Anti depressant drugs
Depression
DEPRESSED PEOPLE,
DEPRESSED PEOPLE EVERYWHERE
Classification

A. Selective Serotonin-Reuptake Inhibitor

B-Serotonin-Norepinephrine Reuptake Inhibitors.
1. Selective serotonin-norepinephrine reuptake inhibitors
2. Tricyclic antidepressants.
Classification

C. 5-HT2 Receptor Modulators.

D-Tetracyclic and Unicyclic Antidepressants.

E. Monoamine Oxidase Inhibitors.
Classification

A-Selective serotonin reuptake inhibitors
1-fluoxetine
2-sertraline
3-citalopram
4-Escitalopram
5-paroxetine
6-fluvoxamine
Classification

B1 - Selective serotonin norepinephrine reuptake inhibitors (SNRI)

- Venlafaxine
- Desvenlafaxine
- Duloxetine
- Milnacipran.
Classification

B2 - TRICYCLIC ANTIDEPRESSANTS.

1-imipramine
2-clomipramine
3-amitriptyline
4-desipremine
5-trimipramine
6-nortriptyline
7-protriptyline
8-doxepin
Classification

C. 5-HT2 Antagonists.

1. Trazodone
2. Nefazodone
Classification

• D-TETRACYCLIC AND UNICYCLIC ANTIDEPRESSANTS
  • Amoxapine
  • Maprotiline
  • Bupropion
  • Mirtazipine
Monoamine oxidase inhibitors

- Phenelzine
- Isocarboxazid
- Tranylcypromine
- Selegiline
- Moclobemide
Pharmacokinetics of Anti-Depressants

ADD’s share many ph features:

- Most have fairly rapid oral absorption
- Achieve peak plasma levels within two to three hours
- Are tightly bound to plasma proteins
- Undergo hepatic metabolism
- Have renal excretion
SSRIs

- SSRIS are a chemically diverse class of agents the primary action of SSRIS are the inhibition of serotonin transporter (SERT).
- Fluoxetine was introduced in the United States in 1988 and quickly became one of the most commonly prescribed medication in medical practice.
- There are currently six available SSRIS.
- They are the most common antidepressants in medical use.
- The popularity of SSRIS are due to their ease of use, safety in overdose, tolerability, cost, and broad spectrum of uses.
Mechanism of action

selective serotonin reuptake inhibitors

1. Inhibits the reuptake of serotonin by binding with serotonin transporter proteins (SERT). The SERT is a glycoprotein imbedded in the axon terminal and cell body membrane of serotonergic neurons.

2. SSRIs inhibits the transporters by binding the receptor.

3. So there is increased availability of serotonin at synaptic and post synaptic level of neurons.
Mechanism of action

• Ssri bind with serotonin transporter protein and inhibit the transport of serotonin from extra to intracellular site.
• So this inc conc of serotonin at its site of action.
Effects of ssris

- Acute increase of serotonergic synaptic activity
- Slower changes in several signaling pathways
- Increase in neurotrophic activity after two weeks
- Antidepressants effects
Pharmacokinetics of SSRIS

- The prototype drug fluoxetine differs from other SSRIS in some respects.
- Flouxetine metabolized to an active product nor fluoxetine.
- Plasma concentration of nor fluoxetine are higher than fluoxetine.
- Elimination half life of nor fluoxetine is about three times longer than fluoxetine. This is the longest half life of all the SSRIS.
- SO fluoxetine should be discontinued four weeks or longer before MAOI can be given to mitigate the risk of serotonin syndrome.
Clinical indications of ssris

- Major depression
- Generalized anxiety disorder
- Panic disorder
- Obsessive compulsive disorder
- Post traumatic stress disorder
- Premenstrual dysphoric disorder
- Eating disorders (bulimia)
Adverse effects of ssris

Increase risk of suicide in patients under the age of 25
Increase serotonergic activity in the gut is associated with Nausea
Gastrointestinal upset
Diarrhea
Improve after 1st wk of treatment
Adverse effects

