

# Letters to the Editor

## Venlafaxine for Pathological Crying After Stroke

**Sir:** Pathological crying after stroke is characterized by outbursts of weeping and tearfulness that are not related to an underlying emotional state, but that can be very distressing to the patient.<sup>1</sup> Disturbed serotonergic transmission is believed to play a role.<sup>2</sup> A number of treatments have been reported as successful, including sertraline,<sup>3</sup> paroxetine,<sup>4</sup> citalopram,<sup>5</sup> fluoxetine,<sup>6</sup> thyrotropin-releasing hormone,<sup>6</sup> levodopa,<sup>7</sup> imipramine,<sup>8</sup> amitriptyline,<sup>9</sup> and nortriptyline.<sup>10</sup> We report the first case of venlafaxine used to successfully treat poststroke pathological crying.

**Case report.** Mr. A, a 67-year-old right-handed man, suffered a hypertensive stroke in 1999 manifested at first by slurred speech and collapse. Computed tomography scan of the head revealed hemorrhage in the left parietal lobe and basal ganglia, compressing the left lateral ventricle, with minimal edema and no midline shift. Also noted were old, small right-sided infarcts with no apparent clinical sequelae.

Mr. A was transferred to the rehabilitation service approximately 2 weeks after his stroke. We were asked to evaluate him at that time for crying spells. He denied any past psychiatric history or past untreated mood symptoms. Since the stroke, he reported having between 5 and 20 crying spells daily that were not associated with any change in mood. He did report feeling distressed by these spells but did not endorse symptoms of depression. He denied episodes of pathological laughter. The Pathological Laughter and Crying Scale (PLACS)<sup>10</sup> was administered, on which the patient scored 14 points.

After informed consent was obtained from the patient, venlafaxine was initiated at a dose of 37.5 mg twice daily. Within 24 hours, the patient reported complete resolution of his crying spells. Follow-up at 2 weeks revealed a score of 0 on the PLACS. We continued to see him at the rehabilitation service and during his stay in the nursing home care unit. Throughout that 6-month period, he remained symptom-free and did not require any increase in dose.

Several tricyclic antidepressants and selective serotonin reuptake inhibitors, as well as other medications, have been reported to dramatically reduce the frequency and severity of pathological crying spells after stroke. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor that may be particularly useful in older patients due to its relatively low protein binding, low anticholinergic effects, low sedation, low orthostatic hypotension, and relatively favorable cytochrome P450 profile.<sup>11,12</sup> While there is the possibility of hypertension with doses over 300 mg daily,<sup>11</sup> which would be a concern in a stroke patient, we found that a low dose of venlafaxine was effective in providing complete relief from this often distressing and embarrassing sequela of stroke.

We considered the possibility that since the patient had a hemorrhagic stroke, he might have had seizures manifested by crying. It is known that seizures occur more commonly with hemorrhagic stroke than with ischemic stroke, particularly when the stroke is cortical in location.<sup>13</sup> Additionally, we know that venlafaxine acts to increase catecholamine levels,<sup>12</sup> and these neurotransmitters have been implicated in having an inhibitory effect on seizures.<sup>14,15</sup> However, the relationship between catecholamines and seizures is complex and not fully understood. Furthermore, venlafaxine has been reported to cause seizures in both rats<sup>16</sup> and humans.<sup>12,17</sup> Most importantly, ictal crying, or dacrytic epilepsy, is quite uncommon, and such crying seizures as a result of stroke are rare.<sup>18</sup>

Another consideration was that the patient may have stopped crying on his own. After examining the evidence, we did not feel that his rapid improvement was due to spontaneous recovery, as he did not regain other functions in such a manner and his dysarthria and right hemiparesis remained even after his lengthy rehabilitation.

There are a few reports in the literature documenting the resolution of pseudobulbar affect within 24 hours of the first dose of medication intended to treat it. We feel that we can now add venlafaxine to the list of possible treatment alternatives.

