. Articles deemed irrelevant were removed, and articles that could potentially contain relevant information were selected for full-text review and were examined in depth to assess eligibility. At this point, each reviewer´s selection was again cross-checked, and discrepancies were resolved by consensus or involvement of a third reviewer.

Inclusion and Exclusion Criteria

Inclusion criteria were cases with (i) author-defined NMS, (ii) ongoing antipsychotic treatment or within 1 injection interval of an LAI, and (iii) adults 18–65 years old (with the upper age limit to avoid potential confusion with organic reasons for presentations that might mimic NMS). Excluded were cases for which (i) the authors did not clearly diagnose NMS (cases diagnosed as, for example, malignant catatonia or malignant hyperthermia); (ii) antipsychotic treatment was given in the context of nonpsychiatric, neurologic, or medical conditions, such as acquired organic disorders (cancer, traumatic brain injury, Parkinson disease, dementia, or postoperative disorders); and (iii) NMS occurred in the context of a voluntary antipsychotic overdose.

Outcomes

The primary focus was to assess and compare cases of NMS occurring during LAI versus OAP-only treatment, both in general and stratified by SGA and first-generation antipsychotic (FGA) treatment, regarding (i) frequency of complete recovery, incomplete recovery, or death; (ii) duration of NMS; and (iii) length of hospital stay related to the NMS. Secondary outcomes included the characterization of clinical characteristics of NMS, such as the severity and frequency of NMS symptoms, the first symptom to start, and the last symptom to stop, as well as interventions used to treat NMS.

Data Extraction

Each included case report was independently reviewed, and demographic, clinical, treatment, and outcome data were independently extracted for each individual NMS case by at least 2 physicians (from among D.G., F.M., J.P., and J.R.) separately. Data extraction files were then cross-checked for inconsistencies and reviewed by a third author to minimize errors. All discrepancies were resolved by consensus. NMS symptom severity was rated using the Francis-Yacoub NMS scale,[27] a 23-symptom scale that encompasses the motor, behavioral, autonomic, and laboratory domains of NMS. Items are rated based on the most severe presentation. If age was provided in imprecise terms or using an age range only, the median of a given range was used. For example, "early 20s" was coded as "23" years of age (median between 20 and 25), "mid 50s" was coded as 55 years of age (median between 50 and 59), and "late 30s" was 37 (median between 35 and 39). If an injection was mentioned without any further specifier and authors could not be contacted, short-acting injection was assumed. If multiple episodes of NMS were described for a

given patient, we characterized only the first episode of NMS. Information was collected about all treatments at the time of NMS. Due to the similar half-life, short-acting injections of antipsychotics were combined with oral treatment. Any data that the authors did not specify in the report and that were not possible to obtain by contacting the authors were considered as missing. These select coding procedures, together with the aforementioned inclusion and exclusion criteria, ensured the selection of case reports meeting the selection, ascertainment, causality, and reporting domains, critical in qualitative evaluation of case reports and series.[28]

Chlorpromazine Equivalents

Antipsychotic dose equivalents were calculated using the chlorpromazine (CPZ) equivalences listed by Leucht and colleagues[29] except for droperidol, for which no conversion factor was available, which is why the method by Gardner and colleagues[30] was used for it. For iloperidone, we followed the conversion factors described by Leucht and colleagues,[31] assuming that their maximum label dose (12 mg twice daily) corresponded to olanzapine 20 mg/d because the investigators of the consensus study had made similar decisions for most other antipsychotics. For cases in which European and American conversion factors differed, such as for lurasidone and paliperidone, our convention was to use the American conversion factors. Given its very high antihistaminic effect and low potency, we considered promethazine very similar to levomepromazine, using its equivalence factor. Blonanserin and perospirone equivalencies were obtained from Inada and Inagaki.[32] We were unable to find conversion factors for cyamemazine, procyclidine, and methotrimeprazine, but only very few patients (n = 5) were treated with these antipsychotics. LAI daily CPZ equivalents were estimated by dividing the total injection dose by the time interval between injections, as previously reported in pharmacokinetic studies comparing long-acting injectable and oral formulations of the same drug.[33,34] For the total CPZ equivalence calculations and subsequent group comparisons, we accounted for all antipsychotic treatments that a patient was taking at NMS onset, summing up the CPZ equivalent doses across the taken antipsychotics. However, in the OAP group, only OAPs were allowed, while in the LAI group, both LAIs and OAPs were allowed. We allowed OAP cotreatment in the LAI group, as our focus was to assess whether the presence of an LAI during the development of NMS influences clinical characteristics and outcomes of NMS. Coprescribed OAPs would not change the outcome relative to the OAP group, except if there would be CPZ equivalence differences, for which we assessed and controlled.

