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Review Article

Pharmacology Section

Cardiovascular and Metabolic Adverse Reactions Associated with the Use of Antipsychotic Drugs: A Narrative Review

PRIYA C PATEL[1], PREETI L NAVIK[2], MANISH J BARVALIYA[3], TEJAS K PATEL[4], HEMANGI A VIRANI[5]

ABSTRACT

The adverse drug reaction profile of antipsychotic drugs includes neurological, endocrinal anticholinergic and cardiovascular effects. The profile of each cardiovascular adverse effects, specific for each antipsychotic medication includes QT prolongation, orthostatic hypotension, myocarditis and metabolic effects, it also reduce the life expectancy of schizophrenic patients. There is a major clinical concern for the patients on long term therapy. This narrative review is focused on the cardiovascular profile of antipsychotic medications. The detailed aetiology, mechanism, monitoring and management of cardiovascular adverse effects are discussed in this review.

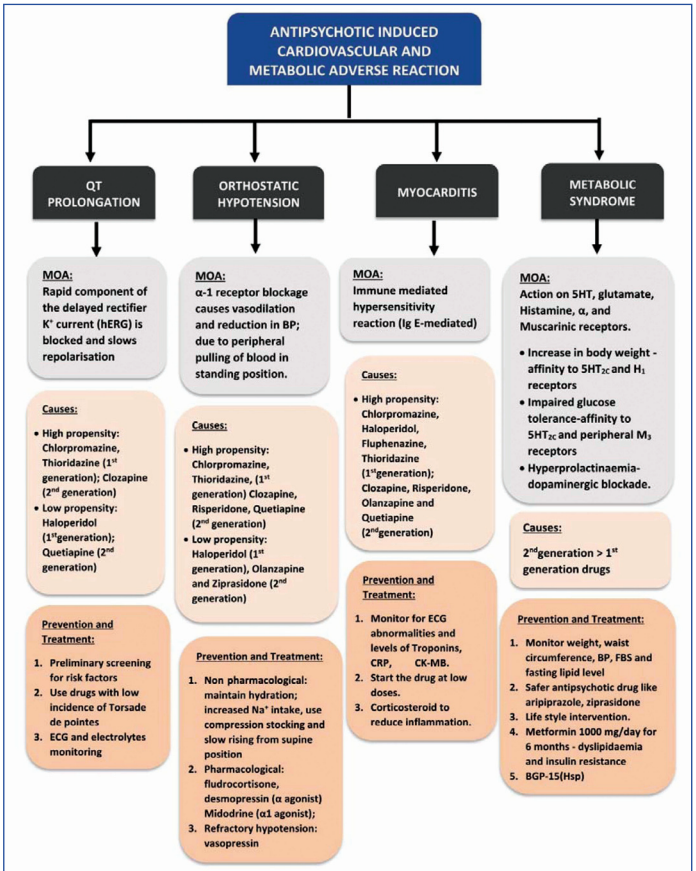
Keywords: Adverse drug reaction, Arrhythmia, Metabolic syndrome, Myocarditis, Neuroleptics

INTRODUCTION

Antipsychotic drugs are widely prescribed for long term treatment of schizophrenia and they are classified as first-generation (typical) and second-generation (atypical) antipsychotic drugs. First generation drugs include chlorpromazine, clopenthixol, clothiapine, flupentixol, fluphenazine, haloperidol, loxapine, prochlorperazine, thioridazine, and trifluoperazine. They are the potent blocker of D2 receptors and generally have a high propensity to cause the extrapyramidal side-effects. Second-generation drugs include amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sulpiride, ziprasidone, and zotepine; which have better action on cognitive function, negative symptoms of schizophrenia, and lower frequency of extrapyramidal side-effects; but have a greater frequency of metabolic and cardiovascular disturbances [1].

The adverse drug reaction profile of antipsychotic drugs includes dose related Central Nervous System (CNS), cardiovascular, metabolic, anticholinergic, endocrinal, and extrapyramidal disturbances. Metabolic side-effects with chronic therapy of certain antipsychotic drugs are a major clinical concern as it increases the risk of cardiovascular mortality. Antipsychotic drugs increase the risk of venous thromboembolism, pneumonia, stroke, hip fracture and ventricular arrhythmia [2]. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) by Goff DC et al., concluded that there is a significant elevation in 10-year Coronary Heart Disease (CHD) in schizophrenia patients than the age, race and gender matched controls [3].