*Dr. Douglas has received honoraria from and has served on the speakers or advisory boards for Wyeth. Drs. Smith, Montealegre-Orjuela, and Jenkins report no financial affiliation or other relationship relevant to the subject matter of this letter.*

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### Reporting Changes in Scores on the Cohen-Mansfield Agitation Inventory Subscales

**Sir:** The study by Ballard et al.<sup>1</sup> of the effects of aromatherapy in reducing agitation among people with severe dementia is of great interest. Because aromatherapy appeared to work so well, the authors posit a need for multicenter trials. Their statement that current pharmacologic management approaches are not based on evidence from double-blind, placebo-controlled studies is erroneous: some are not, but some are.<sup>2,3</sup> Nevertheless, it may be that aromatherapy will be found to be more effective in some types of disturbed behaviors than in others.

Ballard et al.<sup>1</sup> used the Cohen-Mansfield Agitation Inventory (CMAI) when comparing the effects of aromatherapy against those of placebo. Subscales of the CMAI have been developed: Cohen-Mansfield<sup>4</sup> included 6 (out of 29) CMAI items in a physical aggression subscale, 7 in a physical nonaggression subscale, 8 in a verbal nonaggression subscale, and 4 (screaming, cursing, temper outbursts, and making strange noises) in a verbal aggression subscale. Four items were unallocated. An earlier factor analysis<sup>5</sup> resulted in 3 factors, with screaming loading as a verbally agitated behavior, though a replication study<sup>6</sup> found that screaming and cursing loaded with the physical aggression items.

In the study reported in your journal,<sup>1</sup> a significantly greater reduction in the verbal nonaggression score was noted with aromatherapy than that noted with placebo treatment, but there was no difference between the effects of aromatherapy and placebo on verbal aggression. It was therefore surprising to read that the greatest improvement was noted in the domains of restlessness and shouting and that the authors gave shouting and screaming as examples of verbal nonaggression. Was this really what they meant? They did not state which or how many CMAI

items were included when calculating median scores on the 4 subscales.

In order to better understand the data in trials where changes in CMAI subscale scores are used as outcome measures, it would be helpful if authors would report baseline scores and either the number of items or the range of possible scores for each subscale.

*Dr. Snowdon has received grant/research support from Eli Lilly and Janssen-Cilag, has received honoraria from Janssen-Cilag and Pfizer, and has served on the speakers or advisory boards of Janssen-Cilag and Novartis.*

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### Dr. Ballard Replies

**Sir:** As Dr. Snowdon rightly points out, there are indeed placebo-controlled trials of neuroleptics for the treatment of behavioral problems in people with dementia. This is not, however, in disagreement with what we highlighted in our article, which was that there are no placebo-controlled trials specifically in people with severe dementia, which in our view is a major oversight, as this is the group of individuals with the highest frequency of agitation.

Dr. Snowdon makes some interesting points regarding possible mechanisms for improving the reporting of studies utilizing the Cohen-Mansfield Agitation Scale as a primary endpoint. While we will take forward some of these helpful suggestions to further clarify the profile of improvements in the patients treated with aromatherapy, we would also like to clearly state that minor differences in methods for data evaluation clearly cannot explain the large differences between aromatherapy with *Melissa* and with placebo that were identified in our double-blind, placebo-controlled trial.

*Dr. Ballard reports no financial affiliation or other relationship relevant to the subject matter in this letter.*

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### Oral Magnesium Ion Shortens Prolonged QTc Interval

**Sir:** Prolonged QTc interval on the electrocardiogram (ECG) is not an unusual finding in patients hospitalized for mental illness.<sup>1</sup> Prolonged QTc interval may forewarn of torsades de pointes, a ventricular tachycardia that can result in sudden death.<sup>2</sup> Conventional treatment with beta-blockers often is not effective. We have observed that magnesium ion (Mg<sup>++</sup>) administered orally can safely return a prolonged QTc interval to normal.