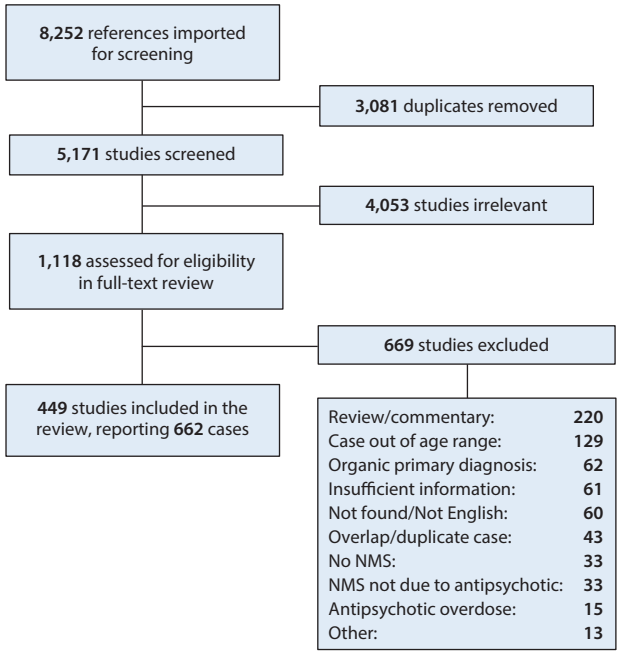
Data Analysis

LAI-related cases could include OAP cotherapy, whereas the OAP group could contain only OAPs, in monotherapy or polytherapy. Patient characteristics and NMS characteristics and interventions were compared between LAI-related and OAP-related NMS cases in univariate analyses, using χ^2 tests for categorical variables, *t* test for normally distributed continuous variables as per Saphiro-Wilk *W* test, and Wilcoxon tests for non-normally distributed continuous variables. Spearman correlation coefficients were used to assess the relationship between clinical severity as measured by the Francis-Yacoub scale and CPZ equivalents. Outcomes of NMS were compared between LAI and OAP groups in potential confounder-adjusted, mixed-models multivariable regression analyses adding to the model all characteristics that were significantly different between LAI and OAP cases in univariate analyses. We also compared NMS cases occurring during FGA-LAI versus FGA-OAP treatment and SGA-LAI versus SGA-OAP treatment, excluding patients treated with both FGA-OAPs and SGA-OAPs, as well as cases in which only formulation, but not drug name or class, was reported. Finally, since CPZ equivalences were not significantly associated with NMS duration ($P = .5764$) or mortality ($P = .6895$), with dose being unavailable in 137 NMS cases, we conducted additional post hoc adjusted regression analyses without CPZ equivalences as a covariate. All analyses were conducted using JMP, Version 13 (SAS Institute Inc, 1989–2019). Network analyses to visualize the frequency and relationship between different symptoms and signs of NMS rated by the Francis-Yacoub Scale were performed using Gephi, version 0.9.2 for Windows (https://gephi.org/).

RESULTS

Search results, articles excluded at full text review, and included articles are detailed in a PRISMA flowchart (Figure 1). Altogether, 662 individual cases of NMS were analyzed.

Figure 1. PRISMA Flowchart of Included and Excluded Studies



Abbreviation: NMS = neuroleptic malignant syndrome.

Sociodemographic Characteristics

LAI-related NMS cases (n = 122; 18.4%) did not differ from OAP-related NMS cases (n = 540; 81.6%) regarding age at time of NMS (median = 36 years, $P = .5983$) or illness duration (median = 10 years, $P = .5661$) (Table 1). LAI-related NMS cases contained more male (LAI = 69.5% vs OAP = 59.4%, $P = .0411$) and Asian patients (LAI = 66.7% vs OAP = 18.5%, $P = .0003$), but fewer white individuals (LAI = 14.3% vs OAP = 61.2%, $P = .0022$), although more LAI-related NMS cases were described in Europe (LAI = 32.8% vs OAP = 19.4%, $P = .0011$). Schizophrenia was the most common primary diagnosis (43.8%), being more frequent with LAIs than with OAPs (60.7% vs 40.0%, $P = .0001$). All other primary and secondary diagnoses, and medical comorbidities were similar across groups (Table 1).

Results were very similar when comparing NMS cases occurring during FGA-LAI (n = 112) versus FGA-OAP (n = 314) treatment, which contributed 426 (64.4%) of the NMS cases. Comparing SGA-LAI (n = 10) vs SGA-OAP treatment (n = 159), no group differences were observed, except for more recent publication times for SGA-LAIs due to later SGA-LAI than SGA-OAP development.

Antipsychotic Agent

All antipsychotic prescriptions at time of NMS are summarized in Supplementary Table 2. Of the 1,039 prescriptions for antipsychotics involved in the 662 NMS cases (292 cases involved receipt of antipsychotic polytherapy), only 11.8% were LAIs, with 92.0% being FGA-LAIs and 8% SGA-LAIs. Altogether, haloperidol was the most frequent antipsychotic associated with NMS (27%), followed by chlorpromazine (9.7%), fluphenazine (8.1%), risperidone (7.0%), olanzapine (6.4%), and clozapine (6.5%). Conversely, fluphenazine was involved in 49.6% of the LAI-related NMS cases, followed by flupenthixol LAI (15.5%), haloperidol LAI (14.6%), and zuclopenthixol LAI (7.3%).

Dose

Total CPZ equivalents were higher in LAI- versus OAP-related NMS cases (median = 813.3 mg/d vs 450 mg/d, $P < .0001$), with doses not reported in 26 (21.3%) of the LAI-related cases and 113 (20.9%) of the OAP-related cases. Likewise, the FGA-LAI group had higher total CPZ equivalents versus the FGA-OAP group (median = 887.5 mg/d vs 487.5 mg/d, $P < .0001$). A similar numerical dose differential comparing the small number of SGA-LAI–related cases versus SGA-OAP-related cases missed statistical significance (median = 577.8 mg/d vs 360 mg/d, $P = .0543$). Regarding individual antipsychotics with ≥ 5 cases, the highest CPZ equivalents were observed with fluphenazine LAI (median = 1,000 mg), followed by zuclopenthixol LAI (median = 800 mg), pipothiazine LAI (median = 700 mg), haloperidol LAI (median = 606 mg), droperidol OAP (median = 606 mg), and haloperidol OAP (median = 563 mg) (Supplementary Table 2).

Comedications

Anticholinergic medications, prescribed in 21.0% of cases, were more frequent in the LAI-related versus OAP-related cases (31.2% vs 18.9%, $P = .0051$) (Supplementary Table 3). No significant LAI versus OAP differences were present for lithium (overall = 14.1%), other mood stabilizers (overall = 10.3%), antidepressants (overall = 10.3%), benzodiazepines (overall = 16.9%) or other psychotropic treatments (overall = 5.7%) (Supplementary Table 3).

