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REVIEW ARTICLE

A Review of Drug-Induced Congenital Heart Defects: Teratogenicity, Mechanisms and Prevention Strategies

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ABSTRACT

Background: Congenital heart defects (CHDs) represent one of the most prevalent types of birth defects, affecting nearly 1% of live births globally. While genetic predispositions contribute to CHDs incidence, increasing evidence highlights the critical role of teratogenic drug exposure during pregnancy.
Objective: This review explores the teratogenic potential of various drug classes—including antiepileptics (valproic acid, phenytoin), isotretinoin, anticoagulants, Angiotensin-Converting Enzyme (ACE) inhibitors, and select antipsychotics—in disrupting fetal cardiac development.
Methodology: The information presented in this review was acquired from different databases including Google, Google Scholar, Elsevier, Wiley, Springer, Taylor & Francis, etc.
Results: The data have revealed that the mechanisms underlying drug-induced CHDs involve oxidative stress, disruption of cardiac signaling pathways, altered folate metabolism, and hemodynamic imbalances. Each agent exhibits unique pathophysiological pathways, such as histone deacetylase inhibition by valproic acid or retinoic acid (RA)-mediated gene dysregulation by isotretinoin, ultimately leading to structural heart anomalies. The review also outlines prevention strategies, emphasizing preconception counseling, alternative drug regimens, early screening, and rigorous pregnancy prevention programs.
Conclusion: As fatal birth threat, a comprehensive understanding of drug-related teratogenicity is crucial to ensuring maternal safety while minimizing fetal cardiovascular risks during gestation.

INTRODUCTION

Congenital heart defects (CHDs) are the abnormalities with the heart's structure that happen while a baby is developing in the womb, which can affect the heart's normal function due to a range of defects, which affect valves and blood vessels. CHDs are among the most common birth defects affecting nearly 1% of live births worldwide (Yang *et al.* 2024). Specific global data on the prevalence and mortality rates of congenital heart disease by gender for the years 2020 to 2024 is limited, but the most comprehensive data available currently only goes up to 2017. A systematic analysis for the Global Burden of Disease Study–2017 reported that in 2017, the global incidence rate of CHDs was 17.9 per 1,000 live births, with 19.1 per 1,000 for males and 16.6 per 1,000 for females (Ray *et al*. 2001; Sun *et al*. 2015). The age-standardized mortality rate (ASMR) for CHDs also decreased from 6.3 per 100,000 population in 1990 to 3.9 per 100,000 in 2017. Men generally had a slightly higher mortality rate than women during this time period. A study in the United States using data from 2017 to 2022 showed that the risk of death for patients with CHD was significantly higher during the COVID-19 pandemic as compared to the past years. The study also found that male CHDs patients had a higher risk of death (Cubeddu 2016).

Although the exact cause is not clearly known, the CHDs can be caused by genes, environmental factors, or when the mother is exposed to teratogenic factors during pregnancy. These defects can be minor and fix themselves or they can be very serious and need surgery(Frommeyer & Eckardt, 2016). Some CHDs are so minor that they go away on their own, while others are very serious and can even be life threatening. Early detection of CHDs has improved, thanks to advancements in diagnostic techniques such as fetal echocardiography. Survival rates have also increased significantly due to improvements in surgical and medical treatments. However, people with a congenital heart defect (CHD) often need lifelong medical follow-up to monitor and manage their condition (Li and Ramos 2017).

In teratogenicity, a drug that can cause birth defects in a baby while it is still developing fetus, and these drugs are called teratogens. They can disrupt the normal growth of baby by causing damage to the cells, interfering with how cells communicate with each other or cause stress to the cells (Taye *et al*. 2024). Many kinds of drugs can be teratogens including some drugs used to prevent seizures, address skin problems, and to prevent blood clots. If certain drugs are taken during pregnancy, they can increase the chances of a baby having a CHD.

Understanding how drugs can cause heart defects is very important for making sure that pregnant women get the best care while also keeping their babies safe (Wang *et al.* 2024). In this review, the information will be provided on how specific medications, especially antiepileptics, anticoagulants, retinoids and ACE inhibitors can lead to problems with a fatal heart development (Lewis-Israeli *et al.* 2021). Focus will be on what can be done to prevent the problems such as carefully assessing the risks of taking certain drugs during pregnancy, using different treatments when possible and making sure that doctors and pregnant women follow guidelines to minimize exposure to harmful drugs.