- Loss of libido
- Delayed orgasm
- Diminished sexual function
- Persists as long as the pt remain on treatment
- Headache
- Insomnia or hypersomnia
- Weight gain
- Discontinuation syndrome 1 or 2 days after dc the Rx
- Dizziness paresthesia
Paroxetine

- Cardiac septal defects are associated with first trimester exposures with paroxetine thus paroxetine is a category D agent.
- SSRI’s are probably associated with post birth complications including pulmonary hypertension.
SNRIS

- Venlafaxine
- Duloxetine
- Desvenlafaxine
MECHANISM OF ACTION

SNRI,s
(selective serotonin noradrenalin reuptake inhibitors)
These drugs bind with both (SERT AND NET) and inhibits them as do the TCAs.

HOWEVER UNLIKE THE TCAs SNRI$s do not have much affinity for other receptors.
MECHANISM OF ACTION OF SNRIS

- Venlafaxine is a potent inhibitor of serotonin reuptake.
- At higher doses it is an inhibitor of norepinephrine reuptake.
- Most drugs of SNRIs more inhibitory effect on SERT than NET.
- Better tolerated than tricyclic drugs because of no significant anti-cholinergic alpha adrenergic receptor blocking or antihistaminic effects.
CLINICAL INDICATIONS OF SNRIS

- MDD
- Generalized anxiety disorder
- Post traumatic stress disorder
- OCD
- Social anxiety disorder
- Panic disorder
- Neuropathic pain
- Back ache
- Muscle ache
Pharmacokinetics
SNRIs

- Venlaflexin is met in the liver via cyp2d6 into desvenaflexine.
- Half life = 11 hrs
- 45% exc unchanged in urine
- Dose = 1 od
Adverse affects of SNRIS

- Nausea
- Dizziness
- Insomnia
- Sedation
- Constipation
- Somnolence
- Sweating
Adverse effects

SNRIs

Inc bp, heart rate. CNS activation, insomnia, anxiety and agitation.

Venlafexine overdose = cardiac toxicity

Duloxetine = hepato toxicity

Discontinuation syndrome
Contraindications

- Duloxetine is metabolized in the liver to many metabolites duloxetine should not be administered to patients with hepatic insufficiency.
- Metabolites are excreted in urine so duloxetine is not recommended in patients with end stage renal disease.
Tricyclic antidepressants

- Dominant class of antidepressants until the introduction of SSRIS in 1980s and 1990s.
- Nine TCAs are available all have a tricyclic core.
- The TCAs block SERT and NET.
- Prototype drug is amitriptyline.
- They all have similar therapeutic efficacy.
- Choice of drug depends on patient tolerance of side effect.
- At present TCAs are used in depression unresponsive to SSRIs and SNRIs.
pharmacokinetics

Tricyclic anti depressents

• Half life = long
• Dose 1 od
• Exc = only 5 % from urine.
Clinical indication of TCAs

- Major Depression
- Panic disorders
- Nocturnal enuresis: imipramine is used by causing contraction of internal sphincter of the bladder
- Chronic pain (neuropathic pain): amitriptyline.
Adverse effects

TCA,S

- Anticolinergic effects
- Dry mouth
- Constipation
- Uri retention
- Blurred vision
- Confusion
- Orthostatic hypotension
- Wt gain
- Sedation
- Arrhythmia
- Sexual side effects
- Discontinuation syndrome.
MECHANISM OF ACTION

5-HT2 ANTAGONISTS

Trazodone and nefazodone = antagonists on 5HT RECEPTORS.
Inhibition of this receptors= antidepressant and anti anxiety
effects.