NMS Clinical Presentation

LAI-related NMS cases were generally indistinguishable from OAP-related cases (Supplementary Table 4). In both groups, the most frequent first sign of NMS was extrapyramidal symptoms (33.2%), followed by hyperthermia (29.2%), autonomic disturbances (24.2%), and altered consciousness (21.8%). Results were similar when comparing FGA-LAI versus FGA-OAP or SGA-LAI versus SGA-OAP.

Altogether, hyperthermia was the most frequently reported symptom (87.0%), followed by creatine phosphokinase elevation (78.4%), severe extremity rigidity (77.2%), mental status changes (58.2%), and autonomic disturbances, eg, tachycardia (58.9%), diaphoresis (46.7%), and systolic blood pressure abnormalities (33.8%). Median Francis-Yacoub scale severity scores were similar when comparing LAI-related versus OAP-related NMS cases (Figure 2) and when comparing FGA-LAI versus FGA-OAP (25.5 vs 22.5, $P = .7067$) and SGA-LAI versus SGA-OAP (26.5 vs 24.0, $P = .6224$) (Supplementary Table 4).

In regression analyses (n = 524, as 138 cases had no antipsychotic dosing information), between-group differences in Francis-Yacoub scale severity scores were influenced by region ($P = .0001$), primary diagnosis ($P = .0001$), and CPZ equivalents ($P = .0264$), but being similar across antipsychotic formulations (median LAI = 26 vs OAP only = 23, $P = .8276$). In a second analysis removing CPZ equivalents (n = 662), results did not change substantially (region: $P = .0001$, primary diagnosis: $P = .0566$, antipsychotic formulation: $P = .4856$).

Results were very similar when comparing FGA-LAI-related versus FGA-OAP-related NMS cases. SGA-LAI-related versus SGA-OAP-related NMS cases were indistinguishable regarding symptom frequencies and severity, as well as total median Francis-Yacoub scale severity score (26.5 vs 24; $P = .7414$).

Relationship Between Antipsychotic Dose and Severity of NMS

In all cases, CPZ equivalences were significantly associated with the Francis-Yacoub scale severity score ($\rho = 0.11$, $P = .0008$). However, this association was statistically significant only in the OAP-related cases ($\rho = 0.16$; $P = .0004$), but not in the LAI-related cases ($\rho = -0.07$, $P = .5206$).

Interventions

The most frequent strategy was antipsychotic discontinuation (63.4% explicitly described vs 36.6%

Table 1. Sociodemographic Characteristics of the Sample[a,b]

