

PRESCRIPTION MEDICATION-INDUCED PSYCHOSIS: A HIGH ALERT FOR DRUG EXPERTS

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ABSTRACT

Psychosis is a complex mental illness of behavioral, psychological, and emotional disturbances. Secondary psychosis can be elicited by prescription medications and literature is replete with examples of such drugs.

Objectives: The goal of this article is to gather information from multiple published sources to highlight the culprit prescription medications that are linked with psychotic episodes and compose the findings into a simplified, stand-alone publication for readers to conveniently become aware of this phenomenon. It is also intended to reiterate the critical role and significance of the pharmacist as a vital player in a health care team. **Methods:** The scientific literature was searched on the PubMed database using the key search phrase “psychosis, medicines or drug or prescription.” The search was limited to the time period from 1960-2019 to ensure the inclusion of the vast majority of previously reported cases of currently available medicines and their related psychoses. **Conclusion:** Commonly-prescribed medications can cause serious, albeit preventable, psychiatric issues. Pharmacists as vital players in patient care can avert the untoward psychotic episode by taking timely steps in notifying the prescribers or counseling the patient on measures to avoid serious and fatal psychotic issues.

Keywords: Psychosis, Drug-induced, Pharmacist, Counseling, Patients

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INTRODUCTION

Psychosis is a multi-factorial mental disorder characterized by delusions, hallucination, incoherent speech, social withdrawal, sleep disturbances etc. More specifically, psychotic symptoms are categorized as positive (delusions, hallucinations), negative (anhedonia, avolition, poverty of thought and motivation, flat affect) and cognitive (impaired attention, concentration, judgment and cognition) [1,2]. It has long been established that elevation in dopamine levels in mesolimbic pathway with some presynaptic dysregulation accounts for psychosis-like symptoms [3]. There is evidence that alterations in serotonin activity are also implicated in pathophysiology of psychosis. Clinically, psychosis is described as primary or secondary based on the causative factors. Primary psychosis is associated with or follows psychiatric conditions such as schizophrenia or bipolar disorder while secondary psychosis is evoked by other medical conditions or drug or medication use or medication withdrawal [4]. Most often, drug-induced psychosis refers to the psychotic episodes caused by abuse of some illicit

psychoactive substances or street drugs such as methamphetamine [5], cannabis [6], cocaine [7], opioid [8], lysergic acid diethylamide (LSD) and/or psilocybin [9], phencyclidine [10] as well as chronic alcohol [11]. However, the purpose of this present article is to focus on psychosis induced by clinically prescribed medications with the intention of refreshing knowledge, increasing awareness and sharing some relevant patient counseling tips for better outcomes.

Below, we discussed some pharmacological agents with a potential for psychotic effects followed by some interesting case reports as examples from the literature and finally, we shared some best practice rules for our community and clinical pharmacists (drug experts) to watch out for offending medications and come up with the intervention plan.

CNS STIMULANTS

CNS stimulants belong to the class of drugs known as sympathomimetics: drugs that mimic the effect of sympathetic nervous system activation. CNS stimulants are not only popular as illicit drugs of

abuse in general population [12] and in psychiatric patients [13], but also have therapeutic significance in the treatment of ADD, ADHD, narcolepsy and obesity. Clinically relevant CNS stimulants include amphetamine and its derivative salts and/ or methylphenidate.

Currently, multiple dosage forms of amphetamine salts are marketed with varying pharmacokinetic characteristics. Some examples are adderall, adderall XR, dexedrine (dextroamphetamine), vyvans (lisdysamphetamine), concerta (methylphenidate) and quillivant (liquid methylphenidate) are closely related to amphetamine mechanistically and are indicated for the same reasons as amphetamine salts.

Although amphetamine or other CNS stimulants are therapeutically successful in achieving goals in their clinical indications, their use is accompanied by a vast array of side effects: gastrointestinal, cardiac, and behavioral or CNS side effects owing to their ability to enter CNS. Most on-label CNS side effects are hyperactivity, insomnia, anorexia, growth retardation, irritability, emotional lability, social withdrawal as well as psychosis.

