



Polypharmacy Induced Delirium: A Case Report Highlighting the Importance of a Thorough Psychiatric History and Physical

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ABSTRACT

A combative aggressive 65 year old female was brought in to the Emergency Room (ED) after found wandering in the streets. Agitated, confused, disoriented in a delirious state, she was admitted to psychiatry for diagnostic clarification. All labs except low platelets were Within Normal Limits (WNL). Imaging was normal. She was not a known neuro-cognitive disorder patient. Poly-pharmacy was ruled in as the etiology of the delirium highlighting the importance of careful prescribing especially in older persons. Moreover, this case highlights the importance of having expert knowledge in (a) the prescribing of psychotropic medication to include mechanism of action, effects, side effects, and interactions, (b) treating delirium, and (c) the importance of a thorough history and physical. From this case report, the authors recommend consulting psychiatry as a standard of care in treating delirium.

Keywords

Delirious, Poly-pharmacy, Delirium

Introduction

Delirium is defined as a transient, usually reversible, cause of mental dysfunction and manifests clinically with a wide range of neuropsychiatric abnormalities [1]. Delirium can occur in any patient population either young or old, however it occurs more commonly in patients who are elderly and who have a neurocognitive disorder [1]. Decreased or change in baseline cognition, attention, or awareness are clinical hallmarks of delirium and often manifests with a waxing and waning type of confusion [1]. Symptoms include: clouding of consciousness, difficulty maintaining or shifting attention, disorientation, illusions, hallucinations, fluctuating levels of consciousness, dysphasia, dysarthria, tremor, asterixis in hepatic encephalopathy, uremia, and motor abnormalities [1].

The diagnosis of delirium is clinical. No laboratory test can diagnose delirium. Diagnostic

criteria: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for delirium are as follows [2],

Disturbance in attention (i.e., reduced ability to direct, focus, sustain and shift attention) and awareness.

Change in cognition (eg., memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia.

The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause.

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Typically anti-psychotics are used as first line agents in treating delirium [3,4]. However as a bit of irony, there is evidence that up to 30% of the cases of delirium in elderly hospitalized patients is caused by medication toxicity to include psychotropic medications [5]. Hospitalized patients and elderly are more at risk of developing cognitive impairment as a result of taking medications. Both age and associated disease states in the elderly especially as it relates to both brain neurochemistry and drug metabolism, are factors making this population at risk [5]. Cases of drug induced delirium can result from Central Nervous System (CNS) toxicity with or without dose dependent manner and with interference of neurotransmitter function [5]. Drug induced delirium can also be an idiosyncratic complication and/or secondary to iatrogenic complications of medication use [5].

Although any drug theoretically can cause delirium, psychoactive drugs are important causes of delirium [5]. Drugs with cholinergic properties such as those used in the Alzheimer's disease spectrum treatments have associated risk in causing delirium [5,6]. So too do anti-psychotics which often have anti-cholinergic properties which can cause delirium. Medication induced delirium is thought to be a temporary psychiatric disorder resulting from a reduced central cholinergic transmission, combined with an increased dopaminergic transmission [6].

The cholinergic and the dopaminergic systems interact not only with each other but with glutamatergic and gamma-amino-butyric acid (GABA) pathways [7]. The cerebral cortex, striatum, substantia nigra, ventral tegmental area and thalamus are all implicated in mental status changes seen in delirium [7]. The thalamus acts as a filter, allowing only the relevant information to travel to the cortex. Psychoactive medications frequently prescribed to hospitalized patients (e.g. benzodiazepines, opioids, antipsychotics) can compromise the thalamic functioning, leading to sensory overload and hyperarousal [7]. Literature [7] proposes that drug-induced delirium would result from the transient thalamic dysfunction caused by exposure to medications that interfere with central glutamatergic, GABAergic, dopaminergic and cholinergic pathways at critical sites of action [7]. A list of drugs believed to cause or prolong delirium or confusional states is seen in the **Table 1**.

Case Report

This is a case of 65 years old female (Ms. M) who was brought in ED by the police. She was found wandering in the streets and knocking on strangers' doors. On presentation she was increasingly confused, disoriented, restless and agitated. Ms. M had psychiatric history of being intermittently treated for bipolar disorder. She

Table 1: Drugs believed to cause or prolong delirium or confusional states [1-12].

Analgesics	Corticosteroids
NSAIDs	Dopamine agonists
Opioids (especially meperidine)	Amantadine
Antibiotics and antivirals	Bromocriptine
Acyclovir	Levodopa
Aminoglycosides	Pergolide
Amphotericin B	Pramipexole
Antimalarials	Ropinirole
Cephalosporins	Gastrointestinal agents
Cycloserine	Antiemetics
Fluoroquinolones	Antispasmodics
Isoniazid	Histamine-2 receptor blockers
Interferon	Loperamide
Linezolid	Herbal preparations
Macrolides	Atropa belladonna extract
Metronidazole	Henbane
Nalidixic acid	Mandrake
Penicillins	Jimson weed
Rifampin	St. John's wort
Sulfonamides	Valerian
Anticholinergics	Hypoglycemics
Atropine	Hypnotics and sedatives
Benzotropine	

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Diphenhydramine	Barbiturates
Scopolamine	Benzodiazepines
Trihexyphenidyl	Muscle relaxants
Anticonvulsants	Baclofen
Carbamazepine	Cyclobenzaprine
Levetiracetam	Other CNS-active agents
Phenytoin	Disulfiram
Valproate	Cholinesterase inhibitors (eg, donepezil)
Vigabatrin	Interleukin-2
Antidepressants	Lithium
Mirtazapine	Phenothiazines
Selective serotonin reuptake inhibitors	
Tricyclic antidepressants	
Cardiovascular and hypertension drugs	
Antiarrhythmics	
Beta blockers	
Clonidine	
Digoxin	
Diuretics	
Methyldopa	

was sleepless for several nights. She was admitted in psychiatric ED with the presumption of having an exacerbation of her bipolar disorder.

