



Evaluation of neuroleptic malignant syndrome induced by antipsychotic drugs using spontaneous reporting system

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A B S T R A C T

Adverse events (AEs) of antipsychotic drugs include neuroleptic malignant syndrome (NMS), which presents complex clinical symptoms, resulting in a fatal outcome. In this study, the association between antipsychotic drugs and NMS was comprehensively evaluated by cluster and association analyses using the Japanese Adverse Drug Event Report (JADER) database.

The analyses were performed using 20 typical antipsychotics (TAPs) alongside 9 atypical antipsychotics (AAPs). The Standardised MedDRA Queries (SMQ) database was used to analyze NMS (SMQ code: 20000044). Reporting odds ratios (RORs) were used for AE signal detection. The relationship between antipsychotic drugs and AEs for NMS was investigated by performing hierarchical cluster analysis using Ward's method.

Between April 2004 and September 2021, the total number of JADER reports was 705,294. RORs (95 % confidence interval) of NMS for haloperidol, chlorpromazine, risperidone, and aripiprazole were 12.1 (11.1–13.3), 6.3 (5.7–7.0), 6.2 (5.8–6.6), and 4.7 (4.4–5.1), respectively. Three clusters were formed, with characteristics as follows: Cluster 1 consisted of only TAPs, such as bromperidol and fluphenazine, whilst having a high reporting rate of hypotension, tachycardia, dyskinesia, and dystonia. Cluster 2 consisted of all AAPs alongside several TAPs, such as haloperidol and chlorpromazine, with higher reporting rates of disturbance of consciousness, extrapyramidal disorders (excluding dyskinesia and dystonia), and serotonin syndrome. Cluster 3 consisted of only perphenazine, whilst having a higher reporting rate of coma, leukocytosis, and Parkinsonism.

The results of this study may therefore aid in the management of NMS using antipsychotic drugs.

1. Introduction

Neuroleptic malignant syndrome (NMS) is primarily caused by the administration, reduction, or cessation of neuropsychiatric drugs and can be characterized by fever, disturbance of consciousness, extrapyramidal disorder, and autonomic nervous system imbalance, with an incidence of 0.07%–2.2 % [1]. Previously, NMS has had a high mortality rate; however, as medical professionals gradually became more aware of it with the progression of clinical research, the prognosis has improved remarkably. However, its etiology and pathophysiology have not yet been fully elucidated [1]. Although it requires prompt treatment, NMS is often diagnosed late in outpatient care. It has a special course, becomes severe, and requires attention in clinical settings. In addition to psychiatry, psychoneurotic drugs are used in psychosomatic medicine, neurology, internal medicine, surgery, and anesthesiology, alongside other

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clinical departments. Therefore, NMS is not only relevant to treating psychiatric problems but also affects health problems reported by other fields [1–5].

The clinical manifestations of NMS include acute fever and disturbance of consciousness, extrapyramidal disorder (muscle rigidity, tremors, dystonia, dyskinesia, etc.), autonomic nervous system imbalance (hyperhidrosis, tachycardia, abnormal blood pressure, etc.), myoclonus, and respiratory failure. In severe cases of NMS, skeletal muscle tissue dissolution occurs and progresses, whilst blood and

Table 1

The number of cases for each preferred terms of standardised MedDRA Queries of neuroleptic malignant syndrome (SMQ^a code: 20000044).

Category	Category for cluster analysis	Preferred terms code	Preferred terms	Case (n)	Case used for the cluster analysis (n)	
Autonomic nervous system imbalance	–	10003840	Autonomic nervous system imbalance	86	86	
	i_Blood pressure abnormal	10005728	Blood pressure abnormal	24	136	
	i_Blood pressure abnormal	10023533	Labile blood pressure	17	–	
	i_Blood pressure abnormal	10005746	Blood pressure fluctuation	95	–	
	–	10019303	Heart rate increased	310	310	
	–	10020642	Hyperhidrosis	473	473	
	i_Hypertension	10005750	Blood pressure increased	2342	5402	
	i_Hypertension	10020772	Hypertension	3060	–	
	i_Hypotension	10005734	Blood pressure decreased	8003	9950	
	i_Hypotension	10021097	Hypotension	1947	–	
Cardiovascular insufficiency	–	10043071	Tachycardia	1508	1508	
	–	10065929	Cardiovascular insufficiency	23	23	
Disturbance of consciousness	–	10001854	Altered state of consciousness	6138	6138	
	–	10010071	Coma	462	462	
	–	10010305	Confusional state	441	441	
	–	10050093	Consciousness fluctuating	10	10	
	–	10012218	Delirium	3059	3059	
	–	10012373	Depressed level of consciousness	2888	2888	
	–	10013395	Disorientation	340	340	
	–	10024855	Loss of consciousness	5375	5375	
	–	10042264	Stupor	130	130	
	Extrapyramidal disorder	–	10007776	Catatonia	62	62
		–	10013916	Dyskinesia	956	956
		–	10013983	Dystonia	603	603
		–	10015832	Extrapyramidal disorder	469	469
		–	10060904	Freezing phenomenon	5	5
–		10020651	Hyperkinesia	32	32	
–		10020852	Hypertonia	27	27	
–		10080149	Malignant catatonia	1	1	
–		10028330	Muscle rigidity	147	147	
–		10028622	Myoclonus	342	342	
–		10030071	Oculogyric crisis	140	140	
–		10030899	Opisthotonus	13	13	
–		10061536	Parkinson's disease	365	1157	
–		10034010	Parkinsonism	792	–	
Hyperthermia malignant	–	10041045	Slow response to stimuli	3	3	
	–	10044565	Tremor	1324	1324	
	–	10045555	Unresponsive to stimuli	75	75	
	–	10020844	Hyperthermia malignant	298	298	
	Leukocytosis	i_Leukocytosis	10024378	Leukocytosis	74	1036
		i_Leukocytosis	10047943	White blood cell count increased	962	–
Neuroleptic malignant syndrome	–	10029282	Neuroleptic malignant syndrome	3461	3461	
	i_Pyrexia	10005911	Body temperature increased	75	14812	
Pyrexia	i_Pyrexia	10020741	Hyperpyrexia	20	–	
	i_Pyrexia	10037660	Pyrexia	14717	–	
	–	10005468	Blood creatine phosphokinase abnormal	11	11	
Rhabdomyolysis	–	10005470	Blood creatine phosphokinase increased	3136	3136	
	–	10028625	Myoglobin blood increased	51	51	
	–	10028631	Myoglobin urine present	10	10	
	–	10028629	Myoglobinuria	32	32	
	–	10039020	Rhabdomyolysis	6750	6750	
	–	10040108	Serotonin syndrome	702	702	

