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Psychiatric Side Effects of Nonpsychiatric Medications

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Numerous medications are capable of causing psychiatric side effects. Drug abuse or misuse, polypharmacy, or physiological changes due to aging may lead to these adverse effects. Drug-induced effects on mental health is a topic of considerable clinical importance and yet it is poorly recognized by health care professionals. This article is a review of psychiatric side effects of prescription and over-the-counter medications, problem recognition, and what can be done to manage and prevent these adverse events. Prevention of drug-induced psychiatric side effects can be aided by avoiding, where possible, medications that can cause these effects; evaluating renal and hepatic function on a regular basis; avoiding agents that can cross the blood-brain barrier; and conducting brief cognitive and behavioural assessments at baseline with follow up on a periodical basis.

Key words: *psychiatric side effect, renal insufficiency, nonpsychiatric medications, adverse drug reactions, cognitive impairment*

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Introduction

Older individuals are frequently the victims of iatrogenic diseases due to the adverse effects of medications. Adverse psychiatric effects, whether due to prescription or over-the-counter-medications, can lead to serious adverse events in the older adult.

Adverse drug reactions are more common in older adults.[1,2] A study of adverse reactions to drugs in general practice showed adverse effects on gastrointestinal and central nervous systems were the most frequently reported and neuropsychiatric reactions account for 30% of the adverse effects.[3] The Canadian Adverse Event Study found that 7.5% of patients admitted to acute care experienced an adverse event, with the second most common cause being drug or fluid therapy. Patients who had adverse events were older than those who did not have adverse events.[4] An Italian study of drug-induced neuropsychiatric side effects over a period of two years in general practice concluded that roughly 10% of the adverse reactions are due to psychiatric side effects.[5] In a Canadian study on older patients, about 10% of the visits to the emergency room were related to adverse drug events.[6]

Pharmacotherapy of the older adult must take into account the effects of age-related changes in the structure and function of the brain and other organs. Because older individuals are excluded from many drug trials, due to physical or cognitive comorbidities or simply due to ageism, we do not have a large body of evidence to describe the type or rate of adverse events from medications in seniors. In this review, we will explore how medications can contribute to the five major types of psychiatric illness: depression, delirium/psychosis, anxiety, insomnia, and cognitive impairment.

Pharmacokinetic and Pharmacodynamic Changes with Aging

The vast majority of adverse psychiatric reactions are Type A adverse drug reactions, which are usually dose dependent or related to the known pharmacological properties of the drug. (A Type B reaction is idiosyncratic and tends to be unrelated to the pharmacology of the medication.) In older adults, response to drugs may be accentuated or modified by age-related changes.

The pharmacokinetic/pharmacodynamic changes that occur with age are illustrated in Figure 1.

Pharmacokinetic Changes

Among those physiologic changes that may play a role are an increase in total body fat, a decrease in lean body mass and water, a possible decrease in albumin, and a decrease in glomerular filtration rate. Pharmacokinetic parameters that change with age generally include an extension of the half-life due to reduced metabolic capacity or decreased renal

elimination and increased volume of distribution for lipid soluble medications. Because of the relative increase in fat mass with aging, lipophilic agents have an increased volume of distribution, thereby extending the half-life of these agents. In contrast, medications that are water-soluble have a smaller volume of distribution, leading to significantly higher concentrations.

Conditions that lead to hepatic or renal insufficiency cause an accumulation of metabolic by-products that can be toxic. Hepatic blood flow (35%) and liver size can decrease with aging (by 44% in older women and 28% in older men) when compared to young persons.[7] Reduced renal function can also contribute to extended high levels of medication. Renal elimination is decreased due to reduced renal blood flow (2% per year after 40), renal mass (10–20% between 40 and 80 years), and glomerular filtration rate (50% between 50 and 90 years). Estimation of renal function may be less accurate in the older adult, often overestimating the actual renal function due to age-related reduction in creatinine, which is secondary to reduced lean body mass.[8] Creatinine clearance can be measured by using inulin or can be calculated using either the Cockgroft-Gault formula or Modification of Diet in Renal Disease (MDRD). A number of institutions are now using calculated GFR.

