

# October

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## HAIR LOSS DUE TO LAMOTRIGINE

*Previous "Psychopharmacology Reviews" columns have discussed the use of lamotrigine for bipolar disorder,<sup>1,2</sup> refractory unipolar depression,<sup>3,4</sup> treatment-resistant schizophrenia,<sup>5</sup> posttraumatic stress disorder,<sup>6</sup> frontal lobe dementia,<sup>7</sup> and post-stroke pathological laughing and crying.<sup>8</sup> Lamotrigine is an anticonvulsant that blocks voltage-gated sodium channels where it inhibits the excessive release of the excitatory amino acids glutamate and  $\gamma$ -aminobutyric acid.<sup>9</sup> In addition to its actions on ion channels, lamotrigine weakly inhibits monoamine transporters. At a concentration of 100–1,000 nM, lamotrigine is an inhibitor of 5-hydroxytryptamine uptake in both rat and human tissues.<sup>10</sup> At similar concentrations, lamotrigine also inhibits norepinephrine and dopamine uptake into rat brain synaptosomes. Now comes a report of a woman with bipolar disorder who developed hair loss as a side effect of lamotrigine.<sup>11</sup>*

A 63-year-old woman was admitted to an inpatient psychiatric unit after developing an episode of bipolar depression. During her hospitalization, from August to September 2003, lamotrigine was initiated. After discharge, lamotrigine was increased gradually to 150 mg/day. Her only other medication consisted of eye drops containing hypromellose. Two to three weeks after beginning lamotrigine, she reported an increase in hair loss, mainly located in the region of the temporal bone. Hemogram and other routine laboratory tests were normal. In November 2003, a classical hair root examination known as the trichogram made by an external consultant dermatologist showed an increase of resting (telogen) and dystrophic hair at the expense of growing (anagen) hair. Due to the probable association of the reported alopecia with lamotrigine, the treatment was discontinued, which resulted in a rapid regression of hair loss.

The temporal sequence of events suggests lamotrigine as the cause of this woman's hair loss. According to the package insert for lamotrigine,<sup>12</sup> alopecia is an infrequent adverse event, occurring in 1/1,000–1/100 patients.

A prior published report<sup>13</sup> of hair loss in a patient treated with lamotrigine exists; however, in that case magnesium val-

proate was also being administered and, given the frequency of its association with alopecia, was implicated as the most likely cause of that patient's telogen effluvium.

Drug-induced alopecia involves an interruption of hair growth when the hair follicles prematurely enter into the resting phase.<sup>14,15</sup> While the mechanism is not known, some have suggested that these medications may chelate zinc and selenium, which are believed to be necessary for hair growth. Generally commencing within 3 months of initiating therapy, alopecia is typically reversible upon dosage reduction or discontinuation of the offending drug.<sup>14,15</sup> Other options for managing this side effect include waiting for accommodation to occur or the use of zinc and selenium.<sup>16</sup> Whether this patient was predisposed to this effect is not known. Nonetheless, it is important to treat alopecia when it occurs, as it is a frequent cause of medication noncompliance. **PP**

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## INTERFERON- $\alpha$ -INDUCED PERSISTENT PSYCHOSIS

Interferon (IFN)- $\alpha$ , a highly purified protein product manufactured by recombinant deoxyribonucleic acid technology, is approved for the treatment of chronic hepatitis C virus (HCV) and for several types of cancer. Its antiviral/antitumor activity is believed to result from direct inhibition of viral replication, antiproliferative action against tumor cells, and modulation of the host immune response. Common adverse effects of this drug include flu-like manifestations and psychiatric symptoms. In particular, depression and suicidality,<sup>1</sup> mania,<sup>2,3</sup> and psychosis<sup>4-6</sup> have been reported. In the latter group of patients, psychosis typically emerged during the period of treatment with IFN- $\alpha$  and resolved shortly after its withdrawal, with or without the adjuvant use of antipsychotics. In the following case report,<sup>7</sup> a patient presents with persistent and refractory psychosis after treatment with IFN- $\alpha$ .

A 50-year-old white male was brought to the emergency room by a family member who had become concerned by his increasing paranoia and bizarre behavior. The patient believed that his building manager had planted hundreds of cameras in his home and on his body. He also reported hearing messages and conversations about him through a device implanted in his brain. He denied symptoms of either mania or depression. His psychiatric history was significant for a 25-year history of narcotic dependence, two brief admissions to substance-dependence treatment facilities, and a remote suicide attempt. There was no known family history of psychiatric illness. At the time of admission, he had been on opioid agonist treatment with methadone for

3 years. He also used clonazepam as needed for initiating sleep. He denied use of other substances, which was corroborated by his toxicologic screening. Ten months before his admission, he had completed a 1-year course of IFN- $\alpha$  for HCV infection.