^a SMQ: Standardised MedDRA Queries.

urinary myoglobin levels increase, leading to acute renal failure [1]. Additionally, NMS can cause metabolic acidosis and disseminated intravascular coagulation [6], with muscle rigidity observed in most cases. Furthermore, some patients show no impairment of consciousness, whereas others present with delirium or coma [7]. As described above, the clinical symptoms are diverse; however, the characteristics of causative drugs remain unknown.

The Spontaneous Reporting System (SRS) for Adverse Events (AEs), published by regulatory authorities in the United States and Japan, has played a major role in the evaluation of drug safety. Based on AE signals obtained by data mining using the SRS database, it is possible to detect unknown AEs that have not been discovered in clinical trials as well as evaluate safety in specific populations and reflect actual clinical uses [8,9]. In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has released the Japanese Adverse Drug Event Report (JADER) database, which contains more than 700,000 total AEs. We conducted a comprehensive drug safety evaluation of NMS using this database.

Cluster analysis (CA) [10,11] and association analysis (AA) [12–14] are useful statistical techniques in data mining. CA is used to find natural groupings within a dataset. Several uses of CA have been reported in the literature, such as characterizing psychiatric patients on the basis of clusters of symptoms [15], identifying the profile of optimal candidates for antipsychotic depot therapy [16], or identifying profiles of functioning and correlations of those profiles in a sample of patients with stable schizophrenia in a real-world setting [17]. This study aimed to comprehensively evaluate the incidence profile of NMS caused by antipsychotic drugs and find useful cluster information. A comprehensive evaluation of 29 types of antipsychotic drugs and 52 AEs was carried out by performing hierarchical CA.

AA is used to find frequent patterns and undetected clinical factor combinations between variables in huge databases, and it may be useful in decision-making by finding relationships between attributes in the database [12–14]. AA has been applied to evaluate the relationship between AEs and their risk factors [9,18–20]. Therefore, herein, we evaluated the relationship between NMS and antipsychotic drugs combinations by performing AA.

2. Methods

2.1. Data source

Data regarding AE reports were collected and fully anonymized by the PMDA to form the JADER database. The AE reports recorded in this database were downloaded from the PMDA website (www.pmda.go.jp). The JADER dataset was also downloaded from the PMDA website. The JADER data were divided into 4 files, “demo,” “drug,” “reac,” and “hist,” with each data table being linked by an

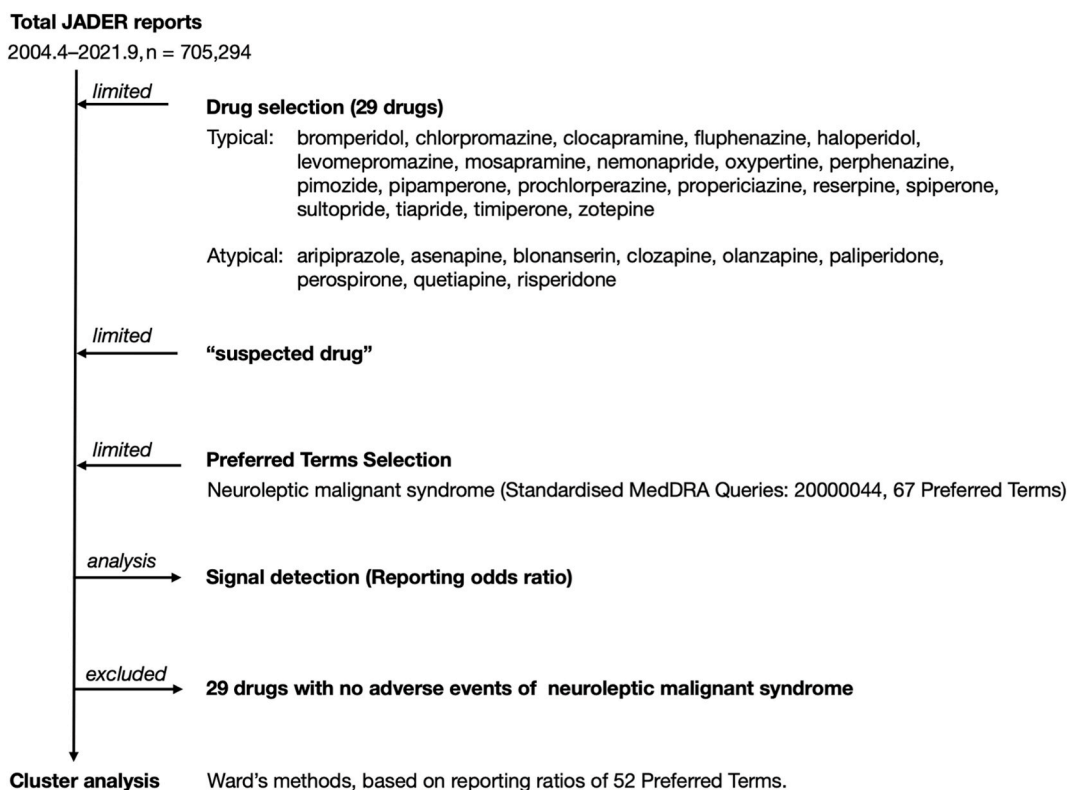


Fig. 1. Flowchart of data analysis.