Metabolic and cardiovascular side-effects of antipsychotic drugs are an important concern as they can reduce life expectancy of schizophrenic patients. Metabolic side-effects like weight gain, dyslipidaemia and hyperglycaemia are important risk factors for cardiovascular events [4]. Therefore, early identification of these side-effects has an important role in clinical practice. In this review, authors have discussed cardiovascular side-effects of antipsychotic drugs with a special focus on arrhythmia, hypotension, myocarditis, and metabolic effects. The mechanism of action, causative drugs and management strategies for cardiovascular adverse effects are summarised in [Table/Fig-1].

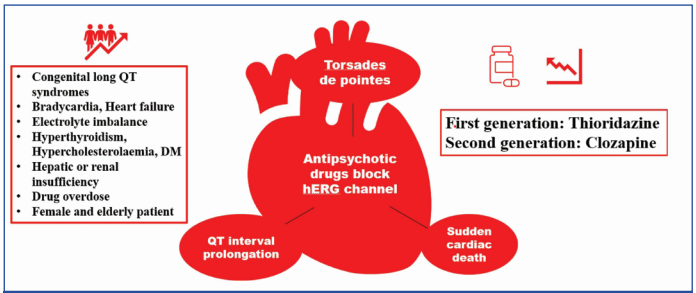


[Table/Fig-1]: Mechanism of action, causative drugs and management strategies of cardiovascular adverse effects due to antipsychotic drugs.
MOA: Mechanism of action; CRP: C-Reactive protein; CK-MB: Creatine kinase-myocardial band; ECG: Electrocardiogram, FBS: Fasting blood sugar; BP: Blood pressure; hERG-human ether-a-go-go-related gene; 5HT-5-hydroxytryptamine

QT Prolongation, Cardiac Arrhythmia and Sudden Cardiac Death

A sudden cardiac arrest probably due to a ventricular tachyarrhy-thmia leads to sudden cardiac death [5]. Sudden cardiac death has been found to be associated with the use of antipsychotic drugs and there are several studies that had evaluated the association of antipsychotic drugs with sudden cardiac death [1,5-7]. It is a rare event but a serious concern for the patients who are receiving the antipsychotic drugs [Table/Fig-2]. Drugs can affect the electrophysiological activity of the heart and drugs those can prolong QT interval can lead to torsade de pointes and ventricular arrhythmia resulting in sudden cardiac death [8]. Both, first and second generation antipsychotic drugs prolong the QT interval and lead to ventricular arrhythmia [5]. The QT prolongation effect varies between various antipsychotic drugs suggesting their different abilities to block the potassium channel and the degree of QT prolongation also varies with the different doses

[5,9,10]. Human ether-a-go-go-related gene (hERG) potassium channels are responsible for the rapid component of the delayed rectifier potassium current which causes phase 3 repolarisation during the action potential [11]. The drugs causing the torsade de pointes block the rapid component of the delayed rectifier potassium current conducted by the hERG potassium channel and slow down the repolarisation [9]. Risks of arrhythmias and sudden cardiac death increase with certain coexisting risk factors like congenital long QT syndromes (hERG mutation), bradycardia, electrolyte imbalance, heart failure, hyperthyroidism, hypercholesterolaemia, Diabetes Mellitus (DM), hepatic or renal insufficiency, overdose of drug (poisoning or slow metaboliser status), female and elderly patient [9,12,13].



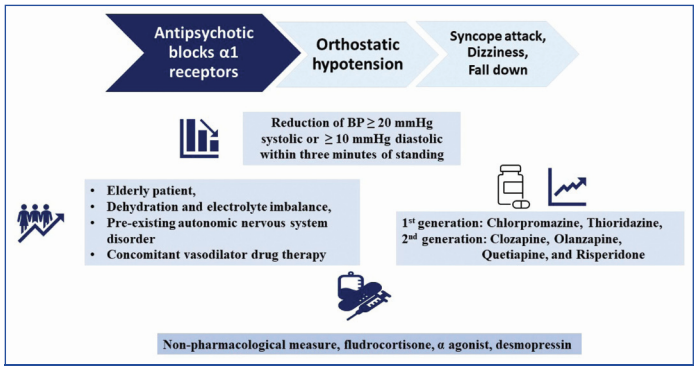
[Table/Fig-2]: Consequences of hERG channel blockade by antipsychotic drugs and factors enhances the risk of QT interval prolongation.
DM: Diabetes Mellitus

