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## CLINICAL UPDATES ON DRUG - INDUCED CARDIOTOXICITY

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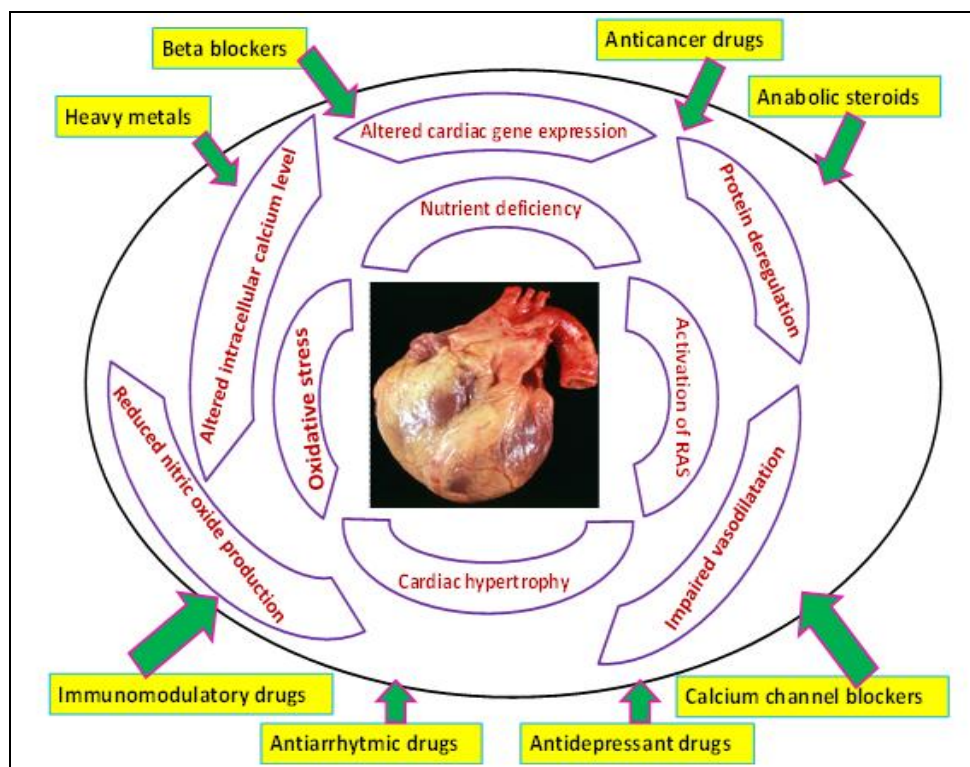
**ABSTRACT:** Cardiotoxicity associated with the clinically used drugs is a global concern of safety for healthcare professionals. Various animal models have been used to study the drug-induced cardiotoxicity but the exact molecular involvement of toxicity is not much clear. Despite the recurrent occurrence 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 cardiotoxicity. 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<sub>10</sub>, 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- $\alpha$  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<sup>1</sup> among which anticancer drugs, specifically anthracycline class of drugs exert severe cardiotoxicity<sup>2</sup>. Other drugs that cause cardiotoxicity are amphetamine, mitomycin, paclitaxel and zidovudine<sup>3, 4</sup>. The common mechanism leading to cardiotoxicity is oxidative stress, generation of free radicals and hypoxia<sup>5</sup>.

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<sup>+</sup> - K<sup>+</sup> ATPase pump)<sup>4</sup>. Exposure to the cardiac-toxic drugs induces prolong cardiac repolarization (QT interval) and causes arrhythmia (Torsades de pointes)<sup>4</sup>. Since these drugs causes cardiotoxicity as side effect, they can be used as cardiotoxicity inducing agents in preclinical experimental models<sup>6</sup>. In this review we are going to focus on the Cardiotoxicity of drugs only and not the experimental models.

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List of cardiotoxic drugs is shown in **Table 1** and effect of cardiotoxic drug is displayed in **Fig. 1** <sup>7</sup>.



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

**TABLE 1: LIST OF CLINICALLY USED DRUGS THAT EXERT CARDIOTOXIC EFFECT** <sup>8</sup>

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	Interferon	Signaling protein	activate JAS-STAT and PI3K/ Akt pathway	Autoimmune disorder, cutaneous, 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	Interfere 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 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: cyclooxygenase

**1. Anthracycline and Cardiotoxicity:** Anthracycline class of drugs are the first line anticancer drugs but their usage are limited due to cardiotoxicity<sup>9</sup>. Doxorubicin (adriamycin) and daunorubicin (daunomycin or rubidomycin) are two members of anthracycline group<sup>10</sup>. These two drugs are obtained from actinobacteria '*Streptomyces peuceitius*'<sup>11</sup>. 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<sup>12</sup>.