identification number and integrated into a relational database. The content of the tables was as follows: The “demo” table contained basic patient information such as sex, age, and reporting year; the “drug” table comprised information on medication, such as the generic name of the drug administered, route of administration, and start and end dates of administration; the “reac” table contained AE, outcome, and date of onset, and the “hist” table included information on the patient’s primary disease. We assessed this database for reports submitted between April 2004 and September 2021. The structure of this database complied with international safety reporting guidelines (International Council on Harmonization E2B).

The “drug” table described the presumed degree of drug involvement in the AEs as follows: “suspected drug,” “concomitant drug,” and “interacting drug.” In this retrospective pharmacovigilance study, data on the “suspected drugs” were extracted and analyzed. We subsequently integrated the relational database based on the four aforementioned tables using the FileMaker Pro 18 Advanced software (FileMaker, Inc. Santa Clara, CA, USA).

2.2. Definition of AEs

The AEs in the JADER database were coded using MedDRA ver. 23.1 (MedDRA/J, www.pmrj.jp/jmo/php/indexj.php). Additionally, the Standardised MedDRA Queries (SMQ) database was used for the analysis of SRSs. SMQ is a grouping of MedDRA terms for a defined condition or area of interest, usually at the Preferred Term (PT) level. We used the SMQ here for NMS (SMQ code: 20000044, containing 67 PTs). In this study, 52 PTs were analyzed, after excluding 15 that had reported no AEs (Table 1).

2.3. Target drugs

In this study, the analyses were performed using 20 typical antipsychotics (TAPs) alongside 9 atypical antipsychotics (AAPs), according to classifications based on the Japanese Society of Neuropsychopharmacology (<http://www.jsnp-org.jp/>) and previous reports (Fig. 1) [4].

2.4. Signal detection

The reporting odds ratio (ROR), which is widely used in post-marketing drug safety evaluations, was used for signal detection [21]. The ROR was calculated from a 2×2 contingency table and was regarded as a signal when the lower limit of the 95 % confidence interval (CI) exceeded 1. Two or more cases were necessary to positively identify such signals (Fig. 2) [8].

2.5. CA

CA was used to analyze the association between each PT of NMS and antipsychotic drugs. CA is an “unsupervised classification method” whereby classification criteria are not predetermined [10,11]. It assigns data to groups with similar properties. In this study, we used agglomerative hierarchical clustering to classify 29 drugs and subsequently analyzed the relationship between the RR of AEs for each drug. Clusters are typically generated from standardized data using Ward’s method with Euclidean distance. Ward’s method merges the clusters to minimize the sum of the squares within the cluster. The distance between clusters is defined as an increase in the sum of squares when two clusters are merged. Clusters of the antipsychotic drugs were formed, with the number of formations being determined based on the characteristics of each cluster. Considering that this analysis is generally not associated with a probabilistic evaluation, it is common for researchers to make appropriate decisions concerning the number of clusters with the greatest perceived significance.

Data analyses in this study were performed using JMP Pro 16.2 (SAS Institute Inc., Cary, NC, USA).

2.6. AA

AA focuses on finding frequent co-occurring associations among a collection of items. Given a set of transactions T (each transaction is a set of items), an association rule can be expressed as X [lhs: left-hand-side, the antecedent of the rule] \rightarrow Y [rhs: right-hand-side, the

	Adverse event of interest	All other adverse event	Total
Drug of interest	a	b	a + b
All other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

$$\text{Reporting odds ratio (ROR)} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$95\% \text{ confidence interval (CI)} = e^{\ln(\text{ROR}) \pm 1.96 \sqrt{1/a + 1/b + 1/c + 1/d}}$$

Fig. 2. Two-by-two contingency table for calculation of reporting odds ratio.

consequent of the rule], where X and Y are mutually exclusive sets of items [12–14]. If the association rule of $X \rightarrow Y$ is true, then *support*, *confidence*, and *lift* values can be calculated to evaluate the correlation indicated by this rule. *Support* determines how often a rule, which in this case is the combination of X and Y, is observed in the database. *Support* was measured using the following formula:

$$\text{Support} = P(X \cap Y) = \{X \cap Y\} / \{D\}$$

where D is the total number of transactions in the database. *Support* is the probability that X and Y are simultaneously true.

