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CLINICAL UPDATES ON DRUG - INDUCED CARDIOTOXICITY

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ABSTRACT: Cardiotoxicity associated with the clinically used drugs is a global concern of safety for healthcare professionals. Various animal models have been used to study the drug-induced cardiotoxicity but the exact molecular involvement of toxicity is not much clear. Despite the recurrent occurrence of toxicities, drugs such as doxorubicin, calcium channel blockers, antiarrhythmics and immunomodulators are regularly used. Anticancer drugs mainly anthracyclines, 5- fluorouracil and cyclophosphamide exert prominent cardio-toxicity. Till date, there is only one drug approved for doxorubicin-related cardiotoxicity *i.e.* dexrazoxane. Few other drugs are used routinely by clinicians to reduce the severity of toxicity which includes ACE inhibitors, L-carnitine, probucol, CoQ_{10}, N-acetylcysteine, Vitamin E and deferoxamine, whereas antidepressants drugs, specifically tricyclic antidepressants are potential candidates for cardiotoxicity. Calcium channel blockers, antiarrhythmic and beta receptor antagonist aggravate cardiac heart failure (CHF) and left ventricular arrhythmia. Interferons, mainly interferon-α is also associated with prominent and dose-dependant toxicity. Some other drugs like zidovudine, chloroquine, cocaine, minoxidil, ketoconazole, prostaglandin E2 and anagrelide are also reported to have cardiotoxic effects. A complication associated with the use of these drugs include hypoxia, coronary ischemia, calcium overload, oxidative stress, contractile dysfunction, left ventricular arrhythmia and cardiomyopathy.

INTRODUCTION: Cardiotoxicity is the common side effect of many drugs [1] among which anticancer drugs, specifically anthracycline class of drugs exert severe cardiotoxicity [2]. Other drugs that cause cardiotoxicity are amphetamine, mitomycin, paclitaxel and zidovudine [3, 4]. The common mechanism leading to cardiotoxicity is oxidative stress, generation of free radicals and hypoxia [5].

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Long-term exposure to cardiotoxic drugs further causes apoptosis and deregulation of myo-contractility. Cardiotoxic effect of drugs can be understood in two ways. (1) Drugs causing cardiac injury by affecting the performance of cardiac muscles. (2) By altering the ion channels and pump (voltage-gated sodium and potassium ion channel and Na^+ - K^+ ATPase pump) [4]. Exposure to the cardiac-toxic drugs induces prolong cardiac repolarization (QT interval) and causes arrhythmia (Torsades de pointes) [4]. Since these drugs causes cardiotoxicity as side effect, they can be used as cardiotoxicity inducing agents in preclinical experimental models [6]. In this review we are going to focus on the Cardiotoxicity of drugs only and not the experimental models.

List of cardiotoxic drugs is shown in **Table 1** and effect of cardiotoxic drug is displayed in **Fig. 1** [7].

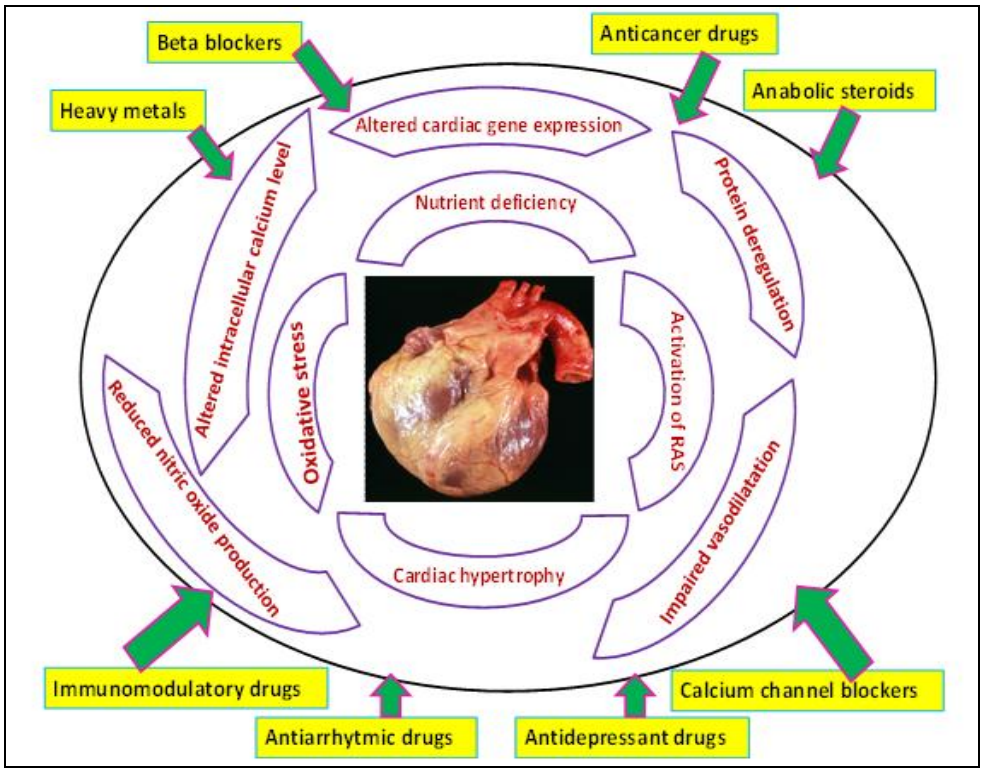

FIG. 1: EFFECT OF CARDIOTOXIC DRUGS ON HEART THROUGH DIFFERENT MECHANISMS

TABLE 1: LIST OF CLINICALLY USED DRUGS THAT EXERT CARDIOTOXIC EFFECT [8]

