# correspondence

## Clozapine in Huntington's disease

**To the Editor:** Bonuccelli et al[1] reported that the administration of clozapine to five patients with Huntington's disease (HD) reduced chorea without producing side effects. Clozapine was incremented at weekly intervals from a dose of 25 mg daily to 150 mg daily. This is an interesting hint that in our opinion is not adequately supported by the evidence provided.

We reviewed the records of eight HD outpatients treated with low doses of clozapine from 1991 on at the movement disorders clinic of the Catholic University. In all but one, clozapine produced appreciable sedation that in most cases was rated as marked. The average (±SD) dose prescribed was 27.34 (±21.63) mg daily; the patients were treated and followed up for an average of 541.75 (±395.74) days; six patients are still on clozapine. In two patients, clozapine successfully controlled aggressive behavior; in two, delusions were attenuated; in three, a reduction of chorea was observed; and in one patient, alcohol intake was also reduced after starting clozapine. Our experience shows that, when given at doses as low as 25 mg daily, clozapine brings about appreciable sedation in HD patients. Based on the common knowledge that chorea is quite sensitive to arousal and to emotional state,[2] we thought that the observed mild benefit on chorea could simply be a nonspecific aftermath of sedation. This view is also confirmed by two other studies. Caine et al[3] observed drowsiness or somnolence in nine of 12 patients treated with clozapine (the dosage was gradually increased to a plateau of 340.42 [±144.56] mg daily). They studied three HD patients: two had a reduction of chorea and somnolence, whereas the third had neither. Sajatovic et al[4] reported that clozapine (up to 175 mg daily) was effective on depression and psychotic symptoms in one HD patient but not on chorea. They did not observe sedation.

Indeed, Bonuccelli et al[1] observed marked somnolence in a patient taking clozapine, but they did not report the dose taken by that patient and did not mention any dose-response correlation. It is rather surprising that they did not observe sedation in any of the remaining four patients, even at doses as high as 150 mg daily. The daily schedule of clozapine was not reported, nor the time of clinical evaluations. (Was it a standard time of day?) Since the patients' reaction speeds and levels of arousal were not evaluated, it may well be that a mild sedation has escaped observation. Considering that chorea is a rather variable dyskinesia, that the number of patients studied was low, and that the study was not blinded, we believe that the reported antichoreic effect of clozapine is not proven data. Finally, we consider that studies such as this should not only compare the drug under study to placebo in double-blind fashion, but they should also compare it to known active drugs (eg, haloperidol) with a crossover design. This would allow more proper differentiation of direct action from the secondary therapeutic effects.

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**Reply from the Authors:** We thank Drs. Colosimo et al for their interest in our findings. They make several criticisms based on a retrospective evaluation regarding eight choreic patients treated with clozapine at low dosages without specifying whether it is a monotherapy or an add-on. This is not an optimal condition for the evaluation of the antichoreic effect of clozapine both because of the low dosages used and because the main objective of the study was to control the psychiatric disturbances associated with chorea. Nonetheless, in three of eight patients, a reduction of chorea was observed, but in seven of eight, an appreciable sedation was present as long as over 2 years after the beginning of treatment. They speculate that the possible antichoreic effect of clozapine could be due to a nonspecific sedative effect of the drug.

The sedative effect of clozapine (present in 20 to 40% of cases) can be noted at the beginning of treatment but disappears with the continuation of treatment (1 to 2 weeks) even with dosages superior to 300 mg/day.[5,6]

In our study, four of five patients presented no degree of sedation. One patient (20% of our series) complained of somnolence at a dosage as low as 25 mg/day, but it was not significant enough to determine the suspension of treatment; moreover, despite the development of tolerance of the sedative effect after approximately 2 weeks, the antichoreic effect persisted. Furthermore, clozapine was administered in two daily doses, and each evaluation was carried out at the same time of day (8 AM) for each patient, before administering the drug, and an effort was made to ensure that the patients were evaluated in the same conditions of environmental stimulation. It is interesting that all patients asked to continue the clozapine treatment at the end of the trial.

In previous studies[7,8] conducted with clozapine for parkinsonian and essential tremor, the antitremor effect of the drug was not correlated to its sedative effect: in some patients, the tremor was reduced or disappeared without inducing sedation; in others, where sedation appeared, the antitremor effect persisted after the development of tolerance of the sedative effect. Moreover, Bennett,[9] in a reply to Quinn,[10] highlighted that his parkinsonian patients treated with clozapine for levodopa-induced dyskinesias[11] had minimal to no daytime sedation during clozapine therapy, despite the fact that they presented a clear antidyskinetic effect and wished to continue clozapine therapy.

