# Bromocriptine for Residual Catatonia Following Neuroleptic Malignant Syndrome: Case Report and Systematic Review

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## INTRODUCTION

**Neuroleptic Malignant Syndrome (NMS)** is a rare but potentially fatal condition associated with either the use of agents that cause dopamine receptor blockade (i.e. antipsychotics) or the abrupt withdrawal of dopaminergic agents:

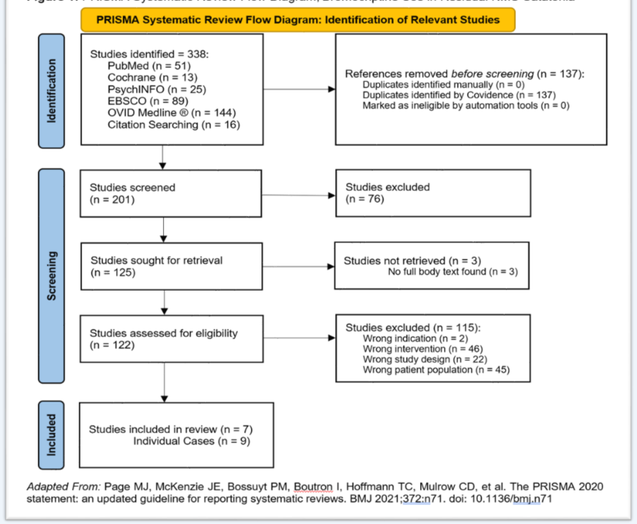
- Incidence of 0.01%-0.03% among those taking antipsychotics, with a mortality rate of 5.4%-7.6%[1,2]
- Theorized to involve dopamine blockade/withdrawal across several central nervous system (CNS) pathways: hypothalamic, nigrostriatal, mesolimbic, and cortical
- NMS is characterized by hyperthermia, autonomic instability, altered mental status, and severe muscular rigidity
- Treatment involves immediate cessation of the offending agent, extensive supportive therapy, and pharmacological treatment/ECT in severe cases
- Most treated cases resolve within weeks; however, in some cases, **residual catatonic symptoms** can persist for **months** after the resolution of hyperthermic and hypermetabolic symptoms[3]
- The utilization of dopaminergic agents, such as **bromocriptine**, to alleviate the catatonic symptoms of NMS has been described in the literature but has not been explored systematically

**Question:** *Given its mechanism as a sympatholytic, $D_2$-agonist, can bromocriptine serve as a second-line treatment for residual NMS catatonia, if traditional management such as benzodiazepine and/or ECT treatment is ineffective or unavailable?*

## METHODS

A systematic literature review of cases where bromocriptine was utilized in the management of residual NMS catatonia was conducted. Exclusion criteria included bromocriptine use limited to acute phase of NMS. **Figure 1** below highlights the review protocol:

**Figure 1:** PRISMA Systematic Review Flow Diagram, Bromocriptine Use in Residual NMS Catatonia




*Adapted From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

## CASE PRESENTATION & LITERATURE REVIEW

- Consult: 21-year-old female patient with psychiatric history of autism spectrum disorder experiencing continued catatonic features following stabilization of aripiprazole-induced NMS [hyperthermia (>102°F), generalized stiffness, jaw clenching, and limited spontaneous movement]
- Persistent Catatonic Features **(shown in Table 1)**: Following NMS treatment with supportive care and lorazepam, she exhibited significant residual catatonic symptoms—including immobility, mutism, rigidity, and posturing—despite improvements in autonomic abnormalities
- Initial Treatments Ineffective; ECT Declined: Further benzodiazepine titration was limited by disinhibition at higher doses and electroconvulsive therapy (ECT) was declined by the patient's parents
- High-Dose Bromocriptine Led to Symptom Resolution: Gradual **titration of bromocriptine up to 25 mg twice daily** over six months resulted in significant improvement and **eventual complete resolution of catatonic symptoms**, with good tolerability
- Post-recovery, genetic testing revealed late-onset Tay-Sachs Disease, possibly contributing to her susceptibility to NMS and prolonged catatonia