Antipsychotics are associated with a 1.5-3 fold increased risk of sudden cardiac death [1,14]. Ray WA et al., evaluated the incidence of sudden cardiac death amongst the current antipsychotic drugs users and found a similar incidence rate ratio for the first 2.00 (95% CI, 1.69–2.35) and second-generation 2.27 (95% CI, 1.89–2.73) antipsychotic drugs [5]. In this study, thioridazine (first generation) and clozapine (second generation) had the highest incidence rate ratio whereas; haloperidol (first generation) and quetiapine (second generation) had the lowest incidence rate ratio of sudden cardiac death [5]. Antipsychotic medications like perphenazine, chlorpromazine, haloperidol, droperidol, flupenthixol, fluphenazine, thioridazine, levomepromazine, trifluprom azine, pimozide, sulpride, sertindole, mesoridazine, ziprasidone, clozapine, olanzapine, risperidone, moperone, pipamperone, cyamemazine, amisulpride, pimavanserin, zotepine, aripiprazole, and sultopride have been reported to be associated with an increased risk of sudden cardiac death [15].

Amongst first generation antipsychotics; chlorpromazine, thioridazine and pimozide have a higher propensity to cause arrhythmia and sudden cardiac death whereas; clozapine and sertindole cause them more frequently amongst second generation [16]. The risk of sudden cardiac death is higher with the higher doses of antipsychotic drugs [5]. In the study by Ray WA et al., the incidence rate ratio was 1.31 (95% CI, 0.97–1.77) for low doses and 2.42 (95% CI, 1.91–3.06) for high doses of first generation whereas 1.59 (95% CI, 1.03–2.46) for low doses and 2.86 (95% CI, 2.25–3.65) for high doses of second generation antipsychotics [5]. Thus, the risk of arrhythmia and sudden cardiac death is dose-dependent for antipsychotic drugs. Preliminary screening for the presence of co-existing risk factors, prescribing drugs with lower risk of causing QT prolongation, avoiding concomitant drugs leading to QT prolongation, titrating the dose with proper risk benefit assessment, controlling other modifiable cardiovascular risk factors, Electrocardiogram (ECG) and electrolytes monitoring can help minimise the risk of arrhythmia and sudden cardiac death [16].

Orthostatic Hypotension

Orthostatic hypotension is defined as the reduction in blood pressure associated with the change in posture from supine to standing. Reduction of blood pressure ≥20 mmHg systolic or ≥10 mmHg diastolic within three minutes of standing can be considered as orthostatic hypotension [17]. It is one of the side-effects of antipsychotic drugs due to α-1 adrenoreceptor blockage [Table/Fig-3]. Stimulation of α-1 adrenoceptors causes vasoconstriction in certain vascular beds and increases peripheral vascular resistance. The blockade of these receptors leads to vasodilation and a reduction in blood pressure. This effect is more prominent in standing position due to peripheral pulling of blood and can cause syncope attack, malaise and dizziness to the patient [17]. Fall due to hypotension may result in fracture and head injury which causes serious concern for both patients and psychiatrists. Orthostatic hypotension may result in cardiovascular consequences like heart failure, stroke, coronary event and also cause cognitive impairment [18,19].



[Table/Fig-3]: Orthostatic hypotension: Case definition, risk factors and common causative agents.