Not only high doses of amphetamine are associated with psychosis, normal therapeutic dose (5-10 mg) after repeated exposure can also produced psychosis marked with delusion and hallucination in healthy volunteers [14-16]. Similarly, in another study, amphetamine 10 mg when taken for 5 weeks precipitated acute symptoms of psychosis in ADHD patients without any personal or family history of psychiatric disorder [17]. This clearly demonstrates the potential of amphetamines for causing psychosis. In this context, two physiological factors are of paramount importance in increasing patient's vulnerability of suffering psychosis: 1) pre-existing psychiatric problems 2) pharmacokinetic interactions. As for the first factor, only one single dose of a stimulant can precipitate psychotic episode in schizophrenic patients with or without acute symptoms. Secondly, pharmacokinetic parameters also play a role in determining the biological half life or therapeutic levels of drugs. Since amphetamine salts are weak base, their renal excretion can be altered by modifying the urinary pH. For instance, ingestion of acidic diet or acidification of urine can increase the renal excretion of amphetamine metabolites and can shorten its half life. While alkalinization of urine can lead to higher renal absorption or increased therapeutic levels of amphetamine, thus prolonging its duration of action which enhances the risk of psychosis [18].

Another grave concern associated with the prolific use of amphetamine or other stimulants is that their early exposure to children or adolescents for clinical reasons might predispose these patients for later drug

abuse. A survey of 9000 college student revealed that students who were prescribed stimulants while in secondary school were three times more likely than naïve students to abuse illicit drugs [19]. However, the same was not true for the students who were prescribed ADHD medications in elementary school. Although data is not conclusive and reports contrary to the first survey also exist, subsequent abuse potential for stimulants in legitimate users cannot be ruled out.

In the past several years, prevalence of ADHD has risen exponentially. According to American Psychiatric Association, about 8.4 % of children and 2.5 % of adults in the United States have ADHD, while CDC reports about 6.1 % (about 4 millions) of US children (2-17 years) were diagnosed with ADHD and 5.1% received ADHD medications [20-22]. Given the alarming increase in ADHD cases and the use of stimulant medications, it is logical to assume that the cases of stimulant-related psychosis may also grow. This demands high level of vigilance from health care providers in patient care.

Examples from Literature

- 1- A 39-years female developed acute psychotic symptoms with confusion, hallucination, personality changes after taking prescribed sibutramine (appetite suppressant) 10 mg a day for 3 weeks. Her symptoms subsided after about 2 weeks of discontinuation of sibutramine [23].
- 2- A 12-year old girl was prescribed adderall 10 mg for ADHD and 2 weeks later she was rushed to the hospital for an anxiety attack which followed prior episodes of insomnia, bizarre behavior and tactile hallucination. All lab results were normal. She has no personal or family history of psychosis or drug abuse except for her mom being a cigarette smoker. Her symptoms improved after discontinuation of adderall for 7 day [24].

CORTICOSTEROIDS

Corticosteroids are a mainstay of treatment for a vast majority of acute or chronic inflammatory or immunological disease including, allergies, asthma, arthritis, lupus, inflammatory bowel disease, chronic pain. Nevertheless, their use or sudden withdrawal is linked with psychiatric problems.

There are numerous reports detailing the incidents of acute psychosis following steroid therapy in both children [25] and adults [26]. Corticosteroid-related psychiatric effects can occur after a single (80mg Depomedrone, hip) [27] or multiple exposures (40 mg Methylprednisolone, intra-articular injection) [28]. Even repeated oral dose (Prednisone 40 mg) has shown to produced reversible symptoms of psychosis in a 12-year old patient with lupus erythematosus [25].

Steroid related psychotic symptoms range from simple episode to transient insomnia or anxiety to much serious effects like confusion, delirium, hallucination, paranoid, violent aggression, cognitive impairment and dementia [28]. There seems to be a possible dose-dependent relationship between steroid and its induced psychosis as prednisone dose higher than 80 mg /day caused psychiatric symptoms in 18.4 % while dose 40-80/day mg caused parallel symptoms in 4.6% of patients, respectively. And doses less than 40 mg/day caused only 1.4% of psychiatric issues [26]. The typical onset for steroid-induced psychiatric problems is 7-11 days [29].

Therefore, it is important that health care providers pay closer attention to the prescribing dose and duration of steroid therapy as well as the concurrent medication as CYP inhibitors can delay the metabolism of steroid and increase its plasma levels and duration of effects [30].

Despite the plethora of studies reporting steroid-induced psychosis, the precise mechanism for corticosteroid-associated psychosis has not been explored or defined in recent years. It seems like corticosteroid-inhibited presynaptic uptake of dopamine is a plausible explanation for psychotic behaviors [31]. Also, there is a need to research the individualized susceptibilities to steroids related psychotic behaviors so that dose adjustment can be performed prior to the treatment.