BRIEF MECHANISMS OF DRUG INDUCED CONGENITAL HEART DEFECTS

The CHDs result from multiple teratogenic mechanisms that disrupt normal cardiac development. The most important of the CHDs are discussed below (Table 1).

Oxidative stress and apoptosis

This occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. Some drugs like valproic acid and phenytoin can increase ROS production. This excess ROS can damage cells, leading to apoptosis or programmed cell death. When apoptosis occurs in the cells that are developing the heart, it can disrupt normal heart formation and lead to CHDs (Xuan *et al*. 2022).

Interference with cardiac signaling pathways

Signaling pathways that are essential for heart development. For example, retinoids can interfere with RA signaling, which is crucial for the migration of cardiac neural crest cells and the formation of the heart tube. Disruptions in these pathways can lead to conotruncal defects and malformations of the outflow tract, which is the part of the heart that pumps blood out to the body (Ho *et al.* 2022).

Folate metabolism disruption

Some medications such as valproic acid can interfere with folate metabolism. This can lead to folate deficiencies which are important for DNA synthesis and cell differentiation. Disruptions in these processes can contribute to both neural and cardiac defects including septal abnormalities (Thorat *et al.* 2024).

Altered hemodynamics

Certain medications such as ACE inhibitors can affect fetal hemodynamics. They can impair fetal kidney function which can reduce amniotic fluid volume and lead to reduced blood flow to the fetus. This hemodynamic instability can cause left-sided heart defects such as hypoplastic left heart syndrome(Nugraha *et al.* 2019).

COMPARING CORONARY HEART DISEASE RISK ACROSS DIFFERENT DRUG CLASSES

Cardiovascular disease, particularly CHD, is a leading cause of morbidity and mortality. Managing risk factors like hypertension and dyslipidemia is crucial in preventing CHD (Nugraha *et al.* 2018).

Among other medications, aspirin is a widely used antiplatelet medication for secondary CHD prevention. The Second Joint Task Force recommends aspirin (at least 75 mg) for coronary patients and those with cerebral atherosclerosis or peripheral disease. With statins and beta-blockers, it lowers all-cause mortality by 90%. Diabetes is a significant CHD risk factor. Managing blood glucose levels with anti-diabetic medications is crucial. However, some anti-diabetic drugs may increase cardiovascular risk, while others have a neutral or beneficial effect (Nugraha *et al.* 2018; Yang *et al.* 2024).

CONFLICTING EVIDENCE IN CHD RISK FACTORS

Several topics have sparked ongoing debates and conflicting evidence regarding their impact on coronary heart disease (CHD) risk. Important of these are briefly described below (Table 1).

Table 1: Different classes of medications causing CHD along with their mechanism, metabolic effects and severity

Medication Class	Mechanism of Increased CHD Risk	Metabolic Effects	Severity of Risk
Antipsychotics (Olanzapine, Clozapine, Risperidone)	- Weight gain - Dyslipidemia - Insulin resistance	Weight gain - Dyslipidemia (increased triglycerides, LDL, decreased HDL) - Insulin resistance (potential progression to type 2 diabetes)	Moderate to High Especially for second-generation antipsychotics (SGAs)
Corticosteroids (Prednisone, Dexamethasone)	Rheumatoid arthritis (RA) is a chronic inflammatory joint disease	Hypertension - Dyslipidemia (increased triglycerides, LDL) - Insulin resistance - Visceral fat deposition (abdominal obesity)	Moderate Especially with long-term use
NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)	Inhibition of COX-1 and COX-2 Endothelial Dysfunction	Altered Lipid Profiles High levels of LDL ("bad" cholesterol) and triglycerides promote atherosclerosis (plaque build-up in arteries), raising the risk of CHD. Increased Oxidative Stress Fluid retention and endothelial dysfunction have been related to use of nonsteroidal anti-inflammatory drugs (NSAIDs), and type 2 diabetes mellitus	Oxidative stress accelerates the development of atherosclerosis, increases inflammation, and promotes clot formation, all of which contribute to the risk of heart disease.
Antihypertensive drugs(Hydrochlorothiazide, Enalapril, Lisinopril, Ramipril)	Hyperuricemia Increased Blood Pressure	Elevate uric acid levels, which may lead to gout. It has been associated as it can cause endothelial dysfunction and contribute to inflammation in blood vessels, further raising the risk of CHD. Increase in cholesterol level, decreases the Chances of HD	Increased LDL Cholesterol and Triglycerides (Moderate to High) Hypokalemia (Moderate), It affects the heart or blood vessels congenital heart defects and peripheral artery disease. “CVD” is used based on t

Fig. 3: Mechanism of Action of *Rumex dentatus* Bioactivities

Testosterone replacement therapy (TRT)

Some studies suggest TRT may increase cardiovascular events, particularly in older men. Other studies propose TRT may improve cardiovascular outcomes in hypogonadal men (Dookun *et al.* 2022).