S. no.	Drug	Class	Mode of action	Use
1	Doxorubicin	Anticancer	Inhibit progression of topoisomerase II	Breast cancer, bladder cancer, lymphoma, Kaposi's sarcoma.
2	Daunorubicin	Anticancer	Inhibit progression of topoisomerase II	Kaposi's sarcoma, lymphoma, myelogenous leukemia
3	Idarubicin	Anticancer	Inhibit progression of topoisomerase II	Acute myeloid leukemia.
4	Cyclophosphamide	Anticancer	Bind at 7 guanine residue and inhibit cell division	Lymphoma, multiple myeloma, ovarian, breast and lung cancer.
5	5 fluorouracil	Anticancer	Thymidylate synthase inhibitor, inhibit DNA replication.	Colon, stomach, esophageal, pancreatic, breast and cervical cancer
6	Chloroquine	Antimalarial	Prevent biocrystallization of hemozoin	Arthritis, malaria, lupus erythematosus
7	Cocaine	Stimulant	Inhibit MAO uptake	Numbing agent
8	Cytarabine	anticancer immunosuppressant	Inhibit DNA and RNA polymerase	AML, CML and non-Hodgkin's lymphoma
9	Paclitaxel	Anticancer	Act on tubulin and causes instability of cytoskeleton causes cell cycle arrest	kapski sarcoma, ovarian, breast, lung, cervical, and pancreatic cancer
10	Mitomycin	Anticancer	Inhibit DNA cross linking	Adenocarcinoma, anal, bladder, breast, cervical, colorectal and lung cancer.
11	Imatinib	Anticancer	Tyrosine kinase inhibitor	CML, gastrointestinal stromal tumors, plexiform neurofibromas.
12	Sunitinib	Anticancer	Tyrosine kinase inhibitor	Renal cell carcinoma and gastrointestinal stromal tumors.
13	Trastuzumab	Monoclonal antibodies	Act through PI3K/Akt pathway	Breast cancer
14	Zidovudine	Antiretroviral	Inhibit HIV's reverse transcriptase enzyme	HIV and HAART

15	Mitoxantrone	Anticancer	Topoisomerase II inhibitor	Metastatic breast cancer, acute myeloid and lymphoblastic leukemia
16	Stibogluconate	Antileishmanial	Topoisomerase I inhibitor	Leishmaniasis
17	Minoxidil	Antihypertensive	Potassium channel opener	Alopecia, hypertension
18	Calcium channel blocker	Antihypertensive	Block calcium entry into cell	Control heart Beat and prevent cerebral vasospasm
19	Interteron	Signaling protein	activate JAS-STAT and PI3K/ Akt pathway	Autoimmune disorder, cutenous, hairy and myeloid leukemia, hepatitis C
20	Cyclosporine	Immunosuppressant	Inhibit the phosphatase activity of calcineurin	Graft rejection, rheumatoid arthritis, psoriasis, UC and dry eye
21	Bromocriptine	Dopamine agonist	Inhibit the release of glutamate	Pituitary tumor, hyperprolactinemia, PD, type-2 diabetes
22	Methylphenidate	CNS stimulant	Dopamine reuptake inhibition	Bipolar disorder and major depressive disorder
23	Amphetamine	CNS stimulant	Enhances dopaminergic activity and inhibit MAO transport	Attention deficit hyperactivity syndrome, narcolepsy, depression
24	Methamphetamine	CNS stimulant	Enhances dopaminergic activity and inhibit MAO transport	Attention deficit hyperactivity syndrome, narcolepsy, obesity and depression
25	Anabolic steroid	Anabolic-androgenic steroid	Binds to the androgenic receptor & initiate anabolism cascade	Bone marrow, growth and appetite stimulant, male contraception, HRT
26	Clozapine	Atypical antipsychotic	Bind with dopamine and serotonin receptor	Psychosis, schizophrenia and parkinsonism
27	Anagrelide	Platelet reducing agent	Inhibit maturation of platelets from megakaryocytes	Essential thrombocytosis and chronic myeloid leukemia.
28	Tricyclic antidepressant	Antidepressant	Block serotonin and norepinephrine transport	Depressive disorder and dysthymia
29	Ephedrine	Adrenergic stimulant	Stimulate adrenergic receptor and increase activity of norepinephrine	Antihypertensive, spinal anesthesia, asthma, nasal congestion and obesity
30	Catecholamine	Neuromodulator	Stimulate adrenergic receptor and increase activity of norepinephrine	Bradycardia, hypotension and hypoglycemia
31	Isoproterenol	Non-selective beta-adrenoreceptor agonist	Stimulate adrenergic receptor	CHF, shock, treatment of airway constriction and bradycardia
32	Pentamidine	antimicrobial	Interfare with host DNA, RNA, protein and phospholipid synthesis	Leishmaniasis, babesiosis and pneumocystis pneumonia.
33	Ethanol	Addictive psychoactive	Bind with GABA and increases the activity	Antiseptic, antidote and medicinal solvent.
34	Arsenic	Heavy metal	Interfere with host DNA, RNA, protein and phospholipids synthesis	In antibiotics, syphilis and trypanosomiasis
35	Cobalt	Heavy metal	Interfere with host DNA, RNA, protein and phospholipids synthesis	Radiation treatment, metabolism regulator and cofactors.
36	Diazoxide	Potassium channel activator	Increase permeability to potassium and block permeability for calcium ion, modulate AMPA and kainate receptor	Malignant hypertension and insulinoma.
37	NSAIDs	COX inhibitor	Non-selective inhibitor of COX enzyme	Analgesic, antipyretic and anti-inflammatory
38	Interleukin-2	cytokines	Stimulate and growth of T cell, release histamine, anti-inflammatory activity	Autoimmune disorder
39	Ketoconazole	Antifungal	Interfere with the fungal ergosterol synthesis and some enzymes	Athlete's foot, ringworm, candidiasis, and other fungal infection
40	Prostaglandin E2	oxytocics	Activate Wnt signaling pathway	Termination of pregnancy and labor induction.
41	Ifosfamide	anticancer	Bind at 7 guanine residue and inhibit of cell division	Testicular, bladder, cervical, ovarian, lung and soft tissue cancer, sarcoma and osteosarcoma.

MAO: Monoamine oxidase, AML: Acute myeloid leukemia, CML: Chronic myeloid leukemia, HAART: highly active antiretroviral therapy, UC: ulcerative colitis, PD: Parkinson's disease, HRT: Hormonal replacement therapy, CHF: Congestive heart failure, COX: cycloxygenase

1. Anthracycline and Cardiotoxicity: Anthracycline class of drugs are the first line anticancer drugs but their usage are limited due to cardiotoxicity [9]. Doxorubicin (adriamycin) and daunorubicin (daunomycin or rubidomycin) are two members of anthracycline group [10]. These two drugs are obtained from actinobacteria '*Streptomyces peucetius'* [11]. Anthracycline-induced cardiotoxicity can be acute which may cause arrhythmia, myocarditis, pericarditis or acute left ventricular failure. These symptoms subside just after withdrawal of treatment but restrict the further use of the drug [12].