The American Heart Association recommends an intravenous injection of magnesium sulfate, as much as 2 g over 2 minutes, to treat torsades de pointes.<sup>3</sup> It seemed reasonable that a smaller dose of Mg<sup>++</sup>, given orally, might correct the cardiac abnormality preceding torsades, namely, a prolonged QTc interval. Thus our first patient came to be treated with oral Mg<sup>++</sup>, and his QTc interval returned to normal.

Over the next 3 years at Eastern Oregon Psychiatric Center (EOPC), 23 additional patients with prolonged QTc intervals were similarly treated, which was viewed as patient care and not as a research project. However, a chart review now suggests that what we observed might prove to be widely useful in psychiatric practice and should be reported, even though we had not planned it as research, and there were no controls.

Table 1 shows 25 observations in 24 patients: 11 women and 13 men, mean age = 43.3 years. Psychiatric diagnoses and respective numbers of patients were schizoaffective disorder, N = 11; schizophrenia, N = 7; bipolar disorder, N = 2; other disorders, N = 4. No patient had hypokalemia, congenital long QTc syndrome, or renal disease. Four patients had cardiac disease controlled by medication.

Patients were being treated with a wide variety of antipsychotic medications, many of which cause prolonged QTc intervals.<sup>4</sup> Several drugs used in general medicine can do likewise.<sup>5</sup> If more than one such medication is used, the effect on the QTc is additive.

Mg<sup>++</sup> was given orally as magnesium oxide (MgO). The mean daily dosage was 15 mg/kg (range, 6–35 mg/kg). Dosage median was 14 mg/kg and mode was 8 mg/kg. Dosages were within the range of MgO as used for other medical conditions. Duration of treatment varied from a few weeks to many months. During MgO treatment, serum Mg<sup>++</sup> levels remained within normal limits. Loose stools occurred in 3 patients.

We monitored the QTc interval (the QT interval corrected for heart rate by Bazett's formula,<sup>6</sup> calculated automatically by our MAC 1200 ECG machine [General Electric Medical Systems, Marquette Division, Milwaukee, Wis.]). To establish persistence, at least 2 ECG tracings were obtained before using oral Mg<sup>++</sup>. Each "before Mg<sup>++</sup>" reading in Table 1 represents an average of the baseline readings. Follow-up ECGs were done at various intervals. A decrease in QTc was usually seen 24 to 48 hours after starting MgO. If it was not, or if the response was judged to be insufficient, the dosage of MgO was raised, and the QTc was monitored.

At EOPC the upper limit of normal for QTc is 0.430 seconds. The mean (95% confidence limits) QTc of the group of patients prior to MgO was 0.489 (0.473, 0.505) seconds. The mean (95% confidence limits) QTc after MgO was 0.420 (0.407, 0.433) seconds. A t test shows the difference between the means to be significant:  $p < 5 \times 10^{-7}$ .

Patient 3 (Table 1), who appears as an exception, actually showed some lowering of his QTc in response to Mg<sup>++</sup>, but after a few days, the patient's QTc returned to higher values. An increased dose of MgO was given, again with a QTc shortening,

