

# Polypharmacy Induced Psychosis and Cognitive Impairment in an Older Adult with Essential Tremor

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## Abstract

**Background:** Polypharmacy represents a common and pressing issue for geriatric patients. It increases the risk of significant drug interactions, adverse effects, and mortality. Here we describe a case of polypharmacy induced psychosis in a 78-year-old male with reversible cognitive impairment.

**Case presentation:** The patient was initially presented with acute encephalopathy and urinary tract infection. In the context of his tremors of unknown origin he was on pramipexole for over three years and amantadine for eight months. Eventually he became psychotic and began threatening family members. Laboratory studies and imaging of the head, chest, and abdomen demonstrated no contributory findings. Admission psychotropics also included a selective serotonin reuptake inhibitor (fluoxetine) and a benzodiazepine (clonazepam). He was transferred to a psychiatric facility on an involuntary basis and continued to demonstrate impaired cognition (Montreal Cognitive Assessment [MoCA] score of 24) and agitation. With discontinuation of the above medications and initiation of risperidone and bupropion, the patient gradually became calmer and cognition improved to near-normal levels (MoCA 26).

**Conclusion:** This case demonstrates the need for caution in prescribing dopaminergic and anticholinergic medications to geriatric patients, since certain combinations of medications may induce subacute states of psychosis and cognitive impairment that may both be reversible with discontinuation, even if the patient previously had appeared to do well on the medications.

**Keywords:** Geriatric Psychiatry; Polypharmacy; Cognitive Impairment; Psychosis; Pramipexole; Amantadine; Risperidone; Dopaminergic

**List of abbreviations:** MoCA: Montreal Cognitive Assessment; PIM: potentially inappropriate medications; STOPP: Screening Tool of Older Person's Prescriptions; UTI: Urinary Tract Infection; HbA1c: Glycated Hemoglobin; TSH: Thyroid Stimulating Hormone; gm: gram(s); IV: Intravenous; mg: milligram(s); mcg: microgram(s); NMDA: N-methyl-D-aspartate; CAD: coronary artery disease; GERD: Gastroesophageal Reflux Disease

## Background

On average, 14 medications, including an average of six pharmaceuticals that may promote geriatric syndromes, are prescribed to patients over the age of 65 [1]. Many of these prescribed medications fall into the category of potentially inappropriate medications (PIM), and a recent study showed that about half of inpatient geriatric patients take PIMs [2]. In addition to potential unpredictable drug interactions, older patients are also at the risk of unknown changes in age-related pharmacokinetics and pharmacodynamics. Moreover, the risk of adverse drug effects increases exponentially with the increase in polypharmacy [3]. Although various strategies, including Beers Criteria and Screening tool of older person's prescriptions (STOPP), are recommended to minimize polypharmacy in geriatric populations, simple methods, such as matching indication with each medication, can be very effective in resolving adverse effects [4-6]. A case of polypharmacy induced psychosis and cognitive impairment in an older adult, and its successful resolution through indication-matched titration of medications, is described here.

## Case Presentation

### History of Presenting Illness

K.H. is a 78-year-old Caucasian male with a history of depression, tremors, diabetes with peripheral neuropathy, arthritis, coronary artery disease, transverse myelitis (on long term steroids), and prostate cancer in remission (with subsequent hypogonadism on

testosterone replacement). He was presented to a hospitalist service for urinary tract infection (UTI) and acute encephalopathy, including visual hallucinations of people invading his home.

The patient appeared confused, paranoid, and unable to give a coherent history. He stated that he was brought to the hospital against his will because he had accused his wife of infidelity with younger men, and denied the visual hallucinations he had previously reported. The patient had no physical complaints and review of systems was negative except for longstanding resting tremor, which was observed at 1-2 per minute involving all four extremities. Complete blood count demonstrated mild neutrophilia and comprehensive metabolic panel demonstrated blood urea nitrogen 52 mg/dl, creatinine 1.85 mg/dl (consistent with acute kidney injury and dehydration), blood glucose of 161 mg/dl (in context of glycated hemoglobin [HbA1c] 6.5%), normal thyroid stimulating hormone (TSH) levels, and mild hyperbilirubinemia. The creatinine clearance ranged from 42 to 47 mL/min, consistent 85 with his long-standing diabetes and associated chronic renal vascular disease. Urinalysis demonstrated positive nitrite and large leukocyte esterase consistent with UTI. Computerized tomography of the head demonstrated only changes of advancing chronologic age (mildly prominent sulci and parenchymal volume loss) and chronic right sphenoid sinus disease, which brain magnetic resonance imaging confirmed. Chest radiography did not reveal any acute findings. Abdominal and retroperitoneal ultrasounds showed no hydronephrosis or cholecystitis, though signs of bladder outlet obstruction and gallstones were present. The patient's medications on admission to the medical facility included clonazepam, amantadine, and pramipexole. Additionally, the hospitalist service started risperidone 0.25 mg daily to control agitation (Table 1). The consult service initiated involuntary psychiatric admission due to ongoing agitation, combativeness, and visual hallucinations placing the patient and his family at risk for harm.