Lsd (lysergic acid diethylamide) and mescaline = agonists to
these receptors and cause anxiety and hallucinations.
Pharmacokinetics

• Goes through extensive hepatic metabolism
• Half life = small so split dosing is req.
• Trazodone = only 5-HT2 antagonist given in single dose.
MECHANISM OF ACTION

• Nafazodone and trazodone primary metabolite m-cpp is a potent 5HT2 antagonist

• nefazodone is a weak inhibitor of both SERT and NET
Tetra cyclic and uni cyclic antidepressants

• Bupropion=pre synaptic release of NE and has no direct effect on serotonin system.
• Mirtazipine= antagonists on alpha adrenoreceptors= releases noradrenalin and serotonin.
• It also has antagonist effect on 5HT2 and 5HT3 receptors.
• Also acts as antagonist on H1 receptors so it has sedative effect.
pharmacokinetics

Tetracyclic and unicyclic agents
Bupropion is rapidly absorbed
Protein binding = 85%
Met = hepatic
Tetra cyclic and uni cyclic antidepressants

- Maprotiline and amoxapine=acts like tricyclic antidepressants. Both inhibit NET more than SERT
- AMOXAPINE moderate inhibitor of post synaptic D2 RECEPTORS
- So amoxapine possesses some antipsychotic properties.
pharmacokinetics

- Excretion = biphasic
  - 1st phase = 1 hr
  - 2nd phase = 14 hrs
- Amoxapine = rapidly absorbed
- Protein binding = 85%
- Half life = variable
- Drug given = divided doses
- Metabolism = hepatic.
Pharmacokinetics

Mao inhibitors
Diff mao inhibitors = met via diff pathways
It has extensive first pass effect so its bioavailability is dec
Abs = git
Bec of prominent first pass effect and their tendency to inhibit mao in the gut alternative routes of administration are being developed
These routes decrease the risk of food interactions and provide increased bioavailability.
Selegeline is available in transdermal and sublingual routes, so it bypass both gut and liver.
Clinical pharmacology

Depression mdd

• Ac episode= 6-14 months
• Goal = remission of all the symptoms
• Benefit starts within 1-2 wks so treatment given for 8-12 weeks

• In 40 % people add given as single therapy and 30-40% patients get remission in 8-12 weeks.
Clinical pharmacology

- If treatment not adequate than
- Switched to another agent
- Eg ssri or snri given with bupropiopn for 6-12 months

- 80 % patients with mdd wil get at least 1 recurrence in lifetime
- Many pts who get multiple recurrence may have tretment reststant disease
Clinical pharmacology

• So MAINTANANCE THERAPY may be given to prevent the disease.

Maintanace therapy = 5 years

Ssri, snri or tca given as maintainance therapy for its protective effects.

If 2 or more serious mdd episodes in 5 years = maintenance therapy indicated.

ADD given for all subtypes of depression
Clinical pharmacology

• Add if given with psychotherapy (cog behav therapy) = more effective.
Clinical pharmacology

Anxiety disorder

all maj anxiety dis eg ptsd ocd , social anxiety gad , panic dis gets treted if add like ssri , snri given

benzodiazepines gives rapid relief in anxiety however add have long term benefit.

Ocd = repetitive anxiety provoking thoughts
Rx= ssri,s and clomipramine.
Clinical pharmacology

Social anxiety disorder
Severe anxiety in social gatherings to the extent that daily life suffers,
Rx = ssri,s and venlafexine

Ptsd( post traumatic stress disorder)
Any trauma or life threatening event results in anxiety provoking thoughts .Rx= ssri,s and psychotherapy .
Clinical pharmacology

Pain disorder

NE and 5 HT reuptake blockers are useful in this disorder
Tca and snrri,s helpful
Duloxetine = Rx for muscle and ch joint pain.
Milnalipram = fibromyalgia
Desvenaflexin = ch backpain and postherpetic neuralgia.
Clinical pharmacology

Premenstrual dysphonic disorder
Anxiety, Depression, fatigue, Insomnia.
Rx = ssris
Fluoxetine and sertraline = 2 weeks

Smoking cessation
Bupropion as effective as nicotine patches
it mimics nicotine effects
Clinical pharmacology

• it antagonize nic receptors.