NSAIDs and CHD risk

COX-2 inhibitors like Celecoxib were initially thought to pose a higher cardiovascular risk. Recent reports suggest Celecoxib may not be worse than traditional NSAIDs like Ibuprofen and Diclofenac in terms of CHD risk (Dookun *et al.* 2022).

Hormonal therapy

Women suffer increased CHD risk with estrogen progestin therapy. Suggests the risk is age-dependent, with lower risks in younger postmenopausal women.

SGLT2 inhibitors

In non-diabetic populations, SGLT2 inhibitors have been shown to reduce CHD risk in diabetic patients. Ongoing studies are assessing potential benefits in non-diabetic populations. These debates highlight the complexity of CHD risk factors and the need for ongoing research to clarify the relationships between these factors and cardiovascular disease (Bonora *et al.* 2019).

Antipsychotics

The trend of antipsychotic use during pregnancy has become a notable concern for the past 10 years. Research does not provide strong evidence that antipsychotics contribute to the development of heart defects, except risperidone (Karmazyn *et al.* 2011). Recent findings show that using atypical antipsychotics i.e. risperidone subtly triggers cardiac malformation, which was noticed three months post birth, but the risk observed might not be reliable because of no known scientific or biological reason (Stanton 2003). If its use causes risk, it seems to be minor (Stanton 2003). The mentioned teratogen is not approved officially to be practiced during pregnancy. Yet they continue to be recommended when necessary and is not always needed to discontinue.

The primary functional organ to be developed in the fetus within the 42 days of beginning of pregnancy is the heart. Throughout this period, special blood vessels evolve, which eventually form the heart. By the crucial period of the second to seventh week of gestation, any disruptions in

development during these weeks might be the period when teratogen leads to congenital abnormalities. Results noticed might have occurred randomly rather than the drug itself. So as to understand the possible dangers of practicing risperidone, it demands future research (Ma *et al.* 2017).

Valproic acid (VPA)

Sodium valproate has been used for over decades for seizure control use. In relation to its benefits, it is linked with its drawbacks by inducing teratogenic risk i.e. neural tube defects and cardiac malformations. In contrast to other antiepileptic drugs such as lamotrigine and levetiracetam, VPA posed the highest risk of congenital malformations (Fischler *et al.* 2012; Ornoy 2009). The exact mechanism by which VPA causes teratogenic effects remains unclear. However, it is believed to act as a Histone Deacetylase (HDAC) inhibitor, affecting transcription factors such as Myocyte Enhancing Factor 2C (Mef2c) (Gurvich *et al.* 2005; Tung and Winn 2011). To investigate its impact on heart development, pregnant mice were treated with VPA, and ultrasound analysis revealed structural abnormalities and changes in cardiac contractility. The study suggests that Mef2c expression is not the primary cause of heart defects in mice. Instead, VPA appears to influence cardiogenesis by altering the activity of specific proteins in cells without directly modifying the genes that regulate them. This interference in how cells interpret and utilize genetic instructions may contribute to developmental issues in the fetus. In contrast to other common antiepileptic drugs, the risk of birth defects is 2–7 times higher with VPA (Ornoy 2009; Fischler *et al.* 2012). Therefore, VPA should not be the first treatment choice unless it is the only option available.

Phenytoin

Phenytoin is a known teratogen that has been linked to various birth defects due to its impact on embryonic development (Danielsson *et al.* 1997; Hansen *et al.* 2021). The possible mechanisms behind these defects include disturbances in folate metabolism, embryonic hypoxia, free radical damage from re-oxygenation, and maternal hyperglycemia (Danielsson *et al.* 1997).

