## Acute Dystonia Caused by Low Dosage of Olanzapine

*SIR*: Clinical studies have shown that although olanzapine has a low frequency of extrapyramidal and neuroendocrine side effects, it may cause acute extrapyramidal symptoms,[1,2] and it appears to be intermediate between risperidone and clozapine in inducing such symptoms. We report two cases of patients who developed acute dystonia while receiving the lowest therapeutic dose, 5 mg/day, of olanzapine.

**Case Reports**

**Case 1**. Mrs. M is a 56-year-old woman with a 20-year history of paranoid schizophrenia. She had previously been treated with haloperidol and trifluoperazine but experienced severe parkinsonism, akathisia, and oculogyric signs, which were controlled with biperiden 12 mg/day. After moderate improvement in her psychotic symptoms, Mrs. M switched to thioridazine 100 mg/day, tapered to 50 mg/day, plus biperiden 4 mg/day. Thioridazine was replaced by olanzapine, starting at 5 mg/day and increasing over 5 days to 10 mg/day. Even at the dose of 5 mg/day, she presented with torticollis and oculogyric signs, and with the dose of 10 mg/day, she manifested akinesia, stiffness, lingual dystonia, and dysarthria, which were not adequately controlled with benzhexol 15 mg/day. She resumed treatment with thioridazine, at 100 mg/day, with benzhexol 10 mg/day; she still manifested oculogyric crises at times. No dystonic symptoms had occurred after previous reductions of neuroleptic dosages.

**Case 2**. Mr. T is a 50-year-old man with schizophrenia since the age of 33. Several trials of antipsychotics had not been effective, and he had experienced severe extrapyramidal symptoms after taking neuroleptics. Recently he had been treated with risperidone 2 mg/day and biperiden 2 mg twice a day. This treatment was discontinued and, after 2 days, olanzapine 5 mg/day was begun. However, a few hours after taking the drug, a disturbing acute dystonic reaction occurred with lingual dystonia and dysarthria, spasm of the patient's neck muscles, and severe torticollis, relieved within 2 hours with biperiden 4 mg and orphenadrine 50 mg orally. Olanzapine was discontinued, and Mr. T resumed treatment with risperidone 2 mg/day and biperiden 2 mg three times a day.

**Comment**

To our knowledge, this is the first report of acute dystonia caused by the lowest therapeutic dose of olanzapine (5 mg), suggesting that olanzapine, despite its chemical and pharmacologic similarities to clozapine, has the potential to cause acute extrapyramidal symptoms even at a very low dosage. In keeping with a previous report,[2] the high propensity of both of these patients to manifest extrapyramidal symptoms during previous treatment with antipsychotics placed them at a higher risk of manifesting acute dystonic reactions. Doses of 5 mg of olanzapine show $D_2$ occupancy of 43%–64%,[3] while the occupancy threshold for obtaining antipsychotic action lies in the range 65%–70%. These unwanted effects are unusual, but they may give a good measure of tolerability of the new antipsychotics beyond the premarketing trials.[4] Clinicians should consider the possibility of the development of acute dystonia in susceptible individuals even with doses insufficient to obtain a true antipsychotic action.

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## Dissociative Symptoms From Combined Treatment With Sertraline and Trazodone

*SIR*: The combined use of sertraline and trazodone is common practice and usually well tolerated. This report highlights the potential for

cognitive impairment and dissociation as adverse effects of this combination.

**Case Report**

Our patient is a 40-year-old active-duty married white female airman who was treated with sertraline 100 mg/day and trazodone 50 mg/night for 1 year for her first episode of major depressive disorder. She was symptom free for 6 months on this regimen when she transferred her care to our clinic. Her medical history and mental status examination were unremarkable, and her medications were continued without change.

