

“The Man Who Would Jump out of His Skin” Olanzapine-Mirtazapine in Whole Body Akathisia and Suicidal Impulsivity

Summary:

A patient presented with suicidal intent, obsessional depression/anxiety, and severe restlessness. He was treated with olanzapine (Zyprexa) and mirtazapine (Remeron). After one week he developed an acute stereotypy in the context of worsening restlessness, despair, and suicidality. The diagnosis of akathisia prompted administration of oral clonazepam (Klonopin) with immediate remission of suicidal ideation and akathisia.

Introduction

In March 2004 United States Food and Drug Administration (FDA) directed antidepressant makers to include with their products new instructions for prescribers. "Health care providers should instruct patients, their families and their caregivers to be alert for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality and worsening depression."¹ Assessment for medication-induced emotional and behavioral hyper-reactivity concomitant with administration or withdrawal of antidepressants is key to diagnosis and treatment. Differentiating akathisia (subjective and objective restlessness) presents special problems in persons subject to comorbid anxiety-depression spectrum disorders, drug-alcohol abuse, personality factors, polypharmacy, and other psychopathological states.² Appropriate diagnosis and treatment may be life-saving.³

Patient Description

TH is a 43 year old white recovered alcoholic. After a minor motor vehicle accident in April 2004 he was ticketed DUI (driving under the influence) and seen at the local emergency room with superficial scalp laceration and "jittery," but with no other medical signs or complaints. He admitted to 3-4 beers consumed at least 8 hours previously. Unenhanced head CT was unremarkable. EKG and chest radiography performed one day later after complaints of chest pain was unremarkable. He returned again in two weeks with chest complaints. On July he was admitted for full medical review of angina with no findings.

In October TH entered his first psychiatric hospitalization with suicidal thoughts and diagnoses of Major Depressive disorder, Alcohol Dependence (by history), and Personality Disorder NOS (with antisocial traits). Absent signs of agitation or alcohol withdrawal, he was treated with paroxetine sustained-release (Paxil-CR) 25 daily for depression and trazodone

¹ "Antidepressant labeling warns of worsening depression and suicidal behavior" *This week in medicine*, MD Consult, 24 June 2004, Conemaugh (Johnstown Pa) Health Information Services

² Akista HS, Benazzi F, Perugi G, Rihmer Z. "Agitated 'unipolar' depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy" *J Affect Disord*. 2005 Apr;85(33):245-258

³ Drake Re, Erlich J "Suicide attempts associated with akathisia" *Am J Psychiatry* 1985 April 142(4):499-501

(Desyrel) 50 mg for sleep. Rapid remission was attended by discharge 5 days post admission. On outpatient review paroxetine was discontinued and mirtazapine (Remeron) begun.

On December 30 he arrived unannounced at the general hospital having discontinued his medication. He attempted to jump off an inner balcony with a two-floor drop. Restrained and escorted to the ER, he was ill-kempt and acutely agitated but absent signs of drug or alcohol intoxication. Rapid calming was achieved with haloperidol (Haldol) 10 mg IM, but the patient refused a voluntary admission because “no one can help me.” He was committed on 302 status (150 hour preventative psychiatric detention) as “a danger to himself as the result of mental illness.”

When I first saw the patient the day following he was intermittently agitated, pacing, arms waving, body in motion, repeating passionately, “I am dead,” “all because of a DUI,” “they took everything from me,” “I’ll be in jail” “I can’t pay the fine” “I have to work.” He would gaze at me briefly, look away, look back, frantic repeating “I’m dead, I’m dead.” He walked out of the office. Walked back in. Walked out. He rebuffed conversation with waving arms and wringing hands, desperate fatalism, “you don’t know” “you have no idea,” “I’m jumping out of my skin.” He revealed no disturbance of intellect or cognition. He was oriented and lucid. Thought was consistent with dysphoric fluctuating affect. Pressure of thought and speech was marked by a fixed obsession of impending imprisonment and doom bordered upon delusional. Drug and alcohol screens and labs were unremarkable.

My initial diagnostic impression was (2) acute depression with suicidal ideation and (2) bipolar (type I, mixed). He was medicated with olanzapine (Zyprexa) titrated to 30 mg. daily and mirtazapine (Remeron) titrated to 45mg. daily. Lorazepam (Ativan) 2mg. po prn for acute agitation was ordered. Modest improvement was noted over the next several days with increased toleration of interpersonal contact, reduced panic, and decreased anxious emotionality accompanying his iterations of futility and inescapable “fine-jail-death” sequence. By the fifth day of hospitalization TH wanted out, but was encouraged to remain on voluntary status for continued treatment and observation.

