A Call for Protocol for the Treatment of Long-Acting Injectable Antipsychotic-Induced Neuroleptic Malignant Syndrome

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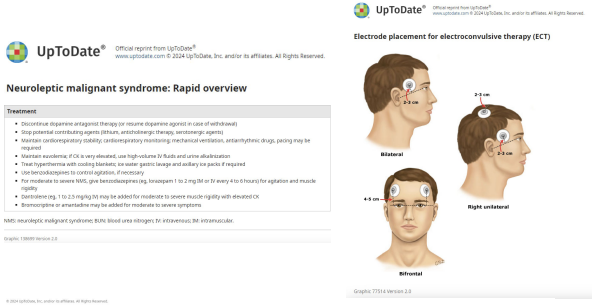
Background:

Neuroleptic Malignant Syndrome (NMS) is a life-threatening reaction to the use of a dopamine-blocking agent or the removal of a dopaminergic agent. With the increasingly common use of long-acting injectable (LAI) antipsychotics, there is an escalating need for protocol to manage LAI-induced NMS. We present two cases with different treatment plans for the management of LAI-induced NMS.



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Neuroleptic malignant syndrome: Rapid overview

Treatment

- Discontinue dopamine antagonist therapy (or resume dopamine agonist in case of withdrawal)
- Stop potential contributing agents (lithium, anticholinergic therapy, serotonergic agents)
- Maintain cardiorespiratory stability; cardiorespiratory monitoring; mechanical ventilation, antiarrhythmic drugs, pacing may be required
- Maintain euvolemia; if CK is very elevated, use high-volume IV fluids and urine alkalinization
- Treat hyperthermia with cooling blankets; ice water gastric lavage and axillary ice packs if required
- Use benzodiazepines to control agitation, if necessary
- For moderate to severe NMS, give benzodiazepines (eg, lorazepam 1 to 2 mg IM or IV every 4 to 6 hours) for agitation and muscle rigidity
- Dantrolene (eg, 1 to 2.5 mg/kg IV) may be added for moderate to severe muscle rigidity with elevated CK
- Bromocriptine or amantadine may be added for moderate to severe symptoms

NMS: neuroleptic malignant syndrome; BUN: blood urea nitrogen; IV: intravenous; IM: intramuscular.

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Electrode placement for electroconvulsive therapy (ECT)

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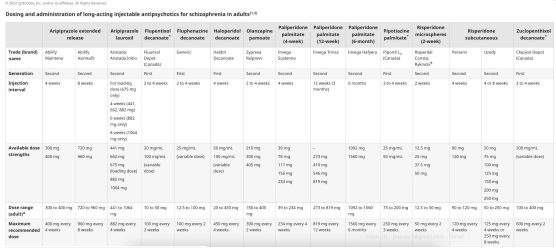

Dosing and administration of long-acting injectable antipsychotics for schizophrenia in adults[1-4]

