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Psychiatric Adverse Drug Reactions (ADRs) associated with Cardiovascularmedications: Review & Analysis of SmPCs and Literature

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Abstract

Introduction : It is well known that prescription drugs can result in a myriad of ADRs, including psychiatric ADRs. Psychiatric effects of drugs can impact sensorium, attention, concentration, memory and higher cognitive functions resulting in distressing physical illness and psychiatric consultation. Generally in regards to psychiatric effects associated with drug therapy, complications such as depression and suicidality (suicidal thinking and behaviour) are those most frequently reported. Prescription drugs with known psychiatric ADRs include: steroids, antibiotics, hormonal drugs, acne drugs, attention-deficit hyperactivity disorder (ADHD) drugs, anti-depressants, anti-parkinsonians, anti-convulsants, anti-malarials, antihypertensives, antihistamines, sedatives tranquillizers, statins, and anti-smoking agents.

Objective and Methodology : To review the SmPCs and literatures of antihypertensive drugs prescribed commonly in medical practice and understand the common, uncommon, rare, very rare psychiatric ADRs and risks associated with these drugs. A list of the most common antihypertensives prescribed in medical practice was prepared and categorised according to the mechanism of action. The most recent SmPCs of the selected drugs from the MHRA website was retrieved and Section 4.8 Undesireable effects was reviewed. Drugs from various treatment categories were included for this analysis: Angiotensin Receptor Blockers (ARBs), ACE Inhibitors; Beta Blockers; Anti arrhythmia drugs; Calcium Channel Blockers (CCB); Centrally acting drugs and Vasodilators

Results : The analysis involved review of the SmPCs and literatures for common, uncommon, rare and very rare psychiatric ADRs based on the Pyschiatric System Organ Class (SOC) effects per MedDRA Preferred Terms (PTs) ranked under headings of frequency. Almost all the drugs from each category reported psychiatric ADRs ranging from common to very rare listed in the SmPCs. Depression, depressed mood, anxiety, nervousness were common for Alpha and Beta blocker group which are the most prescribed drugs in patients with hypertension. Insomia, sleep disturbances, confusion, psychosis were uncommon in all drug treatment categories, while hallucinations, mental confusion, disturbance in attention, depression and personality disorders were rare and very rare ADRs. None of the drug categories listed suicidality or suicide attempt as an ADR.

Conclusion: Identification of psychiatric ADRs related to drug therapy in real world post-marketing setting is difficult. Reporting rates determined on the basis of spontaneously reported post-marketing ADRs are generally presumed to underestimate the risks associated with drug treatment. As a medical student, this exercise will help me to assess patients starting therapy with antihypertensives, identify and report ADRs to the MHRA, monitor ongoing ADRs, and lastly read the SmPC as guidance to good medical practice.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients and each year CVD causes an estimated 17 million deaths worldwide accounting for one-third of all death in the world [1]. More than one-third of these deaths occur in middle aged adults, and in the developed countries Coronary Heart Disease (CHD) and stroke are the leading causes of death amongst men and women. The primary cause of CHD is atherosclerosis that reduces blood flow through the coronary arteries and to the heart muscle resulting in hypertension, angina, myocardial infarction, heart failure and arrhythmias.

Cardiovascular medicines are the most commonly prescribed drugs in the adults and elderly population [2]. The incidence of adverse drug reactions (ADRs) from using these drugs is also highest in these populations and age-related ADRs are a significant cause of morbidity and mortality. It is well known that prescription drugs can result in a myriad of ADRs, including psychiatric ADRs. Psychiatric effects of drugs can impact sensorium, attention, concentration, memory and higher cognitive functions resulting in distressing physical illness and psychiatric consultations. Generally, in regards to psychiatric effects associated with drug therapy, complications such as depression and suicidality (including suicidal ideas and behaviour) are the most commonly reported from the use of cardiovascular medications.

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. Its aims are to enhance patient care and patient safety and to support public health programmes by providing reliable, balanced information for the effective assessment of the benefit-risk profile of medicinal products. The role of PV is to assess whether the benefits of a drug outweigh the risks and it doesn't stop after the drugs are certified. PV is crucial for patient safety and involves ongoing monitoring of drugs to ensure they remain safe for use, especially since previously undetected adverse events can occur at any time. Practicing physicians should understand the risk factors that lead to adverse drug reactions and report adverse drug reactions to the regulatory agencies, so that safer drugs are retained and harmful drugs are withdrawn and adequate measures taken.