Over the next 4 weeks, the patient was treated with olanzapine and showed substantial, albeit incomplete, remission of his symptoms. There was a marked decrease in the frequency and intensity of his auditory hallucinations and he was less preoccupied by his persecutory delusions. He was discharged home on olanzapine 12.5 mg with outpatient psychiatric follow-up and arranged home nursing visits. However, shortly thereafter the patient became nonadherent with treatment and experienced a worsening psychosis that necessitated readmission 2 weeks later. Olanzapine was increased to 25 mg/day. One more month of inpatient treatment resulted in a decrease in auditory hallucinations, but there was no reduction in the persecutory delusions. No longer certifiable, the patient was discharged with case management follow-up in the community.

Interestingly, as pointed out by the authors of this report, there is at least one other published case of persistent psychosis associated with IFN- $\alpha$  treatment for HCV infection involving a man with polysubstance dependence who was also on an opioid agonist treatment.<sup>8</sup> In that case, persistent psychotic symptoms began in the eighth month of therapy. Whether the similarities between that patient and the one described above are coincidental or represent the effect of common risk factors for IFN- $\alpha$ -induced psychosis is unknown at this time. Nonetheless, the temporal sequence of events presented in this case is consistent with IFN- $\alpha$ -induced persistent psychosis that was only partially responsive to olanzapine.

The pathophysiology of IFN- $\alpha$ -induced persistent psychosis is not known precisely but likely involves several different mechanisms. While during short-term treatment IFN- $\alpha$  appears to act as a dopaminergic agonist, after prolonged administration it binds to opiate receptors that seem to modulate presynaptic dopamine release, thereby eliciting a decrease in central dopaminergic activity.<sup>9</sup> After discontinuation of IFN- $\alpha$ , it is possible that this central dopaminergic activity may become reactivated again, with the result including the precipitation of psychotic symptoms. Regardless of mechanism, clinicians prescribing IFN- $\alpha$  ought to be aware of its potential for precipitating psychosis, including as part of a persistent discontinuation syndrome occurring long after its discontinuation. Clinical caution is advised. **PP**

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## PAROXETINE TREATMENT OF PALMAR-PLANTAR HYPERHIDROSIS

Primary palmar-plantar hyperhidrosis (PPH) is a disorder of unknown etiology characterized by excessive, bilateral, and relatively symmetric sweating, affecting the palms, soles, axillae, and craniofacial region.<sup>1</sup> Two types of sweating have been recognized. The first type is thermoregulatory sweating, which is the major mechanism of heat dissipation by eccrine glands present all over the body.<sup>2</sup> It occurs both during the day and at nighttime, and is controlled by the preoptic area of the hypothalamus. In contrast, emotional or mental sweating occurs predominantly over the palms, soles, and axillae during the day and is controlled by the anterior cingulate cortex.<sup>3</sup> Focal hyperhidrosis, like PPH, is a disorder of emotional sweating.<sup>4</sup>

PPH has an estimated incidence of 0.6% to 1%<sup>5</sup> and prevalence of 2.8%.<sup>6</sup> The wet or dripping hands seen with PPH can cause severe functional disability, restrict occupations, and may be socially embarrassing. The accompanying plantar hyperhidrosis may stain and damage shoes. Several treatment options are available, including topical antidepressants,<sup>7</sup> systemic agents such as anticholinergic drugs,<sup>8</sup> tap water iontophoresis,<sup>9</sup> botulinum toxin injection,<sup>10</sup> and surgical procedures such as endoscopic transthoracic sympathectomy.<sup>11</sup> The following is a report in which the selective serotonin reuptake inhibitor (SSRI) paroxetine was found to be useful in amelioration of hyperhidrosis in a patient with PPH.<sup>12</sup>

A 32-year-old man weighing 72 kg (158.4 lbs) presented with a history of excessive sweating of the palms and soles and blushing of the face since childhood, which had increased in severity over the past 6 years. Sweating occurred in both hands and soles throughout the day and hampered day-to-day activities. His symptoms increased on exposure to high temperatures and in situations such as attending meetings in which handling of papers and documents was required, which would result in wet papers and embarrassment, secondarily leading to avoidance of provocative situations. The patient's sweating would lessen

when the room temperature was lowered by air conditioners. There was no history of marked and persistent fear of social situations or exposure to social situations provoking an immediate anxiety response suggestive of social anxiety disorder (SAD). There also was no history of major medical or psychiatric illness, substance abuse, or allergy. The patient's older brother had a similar history of excessive focal sweating, but his symptoms were not severe enough to hamper psychosocial functioning.