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

**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<sup>15</sup>. In practice, determination of exact mechanism of doxorubicin-induced cardiotoxicity is not possible because most of the time patient are on multiple therapies<sup>16, 17</sup>. There are four hypothesis proposed on the subject of anthracycline-induced cardiotoxicity<sup>18</sup>.

(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<sup>18</sup>.

(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<sup>18</sup>.

(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<sup>18</sup>.

(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<sup>18</sup>.

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<sup>9, 19</sup>. Free radicals mainly nitrite free radicals are the major culprit of oxidative stress<sup>20</sup>.

**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**<sup>21, 22</sup>

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 <sub>10</sub>
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)<sup>22</sup>.

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



myopericarditis and myocardial necrosis<sup>25</sup>. If a patient suffers from congestive heart failure (CHF) and get exposed to cyclophosphamide, there is a high chance of death within two weeks<sup>26</sup>. 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<sup>26</sup>.

**3. Paclitaxel and Cardiotoxicity:** Paclitaxel belongs to taxane class of drugs that act by promoting the polymerization of tubulin<sup>27</sup>. 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<sup>27</sup>. Paclitaxel is the choice of drug in ovarian and breast cancer<sup>28, 29</sup>. Asymptomatic bradycardia is most common side effect<sup>30</sup>. 29% of patients undergoing paclitaxel therapy are likely to suffer from bradycardia<sup>31, 32</sup>. In a study, combined therapy of doxorubicin with paclitaxel induces CHF in six patients out of<sup>33</sup>. This occurrence of 18% CHF in patient raised a valid question for combined therapy of paclitaxel and doxorubicin<sup>33</sup>.

**4. Mitoxantrone and Cardiotoxicity:** Mitoxantrone is structurally similar to doxorubicin<sup>34</sup>. This drug is reported to be associated with left ventricular heart failure<sup>35</sup>. 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<sup>36</sup>. 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<sup>37</sup>. It has a direct effect on myocardial cells and on endothelial cells<sup>38</sup>. Mononuclear inflammations and myocardial necrosis have been observed in a patient who died from myocardial infarction followed by 5-FU therapy<sup>39</sup>. 5-FU also induces myocardial hypoxia, CHF and dilated cardiomyopathy have been reported<sup>39</sup>. Capecitabine, on the other hand, causes ischemia<sup>40</sup> and cytarabine has been reported for pericarditis<sup>41</sup>.

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

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

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

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

### 8. Antiarrhythmic drugs and Cardiotoxicity:

Adverse effect related to antiarrhythmic drugs is related to its cardio depressant and negative inotropic effect<sup>65</sup>. If the patient is already suffering from left ventricular dysfunctions, antiarrhythmic drugs can further worsen the situation<sup>66</sup>. Negative inotropy of drugs vary from class to class, as class III antiarrhythmic drugs are devoid of negative inotropy<sup>67</sup>. Antiarrhythmic drugs induced negative inotropy is regulated by an alteration in intracellular calcium concentration<sup>68</sup>. There are randomized double blinded placebo controlled trials which showed the increased risk of CHF in the patients who were taking antiarrhythmic drugs<sup>69</sup>. 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<sup>65</sup>.

### 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<sup>70</sup>. Interestingly when beta blocker was used topically for treatment of glaucoma, it additionally caused CHF<sup>71</sup>. In an epidemiological study, no association between the use of topical beta blockers and CHF was found<sup>72</sup>. Similarly, a trial with carvedilol revealed the reduced mortality in patients suffering from CHF<sup>26</sup>. Thus in order to control beta blocker induced cardiotoxicity (CHF), the initial dose should be low and can be gradually increased<sup>26</sup>.

**10. Interferon and Cardiotoxicity:** There are three types of interferon used clinically *i.e.*

interferon alpha, beta and gamma<sup>73</sup>. Interferon-alpha has been reported with a cardiotoxic effect which includes hypertension and arrhythmia starting from 1<sup>st</sup> day of treatment<sup>74</sup>. It has been reported that almost 5 - 15% of patients suffer from interferon-mediated cardiotoxicity<sup>75</sup>. Other cardiotoxicities of interferon include cardiomyopathy and cardiac ischemia<sup>76</sup>. The possible mechanism proposed for the interferon alpha - induced cardiotoxicity is hypoxia, interference with energy metabolism and increased oxygen demand<sup>77</sup>.