Objective and Methodology

As part of a summer project, the Summary of Product Characteristics [3] (SmPCs) of several antihypertensive drugs that are prescribed commonly in medical practice to understand the common, uncommon, rare, very rare psychiatric ADRs and risks associated with cardiovascular drugs were reviewed. The SmPC is a legal document approved as part of the marketing authorisation for each medicinal product. The SmPC forms the basis of information for healthcare professional on how to prescribe the medicine and its information is updated throughout the life-cycle of the product as new data emerge. SmPCs are the main source of information of medical and pharmaceutical references and electronic prescribing support tools for physicians.

A list of the most common cardiovascular drugs prescribed for the treatment of hypertension in medical practice was prepared based on the mechanism of action. The most recent SmPCs of the drugs included in Table 1 was retrieved from the Medicines and Healthcare Regulatory Authority (MHRA) website and Section 4.8 "Undesireable effects" was reviewed for each of these medicinal products. Section 4.8 "Undesirable effects" provides a summary of safety profile of the medicine with information on the most serious and/or most frequently occurring adverse reactions, including a tabulated list of all adverse reactions with their respective frequency category, presented according to a standard system organ classification, information characterising specific adverse reaction which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice, information on clinically relevant differences in special population such as the elderly and information on a specific risk is also reflected in section 4.4 "Special warnings and precautions for use" when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk.

Commonly prescribed drugs from various treatment categories included for this analysis were ACE Inhibitors – Enalapril, Lisinopril, Ramipril Angiotensin Receptor Blockers (ARBs) – Losartan; Beta Blockers – Atenolol, Metoprolol, Carvedilol; Calcium Channel Blockers (CCB) – Amlodipine, Diltiazem, Nifedipine; Centrally Acting drugs – Clonidine, Methyldopa and Reserpine; Anti-arrhythmic drugs from Class Ia, Ib, Ic and class III and Vasodilators - hydralazine. Only those drugs for which the SmPC included psychiatric ADRs were included in this review.

Additionally, an extensive literature search was also conducted using PubMed using structured terms for each product and psychiatric adverse drug reaction; depression; psychosis; mood swings; delirium; nightmares; sleep disorder; fatigue; insomnia; somnolence; confusion and hallucinations for the medicinal products included in Table 1.

Results

The analysis involved review of common, uncommon, rare and very rare psychiatric ADRs based on the Psychiatric System Organ Class (SOC) effects per MedDRA Preferred Terms (PTs) ranked under headings of frequency as described in Table1. Each of the product SmPCs, used the Council for International Organisations of Medical Sciences (CIOMS) rating for calculation of the frequency for each adverse event terms. The ADRs were then categorised as - very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

Almost all the drugs from each category had psychiatric ADRs ranging from common to very rare listed in the SmPCs. In the ACE inhibitors category, depression and mood alteration occurred at a frequency of ≥ 1/1000 - < 1/100. Depression, depressed mood, anxiety, nervousness were common for Alpha and Beta blocker group which are the most prescribed drugs in patients with hypertension. Insomia, sleep disturbances, confusion, psychosis were uncommon in all drug treatment categories, while hallucinations, mental confusion, disturbance in attention, depression and personality disorders were rare and very rare ADRs. None of the drug categories listed suicidality or suicide attempt as an ADR.

Extensive literature search for these selected medicinal products also reflected similar reports of psychiatric adverse drug reactions as described in Table 1, mainly as single cases or as case series.