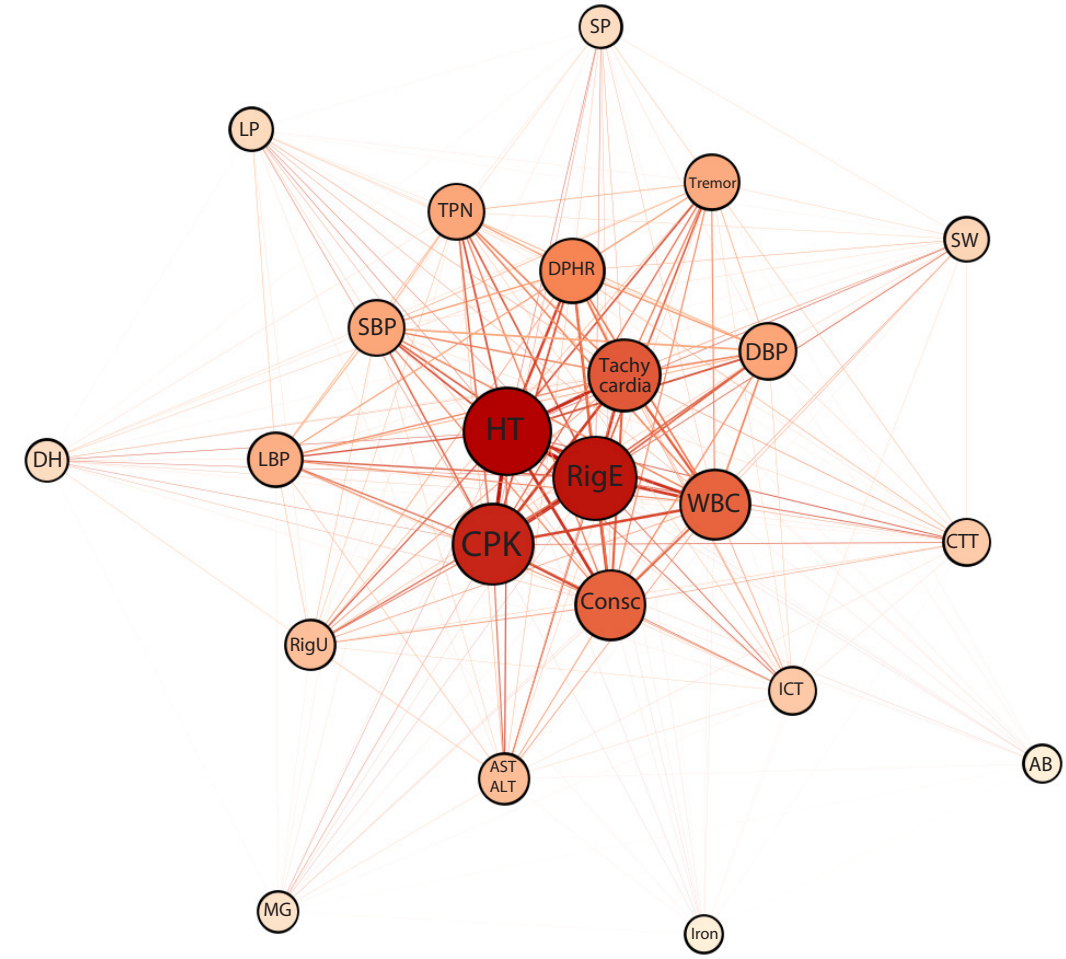
Variable	All Antipsychotics				FGAs				SGAs			
	LAI n = 122 (18.4%)	OAP n = 540 (81.6%)	Total n = 662 (100%)	*P* Value	FGA-LAI n = 112 (26.3%)	FGA-OAP n = 314 (73.7%)	Total n = 426 (100%)	*P* Value	SGA-LAI n = 10 (5.9%)	SGA-OAP n = 159 (94.1%)	Total n = 169 (100%)	*P* Value
Publication year, median (Q_1; Q_3)	1992 (1988; 2000)	2000 (1991; 2010)	2000 (1990; 2009)	**.0001**	1991 (1988; 2000)	1994 (1988; 2000)	1992 (1988; 2000)	.2067	2016 (2014; 2017)	2009 (2002; 2014)	2010 (2003; 2015)	**.0012**
Region				**.0164**				**.0037**				.3613
North America	36 (29.5)	194 (36.1)	230 (34.9)	.1788	33 (29.5)	111 (35.4)	144 (33.8)	.2582	3 (30.0)	62 (39.7)	65 (39.2)	.5707
Asia	33 (27.1)	173 (32.2)	206 (31.3)	.2825	32 (28.6)	110 (35.0)	142 (33.3)	.2131	1 (10.0)	44 (28.2)	45 (27.1)	.2200
Europe	40 (32.8)	104 (19.4)	144 (21.9)	**.0011**	36 (32.1)	50 (15.9)	86 (20.2)	**.0002**	4 (40.0)	34 (21.8)	38 (22.9)	.1714
Africa	3 (2.5)	25 (4.7)	28 (4.3)	.2820	3 (2.7)	25 (8.0)	28 (6.6)	.0527	0 (0.0)	0 (0.0)	0 (0.0)	...
Oceania	10 (8.2)	33(6.2)	43 (6.5)	.3985	8 (7.1)	16 (5.1)	24 (5.6)	.4198	2 (20.0)	13 (8.3)	15 (9.0)	.2022
South America	0 (0.0)	8 (1.5)	8 (1.2)	.1762	0 (0.0)	2 (0.6)	2 (0.5)	.3972	0 (0.0)	3 (1.9)	3 (1.8)	.6612
Age, median (Q_1; Q_3), y	36 (26; 44)	36 (25; 48)	36 (26; 48)	.5983	35 (26; 44)	32 (24; 46)	33 (25; 45)	.6312	41 (37; 56)	40 (28; 49)	40 (29; 55)	.1825
Male	82 (69.5)	311 (59.4)	393 (61.2)	**.0411**	76 (70.4)	175 (58.3)	251 (61.5)	**.0275**	6 (60.0)	97 (61.8)	103 (61.7)	.9104
Race				**.0001**				**.0113**				...
White	3 (14.3)	63 (61.2)	66 (53.2)	**.0022**	3 (14.3)	20 (52.6)	23 (39.0)	.1378	0 (0.0)	33 (68.8)	33 (68.8)	.1083
Black	4 (19.1)	21 (20.4)	25 (20.2)	.7495	4 (19.1)	6 (15.8)	10 (17.0)	.3190	0 (0.0)	9 (18.8)	9 (18.8)	.4394
Asian	14 (66.7)	19 (18.5)	33 (26.6)	**.0003**	14 (66.7)	12 (31.6)	26 (44.1)	**.0010**	0 (0.0)	6 (12.5)	6 (12.5)	.5316
Illness duration, median (Q_1; Q_3), y	9 (4; 18.8)	10 (2.5; 20)	10 (3; 20)	.5651	8 (4; 17.3)	6.5 (1.9; 16)	7 (3; 16.5)	.3272	17 (8.3; 35)	10 (3; 20)	10 (3; 20)	.1654
Primary diagnosis				**.0059**				**.0002**				.6293
Schizophrenia	74 (60.7)	216 (40.0)	290 (43.8)	**.0001**	68 (60.7)	109 (34.7)	177 (41.6)	**.0001**	6 (60.0)	77 (48.4)	83 (49.1)	.4777
Bipolar disorder	14 (11.5)	119 (22.0)	133 (20.1)	**.0085**	14 (12.5)	80 (25.5)	94 (22.1)	**.0045**	0 (0.0)	25 (15.7)	25 (14.8)	.1743
Psychosis	11 (9.0)	43 (8.0)	54 (8.2)	.7010	10 (8.9)	27 (8.6)	37 (8.7)	.9153	1 (10.0)	10 (6.3)	11 (6.5)	.6445
Schizoaffective disorder	8 (6.6)	43 (8.0)	51 (7.7)	.5990	6 (5.4)	15 (4.8)	21 (4.9)	.8077	2 (20.0)	23 (14.5)	25 (14.9)	.6325
MR-autism	5 (4.1)	16 (3.0)	21 (3.2)	.5181	5 (4.5)	8 (2.6)	13 (3.0)	.3114	0 (0.0)	5 (3.1)	5 (3.0)	.5692
Depression	5 (4.1)	51 (9.4)	56 (8.5)	.0553	5 (4.5)	37 (11.8)	42 (9.9)	**.0257**	0 (0.0)	12 (7.6)	12 (7.1)	.3674
Catatonia	1 (0.8)	7 (1.3)	8 (1.2)	.6634	1 (0.9)	6 (1.9)	7 (1.6)	.4669	0 (0.0)	1 (0.6)	1 (0.6)	.8014
Substance use disorder	0 (0.0)	3 (0.6)	3 (0.5)	.4093	0 (0.0)	2 (0.6)	2 (0.5)	.3972	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Other	1 (0.8)	10 (1.8)	11 (1.7)	.4205	1 (0.6)	5 (1.6)	6 (1.4)	.5896	0 (0.0)	3 (1.9)	3 (1.8)	.6612
None	3 (2.5)	32 (5.9)	35 (5.3)	.1222	2 (1.8)	25 (8.0)	27 (6.3)	**.0213**	1 (10.0)	3 (1.9)	4 (2.4)	.1016
Secondary diagnosis				.7659				.6182				.8244
None	114 (93.4)	492 (91.1)	606 (91.5)	.3177	106 (94.6)	297 (94.6)	403 (94.6)	.9818	8 (80.0)	137 (86.2)	145 (85.8)	.5881
MR-autism	6 (4.9)	27 (5.0)	33 (5.0)	.9700	5 (4.5)	7 (2.2)	12 (2.8)	.2197	1 (10.0)	13 (8.2)	14 (8.3)	.8392
Substance use disorder	2 (1.6)	10 (1.9)	12 (1.8)	.8737	1 (0.9)	5 (1.6)	6 (1.4)	.5896	1 (10.0)	4 (2.5)	5 (3.0)	.1755
Depression	0 (0.0)	6 (1.1)	6 (0.9)	.2422	0 (0.0)	2 (0.6)	2 (0.5)	.3972	0 (0.0)	3 (1.9)	3 (1.8)	.6612
Dementia	0 (0.0)	3 (0.6)	3 (0.5)	.4093	0 (0.0)	2 (0.6)	2 (0.5)	.3972	0 (0.0)	1 (0.6)	1 (0.6)	.8014
Other	0 (0.0)	2 (0.4)	2 (0.3)	.5008	0 (0.0)	1 (0.3)	1 (0.2)	.5499	0 (0.0)	1 (0.6)	1 (0.6)	.8014
Comorbidities				.3601				.1802				.2554
Diabetes mellitus	2 (1.6)	18 (3.3)	20 (3.0)	.3235	2 (1.8)	6 (1.9)	8 (1.9)	.9333	0 (0.0)	9 (5.7)	9 (5.4)	.4394
Hypertension	1 (0.8)	21 (3.9)	22 (3.3)	.0876	1 (0.9)	7 (2.2)	8 (1.9)	.3710	0 (0.0)	9 (5.7)	9 (5.4)	.4394
Obesity	1 (0.8)	10 (1.9)	11 (1.6)	.4205	1 (0.9)	4 (1.3)	5 (1.2)	.7479	0 (0.0)	5 (3.1)	5 (3.0)	.5692
Seizure	2 (1.6)	7 (1.3)	9 (1.4)	.7676	2 (1.8)	2 (0.6)	4 (0.9)	.2791	0 (0.0)	4 (2.5)	4 (2.4)	.6117
Serious medical condition	6 (4.9)	30 (5.6)	36 (5.4)	.7791	4 (3.6)	11 (3.5)	15 (3.5)	.9732	2 (22.2)	12 (7.6)	14 (8.3)	.1658

