Antipsychotic Rechallenge After Neuroleptic Malignant Syndrome

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Introduction

Neuroleptic malignant syndrome (NMS) is a life-threatening complication of antipsychotic pharmacotherapy characterized by hyperpyrexia, muscle rigidity, autonomic instability, and elevation of serum creatine phosphokinase (CPK). NMS carries a mortality rate as high as 10-20 percent.[3] In many cases, it occurs in patients who would benefit from long-term antipsychotic therapy, and who therefore must be rechallenged with an antipsychotic after NMS has resolved. It is generally recommended that rechallenge be undertaken with careful monitoring, preferably by titrating from low doses of low-potency antipsychotics, after a period of 2 weeks following resolution of symptoms[8-9].

The symptoms of NMS generally resolve within two weeks of withdrawal of the inducing agent. However, numerous cases of residual catatonia following NMS have been reported[10-12]. For those cases in which catatonic features persist after the resolution of fever and rigidity, it is unclear when the illness can be considered "resolved", and therefore difficult to interpret the existing guidelines on safe reintroduction of antipsychotics.

Major Criteria	Minor Criteria
Fever	Tachycardia
Rigidity	Abnormal blood pressure
Elevated CPK	Tachypnea
	Altered consciousness
	Diaphoresis
	Leukocytosis

All three major criteria or two major plus four minor were considered positive for NMS in this study.

Table 1: Levenson criteria for NMS

Data were gathered from published NMS case reports to evaluate whether time to rechallenge, potency of rechallenge drug, and dose of rechallenge drug were independent predictors of NMS recurrence.

Methods

Through broad MEDLINE and PsycInfo database searches over 500 cases of NMS were identified. Each full-text case report was reviewed by a single investigator. Included in the final analysis were cases that met Levenson criteria for NMS (Table 1)[14] and included information on antipsychotic rechallenge.

The full text of each case was reviewed to extract data including (1) antipsychotic drug, potency, and dose at onset of NMS; (2) drug, potency, and initial and maximum dose at rechallenge; and (3) time between resolution of symptoms and rechallenge.

Continuous variables were reported as means and standard errors. Categorical variables were reported as percentages. Categorical variables were analyzed using chi-square testing. Continuous variables were analyzed using the t-test; when continuous variables were not normally distributed, the Wilcoxon rank sum test was used. Logistic regression was used to determine independent predictors of recurrence. A two-tailed $p < 0.05$ was considered significant.

Results

One hundred thirteen instances of neuroleptic rechallenge in non-catatonic NMS cases and 29 cases of rechallenge in NMS with catatonic features were included in our analysis. Fifty-five cases involved female patients, and 87 male patients. Diagnoses requiring antipsychotic treatment included schizophrenia, acute psychosis, bipolar disorder with psychosis, and dementia.

Patients ranged in age from 12 to 86, with a mean of 37. Of these 142 cases, 55 (39%) resulted in recurrence of NMS and 87 resulted in no recurrence. The recurrence rate was slightly higher in the non-catatonic NMS subgroup (45 cases, 40%) than the catatonic subgroup (10 cases, 35%). Rates of recurrence for all cases and for catatonic and non-catatonic subgroups are summarized in Tables 2-4.

There was no statistically significant relationship found between rate of NMS recurrence and time elapsed before rechallenge, either for all cases or by subgroup.

Although the recurrence rate for patients rechallenged with highest-potency antipsychotics was found to be higher (43% overall) than those rechallenged with lowest-potency drugs (36% overall), the relationship was not significant ($p = 0.518$). Most rechallenge drugs were started at lower doses and gradually increased to therapeutic doses. The maximum antipsychotic dose reached during rechallenge was significantly lower among patients with recurrence of NMS than those who did not recur ($p = .0026$), although this relationship was significant only in the non-catatonic subgroup when the subgroups were analyzed independently. There was no statistically significant relationship between starting dose and recurrence.

