Letters to the Editor

Mirtazapine-Induced Shopping Spree

Dear Editor: Many antidepressants, either alone or in combination, can induce mania. Mirtazapine is a new noradrenergic and specific serotoninergic antidepressant that has been associated with mania when used to augment fluoxetine (1) and with hypomania when combined with sertraline (2). Bhanji and others have recently proposed a “norepinephrine syndrome” of dysphoric mania that is based on mirtazapine’s mechanism of action and a constellation of symptoms it likely caused when prescribed at high dosages (3). We report the case of a young woman who went on a shopping spree after mirtazapine was added to paroxetine that was unsuccessful in treating her depression.

Case Report

The patient is a mother of 3, aged 35 years, with a positive family history of unipolar depression. Seven years earlier, she had been diagnosed with postpartum depression that was successfully treated with paroxetine. After stopping the paroxetine, she remained well until recently, when she presented to her family physician with complaints of fatigue, decreased libido, loss of interest, bouts of tearfulness, and panic attacks. Her doctor started her on paroxetine 10 mg daily and subsequently referred her to the local psychiatrist, who confirmed the diagnosis of a major depressive illness and increased her paroxetine gradually to 50 mg daily. Despite the above regimen, she continued to suffer from depression, except for rare good days when she was able to do some of her housework. To relieve the depression, bupropion, olanzapine, and L-tryptophan were separately added to the paroxetine, but with little success. After stopping the above 3 agents because they failed to boost the antidepressant effect of paroxetine, her psychiatrist added mirtazapine to her treatment. The dosage was gradually increased to 45 mg daily, and she took the combination for 8 weeks. Around this time, the patient was referred to the Mood Disorder Service for consultation. She reported that she had become irritable and impulsive. She described herself as easily “snapping” at people. Her energy had increased and she had started binge eating for the first time. Most dramatically, she began to make large purchases; for example, she bought 10 T-shirts and 5 pairs of shorts for herself, and 8 pairs of shorts for her children, 5 pairs of pants and L-tryptophan were separately added to the paroxetine, but with little success.

The sudden episode of excessive and inappropriate spending resolved promptly when the offending agent, mirtazapine, was discontinued. We believe this is the first case of a shopping spree that was precipitated by the addition of mirtazapine to paroxetine when the latter failed to treat depressive symptoms.

Conclusion

Mirtazapine-induced hypomania was recognized, the mirtazapine was discontinued, and the shopping sprees ceased soon thereafter. The remaining hypomanic symptoms also subsided later. However, the patient experienced depression. Her mood has stabilized with the addition of lithium carbonate.

References


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Age at Onset of Bipolar II Disorder

Dear Editor: Recently, 3 subgroups of bipolar I disorder (BD I), distinguished by different ages at onset, were found (1). Bipolar II disorder (BD II) has been found (according to Kolmogorov–Smirnov test) to have an age-at-onset distribution similar to that of BD I (2). Nevertheless, family studies (an important diagnostic validator) also support a distinction between the 2 disorders (3). The aim of the study reported here was to test whether BD II has 3 age-at-onset subgroups, as reported for BD I.

The study setting, patients, and interview methods are reported in detail elsewhere (4). The study setting was a private practice that has for many years studied BD II (see Benazzi F on PubMed/Medline). The study sample comprised 320 consecutively presenting outpatients (mean age of 41.6 years, SD 13.4) with BD II, 50.2% of whom had a family history of BD, and 68.4% of whom were women. Age at onset of the first major depressive episode (MDE) was assessed with the Structured Clinical Interview for DSM-IV-Clinician Version (5), often supplemented by interviews of family members or close friends.

With regard to onset-age of the first MDE, the mean (SD) age was 22.8 years (10.6), the median age was 20 years, and the age range was 4 to 67 years. Histogram and kernel density estimates were employed to study distribution of age at onset. A histogram results in disproportional representation of density at the centre and in the tails of the distribution, whereas kernel estimators are nonparametric histogram smoothers revealing multimodality. A histogram provides accurate pictures of categorical variables; univariate kernel density estimate is better to represent continuous variables (STATA 7 statistical software; 6). For this sample of patients with BD II, both histogram and kernel density estimate showed 3 age-at-onset subgroups: around age 19 years, around age 27 years, and around age 35 to 40 years (figures available on request from the author). Onset before age 20 years was present in 45.0% (144/320), onset between age 19 and 35 years in 42.8% (137/320), and onset after age 35 years in 12.2% (39/320).