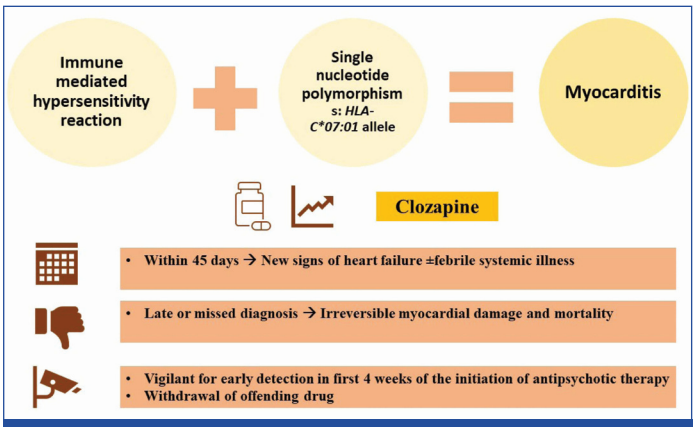
First and second generation antipsychotic drugs are associated with this side-effect which may often restrict the dose titration in patients of schizophrenia. Orthostatic hypotension is observed in around 40-75% of the patients put on antipsychotic drugs [20,21]. The risk of orthostatic hypotension increases in an elderly patient, with dehydration and electrolyte imbalance, pre-existing autonomic nervous system disorder and concomitant vasodilator drug therapy [22]. The agents that commonly cause orthostatic hypotension include chlorpromazine, thioridazine, clozapine, olanzapine, quetiapine, and risperidone [20,21]. Chlorpromazine, thioridazine, clozapine, risperidone and quetiapine have the highest risk whereas haloperidol, olanzapine and ziprasidone have the lowest risk of causing orthostatic hypotension [20-24].

Orthostatic hypotension is a matter of concern during the initial days of therapy as with chronic use, partial tolerance to this side-effect develops. Most of the time, non pharmacological measures can help in reducing the effect of orthostatic hypotension, however; sometimes pharmacological measures are also required in refractory cases [25]. Non pharmacological management includes maintaining hydration and electrolytes; increased sodium intake, use of compression stockings, lower extremities exercise, and slowly rising from the supine position [22,25,26].

Pharmacotherapy should be considered when non pharmacological measures are not sufficient [22,27]. The goal of pharmacotherapy is to improve hypotension without causing supine hypertension. It includes the use of α agonist, fludrocortisone, desmopressin and pyridostigmine [22,27]. Fludrocortisone is the first line therapy considered for the treatment of orthostatic hypotension [27]. Midodrine is a selective α1 agonist which can improve orthostatic hypotension. It is the most effective and fast acting agent for the treatment of chlorpromazine induced orthostatic hypotension in rabbits [28]. In double-blind placebo-controlled trial, 10 mg midodrine two to three times a day was found to improve the neurogenic orthostatic hypotension [29]. Some cases of severe intraoperative hypotension during general anaesthesia have been reported in patients taking antipsychotic drugs [30,31]. In severe and refractory hypotension, vasopressin therapy is effective even if there is no response to α agonist [30,31]. Other drugs which can be considered for the treatment of orthostatic hypotension include droxidopa, atomoxetine, erythropoietin, octreotide, metoclopramide etc., [32].

Myocarditis

Myocarditis is inflammation of the heart muscle histopathologically characterised by inflammatory cellular infiltrate with or without myocardial necrosis [33]. It can be caused by autoimmune disorders, viruses, bacteria, fungus, protozoa and by several medications like sulphonamides, lithium, anticonvulsants and antipsychotic agents [34,35]. Myocarditis can lead to complications like heart failure and arrhythmia due to cardiomyopathy and involvement of the conductive system, respectively [35,36]. As shown in [Table/Fig-4], the mechanism for drug induced myocarditis is thought to be of immune mediated hypersensitivity reaction (Ig E mediated) [37,38].



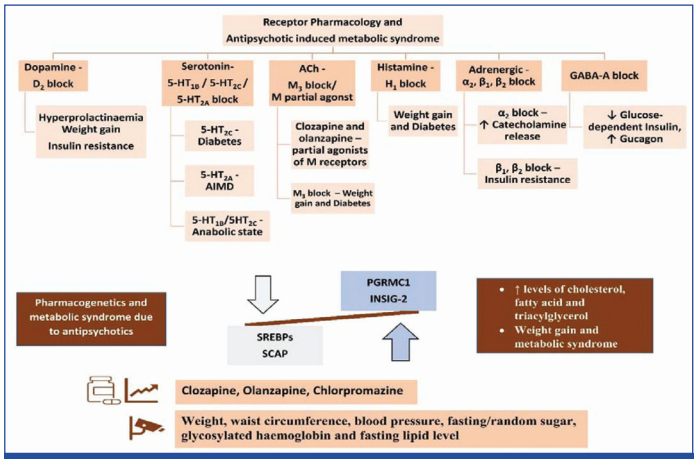
[Table/Fig-4]: Antipsychotic drug-induced myocarditis: mechanism, common causative agent and monitoring requirement.