The blood-brain barrier is composed of tightly formed capillary endothelial cells that allow only certain substances to pass through in order to protect the brain from harmful substances. In a patient who has suffered a stroke or has dementia, there is impaired integrity of the blood-brain barrier function which permits more of a drug to reach the brain. Reduced integrity of blood-brain barrier function is strongly associated with susceptibility to psychiatric side effects as many agents are more likely to move into the brain.[9]

Pharmacodynamic Changes

In addition to pharmacokinetic changes, drugs may interact pharmacodynamically due to changes in drug receptor sensitivity.[10] Drug receptors can change with aging and produce altered, often heightened, drug response. In the older adult, changes in receptor function occur across multiple organs. The net effect of these changes is heightened sensitivity of the brain to adverse drug effects.[11] In older adults, the effects of similar drug concentrations at the site of action may be larger (e.g., opioid analgesics, benzodiazepines, warfarin, angiotensin-converting enzyme inhibitors, calcium channel blockers, and levodopa) or smaller (e.g., beta-agonist bronchodilators and diuretics) than those in younger patients.[12]

Pharmacokinetic drug-drug interactions are also significant. One medication may alter the bioavailablity, rate of metabolism, free fraction, or the volume of distribution of another medication. Pharmacodynamic interactions can also occur between drugs or between a drug and disease state. For example, a patient with Alzheimer's disease has a decrease in cholinergic reserve. By adding an anticholinergic medication, the effect is far more pronounced than in a person without Alzheimer's disease.

It is important to review the medication profiles in older patients for both pharmacokinetic and pharmacodynamic interactions that can contribute to psychiatric side effects.

Types of Psychiatric Side Effects Due to Medications

Cognitive Impairment

Some medications have side effects that mimic the symptoms of dementia. Stopping the medications may reverse these symptoms. Barbiturates, anticholinergics, sedatives, and narcotic analgesics may cause cognitive impairment. Steroids can cause a wide range of psychiatric symptoms including anxiety, depression, cognitive impairment, hypomania, and psychosis. Varney *et al.*, in their study of 1,500 patients, used the term steroid dementia when they saw cognitive deficits in patients using corticosteroids for a long time.[13,14] Cushing's syndrome patients had cognitive deficits and hippocampal atrophy, which is reversible in part when the cortisol level decreases.[15]

Depression

Certain authors have pointed out that individuals with a personal or family history of depression may be at greater risk of developing drug-induced depression.[16,17] Although many drugs have been associated with depression, there is limited evidence only for certain drugs, such as lipophilic beta-blockers, barbiturates, methyldopa, opioids, and cortico-steroids.[18,19] A recent review by Patten indicates that no medications were identified from the literature causing the typical major depressive syndrome, although there is evidence linking some medications like propanolol, corticosteroids, interferon-alpha (IFN-alpha), interleukin 2, and mefloquine with atypical depressive syndrome.[20] Depression may occur during the course of IFN treatment, with depressive symptoms usually appearing within the first 12 weeks.[21]

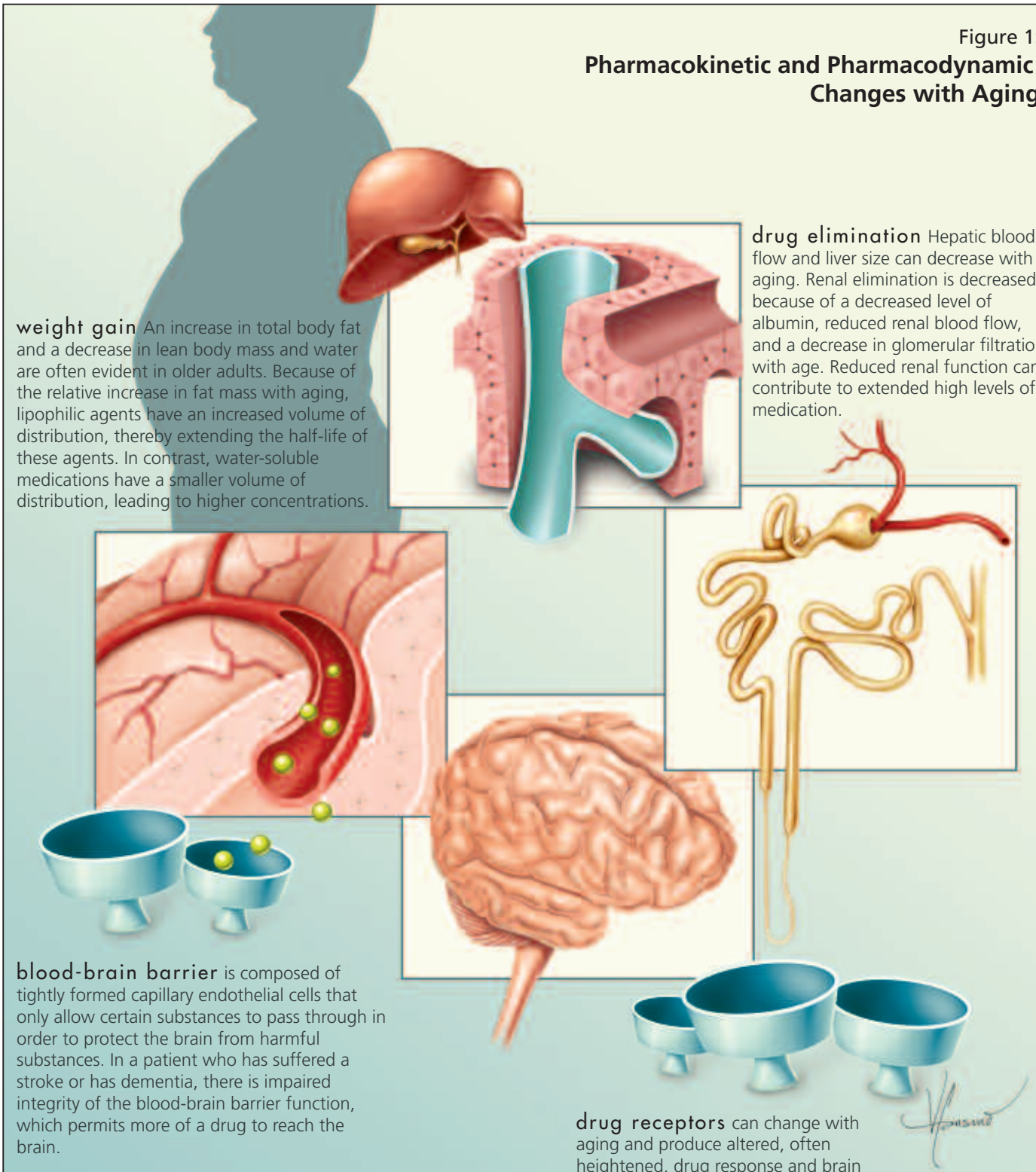
Delirium/Psychosis:

The most common medications that cause delirium include high-dose narcotics, benzodiazepines, and anticholinergics. Anticholinergic activity is also associated with the occurrence and severity of delirium.[22,23] A number of studies have shown that anticholinergic medication use is a common precipitating risk factor.[24,25] While delirium is a multifactorial process, it is estimated that medications alone may account for 12–39% of all cases of delirium.[26]

Some of the medications with anticholinergic effects include antihistamines (e.g., diphenhydramine), meperidine, antiparkinsonian medications (e.g., benztropine), and skeletal muscle relaxants (e.g., cyclobenzaprine).

All antiparkinsonian medications (e.g., L-dopa, dopamine agonists, amantadine, selegiline, COMT inhibitors,

Figure 1:
Pharmacokinetic and Pharmacodynamic Changes with Aging



weight gain An increase in total body fat and a decrease in lean body mass and water are often evident in older adults. Because of the relative increase in fat mass with aging, lipophilic agents have an increased volume of distribution, thereby extending the half-life of these agents. In contrast, water-soluble medications have a smaller volume of distribution, leading to higher concentrations.

drug elimination Hepatic blood flow and liver size can decrease with aging. Renal elimination is decreased because of a decreased level of albumin, reduced renal blood flow, and a decrease in glomerular filtration with age. Reduced renal function can contribute to extended high levels of medication.

blood-brain barrier is composed of tightly formed capillary endothelial cells that only allow certain substances to pass through in order to protect the brain from harmful substances. In a patient who has suffered a stroke or has dementia, there is impaired integrity of the blood-brain barrier function, which permits more of a drug to reach the brain.

drug receptors can change with aging and produce altered, often heightened, drug response and brain sensitivity. In older adults, the effects of similar drug concentrations at the site of action may be larger or smaller than those in younger patients.

and benztropine) can cause delirium due to excessive effects of dopamine. When delirium due to antiparkinsonian medications is suspected, medications can be discontinued in the following order: anticholinergics, selegiline, amantadine, dopamine agonists, entacopone, and, finally, consider tapering L-dopa.[28]

Other classes of medications that can cause delirium include nonsteroidal anti-inflammatory drugs. Indomethacin and ketoprofen, which are the most lipophilic NSAIDs, are particularly causative of delirium.[27]

Insomnia

Medications can affect the sleep cycle. Each person spends roughly one-third of his or her life asleep. Drugs could affect this cognitive state in many different ways. Drugs such as beta-adrenergic blockers, nasal decongestants (pseudoephedrine), methylphenidate, thyroid medications, corticosteroids, phenytoin, and theophylline can induce insomnia.[29–31] Neurotransmitters, including noradrenaline, serotonin, dopamine, histamine, acetylcholine, adenosine, GABA, glutamate, endorphins, and cortisol have all been shown to affect sleep.[32–36] It is therefore no surprise that numerous medications could affect sleep.