Discussion

The similar results achieved from 2 different statistical approaches compared with the Bellivier and others study support the validity of these findings. Age-at-onset distribution in BD II was found to be similar to that in BD I, as reported by Bellivier and others (1). Because onset is an important diagnostic validator (2,7,8), finding 3 similar age-at-onset subgroups in BD I and BD II supports the hypothesis of a closer link between BD I and BD II. When more advanced statistical methods are used, the findings do not replicate the bimodality of onset that Kraepelin describes for manic-depressive insanity (8).

References

Venlafaxine-Associated Hypomania in Unipolar Depression

Dear Editor: Antidepressant-induced hypomania and mania have been reported more commonly in cases of bipolar depression than in cases of unipolar depression (1). Tricyclic antidepressants, monoamine oxidase inhibitors, and even selective serotonin reuptake inhibitors have been associated with this switch (1). Newer antidepressants like venlafaxine, which act on multiple specific receptors, have low propensity for the switch (2) but are not completely safe, particularly in patients with bipolar depression or with family history of bipolarity (3–5). The following case report illustrates that venlafaxine may also be associated with a switch to hypomania in unipolar depression.

Case Report

Mr S, aged 26 years and single, presented to our clinic with a 2-year history of sustained sadness of mood, withdrawal, decreased interest in enjoyable activities, increased tiredness, sadness of mood, withdrawal, decreased interest in enjoyable activities, overactivity, and overtalkativeness. He had been off medication for the 6 months prior to presentation. Two years earlier, his older brother had committed suicide at age 30 years, following an altercation with a psychiatrist but did not perceive significant benefit. He had been off medication for the 6 months prior to presentation. Two years earlier, his older brother had committed suicide at age 30 years, following an altercation with a family member. Apart from this, there was no personal or family history of affective illness, panic disorder, obsessive–compulsive disorder, substance use, or psychosis. No delusions or hallucinations were forthcoming, either at the time of assessment or historically. Results of a general physical examination and laboratory investigation, including a thyroid function test, were normal. He was diagnosed with severe depression without psychotic symptoms, and treatment with venlafaxine 75 mg daily, together with clonazepam 0.5 mg daily to promote sleep, was started. In the next 3 weeks, he reported 50% improvement in overall symptoms. At the end of week 3, venlafaxine was increased to 112.5 mg daily to enhance his improvement.

At the end of 5 weeks of total treatment, he noticed to have decreased sleep, overactivity, overtalkativeness, and excessive cheerfulness. He was cracking jokes, voicing grandiose ideas, spending excessively, and smoking more. During interview, he subjectively complained of racing thoughts and new ideas. He himself had discontinued his increased medication after 2 weeks because he felt well. His symptoms continued until his family members brought him to hospital. Drug-induced hypomanic switch was considered, and lithium carbonate was started, along with benzodiazepine. At the end of 4 weeks, he became asymptomatic.

The patient developed possible venlafaxine-induced switch within 8 weeks of starting the medication (6), and the symptoms continued, although they did not worsen, even after he stopped taking the drug. The presence of predisposing factors for bipolarity (7), that is, early age of onset, long duration of a depressive episode, and a family history of suicide, probably made this patient vulnerable to a switch to hypomania on taking therapeutic dosages of venlafaxine, as shown by similar cases in the literature (3). It is important to acknowledge that it is difficult to prove a causal connection between the introduction of venlafaxine and onset of hypomania, but venlafaxine possibly exposed latent bipolarity in this patient, which led to rapid institution of a mood stabilizer to prevent further morbidity.