The patient was treated with propranolol up to 40 mg/day and alprazolam up to 1 mg/day, as well as nondrug therapies such as reiki, hypnotherapy, acupuncture, and homeopathy. None of these drug and non-drug treatment attempts provided much benefit. Prior to seeking medical help, the patient used to dip his hands in formaldehyde 5% solution. This reduced perspiration to some extent but was not acceptable because of the resultant hardening of the skin.

The patient was diagnosed with PPH and prescribed paroxetine 10 mg/day and clonazepam 0.5 mg twice a day. He was also instructed to avoid secondary anxiety and performance situations. Within 1 month, he reported marked reduction in sweating and improvement in socio-occupational functioning. Paroxetine was increased to 20 mg/day and clonazepam was tapered to discontinuation, after which time the patient maintained complete control of sweating and blushing in all situations. At 6-month follow-up the improvement was sustained without any emergent adverse effects.

A retrospective review of several studies of SAD found that 25% to 32% of patients had hyperhidrosis.<sup>13</sup> The pathophysiology of SAD involves a fear circuit comprising the amygdala, cingulate gyrus, and orbitofrontal and association cortices.<sup>14</sup> Fear- and anxiety-inducing stimuli activate the amygdala, leading to activation of the locus coeruleus, lateral hypothalamus, and consequently, to increased sweating through activation of the sympathetic nervous system. In those with PPH, a cycle may ensue with an increase in sweating leading to a further increase in anxiety, and so on. Treatment that breaks this cycle may be helpful in both conditions. To date, fluoxetine, mirtazapine, gabapentin, botulinum toxin, and endoscopic thoracic sympathectomy have been reported to be useful in decreasing both social anxiety and hyperhidrosis.<sup>13,15,16</sup> Paroxetine is an SSRI effective for the treatment of SAD.<sup>17</sup> It also blocks, in a dose-dependent manner, the cholinergic muscarinic receptors. Anticholinergic drugs stop sweat production by inhibiting acetylcholine receptors on the sweat glands. Thus, there are at least two potential pathways by which paroxetine may be effective in PPH. Additional research is indicated to confirm these preliminary clinical findings. **PP**

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## COGNITIVE DECLINE DUE TO SIMVASTATIN

Statins are the most common drugs used to treat hyperlipidemias. Overall, this class of medications has robust cardiovascular benefits, reducing the risk of death by 14% to 28% in specific populations.<sup>1</sup> Except for concerns about hepato- and myo-toxicity, statins are generally well tolerated and have a safe side-effect profile. Various reports suggest both beneficial<sup>2-5</sup> and detrimental<sup>6,7</sup> effects of statins on memory. Wagstaff and colleagues<sup>8</sup> summarized 60 case reports of statin-induced memory problems in which 39 patients were treated with simvastatin. Approximately 50% of patients treated with simvastatin were noted to have cognitive adverse effects within 2 months of initiation of statin therapy. Approximately 56% of the patients who discontinued simvastatin noted improvement when the drug was discontinued. Memory loss recurred in all four patients who were rechallenged with simvastatin. The following is a report of new-onset cognitive difficulties in an older patient after initiation of simvastatin therapy.<sup>9</sup>

A 64-year-old white male presented with memory problems shortly after initiation of simvastatin therapy. The man had a history of bipolar disorder, characterized predominantly by depressive episodes, which had been stable over the past 2 years. He had one suicide attempt 3 years prior to presentation. However, he had remained stable since attending a psychiatric

day hospital three times a week. In addition, he meaningfully participated in an incentive work rehabilitation program 4 days a week, wherein he worked in the mail room of a local hospital. His medical history was notable for chronic obstructive pulmonary disease and benign hypertrophy of the prostate without urinary obstruction. He had a family history of depression in his mother and sister and Alzheimer's disease in his father. He smoked approximately one pack of cigarettes per day and had a 40 pack/year history of smoking. There had been no alcohol use in the past 5 years.

At baseline, the patient had name- and word-finding difficulties, although his Mini-Mental State Exam (MMSE) score was 30/30. Functional measures at baseline were determined using Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales on which an individual is rated from complete inability to total independence on six ADLs and eight IADLs. The patient scored 23 on the ADL scale and 22 on the IADL scale.