Research using high-frequency ultrasound has shown that phenytoin significantly reduces embryonic heart rate, with some embryos failing to recover even after a 24 h period. These findings suggest that phenytoin-induced malformations result from a combination of embryonic and maternal bradycardia along with hyperglycemia rather than hypoxia alone (Hansen *et al.* 2021). Studies on pregnant Sprague-Dawley rats have demonstrated that the embryonic heart rate (HER) naturally increases with gestational age in control embryos. However, exposure to phenytoin significantly reduces HER, particularly within 4-8 h after dosing, likely due to its ability to cross the placenta. This suggests that phenytoin can directly cause embryonic bradycardia at specific concentrations, leading to adverse developmental effects (Danielsson *et al.* 1997). Further research on mouse and rat embryos cultured with varying concentrations of phenytoin has revealed a dose-dependent decrease in heart rate across all mouse strains, while higher doses in rat embryos resulted in arrhythmias. These observations indicate that phenytoin-induced teratogenic effects are closely linked to embryonic hypoxia caused by impaired heart function (Danielsson *et al.* 1997).

The risks associated with phenytoin are particularly concerning for pregnant women with epilepsy, as they require antiepileptic drugs (AEDs) during pregnancy to maintain seizure control. However, both monotherapy and polytherapy with AEDs have been shown to double or even triple the risk of major birth defects (Hansen *et al.* 2021). Additionally, certain AEDs may also impact cognitive development later in life, further complicating their use during pregnancy. Interestingly, class III antiarrhythmic drugs, such as almokalant, dofetilide, and ibutilide have been found to cause similar teratogenic effects as phenytoin. Like phenytoin, these drugs block the I(Kr) potassium channel and have been shown in animal studies to be highly sensitive to the embryonic heart. Their effects lead to developmental defects by causing bradycardia, arrhythmia, and cardiac arrest, which in turn result in hypoxia, oxidative stress, and altered blood flow (Bénazet *et al.* 2001; Ma *et al.* 2017).

Angiotensin-converting enzyme (ACE) inhibitors

The renin-angiotensin system helps control blood pressure. Medications like ACE inhibitors lower blood pressure by blocking the production or action of angiotensin II. However, using ACE inhibitors during pregnancy can harm the baby, causing congenital heart diseases, kidney problems, low amniotic fluid, lung issues, and poor skull development. These risks are highest in the second and third trimesters. The effects in the first trimester are less clear and may be due to reduced blood flow to the fetus rather than direct harm. Therefore, these medications should not be used during pregnancy, and women who could become pregnant should consider other options (Ma *et al.* 2017).

Drug-induced CHDs

Lisinopril: It is a medication that helps lower blood pressure and treat heart problems. However, it can be harmful to a baby if taken during pregnancy. Taking this drug in the first three months of pregnancy can increase the risk of serious birth defects, especially in the baby's heart and brain. Because of this, it is best to avoid using it during early pregnancy (Lee *et al.* 2016). The harmful effects, also known as teratogenic effects, happen due to several reasons. First, these drugs interfere with the renin-angiotensin system, which is important for regulating blood pressure and fluid balance. Second, they reduce the blood flow from the uterus to the placenta, which means the baby may not get enough

oxygen and nutrients. Third, they can directly affect the growth of heart muscle cells in the baby. Lastly, these drugs can increase the chances of the baby having low blood pressure (hypotension) and reduced blood supply to tissues (ischemia), which can affect proper development (Walters *et al*. 2012).

Captopril: It is a type of medication called an ACE inhibitor, can lead to heart problems and other birth defects in babies if taken during pregnancy, especially in the second and third trimesters. Captopril can cause birth defects if taken during pregnancy, and it works in a way similar to other ACE inhibitors like lisinopril. It can lead to problems in the baby's heart development. Some of the common issues include a hole between the lower heart chambers (ventricular septal defect), and a condition where a blood vessel that should close after birth stays open (called patent ductus arteriosus)(Crisafulli *et al.* 2020).