**Table 1:** Overview of Patient's Symptoms and Outpatient Treatment, August 2020 – August 2021

| DATE OF VISIT | AUGUST 2020 | SEPTEMBER 2020 | OCTOBER 2020 | DECEMBER 2020 | JANUARY 2021 | FEBRUARY 2021 | MARCH 2021 | MAY 2021 | JULY 2021 | AUGUST 2021 |
|---|---|---|---|---|---|---|---|---|---|---|
| MONTHS AFTER DISCHARGE | 0 | 1 | 2 | 4 | 5 | 6 | 7 | 9 | 11 | 12 |
| CATATONIC SYMPTOMS | Immobility, mutism, staring, posturing, rigidity, and withdrawal | Immobility, mutism, staring, posturing, rigidity, grimacing, catalepsy, withdrawal | Improvement with less mutism, minimal posturing, less rigidity, less catalepsy, less withdrawal | Increased mutism, rigidity, posturing, bradykinesia after amantadine discontinued | New ambitendency; improvement in other symptoms with mild staring, rigidity, and catalepsy | Overall improvement with minimal mutism, staring, grimacing, catalepsy | Overall improvement with mild catalepsy | Resolved | Resolved | Resolved |
| BUSH-FRANCIS CATATONIA RATING SCALE (BFCRS) SCORE | 11 | * | * | * | 8 | 6 | 1 | 0 | 0 | 0 |
| **MEDICATION CHANGES FOLLOWING VISIT:** | | | | | | | | | | |
| LORAZEPAM | 0.75 mg QID | ↑0.80 mg QID | 0.80 mg QID | 0.80 mg QID | ↓0.8 mg TID | 0.8 mg TID | ↓0.8 mg BID | ↓0.8 mg nightly | Discontinued | N/A |
| BROMOCRIPTINE | 5 mg BID | ↑10 mg BID | ↑15 mg BID | 15 mg BID | ↑20 mg BID | ↑25 mg BID | 25 mg BID | 25 mg BID | Discontinued w/ taper | N/A |
| AMANTADINE | 200 mg BID | ↓100 mg BID | Discontinued w/ taper | ↑200 mg BID | ↓100 mg BID | ↓100 mg BID | 100 mg BID | 100 mg BID | 100 mg BID | Discontinued w/ taper |