The *confidence* value of the association rule demonstrates the rule's strength. *Confidence* was calculated by the following equation:

$$\text{Confidence} = P(X \cap Y) / P(X)$$

Lift represents the ratio of probability. Given the rule that X and Y occur together to the multiple of the two individual probabilities for X and Y, *lift* was calculated as follows:

$$\text{Lift} = P(X \cap Y) / P(X)P(Y)$$

Lift is a measure of the relationship between X and Y, indicating information regarding an increase in the probability of Y when it is provided with X. Higher *lift* values indicate stronger relationships. If X and Y are independent, *lift* equals 1. If X and Y are positively or negatively correlated, *lift* is > 1 or < 1 , respectively. AA was performed using the apriori function of the *arules* package of R version 4.3.1. In the first step, the apriori algorithm searches for item sets that have more than a given minimum *support*, whereas in the second step, rules are generated by selecting "confident" item sets from those found in the first step. The parameter *maxlen* (maximum length of item set/rule, a parameter in the *arules* package) is the maximum size of mined frequent item sets. To establish association rules efficiently, the thresholds for the optimized *support*, *confidence*, and *maxlen* are defined depending on factors such as the size of the data, the number of items, and the purpose of the research. *Support* and *lift* were visualized using the R-extension package *arulesViz*, which implements visualization techniques to explore association rules. The arguments of the plot in *arulesViz* were set as follows: *method* = "graph," *measure* = "*support*," *shading* = "*lift*." The measures of *support* were used in visualization as the area of the circle. The measures of *lift* were used for the shading of the color of the circle.

3. Results

The JADER database contained 705,294 reports published between April 2004 and September 2021. The respective numbers of

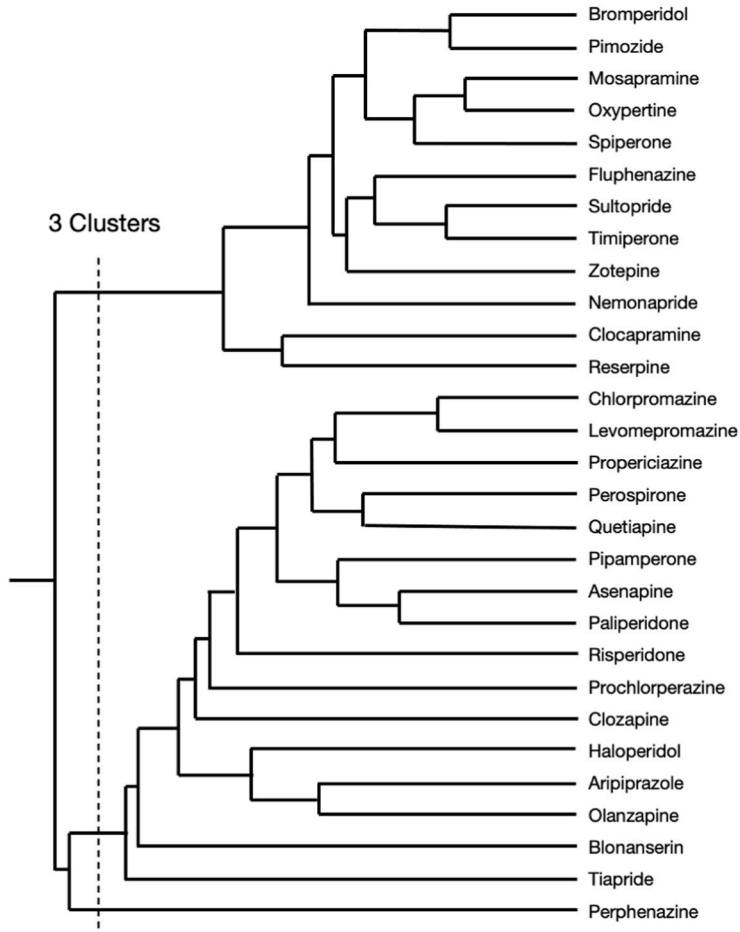
Table 2

Number of reports, reporting ratio, and reporting odds ratio of neuroleptic malignant syndrome (SMQ^a code: 20000044) associated with antipsychotics.

Drugs	Total	Case (n)	Non-case (n)	Reporting ratio (%)	Reporting odds ratio (95 % confidence interval)	
Typical antipsychotics	Bromperidol	169	85	84	50.3	10.0 (7.4–13.5)
	Chlorpromazine	1520	588	932	38.7	6.3 (5.7–7.0)
	Clocapramine	24	11	13	45.8	8.4 (3.7–18.7)
	Fluphenazine	129	74	55	57.4	13.3 (9.4–18.9)
	Haloperidol	1845	1011	834	54.8	12.1 (11.1–13.3)
	Levomepromazine	1110	492	618	44.3	7.9 (7.0–8.9)
	Mosapramine	25	12	13	48.0	9.1 (4.2–20.0)
	Nemonapride	15	5	10	33.3	4.9 (1.7–14.5)
	Oxypertine	18	6	12	33.3	4.9 (1.9–13.2)
	Perphenazine	86	45	41	52.3	10.8 (7.1–16.6)
	Pimozide	60	24	36	40.0	6.6 (3.9–11.0)
	Pipamperone	19	6	13	31.6	4.6 (1.7–12.0)
	Prochlorperazine	220	80	140	36.4	5.6 (4.3–7.4)
	Propicicazine	124	59	65	47.6	9.0 (6.3–12.8)
	Reserpine	18	4	14	22.2	2.8 (0.9–8.6)
	Sipiperone	2	1	1	50.0	– ^b
	Sultopride	82	49	33	59.8	14.7 (9.4–22.8)
	Tiapride	472	192	280	40.7	6.8 (5.7–8.2)
	Timiperone	39	18	21	46.2	8.5 (4.5–15.9)
Zotepine	456	213	243	46.7	8.7 (7.2–10.4)	
Atypical antipsychotics	Aripiprazole	3369	1079	2290	32.0	4.7 (4.4–5.1)
	Asenapine	399	107	292	26.8	3.6 (2.9–4.5)
	Blonanserin	914	398	516	43.5	7.7 (6.7–8.7)
	Clozapine	2512	382	2130	15.2	1.8 (1.6–2.0)
	Olanzapine	2623	812	1811	31.0	4.5 (4.1–4.9)
	Paliperidone	1368	362	1006	26.5	3.6 (3.2–4.0)
	Perospirone	534	246	288	46.1	8.5 (7.1–10.0)
	Quetiapine	2972	852	2120	28.7	4.0 (3.7–4.3)
	Risperidone	3950	1504	2446	38.1	6.2 (5.8–6.6)

^a SMQ: Standardised MedDRA Queries.