On evaluation, Ms. M had waxing and waning level of consciousness with intermittent episodes of wakefulness. She was restless, trying to climb out of bed, and trying to pull her naso-gastric tube and intravenous lines. Her long term memory was deranged and she had difficulty in sustaining her attention. While in the hospital, she was started on haloperidol 5 mg as needed for behavioral control and safety. Laboratory tests revealed blood glucose of 104 mg/dl, hemoglobin of 10.7 g/dl, and her platelet count was low at 70,000. The rest of her tests, complete blood count, urinalysis, chemistry, kidney and liver function were within normal limits. Both brain CT and MRI were normal. She was too paranoid to perform any neuropsychiatric testing.

At the time of evaluation, Ms. M's regular medication regimen was hydroxyzine temazepam (30 mg at bed time), mirtazapine (15 mg at bed time), gabapentin (400 mg three times daily), sodium valproate (500 mg twice daily), lorazepam (0.5 mg three times daily), topiramate (50 mg twice daily). Ms. M was subsequently diagnosed with medication induced delirium. Polypharmacy was tapered and discontinued constituting a medication washout.

Haloperidol was continued due to her agitation and delirium. Sodium Valproate was continued for her bipolar disorder. She showed gradual

improvement of her behavioral and cognitive functioning. She was discharged home with her sedatives weaned off. On follow up visit one week after her discharge, she continued to do well with no behavioral or cognitive sequelae. Her Mini-Mental Status (MMSE) score on follow up visit was WNL.

Discussion

Delirium is common in older persons in hospitals and long-term care facilities, and it may indicate a life-threatening condition [8]. Estimates of the prevalence of delirium vary based on the population studied, the timeframe in which delirium is assessed, and the method of assessment [8]. Nearly 30 percent of older medical patients experience delirium at some time during hospitalization [9]. Drug toxicity causes or contributes to approximately 30 percent of all cases of delirium [9,10]. It has been noted to occur in 11-42% of medical inpatients [11].

Benzodiazepines, anticholinergics, and antipsychotic's, in particular, are often implicated [9,10].

Delirium has been described for hundreds of years, and many case reports and studies have been written on medication induced delirium. The current case highlights a learning point described by Kosari [11].

"Delirium is a multifactorial disorder that can be precipitated by any medical condition in susceptible

person, therefore a comprehensive history and physical (H&P) examination is imperative to guide diagnostic investigations.”

The current case also highlights the importance of expertise and coordination of care among physicians (and non-physician providers) in psychotropic prescribing. It was not clear in the case as to how Ms. M arrived at such a complicated psychiatric medication regimen. It is surmised that with multiple providers and multiple medications, medications are added superfluously, without thorough histories, without coordination among physicians.

The authors of the current case contend that a high level of psychiatry expertise is required for psychotropic management of psychiatric patients. The authors also contend that because delirium is a multifactorial disorder, and psychotropic medications can be dangerous, expert psychiatric consultation is required. This case highlights just how dangerous psychotropic medications can be. Because these psychiatric conditions and delirium are brain diseases, they must be understood to the micro-level. Delirium predisposing factors such as dementia, stroke, Parkinson's disease, advanced age, and sensory impairment [11] must be fully understood by both physicians and non-physician providers prescribing psychotropics. Delirium precipitating factors such as poly-pharmacy, infection, dehydration, immobility, malnutrition, and the use of urinary catheters [11] must be fully elucidated in the H&P. The current case highlights that psychotropic medication management of psychiatric patients and treating delirium needs to either be at the level of residency trained psychiatrists or non-physician providers with physician level oversight.

A thorough psychiatric H&P is especially important in managing delirium. Delirium is a very common medical condition encountered throughout the world and is one of the most

frequent reasons psychiatrists are consulted [12]. The H&P needs to be at the level described in Markowitz and Narasimhan [12] where the physician should search for contributing causes, obtain a complete history, including a careful review of medication usage and illicit drug history, and perform full physical and neurological exams. In performing this H&P, the detailed science of neurobiology and neuropathogenesis needs to be fully appreciated in order to be thorough.

In treating delirium, the authors of the current case recommend consulting a psychiatrist as a standard of care. Psychiatrists understand the neurotransmitters most strongly implicated in delirium pathogenesis such as acetylcholine and dopamine [12]. While decreased acetylcholine and anticholinergic activity is presumed to play a role in delirium, hyperactivity in the dopamine system is also implicated in the pathogenesis of delirium [12]. Psychotropic medications work on these neurotransmitter systems. Less is known about the role of serotonin and gamma-aminobutyric acid (GABA) in delirium pathogenesis. Although these neurotransmitters are involved in the mechanism of action of medications such as anti-depressants and sedatives used in psychiatry [12]. Excess glutamate activity or decreased histamine activity also may be etiologic factors in delirium [12], and certain psychotropic medications involve these neurotransmitters.

Conclusion

In summary, the authors of the current study would like to add to the learning point of Kosari by adding the following addendum:

“Delirium is a multifactorial disorder that can be precipitated by any medical condition in susceptible persons, therefore a comprehensive history and physical (H&P) examination is imperative to guide diagnostic investigations” and expert level psychiatric consultation should be the standard of care.

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