

BRIEF COMMUNICATION

Adverse Reactions to St John's Wort

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Objective: To report 2 cases of adverse reactions to St John's wort, a popular herbal treatment for depression.

Method: We present 2 case histories and review the existing literature regarding St John's wort.

Results: St John's wort may cause serotonin syndrome in sensitive patients. In addition, St John's wort may be associated with hair loss.

Conclusions: For clinical reasons, it is important to recognize and report adverse reactions to herbal remedies and to document that these treatments have side effects commensurate with their potential action on brain neurochemistry.

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Key Words: St John's wort, adverse drug reaction, serotonin syndrome, antidepressant, herbal remedies, herbs, depression

Clinical trials confirm that St John's wort (*Hypericum perforatum*) effectively relieves symptoms associated with mild to moderate depression (1,2). The mechanism by which it exerts this effect is currently unknown. Although early studies noted monoamine oxidase (MAO) inhibition (3), this finding has not been confirmed by subsequent work (4,5). In vitro studies have found that St John's wort may reduce the expression of serotonin receptors (6), increase the numbers of 5-HT_{1A} and 5-HT_{2A} receptors (7), and inhibit synaptosomal serotonin uptake (8,9). It has been questioned whether oral administration of St John's wort extract produces *in vivo* concentrations comparable to those *in vitro* studies. The gamma-aminobutyric acid (GABA) receptor activity of St John's wort has also been investigated without conclusive results (10). Other putative targets of St John's wort include melatonin and cytokine expression, although these reports are preliminary. The potential serotonergic action of St John's wort has raised concerns that it could interact with other serotonergic medications and produce similar side

effects. The first clinical cases of serotonin syndrome associated with the concurrent use of St John's wort and prescription antidepressants (sertraline or nefazodone) have been recently reported (11,12). We report another case of serotonin syndrome in a patient with a history of reactions to serotonergic medications who took St John's wort. In addition, we describe a case of hair loss, which has not previously been associated with ingestion of St John's wort.

Serotonin Syndrome With St John's Wort

Mr X is a 40-year-old man with a history of an anxiety disorder and depression who presented to the emergency room of a psychiatric hospital after taking 450 mg of St John's wort. The brand and preparation of the product are unknown. He had been taking 450 mg daily for the past 10 days for depressed mood. Following dinner, he developed flushing, diaphoresis, agitation, weakness of the legs, dry mouth, tightness in the chest, and an inability to focus. These symptoms differed from his usual panic attacks and did not respond to his usual anti-anxiety coping strategies. He denied excessive use of alcohol. He was currently undergoing cognitive-behavioural therapy for social phobia with panic attacks precipitated by social situations. The panic attacks improved with clonazepam 0.5 mg twice daily, which he had been taking for some months. He was on no other medication.

When he presented to the emergency room, he was hypertensive (172/120 mm Hg) without a postural drop, his heart rate was 94/minute and regular, and his respiration rate was 22/minute. Mr X became progressively more confused over a period of 20 minutes and was disoriented regarding the month, the year, and the fact that it was the Christmas season.

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He did, however, know the name of the hospital. He then became quite tremulous and dizzy and required oxygen to relieve his dyspnea. He complained of chest tightness, but he did not complain of chest pain or radiation. After transport to a general hospital, his blood pressure was 150/96 mm Hg, heart rate 90/minute, and regular and respiration rate was 20/minute. A neurological examination and electrocardiogram were normal. After some hours of observation, Mr X felt better, and his blood pressure normalized at 135/88 mm Hg, at which point he was discharged with a diagnosis of an adverse drug reaction to St John's wort.

In the past, Mr X had experienced manic symptoms at the age of 37, following treatment with a selective serotonin reuptake inhibitor (SSRI) for a depressed mood. He had had 2 admissions to hospital: the first was for a period of 3 weeks in July 1996 when, at the age of 38, he experienced a major depressive episode with psychotic features and suicidal ideation. He also had manic symptoms following treatment with an SSRI. He endorsed a 7-month prior history of heavy alcohol use and occasional binges as a teenager. He was treated with venlafaxine 37.5 mg twice daily and lorazepam 1 mg as needed, up to 4 mg daily. His second admission, in August 1996, for suicidal ideation due to marked psychosocial stressors, occurred 2 weeks after discharge. There were no psychotic features, and he received a diagnosis of adjustment disorder with depressed mood. His blood pressure on this admission was 160/110, with tachycardia and diarrhea that normalized upon stopping the venlafaxine. He was discharged on lorazepam 1 mg daily and referred to a relaxation therapy group and to the care of his community psychiatrist. While he was an outpatient, lorazepam was later changed to clonazepam.