Prior to starting any antidepressant, clinicians should attempt to obtain risk factors for bipolarity that is, cyclothymic or hyperthymic temperament, early onset of depression, acute onset, atypical symptoms, seasonal pattern, and family history of bipolar disorder) to help in early detection and intervention when a manic or hypomanic switch occurs.
complain about the hypnopompic hallucinations, we continued olanzapine therapy for about 2 months. The patient then started to complain more vociferously about sedation and continued to refer to the visual hallucinations mentioned above, which he had previously tolerated. Because these symptoms were totally discordant with the clinical picture drawn before treatment, we decreased the dosage from 20 to 15 mg, and then to 10 mg daily, over a 1-month period. Both sedation and hypnopompic hallucinations persisted at 10 mg daily, but above all, the clinical picture worsened, particularly with regard to social withdrawal. We therefore decided to discontinue olanzapine and replace it with risperidone.

We believe that olanzapine induced the hypnopompic hallucinations claimed by the patient. With regard to olanzapine’s side effects, the drug literature has never reported imperceptive symptoms such as hypnopompic hallucinations. Conversely, cases of hypnopompic hallucinations have been reported during therapy with imipramine, amitriptyline, maprotiline, and donepezil. Schlauch has reported a case of hypnopompic hallucinations during therapy with imipramine and has suggested that such hallucinations may be connected to the decrease in rapid eye movement (REM) sleep caused by imipramine (1). Hemmingsen and Raafaelsen reported 4 cases of hypnopompic and hypnagogic hallucinations during therapy with amitriptyline (2). According to these authors, there is a connection between amitriptyline effects on the brain, sleep patterns, and clinical condition. In our case, hallucinations appeared after a few days of treatment with olanzapine and continued for approximately 2 more months, manifesting themselves every morning as the patient woke up. The patient had never previously suffered hallucinations. They disappeared after the discontinuation of olanzapine therapy and did not reappear when another antipsychotic was administered.

The discontinuation of therapy was not determined by the hallucinations, which our patient tolerated, but by sedative side effects. Olanzapine at a dosage of 5 mg daily significantly increases slow wave sleep, probably by blocking 5-HT2C receptors; it improves the continuity of sleep and the subjective quality of sleep. At a dosage of 10 mg, olanzapine significantly increases the latency of REM sleep and also decreases its duration. Such effects may be a consequence of the antagonist effects of olanzapine at muscarinic cholinergic receptors (3). Inhibition of REM sleep, as we have mentioned above, is a common property of tricyclics. The manifestation of hypnopompic hallucinations caused by olanzapine could be similar to that described for tricyclics and is therefore probably linked to REM-sleep suppression.

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Atypical Neuroleptic Malignant Syndrome Caused by Clozapine and Venlafaxine: Early Brief Treatment With Dantrolene

Dear Editor: Clozapine can cause neuroleptic malignant syndrome (NMS) with a presentation that may be atypical in that it may occur without rigidity, fever, or changes in creatine kinase (CK) (1).

We report a case of possible atypical NMS arising from overdosage of clozapine and venlafaxine that was successfully treated with lorazepam and dantrolene.

Case Report

Mr A, aged 19 years, was diagnosed with schizophrenia. Treatment for 2 years with clozapine 300 mg daily and venlafaxine 150 mg daily helped his condition. After he discontinued his medication for 2 weeks and then took 1000 mg clozapine and 900 mg venlafaxine, he presented to the emergency room, where he went into a coma and was admitted to the intensive care unit. His urine was positive for cannabinoids and clozapine but negative for alcohol, opiates, amphetamines, cocaine, and benzodiazepines. His temperature was 37.2°C.

The following day he emerged from coma and developed delirium, agitation, fluctuating blood pressure, a temperature of 38°C, and leukocytosis. He was without extrapyramidal signs (EPS) and had normal CK. Intravenous lorazepam 12 mg daily was added to his treatment. At day 3, his CK rose to 6700 U/L, and his myoglobin rose to 597 ng/L.

Suspecting NMS, we added dantrolene 1 mg/kg 4 times daily. Twelve hours later, the patient’s CK decreased to 3600 U/L. Glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) rose to 147 U/L and 91 U/L, respectively. After 3 more days, the patient’s CK level was 1750 U/L, his temperature and myoglobin became normal, EPS were absent, consciousness was total, and paranoid delusion and depression emerged. Dantrolene was discontinued, and the patient was transferred to the psychiatric unit.