Table 1. Effects of Oral Magnesium Ion (Mg<sup>++</sup>) on QTc Interval

Patient No.	Age, y	Sex	On Beta Blocker	Dose MgO (mg/kg)	QTc Before Mg <sup>++</sup> (sec)	QTc After Mg <sup>++</sup> (sec)
1	21.8	M	no	8	0.475	0.412
2	57.8	M	yes	10	0.474	0.402
2a			yes	28	0.613	0.402
3	44.8	M	no	16	0.480	0.520
4	64.3	M	no	10	0.471	0.413
5	47.1	F	yes	17	0.490	0.438
6	41.0	M	no	17	0.530	0.440
7	98.5	F	no	8	0.520	0.470
8	45.7	M	yes	18	0.606	0.401
9	40.9	M	no	14	0.483	0.443
10	21.9	M	yes	35	0.450	0.360
11	52.8	F	yes	9	0.460	0.428
12	26.0	F	no	26	0.472	0.430
13	38.3	F	no	13	0.480	0.401
14	35.0	M	no	18	0.479	0.398
15	20.4	F	no	26	0.520	0.447
16	75.0	F	no	8	0.480	0.380
17	43.3	M	yes	8	0.461	0.429
18	50.4	M	yes	6	0.469	0.370
19	39.0	M	no	16	0.470	0.412
20	18.9	F	no	14	0.490	0.440
21	42.2	M	no	8	0.465	0.412
22	40.4	F	no	10	0.459	0.413
23	35.8	F	no	11	0.485	0.409
24	36.9	F	no	19	0.454	0.432
All patients						
Mean					0.489	0.420
SD					0.040	0.032
95% CI					0.016	0.012

Abbreviations: CI = confidence interval, MgO = magnesium oxide.

but again the improvement was not sustained. In his case, the dose of MgO was not increased further.

Despite taking beta-blockers, 8 patients had prolonged QTc intervals prior to oral Mg<sup>++</sup>. Adding Mg<sup>++</sup> to their therapy also decreased the QTc interval in these cases.

Decreasing the dosage of or stopping a QTc-prolonging drug may normalize a prolonged QTc interval. Medication discontinuation can be a risk for psychiatric relapse when a previously nonresponding patient is currently improving with a particular combination of psychiatric medications. Use of oral Mg<sup>++</sup> often enabled the psychiatrist to maintain his treatment of choice. Thus, patient 1 was started on lithium treatment on 2 occasions. Each time, he developed a prolonged QTc interval, and lithium had to be stopped. When oral Mg<sup>++</sup> was administered, he was able to take lithium at the full therapeutic dosage without QTc prolongation developing.

Oral Mg<sup>++</sup> appears to be safe and effective in shortening prolonged QTc intervals. A prospective study using controls will be necessary to verify this thesis.

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### Improvement in Negative Symptoms of Schizophrenia With Antibodies to Tumor Necrosis Factor-alpha and to Interferon-gamma: A Case Report

**Sir:** In 1974, one of us (S.V.S.) proposed that a disturbance in cytokine synthesis may lead to various autoimmune diseases and that the removal of these cytokines could be therapeutic.<sup>1</sup> We also proposed to remove tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) together with certain types of interferon from patients with autoimmune diseases.<sup>2</sup> Cytokine abnormalities typical of autoimmune disorders have been reported in patients with schizophrenia, including interferon- $\alpha$  in the cerebrospinal fluid,<sup>3</sup> elevated TNF- $\alpha$  in the serum,<sup>4</sup> and reduced in vitro production of interferon- $\gamma$ .<sup>5</sup> Recently, significantly elevated TNF- $\alpha$  levels in late pregnancy were connected with greater odds of subsequent development of schizophrenia in offspring.<sup>6</sup> One of us (S.V.S.) has already proposed treating schizophrenia with anticytokine therapy.<sup>7</sup>

**Case report.** To test the effect of an anticytokine therapy in schizophrenia, polyclonal antibodies to TNF- $\alpha$  and to interferon- $\gamma$  were administered to Mr. A, a 56-year-old male patient with residual schizophrenia (DSM-IV). At admission, the patient's attire was not consistent with his age and social status, and he was unkempt. He appeared withdrawn and bored and was spending long periods of time in bed without expressing any interest in his surroundings. His status was characterized mainly by negative symptoms such as flat affect, decreased level of expressivity and gesticulation, emotional flatness, and lack of desire to be involved in social events. Cognitive disturbances were characterized by amorphous and inconcrete thought processes. Mr. A also showed cyclothymic changes involving periods of hypomania and depressive symptoms. No somatic symptoms, such as infections, were observed at admission.