Myocarditis is a rare side-effect of antipsychotic drugs [39]. Amongst first generation antipsychotics, chlorpromazine, haloperidol, fluphenazine, thioridazine, pimozide, trifluoperazine, zuclopenthixol and periciazine have been reported to cause myocarditis whereas amongst second generation antipsychotics, clozapine, risperidone, olanzapine and quetiapine have been reported to induce myocarditis [39-41]. Maximum numbers of cases of myocarditis have been reported with the clozapine [40,42]. For clozapine, the incidence of myocarditis is around 3% [43,44]. In December 2016, a "black box" warning of myocarditis due to clozapine has been added to the label by United States Food and Drug Administration (US FDA) [45]. Lacaze P et al., did the genome analysis and found four single nucleotide polymorphisms that can increase the risk of clozapine induced myocarditis [46]. They identified *HLA-C*07:01* allele responsible for increased risk of clozapine induced myocarditis with an odds ratio of 2.89 (95% CI: 1.11–7.53) which is the same allele associated with clozapine induced agranulocytosis [46]. Clozapine induced myocarditis occurs mostly within first month of starting the drug, hence, close monitoring for this side-effect should be done for the initial period of therapy [17].

Clinical diagnosis of antipsychotic induced myocarditis is difficult because most of the time symptoms are non specific. If the patient has new symptoms within 45 days of starting the drug with new signs of heart failure with or without febrile systemic illness, a possibility of myocarditis should be suspected [47]. The patient may have elevated levels of troponin I, C-reactive protein, and/or creatinine kinase-MB; ECG abnormalities like sinus tachycardia and ST-segment and T wave abnormalities [47,48]. A late or missed diagnosis will lead to irreversible myocardial damage and a poor prognosis with an increased risk of mortality [34]. There is no specific therapy for antipsychotic induced myocarditis. Being vigilant for early detection of this side-effect especially in the first four weeks of the initiation of antipsychotic therapy and withdrawal of an offending drug remains the mainstay of treatment for this adverse reaction [47]. However, withdrawal of clozapine is difficult as it is indicated for refractory cases of schizophrenia. It should be started with low doses and doses should be titrated gradually with proper monitoring of the patient [47]. Supportive care should be considered for heart failure or arrhythmia when present. Corticosteroids can help reduce inflammation, however; routine use of immunosuppressive therapy is not recommended as it increases long term mortality [49].

Metabolic Syndrome

Antipsychotic drugs are one of the risk factors amongst schizophrenic patients for causing metabolic syndrome which is characterised by weight gain, impaired glucose tolerance, insulin resistance, dyslipidaemia, and hypertension [50]. Second generation antipsychotic drugs have a higher incidence rate of causing metabolic syndrome as compared to first generation drugs [50,51]. Antipsychotic polypharmacy and higher potency antipsychotics have a higher risk of causing metabolic syndrome [50,52]. Metabolic syndrome is an important risk factor for cardiovascular disorders. As shown in [Table/Fig-5], mechanisms behind the development of insulin resistance, impaired glucose tolerance, dyslipidaemia are still uncertain.



[Table/Fig-5]: Metabolic Syndrome: receptor pharmacology, pharmacogenetic factors, common causative agents, and clinical monitoring.
AIMD: Antipsychotic-induced metabolic dysfunction; PGRMC1: Progesterone receptor membrane component 1; INSIG-2: Insulin-induced gene-2; SREBP: Sterol-regulatory element-binding proteins; SCAP: SREBP-cleavage-activating protein

Second generation drugs can interplay with numerous other receptors like serotonin, glutamate, histamine, α adrenergic and muscarinic receptors along with dopaminergic receptors [4]. Olanzapine and clozapine which largely affect the body weight have more affinity to serotonergic 5HT2C and histaminergic H1 receptors whereas binding of the drug with the central 5HT2C and peripheral M3 receptors produce impaired glucose tolerance [4]. Hyperprolactinaemia which is common with antipsychotic drugs due to dopaminergic blockade can lead to hyperglycaemia, insulin resistance and weight gain [53]. In an experimental study, clozapine and risperidone treated rats showed increased hepatic expression of Sterol-Regulatory Element-Binding Proteins (SREBPs) and SREBP-Cleavage-Activating Protein (SCAP) along with inhibition of Progesterone Receptor Membrane Component 1 (PGRMC1) and Insulin-Induced Gene-2 (INSIG-2) which can result in increased serum lipid and hormone parameters [54]. SREBPs regulates the cholesterol, fatty acid and triacylglycerol metabolism and excess SREBPs can lead to increased levels of cholesterol, fatty acid and triacylglycerol [54].