Ten days later, all parameters were normalized, especially CK, myoglobin, white blood cell count, G0T, and GPT.

After 10 more days, risperidone 2 mg daily was added and titrated to 3 mg daily. The patient improved and was discharged; 60 days later, he was in good clinical condition.

This patient presented NMS that was atypical in that muscular rigidity was absent during the period with fever, (common with clozapine-related NMS), high CK, altered consciousness and autonomic dysregulation.

NMS occurring after a single dose of venlafaxine has been attributed to a dopamine-inhibiting effect (2) or, alternatively, it has been explained as evidence of central serotonergic overdrive (3). NMS and serotonin syndrome (SS) are often confused, and when considering their clinical overlap, many authors place NMS and SS in the spectrum of the same disorder (4), defined by some as “neurotoxic syndrome” (5) and also including catatony (6).

Dantrolene’s specificity of action remains unknown (7); however, in the case of our patient, adding dantrolene to lorazepam was crucial, even in the absence of rigidity. Early treatment with dantrolene prevented NMS from developing fully. Otherwise, the absence of rigidity is unrelated to this treatment, a characteristic of some NMS with better prognosis.

Fever, altered consciousness, and increased CK and myoglobin indicated treatment with dantrolene.

References

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A Case of de Clérambault Syndrome in a Male Stalker
With Paranoid Schizophrenia

Dear Editor: I describe a case of secondary erotomania in a 43-year-old Moroccan–Canadian single man, a former maintenance worker (collecting disability pension for many years) with a Grade 12 education. Although the syndrome is presumed to be rare in Western patients with schizophrenia, there is evidence for its high prevalence in schizophrenia patients of the paranoid subtype elsewhere. There is also evidence of a robust relation between grandiose delusions and erotomanic symptoms.

Case Report
De Clérambault syndrome, also known as erotomania, erotic paranoid state, delusions of passion, psychopathosistelle, and in the DSM-IV–TR, as delusional disorder of the erotomanic type (1), is documented as an uncommon psychiatric syndrome (2). It is an illness that involves the central delusional theme of being loved by another person. Efforts to contact the object of the delusion through telephone calls, letters, gifts, visits, and even surveillance and stalking are common. While most patients with this disorder in clinical samples are female, in forensic samples, the patients are mostly male. A classic feature of the disorder is that many actions of the target are interpreted by the patient as being paradoxical or contradictory (for example, the target may appear to hate the subject when she really loves him). The paradoxical interpretation of the rejection of the patient’s overtures and of the lack of clear confirmation of his beliefs are viewed as a test of his own love for the target.

The patient was referred from an Ontario Provincial Court under the Mental Health Act for an assessment of his psychological status, pursuant to his being charged with criminal harassment over a 22-year period. He had dated the victim for 4 years prior to the commencement of his harassment, during which epoch he both physically and sexually assaulted her and psychologically and emotionally manipulated her. She then moved to another city, about 200 km away, and ended her relationship with him. He refused to accept this, sending her letters asking that he might live with her and her family. He continued to send packages, gifts, cards, and letters to her, many of which were sent from overseas after he moved back to Morocco with his parents for some time. Some contained menacing messages, and on several occasions, the patient ejaculated on the items and letters before sending them. The victim never responded to any of the messages. At one point, the patient was convicted of possessing a prohibited weapon after he attempted to intimidate the victim into entering his motor vehicle, using brass knuckles. After learning that she was married and had children, he began sending gifts for her children as well.

In addition to a mental status examination, the patient was neurologically examined with the Quick Neurological Screening Test II (QNST-II) and was intellectually and neurocognitively examined with the Test of Nonverbal Intelligence-3 (TONI-3) and the Cognistat Neurobehavioural Cognitive Status Examination (NCSE), respectively. He was also psychometrically examined with the Millon Clinical Multiaxial Inventory-II (MCMI-II), the Minnesota Multiphasic Personality Inventory-2 (MMPI-2), and the Personality Assessment Inventory (PAI). He was further examined with the Spousal Risk Assessment Guide (SARA).

