

LORAZEPAM TREATMENT OF NEUROLEPTIC MALIGNANT SYNDROME

To the Editor:

We enjoyed Drs. Gajwani and Franco-Bronson's case presentation and discussion of a 56-year-old man with fever, muscle rigidity, and autonomic disturbance after use of haloperidol in the April 2001 issue of *Hospital Physician*.¹ The case met criteria for a diagnosis of neuroleptic malignant syndrome (NMS), and the authors reviewed possible treatments including intravenous fluids, cooling blankets, and various pharmacologic agents including anticholinergics, dopamine agonists, and dantrolene sodium. This patient was managed with β -blockers, diphenhydramine, and lorazepam, which was administered for agitation.

We are surprised that the authors failed to consider the administration of lorazepam as effective in relieving the case patient's NMS. A recent article in *Hospital Physician* described 2 cases of NMS that met strict research criteria and were managed successfully with lorazepam.² In addition, a retrospective study of 16 patients who also met research criteria for NMS showed resolution with lorazepam or related benzodiazepines.³ In both of these reports, clinical features of NMS abated within 24 to 72 hours, which compares favorably with the 5 to 10 days reported with only supportive treatments.^{3,4}

In the management of NMS, a consensus exists for discontinuation of the offending pharmacologic agent and for supportive treatments of hydration, physical cooling measures, antipyretics, and monitoring of autonomic signs.^{3,4} Use of specific agents, including dopamine agonists (eg, bromocriptine) and muscle relaxants (eg, dantrolene) is debatable.⁵ Benzodiazepines also have been proposed as specific treatment agents for NMS.

One rationale for use of benzodiazepines relies on changes in dopamine activity by indirect actions involving γ -aminobutyric acid systems of the basal ganglia.³ Another basis for use of benzodiazepines in NMS is the clinical similarity of rigidity and autonomic disturbance in both catatonia and NMS.^{6,7} Lorazepam, in particular, is well established as an effective treatment for catatonia.^{3,6}

For these reasons, we believe that lorazepam may have exerted a specific clinical benefit for NMS in the case reported by Drs. Gajwani and Franco-Bronson.

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In reply:

We completely agree with Drs. Yacoub and Francis. In our article, we hypothesized briefly about the role of γ -aminobutyric acid (GABA) affecting dopamine. At the time of the initial preparation of our article (early 2000), the study by Francis et al¹ had not been published. In reflecting on our case, we would certainly agree that lorazepam, a GABA agonist, was quite likely beneficial, although it may not work in all cases.^{2,3} Over the last year, Dr. Carroll⁴ has described a more complete hypothesis, elucidating the helpful role of GABA-A agonists (ie, lorazepam, zolpidem), the negative effect of GABA-B agonists (ie, baclofen), and the influence of dopamine (as well as of glutamate and serotonin). Another agent, amantadine, affects both dopamine and glutamate receptors and has been used concomitantly with lorazepam. However, dantrolene and bromocriptine may still be tried in very difficult patients who have not responded to adequate trials of lorazepam and are unable to undergo electroconvulsive therapy.

In conclusion, we agree with Drs. Yacoub and Francis that advances are being made rapidly and that the awareness of new hypotheses regarding catatonia and neuroleptic malignant syndrome allows for roles of at least 4 neurotransmitters, including GABA-A. Lorazepam's safety and ease of administration has brought it to the level of a first-line treatment choice.

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