Anthracycline can also cause cardiomyopathy on the chronic use and sometime late-onset of severe arrhythmia and ventricular dysfunction has been seen [12]. It has been observed that rate of survival with anthracycline is much lesser than those of ischemic or dilated cardiomyopathy [13]. Doxorubicin induced cardio-toxicity is dose dependent and controlled monitoring of dose is the best possible way to prevent toxicity [13]. Now-a-days echocardiography is used to monitor doxorubicin-induced cardiotoxicity and this is considered as gold standard test [14].

1.1 Mechanism of Anthracycline - Induced Cardiotoxicity: Generally, chemotherapeutic drugs induced cardiotoxicity is associated with the myocardial cell loss, apoptosis or necrosis which may be mediated by oxidative stress directly or indirectly [15]. In practice, determination of exact mechanism of doxorubicin-induced cardiotoxicity is not possible because most of the time patient are on multiple therapies [16, 17]. There are four hypothesis proposed on the subject of anthracycline-induced cardiotoxicity [18].

(a) Iron and free radical theory in which occurrence of high oxidative stress and depletion of endogenous antioxidant is observed. Myocardium mitochondria are the central point of oxidative stress [18].

(b) Metabolic hypotheses in which C-13 alcoholic metabolite of anthracycline acts on the myocardium and hamper the myocardial energy pathway and intracellular calcium concentrations [18].

(c) Unifying hypothesis in which C-13 alcoholic metabolite is further acted by oxidative stress which results in increased calcium concentration at the interior of myocardial fiber and damages the cell. This may further enhance the lipid peroxidation and loss of selective membrane permeability [18].

(d) Apoptosis hypothesis in which there is upregulation of pro-apoptotic markers like Bax, caspase and cytochrome c, whereas downregulation of anti-apoptotic markers like Bcl-2, Akt, and PIKT3 pathway [18].

Keeping all these theories in view, the role of free radicals occupy the central position. It has been hypothesized that the oxidative stress not only causes myocardial death but directly affects excitation-contraction properties of cardiac muscles [9, 19]. Free radicals mainly nitrite free radicals are the major culprit of oxidative stress [20].

1.2 Cardioprotective Agents Against Anthracycline - Induced Cardiotoxicity: Drugs used clinically for prevention of anthracycline (doxorubicin) induced toxicity are shown in **Table 2**.

TABLE 2: CLINICALLY USED DRUGS FOR PREVENTION OF ANTHRACYCLINE - INDUCED TOXICITY [21, 22]

S. no	Drugs
1	ACE inhibitors**:** systolic heart failure (first line therapy)
2	Dexrazoxane: approved drugs for anthracycline-induced cardiotoxicity
3	L-carnitine
4	Probucol
5	CoQ_{10}
6	N-acetylcysteine
7	Vitamin E
8	Phenethylamine
9	Deferoxamine

Unfortunately, none of the drugs till date is clinically established as a cardioprotective agent against anthracycline (doxorubicin - induced toxicity) [22].

2. Cyclophosphamide and Cardiotoxicity: Cyclophosphamide is an alkylating agent that acts on 7 guanine residue [23]. The active metabolite of cyclophosphamide is responsible for anticancer activity [24]. However, cardiomyopathy which is likely to be diagnosed within 2 weeks of therapy is reported as a side effect [4]. Cardiotoxicity of cyclophosphamide is due to the effect of toxic metabolite on endothelial cells that causes severe

myopericarditis and myocardial necrosis [25]. If a patient suffers from congestive heart failure (CHF) and get exposed to cyclophosphamide, there is a high chance of death within two weeks [26]. In an in-clinic study, 19 women suffering from metastatic breast cancer were given cyclophosphamide at low dose with continuous infusion for 96 hours. It was observed that low dose for the longer duration of therapy increased the therapeutic response and chance of developing CHF [26].

3. Paclitaxel and Cardiotoxicity: Paclitaxel belongs to taxane class of drugs that act by promoting the polymerization of tubulin [27]. Thus microtubule formed due to the activity of paclitaxel is unstable and interfere with the cell division at the interphase of the cell cycle. This interference finally leads to cell death [27]. Paclitaxel is the choice of drug in ovarian and breast cancer [28, 29]. Asymptomatic bradycardia is most common side effect [30]. 29% of patients undergoing paclitaxel therapy are likely to suffer from bradycardia [31, 32]. In a study, combined therapy of doxorubicin with paclitaxel induces CHF in six patients out of [33]. This occurrence of 18% CHF in patient raised a valid question for combined therapy of paclitaxel and doxorubicin [33].

4. Mitoxantrone and Cardiotoxicity: Mitoxantrone is structurally similar to doxorubicin [34]. This drug is reported to be associated with left ventricular heart failure [35]. In a study when mitoxantrone was used in 805 patients, 1.5% of patient developed CHF, whereas another 1.5% of the patient showed decreased left ventricular ejection fraction [36]. In conclusion, mitoxantrone has potential to induce cardiotoxicity and caution must be taken while using it.

5. Antimetabolite [5 –fluorouracil (5-FU), cytarabine and Capecitabine] and Cardiotoxicity: Among all antimetabolites, 5-FU is most extensively studied drugs in term of cardiotoxicity [37]. It has a direct effect on myocardial cells and on endothelial cells [38]. Mononuclear inflammations and myocardial necrosis have been observed in a patient who died from myocardial infarction followed by 5-FU therapy [39]. 5-FU also induces myocardial hypoxia, CHF and dilated cardiomyopathy have been reported [39]. Capecitabine, on the other hand, causes ischemia [40] and cytarabine has been reported for pericarditis [41].

Thus looking into features and shortcomings of these anticancer drugs, some newer drugs have been developed with the aim of targeted therapy [42]. These drugs may offer an advantage in terms of selectivity for cancer cells and less systemic toxicity [42]. Some of these drugs are trastuzumab, imatinib and bevacizumab [43 - 44]. Some of the targeting newer drugs also showed cardiotoxicity *e.g.,* tyrosine kinase inhibitor (sunitinib and imatinib) have been reported with CHF and hypertension [45].