SCAP helps SREBPs for activation and increased transcriptional activities for lipid biosynthesis whereas, INSIG-2 inhibits SCAP induced activation of SREBPs and reduce the lipid biosynthesis [54]. INSIG-2 gene may be the target of antipsychotic drugs. INSIG-2 gene polymorphisms may be responsible for antipsychotic drug-induced weight gain and metabolic syndrome [55,56]. Amongst first generation drugs, chlorpromazine has the highest propensity to cause glucose abnormalities than haloperidol, fluphenazine and perphenazine whereas amongst second generation, clozapine and olanzapine have the higher propensity followed by quetiapine, risperidone, amisulpride, ziprasidone and aripiprazole [57,58]. Clozapine and olanzapine can produce more weight gain as compared to quetiapine, risperidone, amisulpride, ziprasidone and aripiprazole [58].

In matched case-control study by Olfson M et al., clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and first generation antipsychotics were associated with more risk of causing new onset hyperlipidemia [59]. However, aripiprazole and ziprasidone have the lowest risk of causing dyslipidaemia amongst second generation drugs [58]. Patients receiving second generation antipsychotic drugs should be monitored for weight, waist circumference, blood pressure, fasting/random sugar, glycosylated haemoglobin (HbA1c) and fasting lipid level frequently and educated for possible metabolic side-effects and other risk factors for cardiovascular disorders [4,57]. Switch over to safer antipsychotic drugs like aripiprazole, ziprasidone and lifestyle intervention are required if metabolic syndrome develops. The patient should be motivated for regular physical activity, weight loss, healthy diet, stress management and smoking/alcohol cessation. Metformin 1000 mg/day for six months was found effective in improving antipsychotics induced dyslipidemia and insulin resistance [60]. BGP-15 which is a heat shock protein (Hsp) co-inducer can be helpful for the treatment of antipsychotic drug-induced metabolic syndrome [61]. BGP-15 helped to overcome the insulin resistance and reducing weight gain due to risperidone, clozapine and olanzapine in an experimental study [61]. Hypolipidaemic and hypoglycaemic drugs can be helpful for established dyslipidaemia and impaired glucose tolerance.

CONCLUSION(S)

Cardiovascular and metabolic adverse reactions associated with antipsychotic drugs are a matter of concern. QT interval prolongation is a rare adverse effect but, it leads to serious consequences. The control of modifiable cardiovascular risk factors, ECG and electrolytes monitoring is an important aspect of the safe use of antipsychotics. Orthostatic hypotension is common during the initial period of therapy and rarely requires pharmacological interventions. Myocarditis is a rare adverse effect of antipsychotic drugs and maximally reported with clozapine. Genetic association has been found for clozapine induced myocarditis. The interaction of second generation antipsychotics with serotonin, glutamate, histamine, adrenergic, muscarinic and dopaminergic receptors can lead to features of metabolic syndrome like weight gain, insulin resistance, dyslipidaemia, and hypertension. It is a major concern for the patients on long term therapy and further increases the risk of cardiovascular diseases. Schizophrenic patients should be screened for the presence of co-existing risk factors. Antipsychotic drugs should be selected with a proper risk-benefit assessment and titration of dosage should be done based on frequent monitoring of the patients.

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PARTICULARS OF CONTRIBUTORS:
1. Resident, Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India.
2. Resident, Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India.
3. Assistant Professor, Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India.
4. Associate Professor, Department of Pharmacology, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, India.
5. Resident, Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Preeti L Navik,
Resident, Department of Pharmacology, Government Medical College,
Bhavnagar, Gujarat, India.
E-mail: drpreetinavik@gmail.com

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