By day eight marked relapse was apparent. TH signified a death wish for “Dr. Kervorkian,” and tried to negotiate with me for a lethal dose of medication. Upon a call-out to the nursing station, I watched him appear warily at his room door, edge along the wall, dart to the middle, take several steps back, then to the side, clinging to the wall as he approached. Asked if he was OK he said he was trying to avoid stepping on the carpet where it had recently been cleaned. After a short interview characterized by expressions of futile despair, he agreed to a stat dose of 1 mg. oral clonazepam (prescribed twice daily). Within 30 minutes he appeared relatively calm and lucid, discussing various options for engaging in post-discharge work that might help cope with his outstanding fine. No further odd or bizarre motor behavior was observed. The day following the attending psychiatrist noted his marked improvement. TH was discharged on day eleven stable on the above meds. Two weeks later he was readmitted for three days with a similar but less florid presentation.

Discussion

A focus on “restless legs syndrome (RLS), the most readily discriminable form of akathisia, has had the unfortunate consequence of relegating whole body restlessness (WBR) to its shadow. WBR is infrequently diagnosed or studied in the general population relative to its better known half-sibling. WBR is easily confused with delirium, agitation, hyperactive

disorders, bipolar, and psychotic states; and may present as a component of these conditions.

Restless legs syndrome is categorized as a hyperkinesia with stereotypic movements occurring in response to internal restless feeling. The four defining components are (1) desire to move the limbs, often associated with unpleasant sensations; (2) restlessness; (3) worsening at rest somewhat relieved by movement; and (4) increased symptoms in evening or night, often accompanied with sporadic kicking movement during sleep, and occasional cramps. Primary RLS is said to affect between 5 to 10 percent of the general population, worsen with age, and feature an autosomal dominant inheritance. Secondary RLS may be associated with medication, neuropathy, kidney failure, iron deficiency, and pregnancy. Besides resolution of underlying pathology, specific treatments include (1) discontinuation or dose reduction of offending medications; (2) nonselective serotonin antagonists (mianserin, ritanserin, cyproheptadine) for neuroleptic induced akathisia (NIA); and (3) dopamine enhancing meds (pergolide, bromocriptine, etc) for Parkinson syndromes. The α_2 -adrenoreceptor agonist clonidine (Catapres) has been useful. Benzodiazepines are most commonly used for symptomatic relief. Opiates are useful but infrequently prescribed.⁴

Complex rituals and patterned behavioral stereotypies are also found in general human social interaction, isolative behaviors, psychotic states and other psychopathology. Exaggerated chronic forms present in developmental disability, autism, and cerebral palsy. Motor displays may be (1) simple, such as hand flapping, spitting, and head aversion; or (2) complex, such as patterned ambulation forward or sideward, then back, then again forward, sometimes clinging to the wall or following other contextual clues. These behaviors may have a component of self-stimulation, and appear to worsen under conditions of stress or aggravation.

Acute stereotypies may be seen during the active phases of Grand Mal and Jacksonian seizures as well as in Temporal Lobe epilepsy. Chronic forms include Pteridae Syndrome (TS) with characteristic sporadic-repetitive verbal and non-verbal guttural ejaculations, and motor and emotional outbursts. In the acute hospital setting stereotypies are seen in organic states, drug and alcohol withdrawal syndromes, obsessive-compulsive disorder, depression NOS (not otherwise specified), and schizophrenia.

The suppression of acute stereotypies induced by amphetamines, phencyclidine, cocaine, and dopamine serves as baseline evidence for neuroleptic efficacy. The term “neuroleptic” refers to the ability of psychotropic medication to suppress stereotypies in laboratory animals. Psychotropic medication designed for suppression may also induce stereotypy. This is observed with regard to acute dystonic (extrapyramidal, EPS) reactions and tardive syndromes (dyskinesia, dystonia, akathisia).