6. Antidepressant Drugs and Cardiotoxicity: In today's scenario, depression is getting common etiology in most of the chronic disorders [46]. More often antidepressant drugs are used by clinicians [47], which are of 3 major classes (1) tricyclic antidepressant (TCA) (2) selective serotonin reuptake inhibitor (SSRIs) and (3) monoamine oxidase inhibitor (MAO inhibitors) [26]. Among these three classes of drugs, with TCA such as (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline protriptyline and trimipramine), the related cardiotoxicity is more common [48]. Nearly 20% of the patient often suffers from postural hypotension [49]. This side effect becomes more severe when the patient has existing cardiac co-morbid complications [50]. There are reports of altering atrioventricular conduction [51]. A possible mechanism was supposed to be a prolongation of the duration of QRS interval [52]. Sudden death has also been reported with the use of antidepressant drugs [53]. TCA is extensively concentrated in the myocardium [54] and it causes cardiotoxicity by interfering with reuptake of adrenergic amines [55], altering myocardial membrane permeability [55] and by direct action on myocardial [55]. Finally, TCA leads to altered cardiac rhythm and myocardium contractility [55]. There are published evidence of CHF with a number of TCA [56]. On the other hand, SSRIs are related with a lesser incidence of cardiac side effect [57]. Although few study has been performed on the cardio-toxicity of SSRIs [58].

7. Calcium Channel Blockers and Cardiotoxicity: Calcium channel blockers (CCBs) are one of the extensively used drugs in cardiac complications, mainly in angina pectoris [59]. There is an area of debate on the use of CCBs in patients with existing left ventricular dysfunction [60]. Clinically used CCBs are classified into three groups [26].

(1) Phenylethylamine *viz.* verapamil. (2) dihydropyridines *viz.* nifedipine, and (3) benzothiazepines *viz.* diltiazem [26]. There is a report of cardiotoxicity with the use of CCBs which include negative ionotropic effect, activation of rennin-angiotensin system and alteration in membrane calcium transport [61]. There is always a high chance of marked hemodynamic alteration in patients of CHF taking CCBs [62]. In a multicentre dilitiazem post-infarction trial (MDPIT), risk of CHF was found to be increased [63]. It has been seen clinically that the chronic use of nifedipine in a patient of existing CHF exert deleterious effects [64].

8. Antiarrhythmic drugs and Cardiotoxicity: Adverse effect related to antiarrhythmic drugs is related to its cardio depressant and negative ionotropic effect [65]. If the patient is already suffering from left ventricular dysfunctions, antiarrhythmic drugs can further worsen the situation [66]. Negative ionotropy of drugs vary from class to class, as class III antiarrhythmic drugs are devoid of negative inotropy [67]. Antiarrhythmic drugs induced negative inotropy is regulated by an alteration in intracellular calcium concentration [68]. There are randomized double blinded placebo controlled trials which showed the increased risk of CHF in the patients who were taking antiarrhythmic drugs [69]. Thus it can be concluded that almost all antiarrhythmic drug have potential to exert a negative inotropic effect, therefore, utmost caution and monitoring is required while using antiarrhythmic drugs [65].

9. Beta - Adrenoceptor Antagonist and Cardiotoxicity: Beta - Adrenoceptor antagonists are commonly known as beta blockers. These drugs cause negative chronotropic and inotropic effects and exacerbate CHF [70]. Interestingly when beta blocker was used topically for treatment of glaucoma, it additionally caused CHF [71]. In an epidemiological study, no association between the use of topical beta blockers and CHF was found [72]. Similarly, a trial with carvedilol revealed the reduced mortality in patients suffering from CHF [26]. Thus in order to control beta blocker induced cardiotoxicity (CHF), the initial dose should be low and can be gradually increased [26].

10. Interferon and Cardiotoxicity: There are three types of interferon used clinically *i.e.* interferon alpha, beta and gamma [73]. Interferon-alpha has been reported with a cardiotoxic effect which includes hypertension and arrhythmia starting from 1st day of treatment [74]. It has been reported that almost 5 - 15% of patients suffer from interferon-mediated cardiotoxicity [75]. Other cardio-toxicities of interferon include cardiomyopathy and cardiac ischemia [76]. The possible mechanism proposed for the interferon alpha - induced cardiotoxicity is hypoxia, interference with energy metabolism and increased oxygen demand [77].

11. Interleukin-2 (IL-2) and Cardiotoxicity: IL-2 is an approved drug for the treatment of metastatic renal cell carcinoma. IL-2 is associated with deleterious cardiovascular side effects [78]. Reversible left ventricular dysfunction, tachycardia and hypotension are more often reported with the use of IL-2 [78]. Use of IL-2 initiates the production of cytokines which further affect myocardium contractility [78].

12. Amphetamines / Methamphetamines and Cardiotoxicity: Amphetamine class of drugs are the common drugs used by athletes and often associated with doping [79]. These drugs act centrally and cause stimulation which includes euphoria, intensifies emotions and increases sexuality [80]. This drug enhances neuronal reuptake of norepinephrine, serotonin and dopamine [81]. A clinical study has reported the incidence of acute coronary syndrome in 25% of patients taking these drugs [82]. Methamphetamine is reported to be associated with 18% and 40% of incidence of cardiomyopathy [83, 84]. Similarly, in other clinical study methamphetamine is associated with the incidence of 40% cardiomyopathy [84]. There was an animal study which supported the fact that repeated administration of methamphetamine caused cardiac hypertrophy, necrosis, myocarditis, inflammation, left ventricular dysfunction and left ventricular dilatation [85]. Amphetamine and methamphetamine when administered metabolize into catechol that further causes oxidative stress and cardiomyopathy [86].