Medication	Dose	Indication	Note
Cefepime	2 gm/24 hours IV	UTI	Previously on Doxycycline 100 mg/daily and Methenamine 1 mg/daily
Aspirin Metoprolol Atorvastatin	81 mg/daily 50 mg/twice daily 10 mg/daily	CAD	
Amantadine Clonazepam Pramipexole	100 mg/daily 0.25 mg/nightly 1.5 mg/twice daily	Random spasms	Initially thought to be Parkinsonian, but later diagnosed as benign essential tremor
Linagliptin Gabapentin Vitamin B12 Vitamin D3	5 mg/daily 100-200 mg/nightly 1000 mcg/daily 400 units/daily	Diabetes with neuropathy	
Omeprazole	40 mg/daily	GERD	

UTI: Urinary Tract Infection; CAD: Coronary Artery Disease; GERD: Gastroesophageal Reflux Disease.

**Table 1:** List of medications on admission

## Psychiatric History and Mental Status Exam

On arrival to the psychiatric unit, two weeks into his medical hospitalization, risperidone had been increased to 0.5 mg daily, but the patient continued to describe bizarre delusions about his wife having extramarital affairs with multiple men. He also reported distress related to a dispute among partners in his recently retired legal profession, and complained that medical hospital employees were blowing marijuana smoke into his room. He carried prior diagnoses of depression, anxiety, and insomnia, for which he had tried fluoxetine, clonazepam, and zolpidem, respectively, in the past. His mental status exam findings included hyperverbal speech, disturbances of thought process including circumstantiality, tangentiality, and looseness of associations, derailment, and thought content, including visual hallucinations (involving his sitter), paranoid ideation, and delusions. He had incorporated his delusions into his personal history, stating that his wife had been having affairs “for years”, even though his first complaint about them had occurred only three weeks earlier. Family also stated the patient had reported a visual hallucination of someone lying on a road.

## Hospital Course

The treatment team increased risperidone to 0.75 mg twice daily on admission. For the next four days, however, the patient remained paranoid about other patients in the milieu, and would not eat, due to worry about his food being poisoned. He had difficulty catheterizing himself and returned to the emergency department short-term for Foley catheter insertion. He was readmitted to the geriatric psychiatry unit with a MoCA score of 24. The MoCA score for cognitive assessment ranges from 0 to 30, where the average normal score is 27.4 and a score below 26 meets the criteria of cognitive impairment (7). The revised medication regimen in the geriatric unit included discontinuation of amantadine, pramipexole, linagliptin and gabapentin, as well as inclusion of risperidone 0.75 mg twice daily for psychosis, which was later increased to 0.75 mg daily/1 mg nightly day 2, and 1 mg twice daily starting day 3 (Table 2). The patient continued to have insomnia, so trazodone was started at 25 mg nightly as needed for mood and sleep on day 4, which was increased to 50 mg on day 5. Nitrofurantoin treatment was completed on day 4. Though the patient had previously taken fluoxetine for depression, bupropion was started at 100 mg daily on day 5 instead, to avoid worsening of psychosis via serotonergic effects.

By day 7, the patient was denying hallucinations and delusions, demonstrated brighter affect, and sleep had improved to six hours per night. Sitagliptin 100 mg daily (formulary replacement for linagliptin) was resumed in preparation for discharge. By day 8, the patient's wife noted his improvement in mood and behavior and informed the team she felt comfortable with his discharge. The patient was discharged on day 9 with plan to continue risperidone, bupropion, and trazodone, to stay off amantadine and pramipexole, and follow up in ten days with neurology and psychiatry as an outpatient. Repeat MoCA on the day of discharge was 26/30, within normal limits, with the only deficient items including two missed words on 5-minute recall (one recovered on category cue), ten of eleven required words on fluency test, and inattention on backward digit repetition, all consistent with, or improved from, the patient's baseline cognition as reported by family.