During the next year, she developed a number of concerning symptoms. Most prominent was the complaint of "lost and slowed time." She also described poor concentration, low motivation for self-care, anorexia, and apathy. As her condition worsened, she was briefly hospitalized, and her sertraline dosage was increased to 200 mg/day. Depressive symptoms improved, but the patient experienced worsening time distortion and complained of "buzzing" in her ears, orthostatic light-headedness, and frequent nausea. She reported headaches, "stabbing" upper extremity pain, tremulousness, and word-finding difficulties, and she frequently got lost while driving to familiar places. Her Air Force supervisors reported new-onset emotional instability, inability to progress in qualification training, inability to meet duty expectations, difficulty learning new tasks, and frequent tardiness. She had previously been described as "a very dedicated" airman with 18 years of successful service. Psychological testing found no evidence of a personality disorder and supported the diagnosis of depression. Results from a repeated battery of metabolic tests were normal. Magnetic resonance imaging of the brain was normal, and neurological consultation produced no diagnosis. Sertraline was discontinued and all depressive, dissociative, and neurological symptoms immediately resolved. Trazodone was then discontinued. At the time of discharge from outpatient treatment, the patient had been medication free for 1 year and reported no further depressive symptoms.

**Comment**

This patient displayed several dose-related side effects of combination therapy with sertraline and trazodone. The precise mechanism by which this patient's symptoms developed is unclear. Possibilities include the serotonergic activity of sertraline, the serotonergic activity of trazodone or its metabolite meta-chlorophenylpiperazine (mCPP), or the synergistic activity of the combination. mCPP is a potent direct 5-$HT_2$ serotonin agonist. The serotonin agonist activity of trazodone is related to the degree of mCPP accumulation.[1] Administration of mCPP is known to produce anxiety, derealization, and depersonalization.[2]

Serotonergic hallucinogens such as lysergic acid diethylamide, mescaline, and dimethyltryptamine also produce dissociative symptoms via their stimulation of 5-$HT_2$ receptors.[3,4] Furthermore, serotonergic systems heighten sensory processing via the 5-$HT_2$ receptor. Some suggest that dissociation may result from excessive serotonergic activation at the thalamic level, resulting in interference of sensory transmission.[5] Others suggest that hippocampal overstimulation is responsible for dissociative phenomena.[6] The symptoms in this patient may have been caused by an increase in serotonergic activity at thalamic or hippocampal sites, leading to a disturbance of sensory integration and subsequent dissociative symptoms, lending support to the physiological disconnection model of dissociative experience.[5]

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## Favorable Effect of Milnacipran on Depression Induced by Interferon-Alpha

*SIR*: Milnacipran is a novel serotonin and noradrenaline reuptake in-

hibitor. To our knowledge, this is the first report of a patient whose depressive symptoms induced by interferon ameliorated by treatment with milnacipran.

**Case Report**

A 71-year-old man with no history and no family history of psychiatric disorders was admitted to our hospital for renal cancer. He underwent surgery for removal of his left kidney and of a metastatic focus in a lumbar spinal process. One month after the operation, intramuscular injections of interferon-α-2a were started at a dosage of 3 million units three times weekly. One week after the start of interferon therapy, he started to complain of depressive mood, lassitude, and irritability. The dosage of interferon was reduced to 3 million units once a week, and trazodone 100 mg/day was prescribed. Four weeks after beginning the trazodone, the patient's irritability remitted and his depressive mood lessened. His lassitude remained unchanged.

The patient's depressive mood increased during the 2 or 3 days following the interferon injections, and he requested another reduction in the dosage of interferon. It was reduced to 3 million units once monthly, but the patient's depressive mood remained, and it increased during the 2 or 3 days following the injection. We suggested an increase in the dosage of trazodone, but the patient refused because of the side effect of thirst. We suggested trying a different antidepressant, namely, milnacipran, and the patient agreed. The trazodone dosage was reduced to 50 mg/day, and milnacipran 50 mg/day was started. Two weeks later, the trazodone was stopped and the milnacipran dosage was increased to 75 mg/day. One week after the start of the new prescription, the patient's thirst lessened. Four weeks afterward, his depressive mood and lassitude disappeared completely. His mood did not deteriorate during the 2 or 3 days following interferon injections. More than 1 year has passed since his operation. His cancer and depressive symptoms have not returned.