13. Cocaine and Cardiotoxicity: Cocaine is an alkaloid obtained from *Erythroxylon coca* which is a native plant of South America [87]. Initially, it was used as a local anaesthetic but later its use as an ingredient in cola drink started [88]. Pharmacology of

cocaine consists of inhibition of catecholamine uptake by dopamine and norepinephrine transporter at the pre-synaptic neurons. This results in the accumulation of catecholamines at the postsynaptic neuron [89] which causes increased psychomotor and sympathetic activity [89]. Cocaine also causes the release of norepinephrine and epinephrine from the adrenal medulla that result in severe vasoconstriction [89]. Use of cocaine is associated with myocardial ischemia or myocardial infarction [90]. Cocaine also causes tachycardia and increases systolic - diastolic blood pressure [91]. Chronic use of cocaine causes vasoconstriction of coronary artery and thrombosis which together decreases oxygen supply to the myocardium and induces myocardial ischemia [91]. Acute administration of cocaine causes an increase in intracellular calcium concentration and stimulates arrhythmia [92]. Literature supports four mechanisms for the cardiotoxicity of cocaine.

13.1 Promotion of Intracoronary Thrombus Formation: Cocaine administration causes platelet aggregation and increases thromboxane - A2 production which together contributes to the development of cardiomyopathy and left ventricular dysfunction [93].

13.2 Sympathomimetic Effect of Cocaine: Cocaine use results in activation of the beta-adrenergic receptor and increases myocardial contraction which finally leads to increased blood pressure and increased wall stress [93].

13.3 Increased Calcium Flux: Increased myocardial calcium flux into the myocardial cell causes membrane instability and arrhythmia [93].

13.4 Electrophysiological Effects: Use of cocaine causes prolongation of PR, QRS and QT duration that result into arterial fibrillation and tachycardia [93].

14. Anabolic - Androgenic Steroids and Cardio-Toxicity: Inappropriate use of anabolic steroid is associated with left ventricular hypertrophy [94]. Anabolic steroid when administered, binds with androgenic receptors in the heart and in arteries [4]. Anabolic steroid causes hypertension, dyslipidemia atherosclerosis and impaired contraction-relaxation [95]. Animal studies have shown the increased risk of cardiomyopathy and apoptosis in cardiac cells [96]. Further, use of anabolic steroid causes the discrete release of calcium from sarcoplasmic reticulum which additionally worsens the situation of arrhythmia and cardiomyopathy [95]. Some other complications associated with the use of steroid includes endocardial and myocardial fibrosis, cardiac steatosis, myocardial necrosis, coagulation and coronary atheroma [3].

15. Alcohol Abuse / Heavy Metals and Cardio-toxicity: Alcohol abuse primarily affects the central nervous system but it also exerts direct cardiotoxic effects [97, 98]. There are documented evidence for dose-related cardiotoxicity for ethanol that includes left ventricular dysfunction and cardiomyopathy [99]. Alcohol consumption affects the myocardial contractility, systolic-diastolic deregulations and abnormal rhythm [100]. There are also documented evidence for dose-related cardiac depression [100]. Ethanol when exceeds the limit of 75 mg/100 ml in plasma, the force of contraction reduces significantly [101]. Some heavy metals such as cadmium, lead, and cobalt also causes cardiotoxicity [102]. These heavy metal causes a structural change in cardiac cells, alter myocardial contraction and deregulation of some essential enzymes in heart muscles [102].

15.1 Trigger of Torsade de pointis and Cardiotoxicity: QT prolongation is a standard parameter to study cardiac abnormalities [103]. Further, prolongation of QT may be responsible for the sudden death and is called Torsade de Pointes [104]. This type of arrhythmia is defined as the polymorphic ventricular tachycardia [105]. Torsades de pointis are very complicated and serious situation which often shift to ventricular fibrillation [106]. Drugs associated with increased risk of Torsade de Pointes are shown in **Table 3** [107].

TABLE 3: DRUGS ASSOCIATED WITH INCREASED RISK OF TORSADE DE POINTES [107]

S. no.	Drugs	
1	Halofantrine	Probucol
2	Amiodarone	Terfenadine
3	Arsenic trioxide	Quinidine
4	Astemizole	Pentamidine
5	Bepridil	Methadone
6	Chloroquine	Mesoridazine
7	Chlorpromazine	Ibutilide
8	Cisapride	Moxifloxacin
9	Haloperidol	Procainamide
10	Droperidol	Thioridazine
11	Sotalol	Saprofloxacin
12	Levomethadyl	Disopyramide
13	Thioridazine	Erythromycin
14	Vandetanib	Domperidone

CONCLUSION: Now-a-days cardiac complication is increasing day by day. Polypharmacy approach, on the other hand is responsible for the occurrence of secondary disorders such as hypertension and arrhythmia. There are many drugs which are co-administered with existing therapy and further worsen the cardiac complications. Beta blockers, calcium channel blockers, antiarrhythmic drugs, anticancer drugs and immunomodulatory drugs are routinely used by the clinician, thus appropriate monitoring is a prerequisite for the use of these drugs. Particularly in patients with left ventricular dysfunction, utmost precaution should be taken for cardiac toxicity of prescribed medicine. Although, drug - induced cardiomyopathy doesn't occur frequently, a regular monitoring is advised to prevent any such situation while using the discussed therapeutic agents.

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REFERENCES:

1. Shin DD, Brandimarte F, De Luca L *et al*.: Review of current and investigational pharmacologic agents for acute heart failure syndromes. The American journal of cardiology 2007; 99: S4-S23.
2. Kaiserová H: Preventing anthracycline cardiotoxicity: from iron chelation to carbonyl reductase inhibition 2017.
3. Figueredo VM: Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart. The American journal of medicine 2011; 124: 480-8.
4. Klimas J: Drug-Induced Cardiomyopathies: INTECH Open Access Publisher 2012.
5. Lee CS: Mechanisms of cardiotoxicity and the development of heart failure. Critical care nursing clinics of North America 2015; 27: 469-81.
6. Becher PM, Jugdutt BI, Baugh J and Schmack B: Experimental Heart Failure Models and Their Pathophysiological Characterization. BioMed research international 2016.
7. Silverstein D and Hopper K: Small animal critical care medicine: Elsevier Health Sciences 2014.
8. Tripathi K: Essentials of medical pharmacology: JP Medical Ltd; 2013.
9. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM and Yellon DM: Anthracycline chemotherapy and cardiotoxicity. Cardiovascular Drugs and Therapy 2017: 1-13.
10. Cagel M, Grotz E, Bernabeu E, Moretton MA and Chiappetta DA: Doxorubicin: nanotechnological overviews from bench to bedside. Drug discovery today 2017; 22: 270-81.
11. Manivasagan P, Kang KH, Sivakumar K, Li-Chan EC, Oh HM and Kim SK: Marine actinobacteria: An important source of bioactive natural products. Environmental toxicology and pharmacology 2014; 38: 172-88.
12. Cardinale D, Colombo A, Bacchiani G, *et al*.: Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015; Circulationaha. 114.013777.
13. Khouri MG, Klem I, Shenoy C, Sulpher J and Dent SF: Screening and Monitoring for Cardiotoxicity During Cancer Treatment. Cardio-Oncology: Springer 2017; 43-80.
14. Wang L, Tan TC, Halpern EF *et al*.: Major cardiac events and the value of echocardiographic evaluation in patients receiving anthracycline - based chemotherapy. The American journal of cardiology 2015; 116: 442-6.
15. Angsutararux P, Luanpitpong S and Issaragrisil S: Chemotherapy-induced cardiotoxicity: overview of the roles of oxidative stress. Oxidative medicine and cellular longevity 2015.
16. Popat R, Oakervee HE, Hallam S *et al*.: Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up. British journal of haematology 2008; 141: 512-6.
17. Ichikawa Y, Ghanefar M, Bayeva M *et al*.: Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. The Journal of clinical investigation 2014; 124:6 17.
18. Outomuro D, Grana DR, Azzato F and Milei J: Adriamycin-induced myocardial toxicity: new solutions for an old problem? International journal of cardiology 2007; 117: 6-15.
19. Münzel T, Gori T, Keaney Jr JF, Maack C and Daiber A: Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications. European heart journal 2015; 36: 2555-64.
20. Šimůnek T, Štěrba M, Popelová O, Adamcová M, Hrdina R and Geršl V: Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. Pharmacological Reports 2009; 61: 154-71.
21. Vejpongsa P and Yeh ET: Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. Journal of the American College of Cardiology 2014; 64: 938-45.
22. Menna P and Salvatorelli E: Primary Prevention Strategies for Anthracycline Cardiotoxicity: A Brief Overview. Chemotherapy 2017; 62: 159-68.
23. Goldberg MA, Antin JH, Guinan EC and Rappeport JM: Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. Blood 1986; 68: 1114-8.
24. Madondo MT, Quinn M and Plebanski M: Low dose cyclophosphamide: mechanisms of T cell modulation. Cancer treatment reviews 2016; 42: 3-9.
25. Raj S, Franco VI and Lipshultz SE: Anthracycline-induced cardiotoxicity: a review of pathophysiology, diagnosis, and treatment. Current treatment options in cardiovascular medicine 2014; 16: 315.
26. Feenstra J, Grobbee DE, Remme WJ and Stricker BHC: Drug-induced heart failure. Journal of the American College of Cardiology 1999; 33: 1152-62.
27. Benbow SJ, Wozniak KM, Kulesh B, *et al*.: Microtubule-Targeting Agents Eribulin and Paclitaxel Differentially Affect Neuronal Cell Bodies in Chemotherapy-Induced Peripheral Neuropathy. Neurotoxicity Research 2017; 1-12.

