**Disopyramide:**

- **Pharmacologic Effects:** are similar to quinidine, but unlike quinidine and procainamide it produces a greater reduction in Vmax at a depressed membrane potentials than at normal resting potentials. Concentration of disopyramide that does not affect conduction velocity of ERP can reduce automaticity in atrial and ventricular Ts. ECG changes are similar to quinidine but mild. Disopyramide has -ve inotropic effect which can be troublesome in patients with pre-existing heart disease. It can cause vasoconstriction and has an atropine like action.

- **Therapeutic Uses:** it is used as an alternative to quinidine and procainamide.

- **Pharmacokinetics:** well absorbed after oral administration. 50% excreted unchanged in urine. $t_{1/2}$ 5-7hrs.

- **Adverse Effects:** it may cause conduction disturbances, CHF, anticholinergic side effects.

**Class I-B Drugs**

**Lidocaine:**

The I-B agents rapidly bind and unbind from Na channels, therefore their action is manifested when the cardiac cell is depolarizing rapidly. Those drugs are particularly useful in treating ventricular arrhythmia. Lidocaine is the drug of choice in emergency treatment of ventricular arrhythmia after M.I.

- **Pharmacokinetics:** it is an amide L.A., 1st pass effect is 70%, $t_{1/2}$ 1 1/2 hrs. not effective orally.

- **Pharmacologic Effects:** it depresses the rate of phase 4 depolarization in ventricular and purkinjie fibers. Unlike quinidine which suppresses arrhythmia caused by ↑normal automaticity, lidocaine suppresses arrhythmia caused by abnormal automaticity, it suppresses or abolishes ventricular reentry. Lidocaine reduces the duration of AP of purkinjie fibers. Unlike quinidine, lidocaine produces few ECG changes.
It has little effect on the elect. phys. of the atria, thus it has little effect on atria on AV junc. arrhythmia.

- **Therapeutic Uses:** because of its rapid onset and short duration of action, it is particularly useful in treating ventricular arrhythmia arising in emergency situations: 1. Open heart surgery 2. M.I. 3. Dig intoxication.

- **Route of administration:** it is given I.V. to abolish the arrhythmia then followed by continuous infusion because t\(_1/2\) is short, steady state concentration can be reached quickly. It can also be given I.M.

- **Adverse Effects:**
  1. It has wide toxic/therap. ratio.
  2. It shows little impairment of LVF and has no –ve inotropic effect.
  3. CNS effects include: drowsiness, slurred speech, parasthesia, confusion, and convulsions.
  4. Cardiac arrhythmia may also occur.

**Mxiletene and Tocainide:**
They are class I-B similar to lidocaine but are effective orally and are used for chronic treatment of chronic symptomatic ventricular arrhythmia.

- **Side Effect:** include: 1. GIT disturbances 2. Neurologic side effects 3. Tocainide may produce pulmonary fibrosis.

**Phenytoin:**
As anti-arrhythmic, it resembles lidocaine, most useful in treating ventricular arrhythmia associated with dig toxicity and acute M.I.
Class I-C Drugs

Flecainide, Moricizine, Propafenone:
These drugs slowly dissociate from Na\(^+\) channels and show prominent effects even at normal heart rates. They markedly slow phase 0 depolarization causing marked conduction slowing, but only little effect on AP duration or ventricular ERP. They are approved only for refractory arrhythmia (ventricular). They have –ve inotropic effects and can aggravate CHF. They can ppt cardiac arrest. Also approved for AV node tachy in WPW syndrome.

Class II Drugs

(Propranolol, metoprolol (β\(_1\)-selective) and pindolol (ISA),
Acebutalol (β\(_1\)-sel.) and Esmolol)

Propranolol: (β\(_1\), β\(_2\) blocker)
Effect results from β-blockade + direct membrane stabilizing effect. These drugs ↓phase 4 depolarization, thus depress SA node firing → bradycardia. Automaticity is also depressed in purkinjie fibers. They cause a substantial ↑in ERP of AV node prolonging AV conduction. The refractoriness of SA node, atrial and ventricular m. is not as a greatly affected.

- **ECG Effects:** ↑PR interval by its action on AV node.

- **Therapeutic Uses of β-blockers:**
  1. Useful for ventricular arrhythmia caused by ↑sympathetic activity (emotional stress, exercise, thyrotoxicosis).
  2. Useful for AF and atrial flutter and for AV nodal reentrant tachy by slowing conduction through AV node.
  3. It is used sometimes to abolish ventricular arrhythmia caused by dig toxicity.
  4. It reduces the incidence of sudden arrhythmic death after M.I.
  5. May be used in WPW syndrome.

Esmolol:
Is very short acting β\(_1\)-selective blocker used I.V. in acute arrhythmia occurring during surgery or emergency situations.
Class III Drugs

Satolol:

Prolongs repolarization (class III effect) by blocking the K+ outward current and prolongs the duration of the AP and lengthening of the ERP in all cardiac fibers. It has also a non-selective β-blocking activity (class II). The D-isomer of satolol lacks the β-blocking effect while retaining the effect on prolonging the ERP.

- **Uses of satolol:**
  1. It is effective in preventing life threatening ventricular arrhythmia.
  2. May be useful for treatment of SV arrhythmia.

Satolol is better tolerated than Na+ channel blocker and probably more effective in preventing arrhythmia recurrence. However, satolol has a proarrhythmic effect in prolonging the QT interval and may cause torsades de points (3-4 %), t_{1/2}=12 hrs, completely absorbed after oral administration excreted unchanged.