^b n < 2.



Cluster	T ^a or A ^b	Classification	Chlorpromazine equivalent	Major metabolic enzymes
1	T	Butyrophenone derivatives (N05AD)	2	CYP3A4
1	T	Diphenylbutylpiperidine derivatives (N05AG)	4	CYP3A4; CYP2D6
1	T	Other antipsychotics (N05AX)	33	-
1	T	Indole derivatives (N05AE)	80	-
1	T	-	1	-
1	T	Phenothiazines with piperazine structure (N05AB)	2	CYP2D6
1	T	Benzamides (N05AL)	200	-
1	T	-	1.3	-
1	T	Other antipsychotics (N05AX)	66	-
1	T	-	4.5	CYP3A4
1	T	-	40	-
1	T	Rauwolfia alkaloids (C02AA)	0.15	-
2	T	Phenothiazines with aliphatic side-chain (N05AA)	100	CYP2D6
2	T	Phenothiazines with aliphatic side-chain (N05AA)	100	-
2	T	-	20	-
2	A	SDA ^c	8	-
2	A	MARTA ^d	66	CYP3A4
2	T	Butyrophenone derivatives (N05AD)	200	-
2	A	MARTA ^d	2.5	CYP1A2
2	A	SDA ^c	1.5	-
2	A	SDA ^c	1	CYP2D6, CYP3A4
2	T	Phenothiazines with piperazine structure (N05AB)	15	-
2	A	MARTA ^d	50	CYP1A2, CYP3A4
2	T	Butyrophenone derivatives (N05AD)	2	CYP2D6, CYP3A4
2	A	DSS ^e	4	CYP3A4, CYP2D6
2	A	MARTA ^d	2.5	CYP1A2; CYP2D6
2	A	SDA ^c	4	CYP3A4
2	T	Benzamides (N05AL)	100	-
3	T	Phenothiazines with piperazine structure (N05AB)	10	CYP2D6

a: Typical antipsychotics b: Atypical antipsychotics c: Serotonin dopamine antagonist
d: Multi acting receptor targeted antipsychotics e: Dopamine system stabilizer

Fig. 3. Dendrogram representing the clusters (Cluster 1: Consists only of typical antipsychotics, such as bromperidol, fluphenazine, and sultopride, whilst having a high reporting rate of hypotension, tachycardia, dyskinesia, and dystonia; Cluster 2: Consists of all atypical antipsychotics used in this study with several typical antipsychotics such as haloperidol and chlorpromazine. The reporting ratios for disturbance of consciousness, extrapyramidal symptoms (excluding dyskinesia and dystonia) and serotonin syndrome were high; Cluster 3: Consists of only perphenazine and has a high rate of reports of coma, leukocytosis, and Parkinsonism).

NMS (SMQ code: 20000044) reported for haloperidol, chlorpromazine, risperidone, and aripiprazole were 1011, 588, 1504, and 1079. The ROR (95 % CI) for each drug was 12.1 (11.1–13.3), 6.3 (5.7–7.0), 6.2 (5.8–6.6), and 4.7 (4.4–5.1), respectively. Additionally, the reporting ratio (RR) and ROR for each antipsychotic drug are summarized in [Supplementary Tables S1–S52](#). The RRs of NMS for haloperidol, chlorpromazine, risperidone, and aripiprazole were 54.8 % (1011/1845), 38.7 % (588/1520), 38.1 % (1504/3950), and 32.0 % (1079/3369), respectively ([Table 2](#)).

A total of three clusters were formed ([Fig. 3](#)), with the characteristics of each cluster being as follows: Cluster 1 consisted of only TAPs, such as bromperidol, fluphenazine, and sultopride, whilst having a high reporting rate of hypotension, tachycardia, dyskinesia, and dystonia; Cluster 2 consisted of all AAPs used in this study alongside several TAPs, such as haloperidol and chlorpromazine. The RRs of disturbance of consciousness, extrapyramidal disorder (excluding dyskinesia and dystonia), and serotonin syndrome were all high. Furthermore, Cluster 3 consisted of perphenazine only and had a high rate of coma, leukocytosis, and Parkinsonism ([Fig. 4](#)).

We evaluated the possible association between NMS and each antipsychotic. The apriori algorithm of AA identified a set of rules for autonomic nervous system imbalance, disturbance of consciousness, extrapyramidal disorder, NMS, pyrexia, and rhabdomyolysis ([Fig. 5](#), [Supplementary Tables S53–S58](#)). The association rules {Clozapine, Risperidone, Zotepine} → {Autonomic nervous system imbalance} showed the high lift value ([Fig. 5 \(a\)](#), [Table S53 \(id \[1\]\)](#)). The association rules {Chlorpromazine, Fluphenazine, Haloperidol} → {NMS} ([Fig. 5 \(d\)](#), [Table S56 \(id \[1\]\)](#)), {Chlorpromazine, Fluphenazine, Risperidone} → {NMS} ([Fig. 5 \(d\)](#), [Table S56 \(id \[2\]\)](#)), and {Fluphenazine, Haloperidol, Risperidone} → {NMS} ([Fig. 5 \(d\)](#), [Table S56 \(id \[4\]\)](#)) exhibited high scores for lift. The association rules {Haloperidol} → {NMS} exhibited high scores for support ([Fig. 5 \(d\)](#), [Table S56 \(id \[19\]\)](#)).