**Comment**

Interferons have both antiviral and antineoplastic properties that allow them to be used to treat a variety of medical conditions.[1] Symptoms of depression are frequently seen in patients receiving treatment with interferon-α,[2] and treatment of the depression is a matter of concern in clinical practice. Kamata et al.[3] examined the effect of a single intracerebroventricular injection of interferon-α on monoamine concentrations in the rat brain. They found that the levels of serotonin and noradrenaline were reduced in a dose-dependent manner in the frontal cortex. These neurochemical changes are possible mechanisms of depression induced by interferon. In our patient, trazodone 100 mg/day was partially effective, and milnacipran 75 mg/day was completely effective. The primary pharmacological action of trazodone is a blockade of 5-$HT_2$ postsynaptic receptors.[4] The primary pharmacological action of milnacipran is a dual reuptake-inhibition of serotonin and noradrenaline.[5] Given the neurochemical changes reported by Kamata et al.,[3] an antidepressant that activates both serotonin and noradrenaline neurotransmission may be more effective for depression induced by interferon-α.

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## Counterintuitive Antidepressant Properties of Slow rTMS Over the Left Frontal Cortex: A Possible Mechanism

*SIR*: In the summer 2002 issue of the *Journal*, Rosenberg et al.[1] reported antidepressant effects after both slow (1 Hz) and fast (5 Hz) repetitive transcranial magnetic stimulation (rTMS) over the left frontal cortex (FC) in patients with posttraumatic stress disorder (PTSD) and comorbid depression. There were no therapeutical differences between the effects of slow and fast rTMS, which is in fact a striking observation. Depressive symptoms are often accompanied by hypoactivity of the left FC, and there is ample evidence that slow rTMS causes neural inhibition, whereas fast rTMS results in neural excitation of the targeted regions. Thus, the widely applied and obvious parameter in studies of treat-

ment for depression is the higher frequency. Moreover, it has been demonstrated in rTMS neuroimaging studies that fast rTMS leads to normalization of left FC hypometabolism. Only a study by Klein et al.[2] used slow rTMS, but they targeted the right FC, assuming that depression is accompanied by an imbalance in neural activity between the left and right FC, favoring the right. Dampening the right FC activity by slow rTMS would restore homeostasis.

When theorizing on the basis of these findings, the antidepressant effects of slow rTMS over the left FC in the Rosenberg et al. study are counterintuitive. The interpretation the authors provided in terms of rTMS effects adjunctive to antidepressant medication and different patient populations is insufficient to explain their paradoxical finding. A more plausible explanation is that slow rTMS restored the functional connectivity in a cortico-cortical depression circuit[3] that connects the left FC with right parietal cortex (PC). This functional connectivity between different cortical areas can be measured by means of EEG coherence analysis.

Interestingly, a recent endocrinological study published in the fall 2001 issue of the journal demonstrated an inverse relationship between the functional connectivity of the left FC and right PC and cortisol, a biochemical marker for depression.[4] This finding suggests that the functional connectivity in this cortico-cortical circuit is reduced in depression. It should be noted that the functional connectivity between different brain areas is not entirely dependent on cortical arousal, indicating that temporal coupling can be modulated without dramatic changes in activity. Crucially, it has been demonstrated that rTMS over the left FC is capable of the modulation of functional connectivity with the right PC.[5] Working from a model comprising the above-noted depression circuit and the assumed capability of slow rTMS to influence functional connectivity, a recent placebo-controlled study by van Honk and Schutter[3] demonstrated reductions in phenomenological, attentional, and physiological indices of depression after slow rTMS over the right PC. The latter findings are in line with our cortico-cortical depression circuit hypothesis[4] and concur with the slow rTMS results of Rosenberg et al.[1]

In sum, one of the mechanisms by which rTMS studies have established antidepressant effects is the normalization of hypometabolism in the left FC. However, the slow rTMS findings of Rosenberg et al. more likely involve the restoration of the functional connectivity in a left FC–right PC cortico-cortical depression circuit.