** = Telehealth Visit limited BFCRS utilization.*

**Table 2: Cases of Bromocriptine Use in Residual NMS Catatonia**

| **Bromocriptine Use → Catatonia Lysis**<br>**Patient's Residual Catatonia Presentation** | **Treatments Utilized for Catatonia** | **Outcomes** |
|---|---|---|
| 34/M with persistent rigidity, stupor, akinesia, and mutism following haloperidol- and parental chlorpromazine-induced NMS[4] | Bromocriptine (N/A dose)* | Rigidity completely subsided in 5th week after bromocriptine initiation; patient became fully alert and conscious in 6th week but remained psychotic until patient-directed discharge |
| 36/M with persistent mutism, posturing, stereotypic movements, negativism, and increased muscle tone following trifluoperazine-induced NMS[5] | Bromocriptine + ECT initially → Clozapine 75 mg/day six-day trial for continuing psychosis → Restarted on bromocriptine | Bromocriptine/ECT caused initial improvement → following ineffective clozapine trial, bromocriptine led to "gradual" recovery over 4 weeks (no recurrence of NMS symptoms) |
| 66/M with waxy flexibility, posturing, mutism, negativism (BFCRS of 23) following acute NMS[6] | Lorazepam (5 mg/day) → Twice-weekly, bitemporal ECT (11 sessions) → Bromocriptine titrated to 15 mg/day | Lorazepam provided no benefit → 11 ECT sessions provided 65.2% reduction in BFRCS (23 → 8) → Bromocriptine resulted in further improvement as most catatonic symptoms subsided (BFRCS score of 1) |
| 27/M with moderate rigidity, staring, posturing, waxy flexibility following aripiprazole-induced NMS[7] | Lorazepam 1 mg four times daily (QID) → Bromocriptine titrated to 20 mg QID | Bromocriptine 20 mg QID provided rapid improvement to rigidity, tremor, oral intake; other catatonic symptoms resolved after 23 days |
| **Bromocriptine Use → Improved Catatonia**<br>**Patient's Residual Catatonia Presentation** | **Treatments Utilized for Catatonia** | **Outcomes** |
| 30/M with mutism, withdrawal, decreased reactivity to environment, and reduced spontaneous movement following acute NMS[8] | Bromocriptine 5 mg TID + dantrolene 75 mg TID → 30 sessions of ECT | Bromocriptine and dantrolene caused marked improvement in confusion, agitation, and muscular rigidity; however, patient continued having other residual catatonic symptoms until 30 sessions of ECT |
| 21/M with persistent rigidity, stuporous condition, and dystonia following fluphenazine-induced NMS[3] | Dantrolene, bromocriptine, lorazepam, benztropine, ECT (N/A dose) | Bromocriptine and dantrolene brought initial reduction in temperature and rhabdomyolysis; symptoms improved after 190 days |
| 36/M with persistent rigidity, mutism, stupor following perphenazine-induced NMS[3] | Dantrolene, bromocriptine, lorazepam, ECT (N/A dose) | Bromocriptine and dantrolene brought initial reduction in temperature and rhabdomyolysis; ultimate improvement with ECT after 120 days |
| **Bromocriptine Use → No Improvement**<br>**Patient Description** | | **Outcomes** |
| 64/F with continued rigidity, mutism, stupor, and catalepsy following haloperidol-induced NMS[3] | Amantadine, dantrolene, bromocriptine, lorazepam, ECT (N/A dose) | No improvement with bromocriptine; improvement with ECT but patient died due to pneumonia 42 days after symptom onset |
| 60/F with rigidity, mutism, negativism, withdrawal, and stereotypic grasping following quetiapine-induced NMS[9] | Bromocriptine 1 to 40 mg/day; amantadine 100 mg/day; lorazepam-diazepam protocol; ECT | No improvement with bromocriptine or amantadine; residual catatonic symptoms improved after 11 ECT sessions |

## DISCUSSION

**Table 3: Points for Discussion**

| | |
|---|---|
| **Pathophysiological Implications** | Residual NMS catatonia may result from persistent dopamine dysregulation following acute NMS symptom resolution (i.e. hypothalamic dopamine replenishment) |
| **Bromocriptine's Role** | Acting as a $D_2$-agonist, bromocriptine may alleviate catatonic symptoms by replenishing dopamine neurotransmission in affected, intractable CNS pathways |
| **Late-Onset Tay-Sachs Disease (LOTS)** | Case reports of neuropsychiatric manifestations have included catatonia and NMS[10] |

- ECT remains the first-line treatment modality for residual NMS catatonia, as it is effective in refractory cases and most associated with rapid response[3]
- In our case, where ECT was not feasible, targeting residual dopamine dysregulation in cortical and subcortical pathways with dopaminergic agents guided the management approach
  - Including the highlighted case, bromocriptine **improved catatonic symptoms in eight patients (80.0%)** and **lysed catatonic symptoms in five patients (50.0%)**

Limitations:

1. Absence of controlled and randomized conditions impedes a definitive assessment of bromocriptine efficacy
2. Marked improvement in catatonic symptoms occurred during the employment of multiple treatments in a single period, clouding the picture of which modality was most effective
3. Small sample size limits generalizability of these findings

## CONCLUSIONS

- The case and systematic literature review suggest bromocriptine is effective in treating residual catatonia following NMS
- Although making clinical recommendations is difficult in this situation:
  - **Consider bromocriptine when first-line treatments fail or are not feasible**
- Further research is warranted to understand the underlying mechanisms of malignant catatonia and NMS
- Larger studies are needed to establish definitive treatment guidelines and to explore the etiological heterogeneity of catatonia

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