Table 1: Frequency of Psychiatric ADRs for most common cardiovascular drug categories

Drug Treatment Categories	Common ≥ 1/100 - < 1/10	Uncommon ≥ 1/1000 - < 1/100	Rare ≥ 1/10000 - < 1/1000
ACE Inhibitors			
Captopril	Sleep disorders		Confusion, Depression
Enalapril		Depression; Confusion; Insomnia; Somnolence	
Lisinopril		Mood alterations; Sleep disturbances	Mental Confusion
Ramipril		Depressed mood; Anxiety; Nervousness Restlessness; Sleep disorders (somnolence)	Disturbance in attention
Beta Blockers			
Atenolol		Sleep disturbances; Mood change Depression; Anxiety; Nightmares Confusion;Psychosis; Hallucinations	
Carvedilol	Depression Depressed mood	Confusion; Sleep disorders	
Metoprolol			Depression Nightmares Hallucinations Personality disorder
ANGIOTENSIN RECEPTOR BOCKERS (ARBs)			
Losartan			Depression
CALCIUM CHANNEL BLOCKERS (CCBs)			
Amlodipine		Depression; Mood changes (including anxiety); Insomnia	Confusion
Diltiazem		Nervousness; Insomnia	Mood changes (including depression)
Nifedipine		Anxiety reactions; Sleep disorders	
CENTRALLY ACTING DRUGS			
Clonidine	Depression; Sleep disorder	Delusional perception; Hallucination; Nightmare	Confusional state
Methyldopa			Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido
Reserpine	Depression; Sedation		
VASODILATORS			
Hydralazine			Agitation; Anorexia, Anxiety Depression; Hallucinations
ANTI ARRYTHMIA DRUGS			
Class 1a Disopyramide Procainamide Quinidine		 Psychosis Depression; Psychosis with hallucinations	 Depression; Psychosis
Class 1b Lidocaine		Nervousness; Depression	Confusion
Class 1c Flecainide			Hallucination; Depression; Confusional state; Anxiety, Amnesia; Insomnia
Class III Amiodarone Digoxin		 Depression	Confusional state; Delerium Apathy; Confusional state; Psychotic disorder

Discussion

Psychiatric adverse drug reactions are unintended and potential harmful mental and behavioural symptoms resulting from administration of drugs for therapeutic purposes. Numerous cardiovascular medications act on the central nervous system (CNS) through various pathways leading to a variety of psychiatric adverse effects ranging from mood symptoms to cognitive effects to psychosis in very rare conditions [4]. The pharmacological mechanisms that lead to psychiatric adverse events can be categorised into pharmacodynamic and pharmacokinetic mechanisms. Pharmacodynamic mechanisms involve the modifications of major neurotransmitter systems by the prescribed drug, and the mode of action may involve a direct influence on the neurotransmitter systems e.g. dopamine agonists and interleukins or indirectly act on the hypothalamus pituitary adrenal axis. Pharmacokinetic mechanisms may lead to low clearance of the drug due to underlying disease pathology, hepatic enzyme polymorphosim and drug interactions leading to metabolic inhibition. The risk of psychiatric adverse drug reactions may increase due to the increased concentration of the drug. Additionally, several underlying risk factors such as treatment regimen, polypharmacy that may result in drug-drug interaction, elderly patients and narrow therapeutic index of a drug may also lead to psychiatric adverse drug reaction.

The common cardiovascular drugs that are prescribed for the treatment of hypertension such as ACE inhibitors, ARBs, CCBs are all associated with mood symptoms, psychosis and delirium although the frequencies are low [5,6]. Centrally acting drugs such as Clonidine (35%), Methyldopa and Reserpine, beta blockers (> 10%) and ACE inhibitors (>5%) are commonly associated with fatigue and sedation [3,7]. Psychiatric symptoms are frequently reported in patients with cardiovascular disease. Anxiety is a common symptom in patients with coronary artery disease (CAD) especially in patients who have had myocardial infarction (MI). Approximately, 15% of patients with recent MI, congestive heart failure (CHF) suffer from major depressive disorder which is an important confounding factor in cardiac patients who have also been prescribed cardiovascular medication [8]. However, the psychiatric adverse events that are included in the Summary of Product Characteristics (SmPC) in Section 4.8 Undesireable effects are the related adverse drug reactions to the concerned product from the real-world post-marketing setting involving millions of patients exposed to the cardiovascular drugs. Each adverse event reported to the pharmaceutical company is thoroughly evaluated for causality and relatedness taking into consideration all the underlying risk factors and confounders.

There have been several literature reports of association between the use of beta blockers and the development of depression. Many case reports and several reviews have linked propranolol with depression, and a study found that treatment with propranolol was associated with higher rates of antidepressant prescriptions than with other beta blockers [9]. However, a comprehensive review of more than 5800 patients prescribed propranolol found that the drug was rarely associated with depressive symptoms, and that such symptoms usually occurred after long-term use [10].