Medication	Dose	Indication	Note
Nitrofurantoin	100 mg/12 hours	UTI	
Aspirin Metoprolol Atorvastatin Omega-3 fatty acids	81 mg/daily 50 mg/twice daily 10 mg/daily 2 gm/daily	CAD	
Clonazepam	0.25 mg/nightly	Spasms	Discontinued Amantadine and Pramipexole
Vitamin B12 Vitamin D3 Vitamin C	1000 mcg/daily 400 units/daily 1000 mg/daily	Diabetes with neuropathy	Discontinued Linagliptin and Gabapentin
Pantoprazole	80 mg/daily	GERD	Pantoprazole substituted for Omeprazole
Docusate Polyethylene glycol	100 mg/daily 17 gm/daily	Constipation	
Fluticasone	50 mcg/twice daily	Nasal Congestion	
Risperidone	0.75 mg/twice daily	Psychosis	1 mg/nightly day 2 and 1 mg/twice daily starting day 3
Oxycodone-acetaminophen	5-325 mg/eight hours as needed	Moderate pain	

UTI: Urinary Tract Infection; CAD: Coronary Artery Disease; GERD: Gastroesophageal Reflux Disease

**Table 2:** List of medications in the geriatric unit

## Discussion and Conclusion

Polypharmacy is a recurrent problem in the geriatric population. The adverse effect frequency of polypharmacy ranges from 30% in general populations to more than 50% in inpatient settings [1,3,8]. Especially notable is the adverse impact of polypharmacy on mental status and comorbidity of geriatric patients presented to psychiatric services [8,9]. A case of successful resolution of polypharmacy-induced psychosis and mild cognitive impairment, by systematic attrition of polypharmacy, in a 78-year-old male patient is discussed here.

In the population over age 75 years, depression and dementia are often intertwined, and evidence exists for depression as a risk factor for neurocognitive disorder [10,11]. However, the cognitive impairment observed in our patient occurred in the absence of a mood disturbance and was reversible. Similarly, psychosis in an elderly patient with tremor has a broad differential diagnosis, from the various "organic" causes of delirium to the sequelae of Parkinson disease and Lewy body dementia [12]. The dopamine agonists, useful in treatment of tremors, however, themselves carry risk of psychosis due to central dopaminergic stimulation. A previous case report has documented the onset of persecutory delusions in an 89-year-old male following a dosage increase of pramipexole [13].

In this article, we describe the case of a 78-year-old male with the subacute onset of symptoms consistent with a major neurocognitive disorder who was presented in a delirious state while suffering from a urinary tract infection. Despite resolution of the proximate cause of delirium, he remained psychotic until discontinuation of both pramipexole and amantadine. He had been on the former for over three years, while the latter had been added eight months prior to his admission to the inpatient unit. Both were prescribed off-label as an outpatient for disabling essential tremor. Pramipexole, a central dopaminergic agonist, in addition to its use in Parkinson disease and restless limb syndrome, has been proposed for use in treatment-resistant depression and bipolar I depression, as well as treatment of Parkinsonian psychosis itself [14]. It has previously been demonstrated to induce psychosis in a dose-dependent fashion after long term use, including persecutory delusions and vivid visual hallucinations similar to those described in the present case [15]. The higher than recommended dose (maximum renal dosing recommendation is 0.75 mg TID) the patient was receiving, in conjunction with renal vascular disease at the time of admission also may have contributed significantly to the psychiatric presentation. With discontinuation, our patient's cognition subsequently improved as well, such that he no longer met criteria for a neurocognitive disorder. Similarly, amantadine recently has been associated with several documented cases of acute delirium with manic and psychotic features [16,17], yet has also been described as improving catatonia in a subset of previously psychotic patients via its N-methyl-D-aspartate (NMDA) receptor agonism [18]. To our knowledge, this case represents the first

published association of stable long-term dosages of amantadine and pramipexole inducing psychosis and cognitive impairment, each reversible by discontinuation of both medications and initiation of antipsychotics. This case demonstrates the importance of limiting medications in the elderly to the minimal dosage and number necessary to optimize daily function and overall quality of life.

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