Before beginning anticytokine therapy, the patient was maintained on haloperidol, 10 mg, and biperiden, 4 mg, daily. Anticytokine therapy was started after a 7-day washout period. No psychotropic or other drugs were given during the anticytokine therapy.

The level of TNF- $\alpha$  in the patient's blood was 26 pg/mL prior to therapy as tested by ELISA (R&D Systems, Minneapolis, Minn.). Interferon- $\gamma$  was not detected in the patient's blood, but it was speculated that it could be on the surface of the cells. On receiving written consent of the patient, 2 mL each of polyclonal anti-TNF- $\alpha$  and anti-interferon- $\gamma$  antibodies (IgG) (interferon- $\gamma$  and TNF- $\alpha$  neutralizing activity > 66  $\mu$ g/mL as determined by

cell growth inhibition assays) were injected intramuscularly twice daily for 5 successive days. Mr. A's clinical condition was evaluated by a psychiatrist using the Positive and Negative Syndrome Scale (PANSS)<sup>8</sup> on days 0, 5, 12, 19, 26, and 34. Initial PANSS scores were characterized by high negative symptom scores: blunted affect, 5; emotional withdrawal, 5; and passive apathetic social withdrawal, 5. Results on the scale of general psychopathology were characterized by increased scores for depression (5), motor retardation (3), will disturbance (5), and active social withdrawal (3).

By the evening of day 1 of treatment, the patient experienced a substantial increase in energy and improvement in mood. He became friendly and sociable and willingly entered into conversations with other patients and personnel. Subsequently, his mood continued to improve, his level of physical activity and expressive abilities rose, his initiative increased, and he showed a need for activity. Marked changes were observed already by the end of the first week, with behavioral disturbances improving faster than cognitive disturbances.

Mr. A's clinical status was characterized by a very notable decrease in negative symptoms on the PANSS. For example, by the fifth day, the patient's blunted affect score had decreased from 5 to 3; emotional withdrawal, from 5 to 2; passive apathetic social withdrawal, from 5 to 2; depression, from 5 to 3; motor retardation, from 3 to 2; will disturbance, from 5 to 4; and active social withdrawal, from 3 to 2. Subjectively, the patient experienced improvement as well, becoming more active, lively, and interested in activities on his ward and in his surroundings, and he started socializing with other patients. His behavior became more orderly. PANSS scores did not change between day 5 and day 12 except for a 1-point increase in the depression score. By day 34, there was little change except that the patient's blunted affect score increased from 3 to 4; emotional withdrawal, from 2 to 3; and depression, from 3 to 4.

By day 15 since the start of therapy, the patient's circulating TNF- $\alpha$  had dropped to 1 to 2 pg/mL and remained low until beginning to climb on day 31 (Figure 1). On day 12, Mr. A developed hives.