Anxiety

Numerous medications can cause anxiety and even panic attacks. Drugs such as pseudoephedrine (over the counter decongestant), theophylline, salbutamol, prednisone, car-

Table 1: Psychiatric Effects of Nonpsychiatric Drugs

Psychiatric side effect	Central Nervous System (CNS) medication	Cardiovascular System (CVS) medication	Respiratory System (RS) medication	Others
1. Cognitive impairment	Benzodiazepines Barbiturates			Narcotics Steroids Anticholinergics
2. Delirium/ psychosis	Antiparkinsonian (benztropine, dopamine agonist) Sedative withdrawal Anticonvulsants (gabapentin, vigabatrin)	Antiarrythmics (lidocaine, procainamide, digoxin, disopyramide) Beta-blockers Alphamethyldopa	Theophylline (high doses) Steroids (high doses)	Antihistamines (diphenhydramine) Nonsteroidal anti-inflammatory drugs (indomethacin, ketoprofen) Fluoroquinolones
3. Depression	Antiepileptics (vigabatrin, lamotrigine) Antiparkinsonian (amantadine, levodopa)	Beta-blockers Alphamethyldopa Clonidine Digoxin	Steroids	Interferon alpha Vinblastine Vincristine Interleukin-2 Mefloquine
4. Insomnia	Phenytoin Felbamate Methylphenidate	Beta-blockers	Beta agonist (salbutamol) Decongestant (pseudoephedrine)	Thyroid medications
5. Anxiety	Carbamazepine Vigabatrin Amantadine Selegiline Sedative withdrawal	Beta-blockers withdrawal	Salbutamol Theophylline Pseudoephedrine	Corticosteroids

Legend: Psychiatric side effects of medications

bamazepine, and the antiparkinsonian drugs such as amantadine and selegiline are associated with anxiety.[37,38]

Psychiatric Side Effects Caused by Particular Medications

Psychosis due to vigabatrin has been described as schizophrenia-like syndrome. Onset is typically within the first four weeks of therapy. Therapeutic doses have been associated with the emergence of psychosis.[39] Abrupt withdrawal of vigabatrin may produce agitation and hallucinations.[40] Digoxin can cause delirium, psychosis, and depression and delirium. These can occur even at therapeutic drug levels.[41,42] Lidocaine at serum levels > 9 mg/dL can cause psychosis.[43] Theophylline at therapeutic serum ranges (10–20 mcg/mL) can cause restlessness, anxiety, and insomnia.[44] With all quinolones, lethargy, insomnia, and delirium occurs in less than 1% of cases.[45,46] Most cephalosporins can cause delirium as a side effect, especially in patients with renal failure.[47]

See Table 1 for a description of psychiatric effects of medications.

Clinical Approach to the Problem

Older patients, in particular patients with cognitive impairment and/or those on multiple medications, are especially vulnerable to the side effects of medications.[48] If the psychiatric disturbance occurs suddenly, especially in a person with no psychiatric or cognitive history, and shortly after exposure to a drug that can cause psychiatric side effects, it is clearly wise to suspect a drug-induced reaction and, if possible, to discontinue or reduce the dose of the suspected medication. Consider also drug adverse effects if you observe decline in cognitive functions or self-care abilities. Diagnosis of a drug-induced psychiatric side effect remains a matter of clinical judgement.[49] Review all the prescription, over-the-counter, and alternative medications. Assess the patient's cognitive status and look for any pharmacokinetic changes. A drug reaction or medication side effect should be suspected if there is a temporal relationship from the administration of the drug to the side effect or to drug levels, improvement on stopping the drug, and reappearance of symptoms on repeated exposure to the drug.[50]

It is important to keep in mind the difference between association and causation. Medications are usually used in patients who are ill. In some instances the underlying illness may result in depression, delirium, or psychosis, and the medication may or may not be significantly contributing to that effect. A detailed history will also help the clinician assess each patient's risk, which should include the following questions: Is there a history of stroke, dementia, or cognitive impairment? Is there a personal or family history of psychiatric disorders? What prescription medications and over-the-counter medications is the patient currently taking? Was there a recent change to the medications? Are there any coexisting medical conditions that can cause psychiatric symptoms? A personal or family history of affective mental illness can predispose a patient to the psychiatric side effects of steroids.[51] Drug-induced psychiatric symptoms can sometimes occur even with standard dosages and at any time during the course of treatment.

Conclusion

Physicians should be aware of psychiatric symptoms due to nonpsychiatric medications. This will avoid possible misdiagnosis and provide an opportunity for a reversal of symptoms by stopping the medications or decreasing the doses. In general, older adults are more sensitive than young people to both the therapeutic and toxic effects of medications, necessitating lower doses and longer dosing intervals. In addition, when drugs with potential psychiatric side effects are started they should be closely followed and, when managing psychiatric symptoms, medications should be considered in the differential diagnosis.

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