Examples from Literature

1. Our literature search revealed an interesting case of a young 14-years old boy who suffered an acute psychotic episode marked with visual hallucination, delusion and bizarre behavior after switching from Flovent inhaler (steroid) (110 µg; 1 puff; twice daily) to Advair diskus (100 µg/50µg; 1 inhalation twice a day) for his asthma control. Patient has no prior personal or family history of psychotic symptoms. He was taking Focalin for his ADHD and Abilify for intermittent explosive disorder at the time of his presentation to ER with psychotic behavior. Patient's symptoms resolved after discontinuation of his Focalin and Advair diskus [32].
2. An 8-year old white child was prescribed cephalexin, prednisone 50 mg a day; Pulmicort (steroid inhaler) and Nosonex (steroid nasal spray) for his asthma and sinusitis. Five days after the onset of treatment, the child developed visual hallucinations, depression, and suicidal thoughts. His lab and EEG were all normal. No family or personal history of psychosis was noted. His symptoms were subsided after 2 days of stopping prednisone [33].

ANTIBIOTICS

There is a strong evidence from multiple reports that the use of some antibiotics including, penicillins, cephalosprins, fluorquinolones [34, 35], antimalarial

[36] and macrolides [37] carry a risk of neurological side effects. These side effects can range from mere anxiety, depression to seizures, delirium or psychosis [36, 38]. Antibiotics related above side effects can occur within days of treatment (penicillins or cephalosporins) or can be delayed for weeks post antibiotic treatment (metronidazole) [39]. Although patients with prior psychiatric history or use of antipsychotics are more vulnerable to antibiotic associated psychosis, high percentage of naïve patients also experienced acute psychiatric effects that either resolve on discontinuation of antibiotics or required some antipsychotic therapy [40].

We noticed a high prevalence of psychosis in patients especially elderly populations with urinary tract infection treated with ciprofloxacin containing regimen [40, 41]. Similarly, there are numerous reports of acute transient psychotic episodes triggered by *Helicobacter pylori* (*H. pylori*) triple therapy treatment [42] in otherwise healthy individuals without any psychiatric history. And clarithromycin was found to be the offending drug. Others have also reported bizarre and psychotic behaviors initiated by clarithromycin during treatment for *H. pylori* or community-acquired pneumonia [43]. There is a general consensus in literature that ciprofloxacin and clarithromycin are the most notorious antibiotics responsible for “antibiomania”: term used to describe maniac episode following antibiotic therapy [44]. Though antibiomania phenomenon is rare with antibiotic therapy, co-morbid factors can contribute to bring it to fruition. Several mechanisms have been proposed to explain psychiatric side effects of antibiotics and are shown in **Table 1**.

The bottom line is that health care professionals should be wary of the risk factors that predispose a patient to embarrassing and frustrating, albeit transient and reversible, psychotic episodes that might require costly hospitalization or visit to emergency department. Some of these risk factors are poly-pharmacy, advanced age, renal or hepatic impairment, history psychiatric or medication illnesses. These predisposing risk factors should be considered before prescribing or dispensing a medication.

Examples from Literature

1. An 18-years old male was brought to the emergency after self-inflicted gunshot wound to the face resulting in multiple facial fractures and brain lesions. Patient has started a course of sulfamethoxazole-Trimethoprim (SMX-TMP) treatment for toe-nail infection a week ago. Few days into the antibiotic treatment the patient became rude, depressed, withdrawn and started to have visual hallucinations. Patient has no history of psychosis. As for the family history, paternal uncle had committed suicide. Patient

was diagnosed with SMX-TMP induced psychosis which was resolved after discontinuation of therapy [53].

2. A 64-year hospitalized male with a history of hypertension, COPD and bronchiectasis was prescribed cefuroxime, ciprofloxacin and ipratropium inhalations for aggravation of his COPD and possible infected bronchiectasis. Four days later patient's

respiratory symptoms were improved but he became confused, disoriented, and developed visual hallucination. His blood, urine tests were normal as well as his neurology examination. Ciprofloxacin-induced acute psychosis was diagnosed which remitted twenty-four after stopping the medication [41].

Table 1: Proposed mechanisms of some antibiotic-induced psychosis.