4. Discussion

Antipsychotics are classified as either TAPs or AAPs, with TAPs having a very high affinity for dopamine D₂ receptors whilst being generally effective against positive symptoms, such as delusions and hallucinations. AAPs exhibit serotonin 5-HT₂ receptor antagonistic activity in addition to dopamine D₂ receptor antagonistic activity and are effective for negative symptoms such as emotional

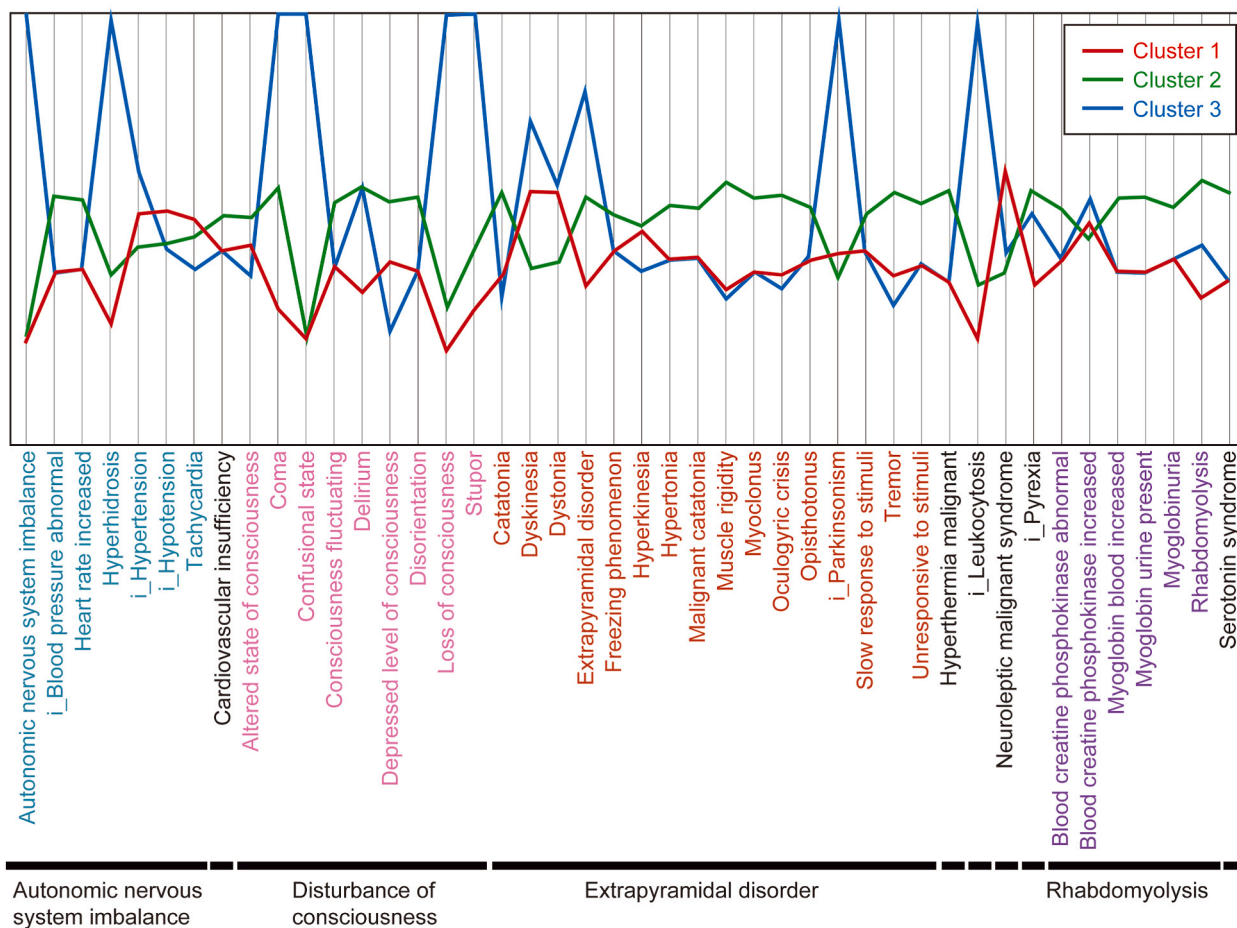


Fig. 4. Cluster mean plots of cluster analysis. The axis ranges from two standard deviations above and below the mean. If a cluster mean falls beyond this range, the axis is extended to include it.