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## In Reply

*SIR*: Schutter et al. present an intriguing and testable hypothesis regarding how and why slow rate (1 Hz) rTMS may be effective for treatment of depression. They suggest that a cortical circuit involving left frontal and right parietal regions is important in depression and that decreased functional connectivity between these regions occurs in depression. They suggest that slow rate magnetic stimulation rather than improving local left frontal cortical function enhances the connectivity of this region with the opposite parietal cortex.

Our finding of a therapeutic effect of slow left frontal stimulation is only "counterintuitive" if left frontal hypofunction is a marker of depression and slow rTMS further causes neural inhibition. In fact, results of functional imaging in depressed patients are not highly replicable and may differentiate subgroups of patients. For instance, a study using single photon emission computed tomography in refractory depressed patients showed hypoperfusion in the inferior frontal, anterior temporal, and anterior cingulate.[1] How does slow rTMS to the dorsolateral frontal cortex modulate this network of altered function? Our patients were suffering not only from refractory depression but also from long-standing post-

traumatic stress disorder (PTSD); which networks (cortical-cortical, cortical-subcortical, cortical-limbic) have altered function? How do these networks interact with the dorsolateral frontal region? How does rTMS at slow or fast rates alter function in the stimulated region and in networks connected to the stimulated region?

As Schutter et al. suggest, data are just beginning to accrue on how rTMS may alter functional connectivity. Jing and Takigawa[2] showed that directed coherence between cortical regions increased after rTMS, particularly in the direction from frontal to parietal; however, they studied only normal subjects after limited rapid (10 Hz) rTMS, and their findings were larger within the hemisphere than between hemispheres. It remains a stretch from this observation to enhancement of left frontal to right parietal functional connectivity. In a more recent study, Strens et al.[3] showed that subthreshold slow (1 Hz) rTMS over the motor cortex increased ipsilateral cortico-cortical coherence and increased coherence between left and right motor cortices. The effects lasted up to 25 minutes after a single session of 1,500 stimuli. However, there are no published data on changes in coherence after a typical course of rTMS treatment of depression (usually 10 treatments over 2 weeks).

We thank Schutter et al. for their hypothesis, which moves the concepts behind rTMS treatment beyond simply altering neuronal excitability in brain regions near the stimulator and moves them into the realm of altering cortical connectivity. We would merely point out the many questions that remain to be answered both with respect to the underlying pathophysiology of depression and PTSD and the mechanisms of brain function modulation by rTMS.

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## A Lesion Approach to Neurobiology of Dissociative Symptoms

*SIR*: Dissociative symptoms such as depersonalization and derealization, though described in neurological conditions, occur infrequently in stroke, and most reports of "organic" depersonalization are limited to seizures and migraine, which often are without neuroimaging correlates.[1] Thus stroke, with its demonstrable focal lesion, provides valuable insights into the neurobiology of dissociative symptoms.

**Case Report**

A 71-year-old woman with history of hypertension, type 2 diabetes mellitus, and two prior episodes of transient ischemic attacks, presented to the emergency department with an episode of "getting disoriented." While driving, the patient suddenly felt that the route seemed unfamiliar, and she inadvertently took a wrong exit, which was brought to her attention by her companions. Meanwhile, she also felt that something was wrong with her own person, as her mind went blank and she felt as is she was in a daze. The whole episode lasted half an hour. In the emergency department, the patient recalled that the trees around the route looked "different" and that everything was happening effortlessly with her being a passive spectator. She denied any changes in perception of color, sound, and recognition of faces and had no neglect symptoms. Her neurological examination was unremarkable except for left inferior quadrantanopia. Magnetic resonance imaging of the brain showed new infarcts in the right occipital cortex, right thalamus, and head of right caudate. The patient had an uneventful hospital stay without recurrence of these symptoms.

**Comment**

The patient's symptoms are redolent of derealization and depersonalization. Although lesions of the occipital cortex have been reported in patients with dissociative symptoms, only rarely has involvement of thalamus been reported.[1] Thalamic hypofunction has been shown in disorders associated with dissociative symptoms such as posttraumatic stress disorder (PTSD).[2] While the involvement of the visual cortex with the resultant visuo-limbic disconnection may in part explain the symptoms of derealization,[3] thalamic dysfunction may contribute to depersonalization by interfering with the initial processing of perceptual information about the "self." This hypothesis is explored below.