[a]Bolded *P* values indicate $P < .05$ (uncontrolled for multiplicity).

[b]Values are reported as n (%) unless otherwise noted. Percentages are reported in relation to the total number of reported cases for each item, not in relation to the total number (title row). For example, in the LAI group, patients in 3 cases are reported as White; 14.3% refers to the percentage of White among all cases of LAI for which race is reported (21 = 3 + 4 + 14), as otherwise percentages would be too small and uninformative. Patients treated with both FGA and SGA OAPs as well as cases in which only formulation, but not drug name or class, is reported (n = 67) are not included in the FGA-OAP or SGA-OAP subgroups.

Abbreviations: FGA = first-generation antipsychotic, LAI = long-acting injectable antipsychotic, MR = mental retardation, n/a = not applicable, OAP = oral antipsychotic, Q_1 = first quartile, Q_3 = third quartile, SGA = second-generation antipsychotic.

Figure 2. Network Analysis of Reported Symptoms of NMS[a]



(continued)

unreported/not discontinued), occurring more frequently with OAP than with LAI treatment (65.7% vs 53.3%, $P = .0098$) (Supplementary Table 5). Prodopaminergic agents (34.4%, mostly bromocriptine [81.1%]), anticholinergics/muscle relaxants (32.0%, mostly dantrolene [73.1%]), and benzodiazepines (31.0%, mostly diazepam [42.9%]) were the most common pharmacologic interventions, while electroconvulsive therapy was uncommon (11.0%). Interventions did not differ across LAI-related versus OAP-related cases, except for greater use of benzodiazepines in OAP-related cases (33.3% vs 20.5%, $P = .0056$).