Amongst the ACE inhibitors, captopril has been reported to be associated with mood effects, potentially due to its transport into the central nervous system (CNS) by a protein carrier[11]. There are fewer reports of mood effects of other ACE inhibitors, though lisinopril has been associated with the induction of mania in a single case report, however, psychosis and delirium have been reported to be rarely associated with ACE inhibitors. Literature reports of ACE inhibitors and angiotensin II receptor antagonists are associated with low rates of psychiatric adverse reactions, though mood symptoms, psychosis, and delirium have been reported frequently.

Similar to the ACE inhibitors, CCBs such as amlodipine, nifedipine and diltiazem are also frequently associated with insomnia and mood changes including anxiety as reflected in the SmPCs for CCBs. However, there are literature reports of rare cases of depression and psychosis, similar to what is included in the SmPCs.

Centrally acting drugs, such as Clonidine is associated with a number of psychiatric adverse effects. Fatigue and sedation are the most common effects reported with clonidine, with sedation occurring in one third or more patients [11,12]. Mood disturbance has been infrequently described with clonidine, however there are several literature reports of depression that occurs in approximately 1% to 2% of patients taking clonidine [11,12]. There are rare reports of hallucinations that can occur with clonidine.

Methyldopa is another centrally acting drug that is not commonly prescribed in routine medical practice, except in patients with pregnancy-induced hypertension, which is a serious condition. Methyldopa acts by reducing blood pressure via central agonism, thereby acting as a false (norepinephrine) neurotransmitter. Similar to other cardiovascular drugs, reports associated with methyldopa use are usually sedation and fatigue, however, depressive symptoms including depression occur frequently with most of the other antihypertensive drugs, and it is thought that this effect may be related to reduced norepinephrine levels.

Of all the cardiovascular drugs prescribed for treating hypertension, reserpine, is one of the older antihypertensive that is rarely used, and has been reported to be associated with adverse psychiatric effects. Reserpine acts by inhibiting the uptake of monoamine neurotransmitters into storage granules, resulting in the metabolism of these neurotransmitters by monoamine oxidase [11]. The depletion of catecholamine neurotransmitters results in its antihypertensive effects and likely contributes to its association with depression and fatigue [11].

Of the anti-arrhythmic medications used commonly in patients with cardiovascular ailments, quinidine a class Ia drug, lidocaine a class Ib and flecainide a class Ic drug are reported to be associated with various psychiatric adverse events ranging from psychosis to delirium as stated in the respected product SmPCs. Class I anti-arrhythmic drugs have been associated with psychosis and delirium in literature reports as well. The common syndrome of cinchonism associated with the use of quinidine may include sensory changes along with delirium.

There are a number of literature reports on two class III anti-arrhythmic drugs, amiodarone and digoxin with several psychiatric adverse drug reactions. Amiodarone is reported to be associated with abnormalities in approximately 15% of patients [13], especially untreated thyroid dysregulation that can lead indirectly to a variety of mood, cognitive, and psychotic symptoms, while digoxin is associated with delirium and other cognitive effects, especially in digoxin toxicity. Visual changes and hallucinations may also occur with digoxin use, even at normal serum levels due to the narrow therapeutic index of the drug which is reflected also in the respective product SmPCs.

Conclusion

Identification of psychiatric ADRs related to drug therapy in real world post-marketing setting is difficult in the absence of a denominator. Reporting rates determined on the basis of spontaneously reported post-marketing ADRs are generally presumed to underestimate the risks associated with drug treatment and also due to massive under-reporting. As a medical student, this exercise will help me to assess patients starting therapy with antihypertensives, identify the adverse psychiatric events reported by the patients and distinguish the reported events from the underlying psychiatric disorders that is common in patients with cardiovascular disease. Furthermore, it will stimulate me in reporting ADRs to the respective health regulatory agencies and to the manufacturers, monitor and manage the ongoing psychiatric ADRs

reported by the patients and in prescribing the correct medicinal product to patients. Lastly, this exercise has helped me to always read the SmPC and to understand the product better before prescribing to patients, as this important document acts as guidance for prescribing medicinal products and adhere to good medical practice.

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