The parietal lobe is one of the regions involved in generating the body schema,[4] and the thalamo-cortico-thalamic loop is implicated in "conscious awareness" in the perceptual domain.[5] The corticothalamic synapses (including those from the parietal lobe) on the relay nuclei of the bilateral thalami are

excitatory and enhance the transmission of peripheral information toward the cortex. The output of the thalamus, however, is to the cortex of the same side.[6] Thus, with the infarction of right thalamus, as in this patient, one speculates a possible corticopetal disconnection between the right thalamus and the right parietal lobe, which in turn reduces the feedback cortical enhancement of the thalami. This may result in a compensatory overactivity in the parietal lobes, thus interfering with the flow of "relevant" information into the thalami and impairing their sensory gating function.[5] The overactivity in the parietal region is supported by a recent positron emission tomography study that showed increased activity in the parietal somatosensory association area in patients with depersonalization disorder.[4] Hence, as highlighted by some investigators,[3] depersonalization and derealization may have separate neuroanatomical correlates, which needs further exploration. Interestingly, glutamate, which is known to increase after stroke and environmental stress, is speculated to cause dissociative symptoms in PTSD,[7] a notion favored by this report.

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## Intermetamorphosis in a Patient With Alzheimer's Disease

*SIR*: Intermetamorphosis is a misidentification syndrome in which familiar persons are believed to have exchanged identities.[1] We report a patient with clinically probable Alzheimer's disease who developed intermetamorphosis for several members of his family. Analysis of this patient's disturbance suggests abnormal processing between the normal face recognition units and the person identity node in the inferior temporal lobe.[2–4]

**Case Report**

A 76-year-old right-handed man had a 3-year history of progressive decline in memory and cognition. His medical history was remarkable only for prior ethanol abuse. The patient had undergone an evaluation for dementia, including neurological examination, laboratory tests, and neuroimaging. Magnetic resonance imaging was significant only for prominence of the temporal horns of the lateral ventricles, suggesting bilateral mesial temporal atrophy, and he was diagnosed with clinically probable Alzheimer's disease.

About 2 years into his illness he began misidentifying family members. Initially, he misidentified his wife as his deceased mother and, later, as his living sister. His substitution of his sister for his wife became firmly established and could not be corrected with explanation. When confronted, he subsequently claimed that he had never been married or that his wife had left him. Gradually, the patient began misidentifying his son as his brother, his daughter as another sister, and his granddaughter as his daughter. These misidentifications persisted even on the telephone. Moreover, on different clinic visits he described the hospital as a meeting hall or a church where he visited to socialize or to help out.

On examination he was cooperative, attentive, and euthymic. His Mini-Mental State Examination Score was 16 (out of 30), and his examination showed deficits in verbal fluency, confrontation naming, delayed recall, complex constructions, and abstractions. The elementary neurological examination was otherwise normal.

We tested the patient with photographs of familiar persons from a photo album. Positive responses were counted when the photo subjects were positively identified or named. The control was his wife, who scored 100% correct answers. The results showed 100% misidentification of his wife as his sister in photographs with 100% persistence of the misidentification over the past without a retrograde gradient, and correct identification of himself through different ages. He did not have prosopagnosia (he recognized 80% of the photographs) and could recognize his own face in a mirror.

**Comment**

We present a rarely described intermetamorphosis syndrome occurring

in a patient with Alzheimer's disease. The patient did not have facial recognition difficulty, a temporal memory gradient for recalling familiar faces, or a failure to integrate prior memories of familiar faces with currently perceived faces. The misidentifications were not limited to the visual modality, as they occurred with the persons' voices as well. This points to a preservation of the abnormal "person identity nodes" across time and across modalities.

These findings, as well as the reduplicative misidentification of the hospital, suggest an inability to correctly identify the source of his sense of familiarity for family members as a result of temporal lobe disease. Frontal lobe dysfunction also may contribute to his misattribution of identity.[5]

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