Our study[1] for the evaluation of the antichoreic efficacy of clozapine represents one of the more common steps used in the validation of the clinical efficacy of a new drug or of new therapeutic indications for an old drug. It is usual to pass from the indications of the utility of the drug in a single case to open-label studies and/or dose finding on small groups of patients; the results are then further confirmed through double-blind studies on larger groups, first versus placebo, then versus drugs that are known to be active.[12]

We reaffirm that it is necessary to continue the evaluation of the effect of clozapine in patients affected by Huntington's chorea through a comparative study of clozapine versus placebo and versus drugs of certain antichoreic properties, such as haloperidol, the chronic side effects of which are, however, probably greater than those of clozapine.

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## Vertebral artery dissections

**To the Editor:** I read with great interest the article by Gomez et al.[1] While addressing the issue of vertebral dissection in association with trauma associated with occult cervical spine fractures, this article serves as a warning that many trauma victims may be undergoing inadequate investigations of the cervical spine. The litany of complaints from trauma victims, including headache, unilateral neck pain, stiffness, and dizziness, are relatively common. Most often these symptoms do tend to remit within a few days to a few weeks. However, all physicians have had the experience of individuals whose symptoms are of much longer duration and much greater severity. All too often the evaluations include MRIs of the head and cervical spine, with plain x-rays of the cervical spine, and stop there. It should be clear to most clinicians that, given the nature of the study provided, it is possible for small cervical fractures to exist without precipitating vertebral dissection. Such fractures may present with many of the symptoms already described. It is unfortunate but not rare that many patients with these complaints who undergo the standard evaluation are often labeled as somatizing due to the absence of any objective findings. One has to wonder about the actual frequency of upper cervical fractures, occult or just unlooked for. This article may be an indicator that we should be pursuing cervical complaints, even those following mild trauma, with more aggressive investigations.

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**Reply from the Authors:** We appreciate very much Dr. Nieves' comments about our paper.[1] We are concerned, as he is, about the potential implications of our findings, particularly as they relate to patients who may have minor neck injuries and numerous complaints related to them. Obviously, the great majority of victims of mild trauma to the cervical spine will not have occult fractures or vertebral artery dissection. It then becomes a matter of clinical importance to identify those who are likely to be found to have such potentially dangerous sequelae from their accidents. It is our opinion that the greatest asset to the physicians involved in the care of these patients is that of having a high index of suspicion regarding this condition. By maintaining an open mind, one should be able to give patients the benefit of the doubt and have them appropriately evaluated should they develop symptoms suggestive of vertebral basilar ischemia. Along these lines, we must point out that the signs and symptoms of vertebrobasilar insufficiency may be relatively unspecific[2-3] and that it will be important to consider the risk factors and age of a patient with complaints referable to the cervical spine.

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## MRI in Guillain-Barré syndrome

**To the Editor:** We read with interest the recent contribution by Crino et al[1] regarding MRI in Guillain-Barré syndrome (GBS). In a report[2] not cited by the authors, we also studied an adult male patient with GBS and urinary retention who had striking enhancement of the conus and cauda equina on MRI. Unfortunately, the current report does not present figures for comparison. We agree that MRI may allow a means to study patterns of disease in GBS and possibly to monitor therapy. We emphasize that abnormal enhancement of the lumbosacral roots and cauda is entirely nonspecific and found in a variety of conditions outlined in our report and by Crino et al. In addition, we have studied two patients with GBS of similar duration and severity with absolutely *normal* enhanced MRIs (unpublished observations). A prospective analysis, perhaps in the context of ongoing therapeutic trials for GBS, would be of value.

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**Reply from the Authors:** We are pleased to respond to Dr. Perry. At least three groups have now observed gadolinium enhancement on MRI of the cauda equina in patients with GBS.[1-3] However, several issues persist regarding the significance of nerve root enhancement in GBS.

First, the clinical presentation in nearly all reported patients was similar and included back pain, leg weakness, and/or voiding dysfunction. Only two had cranial nerve involvement. In all patients, the clinical diagnosis of GBS was supported by an elevated CSF protein (without a significant pleocytosis) and electrophysiologic evidence of demyelination. These patients represent a rather homogeneous sample of the large clinical spectrum of GBS and thus enhancement of the cauda equina may occur in only one subgroup of GBS patients. Further studies to evaluate the more protean manifestations of GBS are indicated.

Second, only one report[3] demonstrated that resolution of gadolinium enhancement corresponded with clinical improvement. Thus, the duration of enhancement relative to clinical recovery remains unclear and may have implications for monitoring patients in clinical trials of therapies for GBS.

Third, an explanation for gadolinium enhancement of spinal nerve roots in GBS is unknown, although postulated mechanisms include radicular inflammation, edema, and/or compromise of the blood-nerve barrier. Whatever the etiology, we agree with Perry et al that the enhancement of the cauda equina is not specific for GBS and may be seen in a variety of neoplastic, inflammatory, compressive, and infectious conditions. We suggest that MRI of the spinal nerve roots may be useful in monitoring patients with GBS, especially in patients participating in therapeutic trials. Finally, since our initial report, we have also studied one patient with mild GBS (he retained the ability to stand and did not suffer voiding dysfunction) in whom gadolinium enhancement was not detected.

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