Eating disorder

• bulimia (food binges followed by ritualistic purging by emesis)
• Hypokalemia may occur which could be dangerous
Clinical pharmacology

- Rx = fluoxitin.
- bupropion = RX of obesity

Other conditions
- Urinary stress incontinence = snri,s given
- Vasomotor symp of peri menopause= desvenlafexine
- Ssri.s
- Nefazodone given
Choice of anti depressant drug.

- Older pts are sensitive to tca,s
- Females respond to ssri,s better than NE inhibitors or tca,s

mdd

Ssri,s = safe tolerable inexpensive so r first line treatment for treating depression
Choice of anti depressant drug

• Bupropion and mirtazipine also 1st line Rx for MDD bec of lil or no side effects.

• TCA and MOA = 2nd or 3rd line for MDD due to lethal overdose, serious adv effects and serious drug interactions

• Used only in resistant depression.
**dose**

*SSRIs, SNRIs*

- Rx starts with the therapeutic dose
- If no benefit – 4 weeks than higher dose given and dose is titrated to its max level.

**TCA and MAO.**

Req titration dose for lethal side effects
Adverse effects

5HT2 antagonists

Sedation
Gi disturbances
Orthostatic hypotension
Hepatotoxicity – hep failure
Adverse effects

TETRACYCLIC AND UNICYCLIC ANTIDEPRESSENTS

SEDATION
SEIZURES
AGITATION
INSOMNIA
ANXIETY.
Adverse effects

MOA

Orthostatic hypotension
Wt gain
Sexual side effects
Activation
Insomnia
Restlessness
Confusion
Sudden discontinuation = delirium like effects e.g. psychosis and confusion
Overdose

- Suicide is unfortunate and serious consequent in dep patients
- 15% risk of suicide in all kinda dep
- Reason = overdose
- TCA frequently involved.
- Overdose lead to lethal arrhythmias vent tachycardia and vent arrhythmias
- Altered mental status eg seizures and bp changes seen in TCA overdose
- 1500 mg of imipramine or amytriptyline is enough to cause overdose and lethal in many pts.
Overdose

- Todellers = 100mg dose causes toxicity.
- Rx = cardiac monitoring
- Airway support
- Gastric lavage
- Sodium bicarbonate is often adm to uncouple TCA from cardiac sodium channel.

MAO

OVERDOSE = autoimmune instability, hyper androgenic symp, psychotic symp, confusion, delerium, fever, seizures.
Overdose

- Rx=cardiac monitoring
- vit sign support
- gastric lavage.

- ssri
- Overdose is uncommon
- Snri also safe
- Vanlafexine = may = cardiac toxicity.
Overdose

- Bupropion = seizures
- If ant dep $+_{ALCOHOL}$ = fatal dose
- $rx =$ emptying of gas tic contents.
Drug interactions

• Sedative effects of antidepressants can be potentiates with other sedatives, eg alcohol, barbiturates, benzodiazepines...

• MAO inhibitors, should not be given along with tyramine containing food, eg cheese, red beer and other fermented food.

• Tyramine is normally destroyed by mao enzymes present in the intestines.
Drug interactions

- MAO INHIBITORS prevent the destruction of tyramine that will cause the release of NE from adrenergic nerve endings.

- NE will cause HTN in the pts.

- Similarly other indirectly acting sympatho mimetics such as EPHEDRINE, PHENYLPROPRANOLAMINE should be avoided along with MAO inhibitors, as they may also cause HTN with MAO inhibitors.
Drug interactions

• NEFAZODONE, and FLUVOXAMINE, inhibits the metabolism of terfenadine, astemizole and cisapride.
• An increase concentration of these drugs in the body leads to cardiac arrhythmias so these drugs should be avoided along with the nefazodone and fluvoxamine.
THANK YOU