Captopril can also cause a hole between the upper heart chambers (atrial septal defect) and a serious condition where the left side of the heart does not grow properly (hypoplastic left heart syndrome) (Crisafulli *et al.* 2020). Because of these risks, it is very important not to use captopril during pregnancy. Women who can get pregnant should use birth control while taking lisinopril and captopril. If they want to become pregnant or find out they are pregnant, they should stop taking lisinopril and switch to a safer blood pressure medication. At around 18 weeks of pregnancy, doctors may recommend an ultrasound and heart check for the baby. Using lisinopril and captopril later in pregnancy can also cause serious problems for the baby (Lancellotti *et al.* 2023). So, it is important for women on lisinopril to talk to their doctor before planning a pregnancy or as soon as they know they are pregnant. To help prevent harm to the baby, several important steps are recommended before and during pregnancy. The women should receive preconception counseling to understand the risks of certain medications and plan safely for pregnancy (Crisafulli *et al.* 2020). A review of all current medications is important, and harmful drugs should be replaced with safer alternatives. For women at high risk, regular pregnancy testing is advised to catch pregnancy early. Early monitoring can help detect any problems in the baby's development as soon as possible. Taking folic acid supplements is also encouraged, as it supports healthy growth of the baby and helps prevent birth defects. Lastly, involving a pregnancy specialist, such as an obstetrician or maternal-fetal medicine doctor, ensures proper care and guidance throughout the pregnancy(Nakamura *et al.* 2022).

Isotretinoin: It is a powerful medication primarily prescribed for severe, treatment-resistant acne. A derivative of Vitamin A works by reducing the activity of sebaceous glands and enhancing the turnover of skin cells. Isotretinoin is a known teratogen, meaning it has the potential to cause birth defects, including CHDs, if taken during pregnancy. The highest risk of teratogenic effects occurs when the drug is used during the first trimester, which is a critical stage for fetal development (Nakamura *et al.* 2022).

Research indicates a notable increase in the incidence of CHDs in infants whose mothers used isotretinoin during pregnancy. Types of CHDs commonly linked to isotretinoin exposure include conotruncal defects, aortic arch artery malformations including transposition of great vessels, double outlet right ventricle, ventricular and atrial septal defects (VSD and ASD) as well as tetralogy of Fallot (Lammer *et al.* 1985; Mark *et al.* 2006). RA treatment induces a broad spectrum of cardiac malformations, ranging from structurally intact hearts with a normal subaortic outflow tract to severe anomalies such as a double outlet right ventricle with a straddling tricuspid orifice or a double inlet left ventricle. A notable finding within this continuum is the strong correlation between inflow and outflow tract defects, which can be attributed to disruptions in the cardiac looping process. This disturbance appears to cause misalignment of septal structures (Tarquini *et al.* 2011). According to a case report by Mondal (2017), a child was born with congenital heart defect, his echocardiography identified congenital cyanotic heart disease, including dextro-transposition of the great arteries, a 4 mm atrial septal defect, and a left-to-right shunt, with normal biventricular function. It was found that the mother had been taking isotretinoin capsule 20 mg/kg/day to treat acne recommended by a dermatologist (Tarquini *et al.* 2011; Hölscher *et al.* 2016). The child was also reported to have many other isotretinoin induced malformations. RA can disrupt the normal development of the heart, affecting the formation of heart chambers and the proper separation of the chambers, which can result in defects such as ASD and VSD, along with other malformations in major blood vessels (Hölscher *et al.* 2016).

PATHOPHYSIOLOGY OF TERATOGENIC ACTION OF ISOTRETINOIN

A major mechanism underlying isotretinoin-induced teratogenesis may be its detrimental effect on cephalic neural-crest cell activity. This disruption plays a critical role in embryonic development, potentially leading to severe congenital anomalies. Notably, interference with these cells has been linked to craniofacial deformities, CHDs, and abnormalities in thymic development(Ma *et al.* 2020). Understanding this mechanism provides valuable insights into the risks associated with isotretinoin exposure during pregnancy. Isotretinoin is a potent teratogen known to disrupt neural crest cell development, leading to severe congenital anomalies. Research indicates that both isotretinoin and its metabolite, 4-oxo-isotretinoin, interfere with cytosolic calcium homeostasis in neural crest cells, triggering cellular stress responses (Ferri *et al.* 2013). This disruption results in membrane blebbing, a characteristic feature of apoptosis, ultimately causing cell death. The loss or dysfunction of neural crest cells during early embryogenesis is a key factor

in the teratogenic effects of isotretinoin. Understanding this mechanism provides valuable insights into the risks associated with isotretinoin exposure during pregnancy. Underscoring the critical need for strict precautions when prescribing it during pregnancy and importance of strict regulatory measures to prevent fetal harm (Varricchi *et al.* 2018).