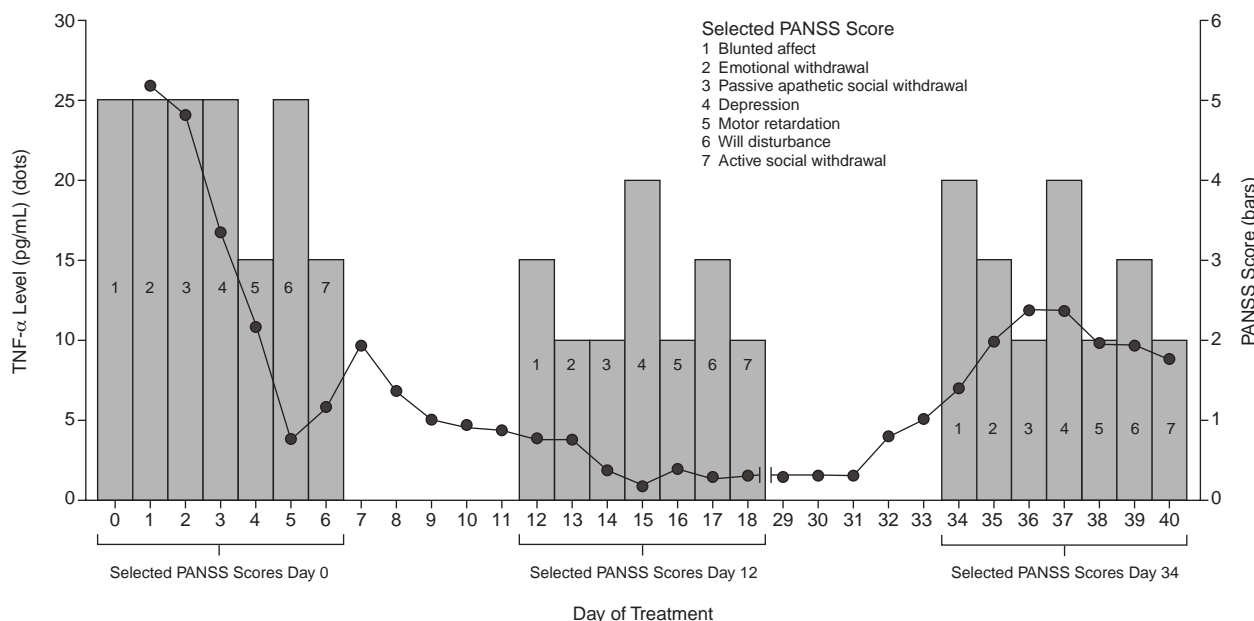
Thus, we observed clinical improvement as measured by changes in PANSS scores of negative symptoms. Motor retardation improved at the beginning of therapy and then remained unchanged throughout the remainder of the period of observation. Scores of will disturbance and active social withdrawal had decreased already toward the end of the first week and later neither decreased nor increased.

A clear association was shown between administration of the 2 antibodies and reduction of negative symptoms in the patient. It was not clear which antibody was responsible for this effect, anti-TNF- $\alpha$ , anti-interferon- $\gamma$ , or both together, although a TNF- $\alpha$  correlation was strong.

Autoimmune diseases, possibly including schizophrenia, may have in common disturbed cytokine synthesis but differ in the clinical manifestations depending on the cells in which the disturbance occurs. We achieved significant clinical effects in treating patients with rheumatoid arthritis and multiple sclerosis with antibodies to interferon- $\gamma$ , though interferon- $\gamma$  was not detected in the blood of most patients.<sup>9,10</sup> Anti-TNF- $\alpha$  is now commercialized for treating rheumatoid arthritis. TNF- $\alpha$  and interferon- $\gamma$  work closely together, and interferon- $\gamma$  can induce TNF- $\alpha$ .

Schizophrenia may result from genetic and environmental interactions. There may be a loss of the TNF- $\alpha$ , interferon- $\gamma$ , or other cytokine transcriptional repressors, leading to a hyperproduction of cytokines, which damages certain brain cells.

**Figure 1. Tumor Necrosis Factor (TNF)- $\alpha$  Levels and Positive and Negative Syndrome Scale (PANSS) Scores in a Patient With Residual Schizophrenia Before and After Anticytokine Treatment<sup>a</sup>**



<sup>a</sup>Anticytokine therapy (anti-TNF- $\alpha$  and anti-interferon- $\gamma$  antibodies) was given on days 1 through 5.

A more prolonged therapy, using humanized monoclonal antibodies to interferon- $\gamma$  and to TNF- $\alpha$ , and possibly to interferon- $\alpha$  and to IL-6, separately or combined, may lead to more pronounced and long-lasting improvement. The marked effects found in 1 patient encourage further pursuit of an anticytokine therapy in treating schizophrenia.

*Polyclonal antibodies to interferon- $\gamma$  and TNF- $\alpha$  were provided by Advanced Biotherapy, Inc., Woodland Hills, Calif.*

*Drs. S. V. Skurkovich and B. Skurkovich are officers, board members, and shareholders of Advanced Biotherapy Inc.*

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