No evidence of gross neurological disease or of neurocognitive impairment was uncovered, although the patient’s level of fluid and nonverbal intellectual functioning appeared to be somewhat limited (that is, within the low average range at the 14th percentile). Further medical assessment also yielded remarkable findings, other than a self-report of occasional headaches and a documented history of acute dystonia with haloperidol. There was no history of alcohol or drug abuse. He was currently being treated psychopharmacologically with olanzapine (2.5 mg orally at bedtime) and fluphenazine decanoate (15 mg IM).

The patient displayed no evidence of a formal thought disorder or of perceptual abnormalities (such as hallucinations) of any kind. However, he was blatantly delusional (for example, he falsely believed he had been raped at knifepoint by a coworker); he was grandiose (he believed he was an eminent inventor of children’s toys, although he had never been recognized as such); and he evinced markedly narcissistic, obsessive–compulsive, and dependent personality features. Also indicated and underlying his intense oppositional resentment and anger were extreme cynicism and suspiciousness and (or) mistrust of others’ motives, along with very low levels of heterosexual activity (his only intimate relationship was with the victim). The combination of impulsiveness, resentment, and good energy levels portended the likelihood that the patient might lash out at those whom he felt had slighted him in some way. The findings were also consistent with one of the prototypes of male spouse abusers, and the patient evinced several risk factors indicating an elevated risk for future spousal or romantic partner assault. The presence of delusions with an absence of prominent disorganized speech, disorganized or catatonic behaviour, or flat or inappropriate affect supported a diagnosis of schizophrenia of the paranoid subtype.

This case exemplifies previous findings of a relation between erotomanic symptoms and schizophrenia of the paranoid subtype and of a robust relation between grandiose delusions and erotomanic symptoms. It further exemplifies Kraepelin’s original 1921 formulation, which classified erotomanic delusions as a subcategory of grandiose delusions (3,4). It remains unclear whether the currently presumed rarity of erotomanic symptoms in Western patients with schizophrenia is a result of a cultural disparity or a consequence of unreported characteristics of schizophrenia. This case illustrates that at least a systematic search for erotomanic symptoms, both during acute episodes of schizophrenia of the paranoid subtype and in the presence of grandiose delusions, should be conducted.

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Calcitonin Treatment for Phantom Limb Pain

Dear Editor: Phantom limb pain (PLP) and phantom limb sensation (PLS) describe sensation that is localized to a paralyzed or amputated appendage; PLP is painful, whereas PLS is not (1,2). There is little evidence from randomized controlled trials (RCTs) to guide treatment (3), and the management of phantom limb continues to challenge clinicians. Traditionally, combined tricyclic antidepressants (TCAs) and opioids have been used effectively in the management of PLP, but increasing attention is being focused on the role of calcitonin (4–7). In a small, double-blind RCT, Jaeger and Maier reported complete resolution of PLP in 76% of amputees at 1 week and in 71% of amputees at 2 years after treatment with intravenous calcitonin (6). Related studies have shown that intranasal calcitonin is an effective analgesic agent in bone pain owing to osteoporosis and malignancy (8–10). We describe the use of intranasal calcitonin for the treatment of PLP after spinal cord injury, which has not been previously described in the literature.

Case Report

Mr S, aged 60 years, with no psychiatric history, was the pedestrian victim of a hit-and-run accident that rendered him quadriplegic owing to a C5 lesion. Five days after admission, he complained of paresthesias and feelings of uncontrolled movement in his arms. Over the next 17 days, the symptoms interfered with his sleep and made him anxious, despite routine administration of diazepam and immovane. The psychiatric team was consulted and suggested that Mr S take a moderate dosage of clomipramine. The team was unable to give an opioid in combination with the TCA because he had experienced visual hallucinations on morphine earlier that week. Mr S complained that his PLS worsened, and the clomipramine was discontinued.