According to the research of Bouman (1995) on chicken hearts after administering RA treatment he observed VSD and DORV showing dextraposed arterial pole and many other abnormalities. He concluded that RA treatment in chickens induces a broad spectrum of cardiac malformations. A notable finding within this continuum is the strong correlation between inflow and outflow tract defects, which can be attributed to disruptions in the cardiac looping process (Varricchi *et al.* 2018). These insights highlight the critical role of cardiac looping in proper heart development and the potential teratogenic effects of RA exposure. RA influences heart tissue specification, structural patterning, and neural crest development. While its deficiency can disrupt heart formation, excessive RA exposure has been linked to congenital defects in animal models. The active form of isotretinoin, RA, interferes with normal fetal development by affecting processes like cell differentiation, programmed cell death (apoptosis), and blood vessel formation (angiogenesis) (Iqubal *et al.* 2018).

RETINOID IMPACT ON GENE REGULATION

Isotretinoin works by binding to nuclear RA receptors (RARs and RXRs), which regulate the expression of specific genes involved in cellular differentiation, tissue maintenance and embryonic development. RA influences genes responsible for heart formation by regulating transcription factors involved in cardiogenesis. Disruption of these factors can lead to abnormalities in the folding, septation, and overall formation of the fetal heart (Iqubal *et al.* 2018). RA balance is very important for embryo development at every stage. RA levels are precisely regulated through a complex interplay between synthesizing and metabolizing enzymes. Retinoids bind to RA and retinoid X receptors (RARs and RXRs), initiating a regulatory cascade that governs the expression of tissue-specific genes. Genetic or nutritional disruptions in RA signaling may serve as a significant risk factor, contributing to an increased prevalence of congenital heart diseases in humans(Florescu *et al.* 2013). According to Liu (2018), isotretinoin exposure disrupts mesodermal differentiation by altering gene expression and chromatin accessibility. RNA-seq analysis reveals dysregulation of key signaling pathways, such as TGF-beta, while ATAC-seq indicates increased DNA binding of transcription factors like HNF1B, SOX10, and NFIC near affected genes. These findings suggest potential molecular mechanisms through which isotretinoin interferes with mesodermal differentiation, impacting cardiac development(Varga *et al.* 2015).

CHD-DRUGS PREVENTION STRATEGIES

Research suggests that isotretinoin therapy at a dosage of 0.8 mg/kg/day poses no significant risk of polymorphic ventricular tachycardia, making it a safe option for acne treatment. This dosage appears to maintain cardiac safety while effectively addressing dermatological concerns, reinforcing its suitability for clinical use. To prevent the isotretinoin induced CHD and other abnormalities, pregnancy prevention programs (PPPs) should be implemented worldwide (Varga *et al.* 2015). It is seen that in those countries where there are no PPP's, it is estimated that around 80% of pregnant women come into contact with isotretinoin either within the advised 30-day contraception period or while they are pregnant. Studies indicate that women who continue taking isotretinoin beyond the 15th day after conception face a 35% risk of their offspring developing isotretinoin embryopathy and 40% risk of abortion and stillbirth. Pregnancy during isotretinoin treatment indicates a failure of preventive measures. To minimize risk, two forms of contraception should be used starting one month before treatment begins and continuing until one month after discontinuation (Varga *et al*. 2015).

CONCLUSIONS

CHDs basically affect about 1% of live births worldwide, which makes it one of the pervasive birth defects. Either these defects may be minor or might need surgery for its cure. There are certain types of drugs discussed above that can cause birth defects within the babies. The drug classes that lead to birth defects are described above. Normal heart formation is affected when following mechanisms take place by taking the specific type of drug, oxidative stress, apoptosis, folate metabolism disruption, interference with cardiac signaling pathways, altered hemodynamics etc. Moving towards the classes of the drugs that lead to CHDs, these drugs which show the risk of the CHDs are needed to be replaced with the drugs that have less risk factor of CHDs. Considering anti-psychotics, all their types somehow show CHDs risk except for the drug risperidone as it shows the risk but it is not as the other drugs, rather it is one of the minor risks which can be treated. During pregnancy it is mentioned for the patient only if necessary.

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AUTHOR CONTRIBUTIONS

All authors made equal contributions to the conception, design, execution, and writing of this study.

CONFLICTS OF INTEREST

The authors declared no conflict of interest.

DATA AVAILABILITY

The data will be made available on a fair request.

ETHICS APPROVAL

Not applicable

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