Amiodarone:

It contains iodine and is structurally related to thyroxine. It has complex effects slowing class I, II, III, IV effects.

- **Pharmacologic Effects:**
  1. It ↑the AP duration and ERP in atrial and ventricular m, AV node automaticity.
  2. It ↓the SA node automaticity.
  3. It ↑the PR, QRS, and QT intervals.
  4. It induces α and β adrenergic blockade (by non-competitive antagonism), therefore it can cause sys. And coronary vasodilation.

- **Uses of Amiodarone:** it is considered the most powerful anti-arrhythmic available for the treatment and prevention of both atrial and ventricular arrhythmia. Side effects are frequent even with short term use, therefore, its use is reserved for the treatment of life threatening arrhythmia refractory to other anti-arrhythmias. It is the drug of 1st choice in WPW syndrome.

- **Pharmacokinetics:** highly lipid soluble. t_{1/2} = 20-100 days, full clinical effects may not be achieved until 6 weeks after initiation of therapy.
**Adverse Effects:** with prolonged use, it occurs in 50% of patients which may lead to discont. Of the drug:

1. Pulmonary fibrosis (usually reversible).
2. Cardiac effects: AV block, sinus brady, and torsades de pointes.
3. Corneal microdeposits and blurred vision.
4. Photosensitivity.
5. Bluish discoloration of skin due to iodine accumulation.
6. Hyper- or hypo- thyroidism due to interference with conversion of $T_4$ to $T_3$.
7. Neurological: ataxia, dizziness, tremor, peripheral neuropathy and myopathy.
8. GIT intolerance – nausea, vomiting and anorexia.
9. Serum levels of dig, diltiazem, and quinidine are ↑ with amiodarone use.

**Dronedarone:**

same as amiodarone but lacks iodine atoms t half is only 24 hrs. Has no thyroid or pulmonary toxicity

**Bretylium:**

Is an adr. neuronal blocker, has no. of direct and indirect actions, the most prominent of which is prolongation of the ERP and duration of AP in atrial, ventricular m. and AV node. It also ↑the VF threshold and AV node. It also has ECG effects: ↑PR and QT intervals.

**Uses of bretylium:** reserved for life threatening arrhythmia refractory to other therapy.

**Side Effects:** hypotension, n and v after rapid I.V. administration.

**DOFETILIDE**

Dofetilide has class 3 action potential prolonging action. This action is effected by a dose-dependent blockade of the rapid component of the delayed rectifier potassium current, $I_{Kr}$. Dofetilide is 100% bioavailable. Dofetilide is approved for the maintenance of normal sinus rhythm in patients with atrial fibrillation. It is also effective in restoring normal sinus rhythm in patients with atrial fibrillation. It increases QT interval.
IBUTILIDE
Ibutilide slows cardiac repolarization by blockade of the rapid component (I_{Kr}) of the delayed rectifier potassium current. Intravenous ibutilide is used for the acute conversion of atrial flutter and atrial fibrillation to normal sinus rhythm. The drug is more effective in atrial flutter than atrial fibrillation, with a mean time to termination of 20 minutes. The most important adverse effect is excessive QT interval prolongation and torsade de pointes. Patients require continuous ECG monitoring for 4 hours after ibutilide infusion or until QT_c returns to baseline.

Class IV Agents

**Ca\(^+\) channel blockers:** (verapamil and diltiazem)

They block the inward current carried by Ca\(^+\) resulting in the ↓ in the rate of phase 4 depolarization. They slow conduction and ↑ERP in Ts dependant on Ca\(^+\) current e.g. AV node. They shorten the AP. These drugs bind only to open depolarization channels. They are therefore used dependent (i.e. they block most effect where the heart is rapidly (use or state dependence)

- **Use of Class IV drugs:**
  1. Are more effective against atrial than ventricular arrhythmia.
  2. Very effective in the termination of SVT due to AV re-entry when given I.V.
  3. They reduce ventricular rate in atrial flutter or AF and may enhance the effect of digoxin in this regard.

- **Adverse Effects:**
  1. Because of its effect on AV node, they should not be used in patients with AV nodal dysfunction.
  2. They depress M. contractility, therefore care should be taken when used in patients with CHF.
  3. It is contraindicated in patients with AF who have the WPW syndrome.
  4. Hypotension.
  5. Leg edema.
Adenosine:
Is naturally occurring nucleoside, but at high doses it decreases conduction velocity and prolongs the Ref period and ↓automaticity in AV node. I.V. adenosine has become the drug of choice for abolishing SVT and is replacing verapamil in this regard. It has low toxicity, but causes flushing, chest pain and hypotension. It has an extremely short duration of action (15 seconds).

MAGNESIUM
Originally used for patients with digitalis-induced arrhythmias who were hypomagnesemic, magnesium infusion has been found to have antiarrhythmic effects in some patients with normal serum magnesium levels. The mechanisms of these effects are not known, but magnesium is recognized to influence Na⁺,K⁺ ATPase, sodium channels, certain potassium channels, and calcium channels. Magnesium therapy appears to be indicated in patients with digitalis-induced arrhythmias if hypomagnesemia is present; it is also indicated in some patients with torsade de pointes even if serum magnesium is normal. The usual dosage is 1 g (as sulfate) given intravenously over 20 minutes and repeated once if necessary.