	N	Recurrence	No Recurrence	p value
ALL CASES				
Before sx resolved	25	10 (40%)	15 (60%)	
After sx resolved	101	43 (43%)	58 (57%)	0.815
< 5 days after sx resolved	42	15 (36%)	27 (64%)	
> 5 days after sx resolved	59	30 (51%)	29 (49%)	0.132
< 2 wks after sx resolved	58	20 (35%)	38 (65%)	
> 2 wks after sx resolved	49	26 (53%)	23 (47%)	0.053
NON-CATATONIC CASES				
Before sx resolved	17	7 (41%)	10 (59%)	
After sx resolved	80	36 (45%)	44 (55%)	0.773
< 5 days after sx resolved	31	12 (39%)	19 (61%)	
> 5 days after sx resolved	48	23 (48%)	25 (52%)	0.42
< 2 wks after sx resolved	44	16 (36%)	28 (64%)	
> 2 wks after sx resolved	41	21 (51%)	20 (49%)	0.167
CATATONIC CASES				
Before sx resolved	8	3 (62%)	5 (38%)	
After sx resolved	21	7 (33%)	14 (67%)	0.833
< 5 days after sx resolved	11	3 (27%)	8 (73%)	
> 5 days after sx resolved	11	7 (64%)	4 (36%)	0.083
< 2 wks after sx resolved	14	4 (29%)	10 (71%)	
> 2 wks after sx resolved	8	5 (63%)	3 (37%)	0.119

Table 2: Risk of recurrence by time to rechallenge

Discussion

Time Frame

Although several past studies have suggested a significant relationship between time frame and likelihood of recurrence[2,5,6], that relationship was not borne out by the analysis performed here. While it is possible that our study did not include enough case reports to identify a significant trend, our findings suggested that recurrence is in fact more likely when rechallenge is undertaken *greater* than two weeks after resolution of symptoms.

	Recurrence		No Recurrence		p value
ALL CASES	Mean	St Err	Mean	St Err	
Starting Dose	115.8	28.4	156.1	25.2	0.292
Maximum Dose	173.6	52.4	388.0	45.5	0.0026
NON-CATATONIC CASES	Mean	St Err	Mean	St Err	
Starting Dose	124.9	33.1	169.7	31.4	0.331
Maximum Dose	173.8	63.0	412.1	55.4	0.006
CATATONIC CASES	Mean	St Err	Mean	St Err	
Starting Dose	56.5	31.0	112.4	20.7	0.162
Maximum Dose	172.9	81.6	307.0	67.9	0.221

Table 3: Risk of recurrence by dose (chlorpromazine equivalents)

Discontinuing the precipitating medication is the well-supported mainstay of treatment for NMS, and it therefore remains prudent to withhold antipsychotics while fever and rigidity persist; however, our data suggest that antipsychotics may be safely reintroduced earlier than is generally recommended.

Potency of Rechallenge Drug

Our findings, although statistically insignificant, were consistent with past literature reviews suggesting a higher risk of recurrence with higher-potency antipsychotics[1-4,7]. We generally recommend choosing a lower-potency second-generation drug for rechallenge. However, individual cases may warrant other choices.

	N	Recurrence	No Recurrence	p value
ALL CASES				
Highest Potency	23	10 (43%)	13 (56%)	
Lowest Potency	75	27 (36%)	48 (64%)	0.518
NON-CATATONIC CASES				
Highest Potency	17	7 (41%)	10 (59%)	
Lowest Potency	65	23 (35%)	42 (65%)	0.659
CATATONIC CASES				
Highest Potency	6	3 (50%)	3 (50%)	
Lowest Potency	10	4 (40%)	6 (60%)	0.696

Table 4: Risk of recurrence by potency

Dose of Rechallenge Drug

The significant inverse relationship found between maximum dose and risk of rechallenge can be explained by the fact that NMS recurred at subtherapeutic doses in many patients, and antipsychotics were discontinued early in the dose titration.

The lack of significant relationship between starting dose and recurrence risk is consistent with findings from past studies[2]. Antipsychotic drugs should always be started at low doses and increased to the lowest possible therapeutic dose to minimize side effects.

Conclusions

NMS is a syndrome whose onset is difficult to predict and which may recur; however, many patients are successfully restarted on antipsychotic medication. Based on our analysis, time between resolution of symptoms and rechallenge may have no bearing on risk of recurrence, in contrast to current recommendations. Dose of rechallenge drug is also unlikely to be an independent predictor of recurrence. Several studies, including ours, have shown a statistically insignificant but consistent positive relationship between potency of rechallenge drug and risk of recurrence. Clinicians should consider the severity of patient symptoms and the patient's past responses to different medications when choosing the appropriate time and drug for rechallenge, and always reintroduce antipsychotics with careful monitoring of vital signs and laboratory values. Further study of recurrence risk, as well as NMS with catatonic features, will improve our ability to make the best choices for our patients.

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