28. Chan JK, Brady MF, Penson RT, *et al*.: Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. New England Journal of Medicine 2016; 374: 738-48.
29. Vashishtha H and Ginsburg DS: Effects of Tip60 and Paclitaxel on Breast and Lung Cancer. Clinical Laboratory Science 2016; 29.
30. Spencer CM and Faulds D: Paclitaxel. Drugs 1994; 48: 794-847.
31. Rowinsky E and Donehower R: Paclitaxel (taxol) N Engl J Med. 1995; 332: 1004–1014. doi: 10.1056. NEJM199504133321507[PubMed][Cross Ref].
32. Schlitt A, Jordan K, Vordermark D, Schwamborn J, Langer T and Thomssen C: Cardiotoxicity and oncological treatments. Deutsches Ärzteblatt International 2014; 111: 161.
33. Gianni L, Munzone E, Capri G *et al*.: Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. Journal of Clinical Oncology 1995; 13: 2688-99.
34. White RJ and Durr FE: Development of mitoxantrone. Investigational new drugs 1985; 3: 85-93.
35. Shaikh AY, Suryadevara S, Tripathi A *et al*.: Mitoxantrone-Induced Cardiotoxicity in Acute Myeloid Leukemia - A Velocity Vector Imaging Analysis. Echocardiography 2016; 33: 1166-77.
36. Mather F, Simon R, Clark G and Von Hoff D: Cardiotoxicity in patients treated with mitoxantrone: Southwest Oncology Group phase II studies. Cancer treatment reports 1987; 71: 609.
37. Thomas SA, Grami Z, Mehta S and Patel K: Adverse effects of 5-fluorouracil: Focus on rare side effects. Cancer Cell and Microenvironment 2016; 3.
38. Altieri P, Murialdo R, Barisione C *et al*.: 5-fluorouracil causes endothelial cell senescence: potential protective role of glucagon-like peptide 1. British Journal of Pharmacology 2017.
39. Polk A, Vistisen K, Vaage-Nilsen M and Nielsen DL: A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity. BMC Pharmacology and Toxicology 2014; 15: 47.
40. Lestuzzi C, Berretta M and De Paoli A: Capecitabine cardiotoxicity: How to limit life-threatening events. International Journal of Cardiology 2017; 229: 5.
41. Sato M and Park M: Case Report: Cytarabine-Induced Pericarditis and Pericardial Effusion. The Medicine Forum 2017; 10.
42. Lancellotti P, Moonen M and Jerusalem G: Predicting Reversibility of Anticancer Drugs-Related Cardiac Dysfunction: A New Piece to the Routine Use of Deformation Imaging. Echocardiography 2016; 33: 504-9.
43. Sharma A, Burridge PW, McKeithan WL *et al*.: High-throughput screening of tyrosine kinase inhibitor cardiotoxicity with human induced pluripotent stem cells. Science translational medicine 2017; 9: eaaf2584.
44. Gharwan H and Groninger H: Kinase inhibitors and monoclonal antibodies in oncology: clinical implications. Nature reviews Clinical oncology 2016; 13: 209-27.
45. Gronich N, Lavi I, Barnett-Griness O, Saliba W, Abernethy D and Rennert G: Tyrosine kinase-targeting drugs-associated heart failure. British Journal of Cancer 2017.
46. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V and Ustun B: Depression, chronic diseases, and decrements in health: results from the World Health Surveys. The Lancet 2007; 370: 851-8.
47. Palmer S, Vecchio M, Craig JC *et al*.: Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney international 2013; 84: 179-91.
48. Conrad SK, Catalano MC and Catalano G: The use of fluoxetine in a patient with Takotsubo cardiomyopathy. Journal of Psychiatric Practice® 2016; 22: 234-8.
49. Glassman A, Bigger JT, Giardina E, Kantor S, Perel J and Davies M: Clinical characteristics of imipramine-induced orthostatic hypotension. The Lancet 1979; 313: 468-72.
50. Coupland C, Hill T, Morriss R, Moore M, Arthur A and Hippisley-Cox J: Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using primary care database. bmj 2016; 352: i1350.
51. Nezafati MH, Vojdanparast M and Nezafati P: Antidepressants and cardiovascular adverse events: A narrative review. ARYA atherosclerosis 2015; 11: 295.
52. Fukushima N, Nanao K, Fukushima H, Namera A and Miura M: A neonatal prolonged QT syndrome due to maternal use of oral tricyclic antidepressants. European journal of pediatrics 2016; 175: 1129-32.
53. Ray WA, Meredith S, Thapa PB, Hall K and Murray KT: Cyclic antidepressants and the risk of sudden cardiac death. Clinical Pharmacology and Therapeutics 2004; 75: 234-41.
54. Amsterdam J, Brunswick D and Mendels J: The clinical application of tricyclic antidepressant pharmacokinetics and plasma levels. Am J Psychiatry 1980; 137: 653-62.
55. Isbister GK: Electrocardiogram changes and arrhythmias in venlafaxine overdose. British journal of clinical pharmacology 2009; 67: 572-6.
56. Rossman I and Veith RC: Depression in the elderly: Pharmacologic considerations in treatment. Journal of the American Geriatrics Society 1982; 30: 581-6.
57. Álamo C, López-Muñoz F, García-García P and García-Ramos S: Risk–benefit analysis of antidepressant drug treatment in the elderly. Psychogeriatrics 2014; 14: 261-8.
58. O'Leary OF, Dinan TG and Cryan JF: Faster, better, stronger: towards new antidepressant therapeutic strategies. European journal of pharmacology 2015; 753: 32-50.
59. Godfraind T: Calcium channel blockers in cardiovascular pharmacotherapy. Journal of cardiovascular pharmacology and therapeutics 2014; 19: 501-15.
60. Beevers D and Sleight P: Short acting dihydropyridine (vasodilating) calcium channel blockers for hypertension: is there a risk? BMJ: British Medical Journal 1996; 312: 1143.
61. Whyte I, Buckley N and Dawson A: Calcium channel blockers. Medicine 2016; 44: 148-50.
62. Girouard C, Grégoire J-P, Poirier P and Moisan J: Effect of contraindicated drugs for heart failure on hospitalization among seniors with heart failure: A nested case-control study. Medicine 2017; 96.
63. Solomon R and McCord J: Medications to Avoid in Acute Decompensated Heart Failure. Current Emergency and Hospital Medicine Reports 2017; 5: 83-7.
64. Aurora L and McCord J: Drugs to Avoid in Acute Decompensated Heart Failure (ADHF): Contraindicated Medications and Interactions. Short Stay Management of Acute Heart Failure: Springer; 2017: 261-8.
65. Honerjäger P, Loibl E, Steidl I, Schönsteiner G and Ulm K: Negative inotropic effects of tetrodotoxin and seven class 1 antiarrhythmic drugs in relation to sodium channel blockade. Naunyn-Schmiedeberg's archives of pharmacology 1986; 332: 184-95.