Outcomes

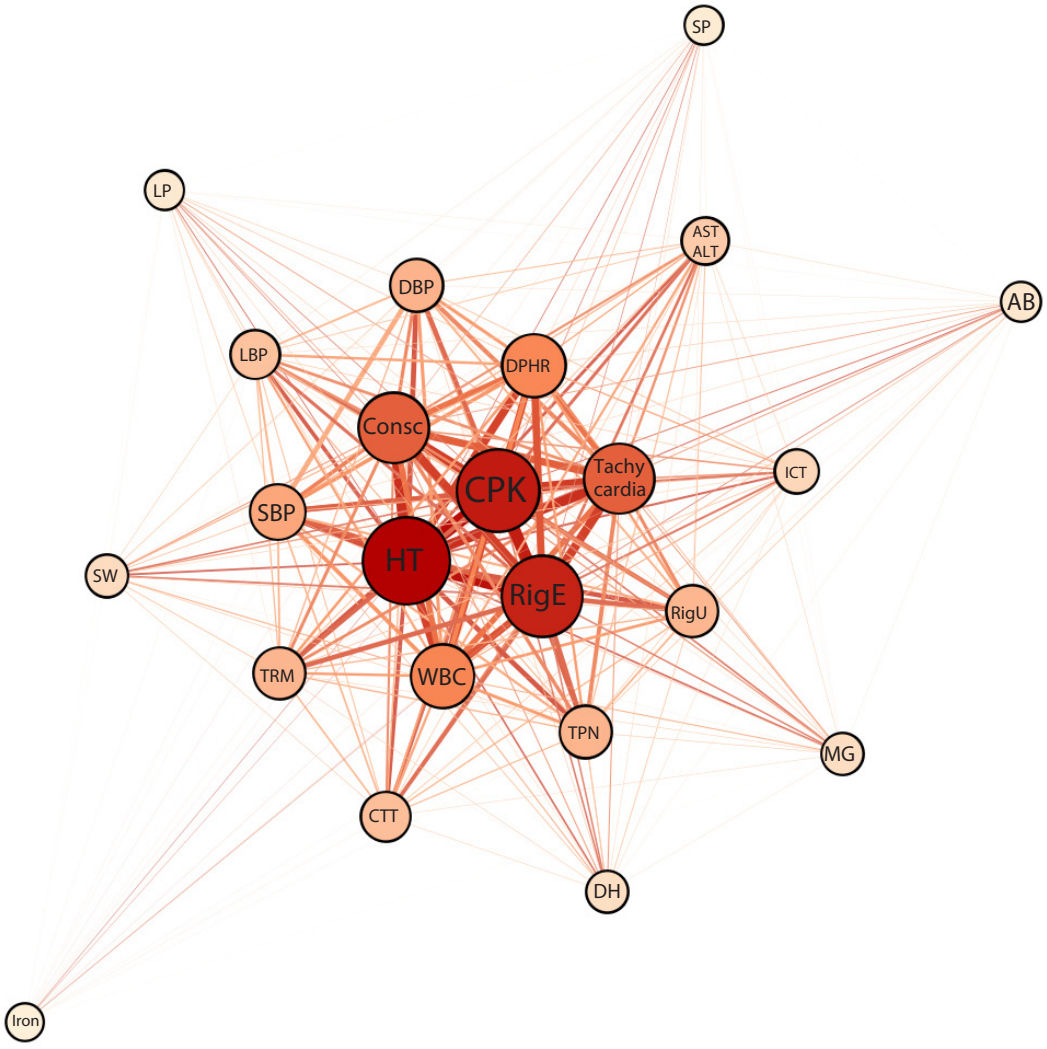
Overall, 86.3% of NMS patients recovered completely (LAI = 82.0% vs OAP = 87.2%, $P = .2887$). Incomplete recovery was similar (LAI = 7.4% vs OAP = 6.1%, $P = .7489$), despite a significantly lower rate of cardiovascular sequelae in the LAI group ($P = .0001$), but this finding was rare (0.30%) and was reported exclusively with OAPs. Death also did not differ significantly between groups (LAI = 10.7% vs OAP = 6.7%, $P = .0861$) (Table 2). The median NMS duration was 4.2 days longer in LAI-related cases (LAI = 2.0 weeks vs OAP = 1.4 weeks, $P = .0801$). The median duration of hospitalization also did not differ between groups (LAI = 5 weeks vs OAP = 3.8 weeks, $P = .8322$). Need for ($P = .9709$) and duration of ($P = .4006$) intensive care treatment were also similar (Supplementary Table 5).

Post hoc, adjusted multivariable regression analyses, removing CPZ equivalents that were unrelated to NMS duration and mortality, which excluded 137 NMS cases from the primary model, yielded a significantly longer NMS duration of LAI-related versus OAP-related cases (2.6 vs 1.8 weeks, $P = .0339$), but even less difference regarding mortality ($P = .1532$). All other outcomes remained unchanged after optimizing the model.

Duration of NMS was also significantly longer with FGA-LAI versus FGA-OAP treatment ($P = .0357$), a difference that became more significant ($P = .0031$) after removing CPZ equivalences, which had not been associated with duration of NMS in that model ($P = .4957$). Conversely, the median NMS duration did not differ across SGA-LAI-related versus SGA-OAP–related cases (1.6 vs 1.3 weeks, $P = .9829$). Similarly, remaining outcomes did not differ across cases related to FGA-LAIs versus FGA-OAPs or SGA-LAIs versus SGA-OAPs (Table 2).

Figure 2 (continued).

B.



[a]Network analysis of the reported symptoms and signs on the Francis-Yacoub scale for cases of NMS happening during (A) LAI antipsychotic and (B) OAP antipsychotic treatment. The symptoms/signs are depicted as nodes, the size of which are proportional to the frequency in which the event is reported. The thickness of the edges connecting the nodes is proportional to the frequency of co-occurrences between symptoms, thus creating networks of symptoms. The strength of the color of the nodes represents closeness centrality and interconnectedness.

Abbreviations: AB = acid-base balance alterations, AST/ALT = serum aspartate/alanine aminotransferase alterations, Consc = consciousness alteration, CPK = serum creatine phosphokinase alterations, CTT = catatonia, DBP = diastolic blood pressure alterations, DH = dehydration, DPHR = diaphoresis, HT = hyperthermia, ICT = incontinence, Iron = serum iron level alterations, LAI = long-acting injectable antipsychotic, LBP = labile blood pressure, LP = labile pulse, MG = myoglobinemia/myoglobinuria, NMS = neuroleptic malignant syndrome, OAP = oral antipsychotic, RigE = rigidity of extremities, RigU = rigidity of neck and/or upper trunk, SBP = systolic blood pressure alterations, SP = pharyngeal/speech alterations, SW = pharyngeal/swallowing alterations, TPN = tachypnea, TRM = tremor, WBC = white blood cell count alterations.

DISCUSSION

To our knowledge, this study constitutes the first systematic review and pooled, patient-level analysis of individual cases comparing characteristics and outcomes of NMS occurring during LAI versus OAP therapy.