Antibiotic	Mechanism of psychosis	References
Clarithromycin	Direct neurotoxicity Possible modulation of glutamatergic or G-aminobutyric acid pathways Alterations of cortisol and prostaglandin metabolism	[45, 46]
Ciprofloxacin / Metronidazole	Possible inhibition of GABA _A receptors	[47]
Sulfamethoxazole-Trimethoprim	Inhibition of Dihydrofolate reductase and depletion of tetrahydrobiopterin and folic acid	[48]
	Hypofunctioning of NMDA receptors	[49]
	Destruction of bacterial flora that produces D-alanine	[49]
Cephalosporins	Enhanced TNF α release that causes neurotoxicity	[50]
Antivirals (Acyclovir, Ganciclovir, Valacyclovir)	Unknown (crosses BBB; probably direct toxicity in renal impairment)	[51]
Antimalarial (quinidine, mefloquine)	Disruption of endoplasmic reticulum Ca homeostasis	[52]

ANTIEPILEPTICS

Mood and behavioral disorders are frequent adverse effects of antiepileptic medicines. Examples of common antiepileptics with reported psychotic potentials are topiramate, vigabatrin, zonisamide, ethosuximide, pregabalin. Careful selection of right medications, patients risk factors, benefits versus side effects ratio and gradual dose titration are among the vital parameters to take into account for pharmacological management of epilepsy [54].

Examples from Literature

- 1- A 29-year old white female with cerebral palsy suffered an attack of myoclonus and acute psychosis highlighted with paranoid thoughts two weeks after her topiramate 25 mg twice a day was increased to 50 mg twice a day. She has no history of psychosis and was prescribed topiramate for migraine prophylaxis. Her lab and EEG were normal. Her conditions improved after her topiramate dose was reduced and tapered off over 4 days period [55].
- 2- An 11-year old girl was prescribed levetiracetam 500 mg twice daily for her generalized tonic convulsion. The patient misunderstood the directions and took 1000 mg twice daily for 7 days before experiencing restlessness, visual hallucination and soliloquy. She has no history of psychiatric problems. Her lab and neurological examination was normal. Her symptoms

subsided after stopping levetiracetam, and olanzapine was prescribed for 10 days [56].

CARDIOVASCULAR AGENTS

A vast majority of cardiovascular medications cause sedation and fatigue as side effect but the use of some select medicines is correlated with clinical neuropsychiatric issues either alone or in combination with other medicines [57].

Diuretics (thiazide and loop diuretics) are associated with neuropsychiatric symptoms, albeit, at low rates, owing to their electrolyte depleting effects. Thiazide diuretics related hyponatremia can also exacerbate SSRI or lithium-induced toxic effects that manifest as neuropsychiatric symptoms [58, 59] so careful monitoring is warranted in case of above combinations. According to a report by [60] 50-90% of patients taking 40-80 mg of furosemide for congestive heart failure have severe thiamine deficiency and are at high risk of developing Wernicke's encephalopathy.

Of other cardiovascular medications, hydralazine and digoxin are linked with psychiatric side effects. Confusion and visual hallucination are common side effects of digoxin and occur at therapeutic doses, while delirium and delusion are seen at toxic doses [61]. Interestingly, there are few reports of the link between the use of some angiotensin receptor blockers e.g. losartan and valsartan-HCTZ and

neuropsychiatric symptoms that resolve after discontinuation of medications [62, 63].

ANTICHOLINERGICS / ANTIHISTAMINES

Anticholinergic drugs are extensively used for a number of medical conditions: peptic ulcer (prinzepine, glycopyrrolate), asthma or COPD (ipratropium), motion sickness (scopolamine), urinary bladder control (oxybutinin), extrapyramidal side effects (benztropine or trihexyphenidyl) etc. Similarly, antihistamine especially first generation antihistamines are popular anti-allergy medications. Both class of medications are antagonists at muscarinic receptors and have the ability to increase presynaptic dopamine levels and thus have the potential to cause inattention, confusion, delirium and hallucination at high doses. Psychotic effects of these medications are more prominent in geriatric patients with cognitive impairment [64].

Despite their undesirable psychotic effects, anticholinergic drugs are primarily employed to treat acute dystonia and extrapyramidal side effects ensuing therapy with antipsychotic medications. However, long term or concurrent use of anticholinergics is not recommended with antipsychotics for fear of exacerbation of cognitive or psychotic side effects especially in elderly patients [65]. Given the above drawbacks, it is imperative that health care professional pay due attention to the medication list of all patients to prevent likely decline in neurological functions and avoid psychotic side effects.