A trial of calcitonin was subsequently administered, initiated slowly owing to the potential for anaphylaxis as well as for less deleterious side effects such as nausea and vomiting. Intravenous calcitonin was not available at our centre, so intranasal calcitonin was started instead. After a trial of 1 IU calcitonin intradermally, Mr S was given 200 IU of intranasal calcitonin and reported an alleviation of PLP symptoms for several hours, during which he slept. Two days later, he received 400 IU of intranasal calcitonin, with only a transient improvement in symptoms.

Discussion

This case report on PLP does not support the beneficial effects of calcitonin on PLP reported in previous studies (2). Our report differs from the literature in 2 important respects. First, intranasal administration has not been studied, and it is likely that the optimal dosage was not used in this patient’s care. Further, previous studies all involve patients experiencing PLP symptoms after amputation, not PLP after spinal cord injury. This case report does highlight that intranasal calcitonin is well tolerated and convenient and may be effective as an acute pain reliever in patients who cannot tolerate traditional PLP or PLP pain medications. There continues to be a need for additional research to define the role of intranasal calcitonin in PLP pain management.

References


The Use of Atomoxetine Adjunctively in Fibromyalgia Syndrome

Dear Editor: Fibromyalgia syndrome (FMS) is a chronic disease characterized by widespread musculoskeletal pain (1). It is also accompanied by persistent fatigue, non-restorative sleep, generalized morning stiffness, and multiple tender points (2). FMS occurs more often in women than in men and has an overall prevalence rate of 1% in the population (3). The pathophysiology of FMS is unknown; however, central monoaminergic transmission may be involved (4). No single medication has been found to effectively treat all symptoms of FMS. Selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, hypnotic agents, anticonvulsants, and analgesics have been used to treat the syndrome. The following cases discuss using atomoxetine adjunctively in FMS. To my knowledge, this is the first description of atomoxetine used in the pharmacologic treatment of FMS.

Case Report 1

Ms A is hispanic and aged 35 years. She was referred by her primary care physician for assistance with the pharmacologic management of her fibromyalgia. She had been diagnosed with fibromyalgia 1 year prior to consultation and took sertraline 150 mg daily and cyclobenzaprine 10 mg 3 times daily, as needed. She had a psychiatric history significant for a major depressive episode that had been in remission for about 2 years. She had no active symptoms associated with depression. Her biggest concerns were ongoing fatigue, coupled with a worsening of pain in her tender points, that interfered with her ability to work a consistent 40 hours weekly (she was able to work about 20 hours weekly). She had no other medical problems: recent laboratory test including a complete blood count, comprehensive metabolic panel, liver function test, thyroid-stimulating hormone, erythrocyte sedimentation rate, urinalysis, and pregnancy test were either within normal limits or negative. She did not want to discontinue taking sertraline because she had not tolerated other antidepressants (including venlafaxine and paroxetine) during her depressive episode. She gave informed consent to a trial of atomoxetine to target her symptoms and began atomoxetine 40 mg daily, which was titrated to 80 mg over 1 week with no significant side effects. During the next 3 weeks, she began to note a reduction in pain and an increase in her energy level. She gradually began to increase her workweek by 5 hours.
weighing both the risks and the benefits, compared with agents that are already FDA-approved for the particular condition. In the case of fibromyalgia, where there is no particular FDA-approved agent, it is important to compare it with agents that have been most widely used in the treatment of fibromyalgia.

References

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Re: Autism—Its Detection, Causes, and Treatment

Dear Editor: I welcome the reviews of autism in the September 2003 issue of the CJP. I was a little saddened that there was no reference to the research I have conducted, but not surprised. After all, I concluded that the “pathology” of autism is not an illness or deficit but, rather, a condition of being extra sensitive. It is less a case of autism sufferers being abnormal in a normal environment than it is of their being supernormal in an abnormal environment. This accords with the parents’ accounts of their children’s behaviour as extremely responsive to distant sirens when no one else in the family (apart from, possibly, household animals) could hear the sound. We found the auditory evoked potentials to be quite unusual in autistic children—larger and faster, but not necessarily abnormal. Additionally, the typical autistic child is very good looking. That is partly what creates such deep dilemmas for the parents. Can anybody think of a single genetic disorder that leaves the child looking more, rather than less, beautiful? I can’t.

Reference