Antipsychotic medications and antidepressants including those that inhibit the reuptake of serotonin (SSRI's) are well known for potent adverse effects including akathisia.⁵ Akathisia has been identified in potentiating the emergence of suicidal ideation and self-lethal behavior, especially at the inception of treatment, upon dose changes, or in the withdrawal phase. Atypical second generation (atypical) antipsychotics including olanzepine are broadly promoted for their ability to counteract both positive and negative symptoms in acute and chronic psychiatric

⁴ Goetz, *Textbook of Clinical Neurology* 2nd Edition (Elsevier, 2003), 280, 730-731

⁵ Benazzi F “Agitated depression: a valid depression subtype” *Prog Neuropsychopharm Biol Psychiatry* 2004 December 28(8):1279-1285

disability absent severe dystonic, akathisia, and tardive effects. Expanding indications for their use include acute stress disorders, panic, compulsive and phobic anxiety, severe agitation, bipolar excitement and depression. Adverse interactions in combination with SSRI antidepressant and paradoxical reactions to their use are still under-reported.

New generation antidepressant medication is generally correlated with lower suicide rates in depressed study populations.⁶ The antidepressant mirtazapine, while related to the SSRI's, has a distinctive mechanism with effects upon both noradrenergic and serotonergic function.⁷ In twenty-six schizophrenic patient with neuroleptic induced akathisia (NIA) mirtazapine improved both psychotic and parkinsonian symptoms, with mild sedative side effects⁸ One study found it superior to placebo and comparable to amitriptyline (Elavil) in the treatment of major depression with anxiety-agitation and anxiety-somatization.⁹ However mirtazapine used in depressed patients has been reported to induce an acute akathisia with restlessness of the lower extremities.¹⁰ One instance of the primary (genetic) form of restless legs syndrome (RLS) with depression worsened by the administration of mirtazapine has been reported.¹¹ In addition mirtazapine was associated with a suicide attempt six months after termination of interferon alpha (IFNalpha) treatment for hepatitis;¹² and psychosis in a Parkinson's patient subject to a chronic levodopa regimen.¹³

⁶ Gibbons RD, Hur K, Bhaumik DK, Mann JJ "The relationship between antidepressant medication use and rate of suicide" *Arch Gen Psychiatry* 2005 February 62(2):165-172

⁷ Hartmann PM, "Mirtazapine: a new antidepressant" *Am Fam Physician* 1999 Jan 1; 59(1):159-161

⁸ Poyurovsky M, Epshtein S, Fuchs C, Schneidman M, Wizmen R, Wizman A "Efficacy of low-dose mirtazapine in neuroleptic-induced akathisia: a double-blind randomized placebo-controlled pilot study" *J Can Psychopharmacol* 1003 June 23(3):305-308

⁹ Fawcett J, Barkin RL, "A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety" *J Can Psychiatry* 1998 March 59(3):123-127

¹⁰ One patient gained rapid relief on clonazepam. Girishchandra BG, Johnson L, Cresp RM, Orr KGD "Mirtazapine-induced akathisia" *Med J Australia* 4 March 2002 176(5):242

¹¹ Tieve Ha, de Quadros A, Barros Fc, Weneck LC "Worsening of autosomal dominant resless legs syndrom after use of mirtazapine: case report" *Arq Neuropsiquiatri*. 2002 December 4:1025-9. Pub. 2003 Jan

¹² Nickel T, Xonntag A, Backmund M, Pollmacher T "Depression during therapy with interferon alpha-how long should an antidepressant treatment last?" *Pharmacopsychiatry* 22005 March 38(2):102-104

¹³ Normann C, Hesslinger B, Frauenknecht S, Berger M, Walden J "Psychosis during chronic levodopa therapy triggered by the new antidepressive drug mirtazapine"

Conclusion

This case illustrates a severe complication of a second generation neuroleptic (olanzepine) use in combination with an atypical antidepressant (mirtazapine). Toward the end of his first week of pharmacologic intervention, TH presented with an increased anxiety/depression, whole body restlessness, and a drastic sense of impending doom with projected relief by suicide.. An acute onset complex behavioral stereotypy focused diagnostic attention on drug-induced akathisia. Rapid relief afforded by oral clonazepam underlines the significance of making the diagnosis of akathisia in reversing acute lethal preoccupation in a patient presenting with panic and depression. Long term relief from this whole-body akathisia syndrome remains problematic unless causal agents are better identified and carefully withdrawn when necessary.¹⁴

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April 2005

Pharmacopsychiatry 1987 November 30(6):263-265

¹⁴ Brasic JR, Barnett JY, Aisemberg P, Ahn SC, Nadrich RH, Kaplan D, Ahmad R, Mendonca MF "Dyskinesias subside off all medication in a boy with autistic disorder and severe mental retardation" *Psychol Rep* 1997 December 81(3Pt1):755-767