**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<sup>78</sup>. Reversible left ventricular dysfunction, tachycardia and hypotension are more often reported with the use of IL-2<sup>78</sup>. Use of IL-2 initiates the production of cytokines which further affect myocardium contractility<sup>78</sup>.

### 12. Amphetamines / Methamphetamines and Cardiotoxicity:

Amphetamine class of drugs are the common drugs used by athletes and often associated with doping<sup>79</sup>. These drugs act centrally and cause stimulation which includes euphoria, intensifies emotions and increases sexuality<sup>80</sup>. This drug enhances neuronal reuptake of norepinephrine, serotonin and dopamine<sup>81</sup>. A clinical study has reported the incidence of acute coronary syndrome in 25% of patients taking these drugs<sup>82</sup>. Methamphetamine is reported to be associated with 18% and 40% of incidence of cardiomyopathy<sup>83, 84</sup>. Similarly, in other clinical study methamphetamine is associated with the incidence of 40% cardiomyopathy<sup>84</sup>. 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<sup>85</sup>. Amphetamine and methamphetamine when administered metabolize into catechol that further causes oxidative stress and cardiomyopathy<sup>86</sup>.

**13. Cocaine and Cardiotoxicity:** Cocaine is an alkaloid obtained from *Erythroxylon coca* which is a native plant of South America<sup>87</sup>. Initially, it was used as a local anaesthetic but later its use as an ingredient in cola drink started<sup>88</sup>. 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<sup>89</sup> which causes increased psychomotor and sympathetic activity<sup>89</sup>. Cocaine also causes the release of norepinephrine and epinephrine from the adrenal medulla that result in severe vasoconstriction<sup>89</sup>. Use of cocaine is associated with myocardial ischemia or myocardial infarction<sup>90</sup>. Cocaine also causes tachycardia and increases systolic - diastolic blood pressure<sup>91</sup>. Chronic use of cocaine causes vasoconstriction of coronary artery and thrombosis which together decreases oxygen supply to the myocardium and induces myocardial ischemia<sup>91</sup>. Acute administration of cocaine causes an increase in intracellular calcium concentration and stimulates arrhythmia<sup>92</sup>. Literature supports four mechanisms for the cardiotoxicity of cocaine.

**13.1 Promotion of Intracoronary Thrombus Formation:** Cocaine administration causes platelet aggregation and increases thromboxane - A<sub>2</sub> production which together contributes to the development of cardiomyopathy and left ventricular dysfunction<sup>93</sup>.

**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<sup>93</sup>.

**13.3 Increased Calcium Flux:** Increased myocardial calcium flux into the myocardial cell causes membrane instability and arrhythmia<sup>93</sup>.

**13.4 Electrophysiological Effects:** Use of cocaine causes prolongation of PR, QRS and QT duration that result into arterial fibrillation and tachycardia<sup>93</sup>.

**14. Anabolic - Androgenic Steroids and Cardio-Toxicity:** Inappropriate use of anabolic steroid is associated with left ventricular hypertrophy<sup>94</sup>. Anabolic steroid when administered, binds with androgenic receptors in the heart and in arteries<sup>4</sup>. Anabolic steroid causes hypertension, dyslipidemia atherosclerosis and impaired contraction-relaxation<sup>95</sup>. Animal studies have shown the increased risk of cardiomyopathy and apoptosis in cardiac cells<sup>96</sup>. Further, use of anabolic steroid causes the discrete release of calcium from sarcoplasmic reticulum

which additionally worsens the situation of arrhythmia and cardiomyopathy<sup>95</sup>. Some other complications associated with the use of steroid includes endocardial and myocardial fibrosis, cardiac steatosis, myocardial necrosis, coagulation and coronary atheroma<sup>3</sup>.

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

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

**TABLE 3: DRUGS ASSOCIATED WITH INCREASED RISK OF TORSADE DE POINTES**<sup>107</sup>

S. no.	Drugs	
1	Halofantrine	Probuocol
2	Amiodarone	Terfenadine
3	Arsenic trioxide	Quinidine
4	Astemizole	Pentamidine
5	Bepidil	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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