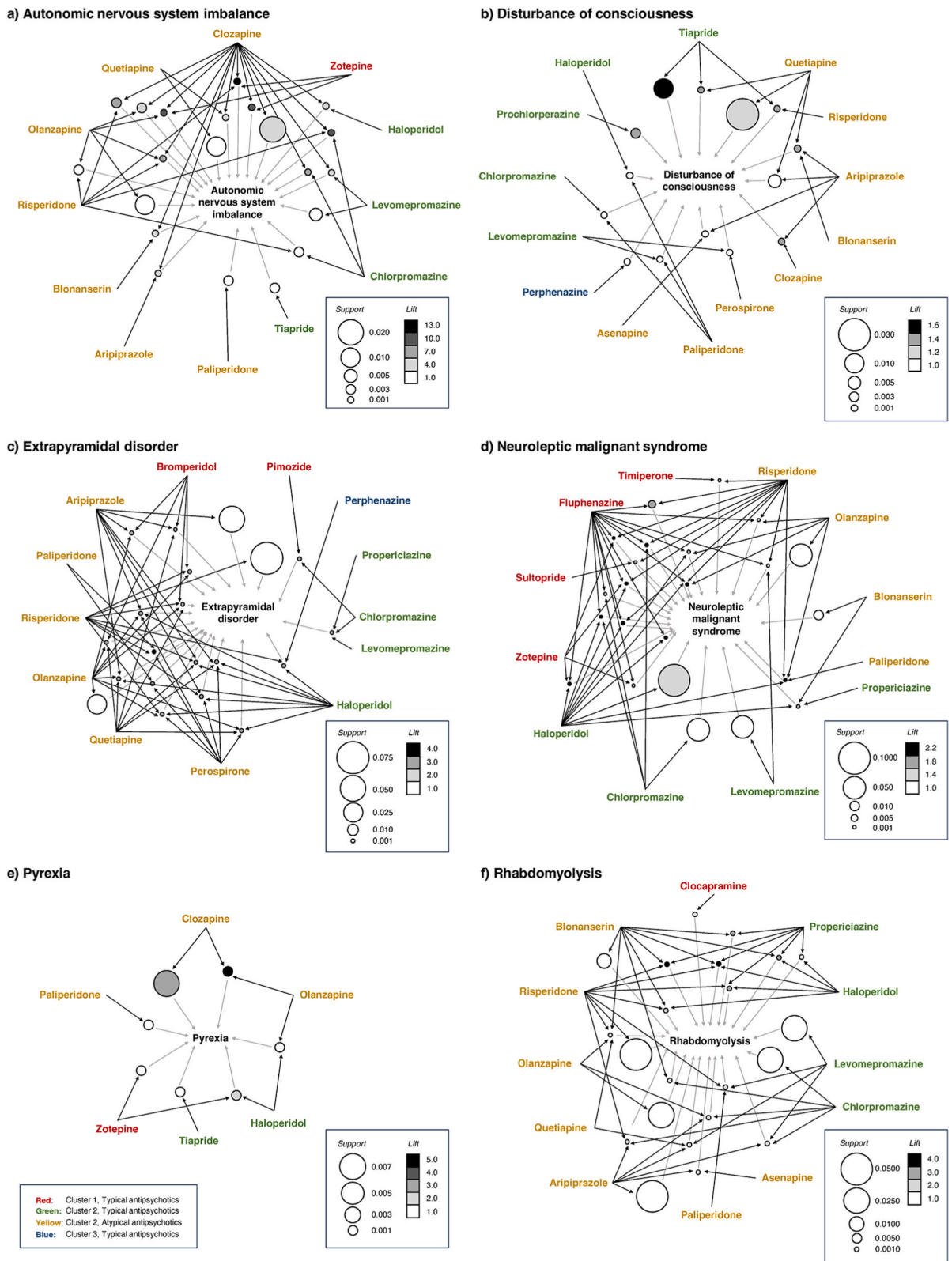


Fig. 5. Visualization of correlation rules established by performing association rule analysis.

dullness and lack of spontaneity [22,23]. Although the etiology of NMS remains unknown, most NMS symptoms probably result from a rapid decrease in central dopaminergic activity because of the blockade of D₂ receptors or the abrupt cessation of D₂ receptor stimulation. In this regard, higher doses of neuropsychiatric drugs are correlated with a greater risk of developing NMS.

The reason for the higher risk of NMS when using TAPs is related to the high dopamine D₂ receptor affinity of the drug and low binding dissociation from the receptor. AAPs are currently the drug of choice for treating the first episode of schizophrenia [24,25]. Considering that AAPs have fewer drawbacks than those of TAPs, they are more likely to exert an effect on negative symptoms and are less likely to cause extrapyramidal disorder [26]. However, no theory has been established for comparing TAP-related NMS risk with AAP-related NMS risk. A balanced dopamine D₂ and 5-HT receptor blockade, particularly 5-HT_{2A} receptor blockade [27], in AAPs has been proposed as a reason for lower NMS risk associated with AAPs than that with TAPs; however, it is not conclusive. Additionally, the possibility of publication bias has been proposed. All neuropsychiatric drugs have been reported to have the risk of NMS associated with their administration at standard doses and all routes of administration. Moreover, the present AA results showed that in extrapyramidal disorders, AAP-related rules were more common than TAP-related rules (Fig. 5 (c)), and in NMS, TAP-related rules tend to have higher *lift* values than those observed for AAP-related rules (Fig. 5 (d)).

Of the 29 drugs included in this study, the lower 95 % CI for the ROR of 27 NMS (SMQ code: 20000044) drugs, excluding reserpine and spiperone, exceeded 1. As a result, a relationship between antipsychotic drugs and NMS was proposed here. NMS was included among the serious AE items in the package inserts of all drugs used in this study, except for reserpine. Healthcare professionals should pay close attention to NMS in a patient who is administered not only TAPs but also AAPs, which are sought to have a relatively low risk of NMS compared with the risk associated with TAPs according to the previous reports [26,28].

CA defines similarities between multiple drugs and classifies them into homogeneous clusters, and it is an exploratory data analysis technique used to summarize the tendencies of sets such as unknown databases and to intuitively understand their content. Clustering is based on subjectivity or a point of view and can be divided into arbitrary clustering numbers by the researcher. The validity of clustering results can only be subsequently determined through external knowledge, such as the intended use of the division. If the user can interpret the division result, then it can be said that the correct number of clusters has been formed [10]. Therefore, the validity of clustering results must always be examined based on the purpose of their use. Here, we assigned a clustering number of three based on the similarity in expression profiles across the 52 AEs.

The characteristic information for each cluster shown in Fig. 3 demonstrates the trend in the occurrence of AEs common to drug groups belonging to the cluster information. This provides information on the reporting rates of AEs associated with NMS for each antipsychotic drug. Healthcare professionals can use Figs. 3–5 to obtain an overview of AEs that should be noted in advance for each drug used.