	Aripiprazole extended release		Aripiprazole lauroxil	Fluspirilene decanoate[1]	Fluphenazine decanoate	Haloperidol decanoate	Olanzapine pamoate	Paliperidone palmitate (4-week)	Paliperidone palmitate (12-week)	Paliperidone palmitate (6-month)	Pipotiazine palmitate[1]	Risperidone microsphere (2-week)	Risperidone subcutaneous	Zuclopenthixol decanoate[1]
Trade (brand) name	Abilify Maintena	Abilify Asimtufii	Aristada, Aristada Initio	Fluanxol Depot (Canada)	Generic	Haldol Decanoate	Zyprexa Relprevv	Invega Sustenna	Invega Trinza	Invega Hafyera	Piportil L_4 (Canada)	Risperdal Consta, Rykindo®	Perseris	Uzedy	Clopixol Depot (Canada)
Generation	Second	Second	Second	First	First	First	Second	Second	Second	Second	First	Second	Second	Second	First
Injection interval	4 weeks	8 weeks	For loading dose (675 mg only): 4 weeks (441, 662, 882 mg) 6 weeks (882 mg only) 8 weeks (1064 mg only)	2 to 4 weeks	2 to 4 weeks	4 weeks	2 to 4 weeks	4 weeks	12 weeks (3 months)	6 months	3 to 4 weeks	2 weeks	4 weeks	4 or 8 weeks	2 to 4 weeks
Available dose strengths	300 mg 400 mg	720 mg 960 mg	441 mg 662 mg 675 mg (loading dose) 882 mg 1064 mg	20 mg/mL 100 mg/mL (variable dose)	25 mg/mL (variable dose)	50 mg/mL (variable dose)	210 mg 300 mg 405 mg	39 mg 78 mg 117 mg 156 mg 234 mg	– 273 mg 410 mg 546 mg 819 mg	1092 mg 1560 mg	25 mg/mL 50 mg/mL	12.5 mg 25 mg 37.5 mg 50 mg	90 mg 120 mg	50 mg 75 mg 100 mg 125 mg 150 mg 200 mg 250 mg	200 mg/mL (variable dose)
Dose range (adult)[4]	300 to 400 mg	720 to 960 mg	441 to 1064 mg	50 to 50 mg	12.5 to 100 mg	20 to 450 mg	150 to 405 mg	39 to 234 mg	273 to 819 mg	1092 to 1560 mg	75 to 200 mg	12.5 to 50 mg	90 to 120 mg	90 to 250 mg	100 to 400 mg
Maximum recommended dose	400 mg every 4 weeks	960 mg every 8 weeks	882 mg every 4 weeks	100 mg every 2 weeks	100 mg every 2 weeks	100 mg every 2 weeks	300 mg every 2 weeks	234 mg every 4 weeks	819 mg every 12 weeks	1560 mg every 6 months	150 mg every 3 weeks	50 mg every 2 weeks	120 mg every 4 weeks	125 mg every 4 weeks or 250 mg every 8 weeks	600 mg every 2 weeks

Cases:

RH is a 57 year old female with Schizoaffective Disorder who presented with altered mental status and psychosis who developed NMS following initiation of haloperidol decanoate. She had hyperthermia, intermittent tachycardia, and rigidity on exam. Her serum iron was low at 38 micrograms/dL, however, her total creatine kinase never rose about 37 U/L. Initially, after antipsychotics were held, she was managed with lorazepam 1 mg every 6 hours, iron sucrose IV 200 mg daily for 5 days, and supportive care, however, the response was not optimal. Eventually, she underwent a course of electroconvulsive therapy (ECT) that ultimately resolved her NMS.

KC is a 49 year old female with Bipolar 1 Disorder who presented with acute mania following treatment with 3-month paliperidone 546 mg injection and oral paliperidone 3 mg daily. Her course was complicated by NMS after she was treated with 1-month paliperidone 156 mg, oral paliperidone 6 mg twice daily, oral chlorpromazine 100 mg, and lithium 450 mg twice a day over an eleven-day period. She had autonomic instability without developing hyperthermia and was rigid on physical exam. Her serum iron was low at 46 micrograms/dL with an elevated total creatine kinase of 782 U/L. All antipsychotics were held, and her NMS was treated with lorazepam IV 2 mg every 6 hours, supportive care, and discontinuation of her lithium, with her NMS resolving after one week.

Discussion:

The cornerstone of treatment for NMS is benzodiazepines and ECT (Stern, 2018), however, there is limited data for treatment of prolonged NMS due to LAI use. Literature suggests that decreased serum iron may play a role in NMS (Rosebush, 1991), which may suggest use of iron supplementation in treatment of the syndrome. The use of dopaminergic agents and muscle relaxants can additionally improve the outcome and mortality of NMS (Sakkas, 1991). Both cases had resolution of NMS with use of different treatment plans, however, the development of a standardized protocol could lead to quicker resolution, decreased length of hospital stay, and many other benefits. The multitude of variables and possible treatment options for NMS highlights the need to establish protocol for persistent cases, especially as the use of LAI's become more commonplace in psychiatry.

References:

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