PHARMACIST'S ROLE

In this article we reviewed the literature to search for any major class of medications or medications that have been reported to have any psychiatric side effects. Among other health care providers, pharmacists are considered drug experts. With the steadily growing public perception of pharmacist's scope of knowledge and professional responsibilities, more and more patients approach pharmacist to discuss their disease states, medications and corresponding side effects and drug interactions. Therefore, pharmacist must leverage the patients trust and must be equipped with in-depth knowledge and understanding of the currently available therapeutic agents to disseminate information to their patients. Following are few suggestions or ideas whereby pharmacist can play a valuable role in preventing their patients from experiencing menacing psychotic attacks.

It is imperative that during their counseling session, pharmacist discuss the potential for above medications to trigger psychotic symptoms, so patients are prepared as to what to expect and can seek help when appropriate. It is especially important

in the case of young children taking medications in question so that family or school teachers are educated on this matter and can take measures to handle the psychotic episodes especially if maniac or violent episode of psychosis kicks off in public places or away from emergency or hospital.

Pharmacist must remind family or caregivers, that all vulnerable patients including, children, adults, or senior patients must be monitored for signs and symptoms of psychosis to prevent self injury or harm to others.

It is pharmacist's professional responsibility to thoroughly review patients profile to look for any drug-drug, drug-disease interactions or allergy information before authorizing to fill the prescription. Patients must be asked regularly if they are taking any OTC, herbal, or nutritional supplements or medications prescribed by other providers. All of the above information must be input in patient's profile for future references. Sometimes, things as simple as taking an OTC antacid, or proton pump inhibitors can elevate the blood levels of amphetamine salts and predispose the patient to unsuspecting psychotic episode.

Since sudden withdrawal of CNS stimulants or other psychotropic medication can also precipitate acute psychotic symptoms, patients must be reminded not to stop the medications without their prescriber's consultation. On that note, any non-compliant patients of important medications must be reported to their health care provider.

It is never too late to discuss the value of healthy life style with your patients. Balanced careful diet, good night sleep, amiable company and stressors free life are extremely beneficial to maintaining good mental health. Sleep deprivation or high consumption of caffeine can easy trigger psychosis in patients with or without psychotic history [44, 66].

Social stigma attached to psychosis in certain ethnic cultures or patients with low educational background, or with some religious beliefs, may prevent patients or families to seek medical advice. As a responsible member of community health care team, pharmacists must carefully educate these groups of patients to bring any unusual behavior or symptoms to the attention of medical team. For example, postpartum psychosis, although rare (0.1 – 0.2 % of deliveries), is a medical emergency due to risk of potential harm to mother and new-born baby and must be reported immediately. Symptoms of postpartum psychosis usually occur days or weeks after childbirth and may manifest as impaired cognition, hallucination, confusion, abnormal thoughts and behavior [67].

It is also worth mentioning that pharmacist must also be cognizance of plethora of medical conditions that lead to acute psychosis or psychotic symptoms.

Examples of such medical conditions are endocrinological abnormalities (alterations in thyroid, parathyroid levels, Cushing syndrome, sex hormone imbalances causing menstrual and postpartum psychosis); electrolyte imbalances, neurodegenerative diseases (Parkinson's, Alzheimer, dementia, multiple sclerosis, stroke, malignancy like brain tumor); infections (syphilis, encephalitis, HIV, malaria); parasitic infestations such as neurocysticercosis; poisoning by some environmental toxins or medication use; some autoimmune disease; some inborn metabolic disorders such as succinic semialdehyde dehydrogenase deficiency, porphyria and metachromatic leukodystrophy and some nutritional deficiencies like Vitamin B₁₂ deficiency are reported to be linked with psychotic behavior [68].

With all the above-mentioned information and careful review of our patient's profile, Pharmacist can make a difference in curtailing the growing

problem of medication-precipitated psychosis. Pharmacist must also advise their patients to bring any unusual behavior or feeling to their prescriber attention.

CONCLUSION

A large collection of prescription medicines including CNS stimulants, steroids, antibiotics, antihypertensives can precipitate transient or long-term psychotic attacks, which can lead to emergency situations and fatal consequences. The exponential growth of available medicines demands further expansion of the scope of the pharmacist's responsibilities; pharmacist intervention can significantly decrease the number of such insalubrious incidents.

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