Serotonin Syndrome

There have been many reports in the literature of serotonin syndrome occurring with various single agents or combinations of medications, including SSRIs, MAOIs, clomipramine, clorgyline, lithium, carbamazepine, benzodiazepines, bromocriptine, L-dopa/carbidopa, levothyroxine, and others. Usually, the syndrome is seen in combinations of serotomimetic agents with MAOIs, develops after initiation or dose increases, and may be dose-dependent (13). The typical signs and symptoms of serotonin syndrome include changes in mental status (agitation, confusion, hypomania, restlessness, disorientation, or coma), autonomic changes (diaphoresis, flushing, blood pressure lability, tachycardia, tachypnea, pupillary changes, or low-grade fever), and neuromuscular changes (tremor, hyperreflexia, myoclonus, rigidity, or incoordination), in addition to headache, nausea, anxiety, diarrhea and shivering (13–15). There are no reliable laboratory changes to help in the detection of this syndrome; thus, the diagnosis is a clinical one. There are sporadic reports of mild leukocytosis and

increased creatinine kinase (CK). In severe cases, seizures, nystagmus, opisthotonus, renal failure, cardiac arrhythmias, coma, and death can occur (15).

It has been hypothesized that activation of the 5-HT_{1A} receptor is involved in the pathophysiology of serotonin syndrome. Other hypotheses include stimulation or modification of serotonin receptors in the dorsal and median raphe nucleus in the brainstem (the main location for serotonin neuron cell bodies), enhancement of overall 5-HT transmission, and combined activation of cyclic adenosine monophosphate (cAMP)-related 5-HT_{1A} receptors and phosphatidylydrolysis-linked 5-HT₂ receptors (15). The incidence of serotonin syndrome is unknown. It is likely under-reported, and it can be confused with neuroleptic malignant syndrome (16). Treatment includes prompt recognition, removal of the offending agent(s), close observation until resolution, and the use of such various supportive measures as adequate hydration, attention to electrolyte and acid-base balances, cooling baths, and antipyretics (17). No benefit has been demonstrated with the use of benzodiazepines, anticholinergics, antihistaminergics, chlorpromazine, muscle relaxants, and membrane stabilizers such as dantrolene (14). Anecdotal use of cyproheptadine, a serotonin antagonist, and methysergide have been reported to decrease the duration of this syndrome, which is usually short-lived (14). In the case of Mr X, the possibility that ingestion of St John's wort caused serotonin syndrome is supported by the chronology of events and the fact that he has experienced prior adverse reactions to serotonergic medications. Other possible causes for his symptoms include an atypical panic attack and an adverse reaction to something he ate at dinner.

Hair Loss With St John's Wort

Ms X, a 24-year-old, university-educated woman, began suffering non-specific symptoms in 1996, for which she was prescribed herbal remedies by her traditional Chinese medicine practitioner. She subsequently developed prominent paranoid delusions of reference from the radio and from television, accompanied by delusions of thought broadcasting and grandiosity, and was diagnosed with schizophrenia in 1997. Her psychotic symptoms responded well to treatment with olanzapine at a dose of between 5 mg to 10 mg daily. Beginning in June 1998, still on olanzapine and feeling depressed, Ms X began taking St John's wort at a dose of 300 mg 3 times daily. Five months after initiating St John's wort, she began to experience hair loss on both her scalp and eye brows that persisted for 12 months. She had no history of medical illnesses, and hematology results, including CBC, differential, and microscopy were normal. Clinical chemistry, including creatinine, total bilirubin, alkaline phosphatase, aspartate transaminase (AST) and thyroid-stimulating hormone (TSH) were normal. Prolactin was slightly elevated at 51 mg/L (secondary to olanzapine). Microscopic examination of hairs

revealed a mixed telogen and normal anagen morphology that suggests a drug reaction.

Both tricyclic and SSRI antidepressants have been associated with hair loss (18–27). Although spontaneous and coincidental hair loss is possible, both the 5-month delay between onset of St John's wort use and the type of hair loss (telogen) suggest drug induction (28). The duration of hair loss (12 months) is consistent with this conclusion, as is the microscopic appearance of the hair.

Conclusion

Although herbal remedies have pharmacological properties that may render them effective treatments, these case reports demonstrate that they also have serious side effects. It is important that clinicians recognize and educate their patients about these risks, and inquire about the use of alternative therapies, as part of a thorough medical history. Adverse reactions to herbal products should be reported in the same manner as are conventional medications—directly to Health Canada, or via regional reporting centres. The relevant forms are available in the Compendium of Pharmaceuticals and Specialties (CPS).

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Résumé— Effets indésirables du millepertuis

Objectif: Rapporter 2 cas d'effets indésirables du millepertuis, traitement populaire, d'origine végétale, de la dépression.

Méthode: Nous présentons 2 cas concrets et examinons la documentation existante en ce qui a trait au millepertuis.

Résultats: Le millepertuis peut causer un syndrome de sérotonine chez les patients sensibles. En outre, il peut être associé à la perte de cheveux.

Conclusions: Pour des raisons cliniques, il importe de reconnaître et de déclarer les effets indésirables des remèdes à base de plantes médicinales, et d'étayer le fait que ces traitements ont des effets secondaires correspondant à leur action puis santé sur la neurochimie du cerveau.