The extrapyramidal disorder is less likely to occur in patients receiving AAPs compared with those receiving TAPs [26,29]. However, several previous studies have indicated that AAPs can cause extrapyramidal disturbances to the same extent as TAPs [30]. However, multiple other studies have also suggested that AAPs and TAPs carry similar risks of extrapyramidal disturbance [31,32]. Cluster 2, which included all AAPs alongside several TAPs, was more likely to have AEs related to NMS (especially extrapyramidal symptoms, excluding dyskinesia and dystonia) compared with Cluster 1, which consisted of only TAPs. Cluster 2 included several TAPs in addition to AAPs; therefore, the results should be interpreted with caution.

Recently, several studies have investigated the association between NMS and CYP2D6 deletion. CYP2D6 activity has been shown to have genetic alterations that show differences in activity among ultra-rapid, extensive, intermediate, and poor metabolizers, with the percentage of intermediate metabolizers in Japan being 40%–50 % [33]. Several previous studies have also suggested that the delayed degradation of antipsychotic drugs metabolized by CYP2D6 may increase the risk of AEs [34]. Furthermore, one report found that those with CYP2D6*5 polymorphism (poor metabolizer type) were significantly more likely to develop NMS [35]. In addition, Kirchheiner et al. reported that it was better to adjust the dose of antipsychotic drugs by a factor of 0.33–1.5, based on the metabolic capacity of CYP2D6 [36]. Among the drugs used in this study, the TAPs pimozide, fluphenazine, chlorpromazine, perphenazine, and haloperidol, alongside AAP, such as aripiprazole, olanzapine, and risperidone, were all metabolized by CYP2D6 [37]. Because chlorpromazine (TAP) and asenapine (AAP) inhibit CYP2D6 [38,39], their concomitant use with other neuropsychiatric drugs metabolized by CYP2D6, such as risperidone and olanzapine, may increase blood concentration levels of these drugs and increase the risk of NMS. However, the present AA results showed no clear concomitant interactions. In addition to neuropsychiatric drugs, many other CYP2D6 inhibitors are known, including paroxetine (selective serotonin reuptake inhibitor), amiodarone (antiarrhythmic), cimetidine (H₂-receptor antagonist), and quinidine (antiarrhythmic) [2,5,40]. We did not examine these concomitant medications in this study, and we believe that future studies should examine the mentioned CYP2D6 inhibitors.

An interesting approach could be investigating the relationship between NMS and the metabolic enzymes of antipsychotics. Whether the characteristics of the three clusters could be explained by metabolic enzymes or other genes is a subject for future investigation.

The limitations of analyses using SRS should be noted here. SRS uses insufficient information in terms of patient background, whilst under-reporting or over-reporting confounding factors, and no control population or reference group. To date, no widely accepted method has been established for adjusting the covariates in studies using SRS datasets. Multiple logistic regression methods have been reported to partially adjust for confounding factors [18]. Propensity scores may be used to reduce bias by equating groups based on possible confounders [41,42]. Alternately, some recent studies have provided some approaches to address these issues in a high-dimensional context [43–45]. Therefore, future studies should investigate problems such as adjusting covariates and reducing biases. Moreover, the present results must be carefully interpreted considering the limitations of this study. Furthermore, we need to consider external factors, such as the release of safety information from administrative authorities and market trends, and the possibility of overlooking delayed AEs. Considering the inherent problems of SRS, it should not be used for true risk assessment [8,21].

Drug therapy for patients with schizophrenia is based on the single-agent administration of AAPs. Depending on the efficacy and side effects of a drug, there are many cases of changes or additions to other drugs, as well as several cases of multidrug therapy [46,47]. Previous reports have shown that polypharmacy is a risk factor for NMS [48]. However, our analysis did not adequately consider polypharmacy. Malignant syndrome is considered to be less affected by the male-to-female ratio and age of onset [1]; therefore, we did not examine this by sex or age. In addition, we did not consider the potency or dosage of each antipsychotic drug. Therefore, an analysis that considers these factors will be conducted in the future.

Despite these analytical limitations, the findings obtained herein from JADER, a large-scale AE database that accumulates long-term cases collected from actual clinical settings, are considered useful. Therefore, it is important to continue medication for the treatment of schizophrenia. Owing to the long-term treatment, many patients stop taking the drug of their own accord. Additionally, AEs of antipsychotics can lead to their discontinuation. As a result of knowing the AE profile in advance, it is considered possible for medical professionals to predict characteristic NMSs that are likely to occur in a patient. The findings of this study can be further applied to CA and AA by incorporating datasets on individual susceptibility to NMS and psychological and social factors in order to develop a program to predict the risk factors of NMS in clinical practices. Overall, we believe that the results of this study will contribute to the treatment of schizophrenia.

5. Conclusion

Using the JADER database, we demonstrated the potential risks of NMS associated with antipsychotics based on RORs. Drugs were then classified based on their AE profiles by performing CA and AA. It is important to provide information to other healthcare professionals and patients, considering the characteristics of AEs reported in each cluster or the effects of concomitant antipsychotic drugs. Our study results may aid in the management of NMS using antipsychotic drugs.

Ethics approval

Ethical approval was not sought for this study because the study was a database-related observational study without directly involving any research subjects. All results were obtained from data openly available online from the PMDA website (www.pmda.go.jp). All data from the JADER database were fully anonymized by the relevant regulatory authority before we accessed them.

Funding statement

This research was partially supported by JSPS KAKENHI Grant Number, 21K06646 and 21K11100.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mitsuhiro Nakamura reports financial support was provided by Japan Society for the Promotion of Science.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2023.e21891>.

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