At the time of presentation, the patient's medications included venlafaxine 150 mg/day, quetiapine fumarate 25 mg BID, simvastatin 40 mg/day, terazosin 4 mg hs, and carbamazepine extended-release 200 mg/day. Simvastatin 40 mg had been initiated by the patient's primary care physician for dyslipidemia. Within 1 week of starting simvastatin, the patient complained of additional memory problems. In addition to the baseline problems with word-finding and names, a semistructured interview with a geriatric psychiatrist revealed difficulties with short-term and long-term memory, item misplacement, attention span, and concentration. After 2 weeks of treatment with simvastatin, the patient's MMSE dropped to 27/30; specifically, he lost one point each in orientation to time, serial 7s, and recall. His ADL score was 21; he lost one point each on bathing and grooming. His IADL score was 19; he scored one point less on shopping, cooking, and finances. Simvastatin was discontinued. Six weeks later, the patient's new-onset memory problems resolved. His MMSE returned to 30/30, and his ADL and IADL scores returned to baseline values.

After obtaining proper informed consent, simvastatin was restarted, but at half the original dose (ie, 20 mg/day). Within 2 weeks, the patient reported a recurrence of memory problems, as evidenced by a decline in his MMSE score to 28. This time, he lost one point each in serial 7s and 3 stage command. Simvastatin was discontinued. Over the next 4 weeks, the patient's new-onset memory problems resolved. His MMSE score was again 30/30. Functional status was not assessed during this challenge phase.

The temporal sequence of events supports a highly probable association between simvastatin and cognitive decline

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in this patient.<sup>10</sup> The mechanism by which statins might worsen cognition is not known. Since cholesterol is essential in the myelination of neurons, some have suggested that excessive inhibition of cholesterol synthesis could lead to adverse cognitive effects.<sup>11</sup> Simvastatin is the most lipophilic of all the available statins. In general, lipophilic statins have been shown to be pro-inflammatory in the brain, which could represent another possible mechanism for worsening cognition.<sup>12</sup> Regardless of mechanism, it appears that lipophilic statins like simvastatin may be associated with cognitive decline, particularly in elderly patients with preexisting memory problems. **PP**

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## DOSE-DEPENDENT OLANZAPINE-INDUCED URINARY RETENTION

Currently Food and Drug Administration approved for the treatment of schizophrenia and mania, olanzapine is an atypical antipsychotic that binds to multiple sites including serotonin (5-HT)<sub>2A</sub> and 5-HT<sub>2C</sub>, dopamine (D)<sub>2</sub>, D<sub>4</sub>, D<sub>1</sub>, muscarinic-1, histamine-1, and  $\alpha_1$ -adrenergic receptors.<sup>1</sup> Atypical antipsychotics are known to have anticholinergic adverse events (AEs), including urinary retention.<sup>2</sup> The incidence of olanzapine-induced anticholinergic AEs is approximately 10%.<sup>3</sup> The following may be the first published report of urinary retention in an olanzapine-treated patient.<sup>4</sup>

A 24-year-old white man with paranoid schizophrenia was hospitalized for a psychotic episode characterized mainly by paranoid ideas and auditory hallucinations. He consumed alcohol and cannabis regularly and was an active smoker.

He did not take cold remedies. Upon admission the patient received olanzapine 20 mg/day, but no other medication on a regular basis. Four days following admission, he received haloperidol 5 mg and lorazepam 2 mg orally. Two days later, he began to show clinical improvement consisting of decreased hallucinations and agitation and improved social interactions. However, he had difficulty initiating urination and was completely unable to void. On two occasions, 1,350 and 1,950 cc of urine were removed by means of a catheter. The patient did not develop any other anticholinergic AEs. Urinalysis, urine culture, complete blood count, electrolytes, urea, creatinine, and rectal examination failed to reveal any etiology for the urinary retention. Olanzapine was discontinued, with the urinary retention progressively disappearing over the next 24 hours.

Given the significant psychiatric improvement attributable to olanzapine, it was restarted at a dose of 5 mg/day for 2 days, and then increased to 10 mg/day thereafter. No urinary retention occurred with this dose and the clinical improvement was maintained. The patient was transferred to another service and then eventually discharged from the hospital with no signs of urinary retention. He was given a prescription for outpatient use of olanzapine 5 mg/day but became noncompliant with treatment. Of note, at no point during this time was there any urinary retention.

Three months later, the patient presented at the hospital's psychiatric emergency department with persecutory delusions, agitation, and hallucinations. Again he was prescribed olanzapine 20 mg/day. On the same day, he also received one dose of haloperidol 5 mg and lorazepam 2 mg. Five days later, urinary retention reappeared. The dose of olanzapine was reduced to 10 mg/day and the urinary retention resolved.

The temporal sequence of events described above is consistent with a probable and dose-dependent association between use of olanzapine and urinary retention.<sup>5</sup> For olanzapine-treated patients who develop new-onset urinary retention, dosage reduction ought to be considered as a first approach, being mindful to monitor carefully for worsening of the core psychiatric symptomatology. **PP**

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