66. Greene HL, Richardson DW, Hallstrom AP *et al*.: Congestive heart failure after acute myocardial infarction in patients receiving antiarrhythmic agents for ventricular premature complexes (Cardiac Arrhythmia Pilot Study). The American journal of cardiology 1989; 63: 393-8.
67. Özkaya E and Yazganoğlu KD: Class III Antiarrhythmic Drugs. Adverse Cutaneous Drug Reactions to Cardiovascular Drugs: Springer 2014; 123-8.
68. Driessen H, Bourgonje V, van Veen T and Vos M: New antiarrhythmic targets to control intracellular calcium handling. Netherlands Heart Journal 2014; 22: 198-213.
69. Jafib B, Doctor M, Panel D *et al*.: Risk of cardiovascular events, stroke, congestive heart failure, interstitial lung disease, and acute liver injury: dronedarone versus amiodarone and other antiarrhythmics 2013.
70. Prins KW, Neill JM, Tyler JO, Eckman PM and Duval S: Effects of beta-blocker withdrawal in acute decompensated heart failure. JACC: Heart Failure 2015; 3: 647-53.
71. Pinnock C, Yip JL, Khawaja AP *et al*.: Topical Beta-Blockers and Cardiovascular Mortality: Systematic Review and Meta-Analysis with Data from the EPIC-Norfolk Cohort Study. Ophthalmic Epidemiology 2016; 23: 277-84.
72. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Choodnovskiy I and Avorn J: Topical glaucoma medications and cardiovascular risk in the elderly. Clinical Pharmacology and Therapeutics 1994; 55: 76-83.
73. Chen H, Ye L, Su J, *et al*.: Effects of different types of interferon on the expression of HCV replication-related microRNA. Zhonghua yi xue za zhi 2014; 94: 776-9.
74. Zimmerman S, Adkins D, Graham M, *et al*.: Case report: Irreversible, severe congestive cardiomyopathy occurring in association with interferon alpha therapy 2009.
75. Ferreira L, Frade AF, Baron MA *et al*.: Interferon-γ and other inflammatory mediators in cardiomyocyte signaling during Chagas disease cardiomyopathy. World journal of cardiology 2014; 6: 782-90.
76. Sleijfer S, Bannink M, Van Gool AR, Kruit WH and Stoter G: Side effects of interferon-α therapy. Pharmacy world and science 2005; 27: 423-31.
77. Rochette L, Guenancia C, Gudjoncik A *et al*.: Anthracyclines / trastuzumab: new aspects of cardiotoxicity and molecular mechanisms. Trends in pharmacological sciences 2015; 36: 326-48.
78. Tan MCC, Ortega-Legaspi JM, Cheng SF and Patton KK: Acute myocarditis following high-dose interleukin-2 treatment. Journal of Cardiology Cases 2017; 15: 28-31.
79. Deventer K, Van Eenoo P and Delbeke F: Screening for amphetamine and amphetamine-type drugs in doping analysis by liquid chromatography / mass spectrometry. Rapid communications in mass spectrometry 2006; 20: 877-82.
80. Samanin R: Central mechanisms of anorectic drugs. Medicinal Chemistry Advances: Proceedings of the Seventh International Symposium on Medicinal Chemistry, Torremolinos, Spain. Elsevier 1980; 2016; 271.
81. Hutson PH, Tarazi FI, Madhoo M, Slawecki C and Patkar AA: Preclinical pharmacology of amphetamine: Implications for the treatment of neuropsychiatric disorders. Pharmacology and therapeutics 2014; 143: 253-64.
82. Turnipseed SD, Richards JR, Kirk JD, Diercks DB and Amsterdam EA: Frequency of acute coronary syndrome in patients presenting to the emergency department with chest pain after methamphetamine use. The Journal of emergency medicine 2003; 24: 369-73.
83. Wijetunga M, Seto T, Lindsay J and Schatz I: Crystal methamphetamine-associated cardiomyopathy: tip of the iceberg? Journal of Toxicology: Clinical Toxicology 2003; 41: 981-6.
84. Yeo KK, Wijetunga M, Ito H *et al*.: The association of methamphetamine use and cardiomyopathy in young patients. The American journal of medicine 2007; 120: 165-71.
85. Solís-Olivares CA and Ramírez-García HA: Amphetamine-related dilatated cardiomyopathy: a growing phenomenon. Case report. Rev Mex Cardiol 2017; 28: 35-9.
86. Bolton JL, Trush MA, Penning TM, Dryhurst G and Monks TJ: Role of quinones in toxicology. Chemical research in toxicology 2000; 13: 135-60.
87. Aniszewski T: Alkaloids: Chemistry, Biology, Ecology, and Applications: Elsevier 2015.
88. Braam C: From Coca to Cocaine. Shooting Up: A Short History of Drugs and War 2016; 91.
89. Sable H, Miller M, Nelms J *et al*.: Behavioral pharmacology of cocaine and amphetamine in rats perinatally exposed to polychlorinated biphenyls (PCBs). Neurotoxicology and Teratology 2014; 88.
90. Pallavi R, Talebi S, Hassen G, Visco F and Popis-Matejak B: 1259: Cocaine Induced Cardiotoxicity. Critical Care Medicine 2014; 42: A1654.
91. Liaudet L, Calderari B and Pacher P: Pathophysiological mechanisms of catecholamine and cocaine-mediated cardiotoxicity. Heart failure reviews 2014; 19: 815-24.
92. Maraj S, Figueredo VM and Lynn Morris D: Cocaine and the heart. Clinical cardiology 2010; 33: 264-9.
93. Awtry EH and Philippides GJ: Alcoholic and cocaine-associated cardiomyopathies. Progress in cardiovascular diseases 2010; 52: 289-99.
94. Giannotti S, Ghilardi M, Dell'Osso G, Bugelli G and Guido G: Left ventricular hypertrophy and spontaneous rupture of the Achilles tendon after anabolic steroids in bodybuilder. European Orthopaedics and Traumatology 2014; 5: 363-5.
95. Tsitsimpikou C: Cardiotoxicity of anabolic steroids; animal case study of oral turinabol and methanabol. Toxicology Letters 2014; S21.
96. Shamloul RM, Aborayah AF, Hashad A and Abd-Allah F: Anabolic steroids abuse-induced cardiomyopathy and ischaemic stroke in a young male patient. BMJ case reports 2014; bcr2013203033.
97. Gardner JD and Mouton AJ: Alcohol effects on cardiac function. Comprehensive Physiology 2015.
98. Gardenhire DS: Drugs Affecting the Central Nervous System. Rau's Respiratory Care Pharmacology-E-Book 2015; 330.
99. Wang Y, Li G, Sun Y, Shan G, Xu R and Guo L: Left ventricular strain and rotation by 2-D speckle tracking echocardiography identify early alcoholic cardiomyopathy. Ultrasound in medicine and biology 2016; 42: 1741-9.
100. Fernández-Solà J: Cardiovascular risks and benefits of moderate and heavy alcohol consumption. Nature Reviews Cardiology 2015; 12: 576-87.
101. Knochel JP: Cardiovascular effects of alcohol. Annals of internal medicine 1983; 98: 849-54.
102. Oyinloye BE, Ajiboye BO, Ojo OA, Nwozo SO and Kappo AP: Cardioprotective and antioxidant influence of aqueous extracts from *Sesamum indicum* seeds on oxidative stress induced by cadmium in wistar rats. Pharmacognosy magazine 2016; 12: S170.

103. Keirns J, Desai A, Kowalski D, *et al*.: QT interval Shortening with Isavuconazole: *In vitro* and *in vivo* Effects on Cardiac Repolarization. Clinical Pharmacology and Therapeutics 2017.
104. Schlit AF, Delaunois A, Colomar A *et al*.: Risk of QT prolongation and torsade de pointes associated with exposure to hydroxyzine: re-evaluation of an established drug. Pharmacology Research and Perspectives 2017; 5.
105. Passman R and Kadish A: Polymorphic ventricular tachycardia, long QT syndrome, and torsades de pointes. Medical Clinics of North America 2001; 85: 321-41.
106. Weiss JN, Garfinkel A, Karagueuzian HS *et al*.: Perspective: a dynamics-based classification of ventricular arrhythmias. Journal of molecular and cellular cardiology 2015; 82: 136-52.
107. Salvi V, Karnad DR, Panicker GK and Kothari S: Update on the evaluation of a new drug for effects on cardiac repolarization in humans: issues in early drug development. British journal of pharmacology 2010; 159: 34-48.

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