Our main finding is that clinical presentation, severity, and outcomes of NMS, including mortality, did not differ significantly between LAI-related and OAP-related NMS cases. These results are relevant, as they can inform clinical decision making on increasingly available LAIs[13] in view of the potential risk of NMS and its sequelae, while no other higher level of evidence exists. This information is especially important given the expansion of the injection interval to currently 3 months,[35,36] with a 6-monthly LAI under investigation.[37] Furthermore, LAI indications and use have also expanded beyond schizophrenia.[38] Nonetheless, the inability to stop treatment in case of a serious adverse event, like NMS, has been cited as an argument against LAIs.[6,13,25] However, synthesis of the available data does not support the concern that LAIs may lead to more serious adverse outcomes should NMS develop, which should therefore not detract from offering LAIs that have remained underutilized, despite data indicating superiority versus OAPs for treatment engagement, relapse, hospitalization, and even mortality.[13,15,17–20]

Table 2. Outcomes of Neuroleptic Malignant Syndrome (NMS)[a,b]

Outcome	All Antipsychotics				FGAs				SGAs			
	LAI n = 122 (18.4%)	OAP n = 540 (81.6%)	Total n = 662 (100%)	*P* Value	FGA-LAI n = 112 (26.3%)	FGA-OAP n = 314 (73.7%)	Total n = 426 (100%)	*P* Value	SGA-LAI n = 10 (5.9%)	SGA-OAP n = 159 (94.1%)	Total n = 169 (100%)	*P* Value
Complete recovery	100 (82.0)	471 (87.2)	571 (86.3)	.2887	91 (81.3)	265 (84.4)	356 (83.6)	.3916	9 (90.0)	146 (91.8)	155 (91.7)	.9973
Death	13 (10.7)	36 (6.7)	49 (7.4)	.0861	12 (10.7)	25 (8.0)	37 (8.7)	.1423	1 (10.0)	6 (3.8)	7 (4.1)	.6620
Incomplete recovery (sequelae)	9 (7.4)	33 (6.1)	42 (6.3)	.7489	9 (8.0)	24 (7.6)	33 (7.8)	.7724	0 (0)	7 (4.4)	7 (4.1)	.3663
Neurologic sequelae[c]	7 (100)	22 (75.9)	29 (80.6)	.8505	7 (100)	17 (77.3)	24 (82.8)	.9619	0 (0)	4 (80)	4 (80)	.5808
Cardiovascular sequelae[c]	0 (0)	2 (6.9)	2 (5.6)	**.0001**	0 (0)	2 (9.1)	2 (6.9)	.2909	0 (0)	0 (0)	0 (0)	…
Other sequelae[c]	0 (0)	5 (17.2)	5 (13.9)	.1221	0 (0)	3 (13.6)	3 (10.3)	.3288	0 (0)	1 (20)	1 (20)	.8384
Duration of NMS, median (Q_1; Q_3), wk	2.0 (1; 4.3)	1.4 (0.9; 2.3)	1.4 (0.9; 2.6)	.0801	2 (1; 4.3)	1.4 (0.9; 2.4)	1.4 (0.9; 2.9)	**.0357**	1.6 (1; 3.3)	1.3 (0.9; 2.1)	1.3 (0.9; 2.1)	.9829
Time onset-death[d], median (Q_1; Q_3), wk	4.6 (0.9; 9)	1.1 (0.7; 3.1)	1.4 (0.8; 4.8)	.3852	4.6 (0.8; 9)	1 (0.7; 4.3)	1 (0.7; 5.1)	.9154	10 (10; 10)	1.6 (0.1; 3.1)	3.1 (0.1; 10)	n/e
Hospital stay, median (Q_1; Q_3), wk	5 (2.1; 8.4)	3.8 (2; 6.2)	4 (2; 6.7)	.8322	6 (2.1; 8.6)	4 (2.3; 9)	4 (2.1; 8.6)	.5169	2.7 (2; 10)	3 (1.3; 4.3)	2.9 (1.3; 4.5)	.8727

[a]Values are shown as n (%) unless otherwise noted. Bolded *P* values indicate $P < .05$.
[b]Results show *P* values after adjusting for between-group significant variables. Cases for which no outcome was reported were presumed to be full recovery, since death or sequelae would most likely have been reported. Results for LAI versus OAP comparisons show *P* values after adjusting for antipsychotic strength, year of publication, race, region, sex, and primary diagnosis. Results for FGA-LAI versus FGA-OAP comparison show *P* values after adjusting for antipsychotic strength, race, region, sex, and primary diagnosis, since publication year was no different. Results for SGA-LAI versus SGA-OAP are adjusted for year of publication, the only between-group significant variable. Patients treated with both FGA- and SGA-OAP as well as cases in which only formulation, but not drug name or class, is reported (n = 67) are not included in the FGA-OAP or SGA-OAP subgroups.
[c]Percentages are reported in relation to the total number of reported cases of incomplete recovery, not in relation to the total number (title row).
[d]Time from NMS onset to death.
Abbreviations: FGA = first-generation antipsychotic, LAI = long-acting injectable antipsychotic, n/e = non-estimable, OAP = oral antipsychotic, Q_1 = first quartile, Q_3 = third quartile, SGA = second-generation antipsychotic.

While the overall mortality of 7.4% across all reported NMS cases is similar to findings of a recent nationwide inpatient study (5.1%–8.3%)[39] and a register-based case-control study (8.4%),[40] our finding is lower than what had been previously reported, with mortality figures ranging from 15% to 22%.[41–44] Additionally, although not the focus of these analyses, which were adjusted statistically for variables differing across antipsychotic formulations, mortality associated with NMS may even be lower with SGAs (4.5%) than with FGAs (10.5%), which has been suggested before.[39,45–47] However, additional studies and analyses are needed to examine this possibility.

Consistent with our results, a meta-analysis of 52 RCTs comparing overall mortality with LAIs vs OAPs in schizophrenia[48] reported similar mortality between LAIs and OAPs. Additionally, a nationwide register study investigating all-cause mortality in schizophrenia[20] showed that the lowest cumulative all-cause mortality (mean follow-up = 7.5 years) was observed for SGA-LAIs (8.5%). In pairwise comparisons, the overall mortality risk was 33% lower with LAIs versus equivalent OAPs.[20] Notably, we found only 10 cases of NMS with SGA-LAI therapy (1.5% of all cases), with only 1 death.[49] However, that patient was receiving risperidone 100 mg twice weekly, but also oral risperidone, oral olanzapine, topiramate, and lithium, weakening the association with LAI use. Notably, no cases of incomplete recovery or sequelae were reported with SGA-LAIs.

NMS duration was longer in the LAI group after adjusting for significant between-group factors and maximizing the sample size in the model. This finding could be explained by the prolonged half-life of LAIs versus OAPs. However, this finding was evident only when comparing FGA-LAIs versus FGA-OAPs, but not SGA-LAIs versus SGA-OAPs, although the small sample size may have reduced the power to detect significant differences. While further studies with more SGA-LAI-related NMS cases, including LAIs with more than monthly injection intervals, for which no case reports of NMS cases have been reported yet, are needed, the difference in NMS duration was only 4 days, and NMS outcomes did not differ. Results are consistent with previous reports of a longer NMS duration with FGA-LAIs versus FGA-OAPs (2.5 weeks vs 2.0 weeks).[44]

NMS was predominantly reported in men (61.2%), affected with schizophrenia (43.8%) and having a median age of 36 years, none of which differed by antipsychotic formulation. These results are consistent with those of previous studies and recent data suggesting that NMS more frequently affects young adult males.[47,50,51] Interestingly, fluphenazine LAI accounted for 50% of all LAI-related NMS cases and > 90% of FGA-LAI-related cases. This finding could be explained by the fact that FGAs have been available for much longer, but the role that FGAs versus SGAs and D_2 affinity may play in NMS requires consideration.[46,50] Nevertheless, in the analyzed cases, the presentation, global severity and outcomes were similar in LAI-related versus OAP-related NMS. Unlike previous studies,[40] ours did not find lithium to be associated with NMS outcomes.

This study has several limitations. First, information was collected from case reports, which do not constitute controlled evidence and may be sensitive to higher uncertainty and reporting bias. However, since death and sequelae are serious outcomes that will more likely lead to a case report publication, the frequency

of mortality and sequelae relative to case reports describing positive outcomes may be less vulnerable to underreporting. The same may be true for the very infrequent SGA-LAI–related NMS cases. Given that many more reports on SGA-OAPs exist, there may be less risk of underreporting of LAI-related NMS cases. Second, drawing on case reports means relying on the quality and comprehensiveness of the authors' NMS assessment and description. However, we quantified severity ratings using the Francis-Yacoub symptom scale, enhancing the reliability of the analyzed data. Third, we included cases that authors declared as NMS, regardless of the diagnostic criteria they used. Although this procedure may have introduced variability, we used an inclusive approach, consistent with those of similar studies,[46] since exact diagnostic criteria for NMS have been debated.[8,51] Nevertheless, we excluded cases related to medical or neurologic disorders to reduce confounding variables. Fourth, we allowed LAI-OAP cotreatment to avoid making assumptions about what the causal agent of NMS was, focusing on whether presence of LAI treatment influenced NMS characteristics and outcomes. However, we conducted multivariable regression analyses, controlling the LAI versus OAP comparisons for between-group variables. Finally, since we abstracted only the first report of NMS in a given patient, we cannot comment on potential differences of NMS characteristics and outcomes between a first and subsequent occurrence of NMS. However, this will the topic of a future investigation.

Since the infrequent adverse effect of NMS is very difficult to study prospectively, results from this study provide relevant information and should contribute to mitigating safety concerns regarding LAI therapy, even when NMS arises. However, due to the aforementioned limitations, results should be interpreted with caution, and clinicians should remain vigilant for NMS regardless of antipsychotic formulation used.

CONCLUSION

Clinical presentation, severity, recovery, and mortality did not differ significantly between patients developing NMS during LAI versus OAP treatment. NMS duration was slightly longer with LAIs, but not with SGA-LAIs, and differences were small and did not translate into increased length of hospitalization or worse outcomes. Results are encouraging but should be interpreted cautiously, being based on case reports. Prospective and/or database studies are needed to further clarify the safety of LAIs versus OAPs.

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Potential conflicts of interest: **Dr Misawa** has received speaker's honoraria from Sumitomo Dainippon, Eli Lilly, Janssen, Novartis, Otsuka, and Pfizer. **Dr Rubio** has received advisory board and speaker honoraria from Lundbeck and consultant honoraria from the ZeroCopayProgram. **Dr Guinart** has been a consultant for and/or has received speaker honoraria from Otsuka America and Janssen Pharmaceuticals. **Dr Kane** has been a consultant and/or advisor for or has received honoraria from Alkermes, Allergan, LB Pharmaceuticals, H. Lundbeck, Intra-Cellular Therapies, Janssen, Johnson & Johnson, Merck, Minerva, Neurocrine, Newron, Otsuka, Pierre Fabre, Reviva, Roche, Sumitomo Dainippon, Sunovion, Takeda, Teva, and UpToDate and is a shareholder in LB Pharmaceuticals and Vanguard Research Group. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, Intra-Cellular Therapies, Janssen/Johnson & Johnson, LB Pharmaceuticals, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva; has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka; has served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva; has received royalties from UpToDate and grant support from Janssen and Takeda; and is also a shareholder of LB Pharmaceuticals. **Drs Pereira**, **Sharma**, and **Schoretsanitis** have no conflict of interest.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Joseph F. Goldberg, MD, at jgoldberg@psychiatrist.com.

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