**ANTIDEPRESSANTS: Heterocyclics** (p.l)

1. **Introduction**

heterocyclics (3 rings or more), includes tricyclic antidepressants(TCAs)
have antidepressant, anxiolytic, & analgesic properties
traditional TCAs are the standard against which other antidepressants are measured; TCAs are very effective & have fairly rapid onset of effect

2. **Pharmacokinetics**

are **very lipid soluble**
well absorbed through GI tract, peak plasma levels in ½ to l hour
distributed rapidly, accumulate in brain, liver & kidneys
binding to blood proteins vary widely across different drugs
some bind extensively (80-90%) ½ hour after absorbed
takes **5 to 10 days to reach a steady state** plasma level
**therapeutic effect may take 1 to 4 weeks to be observed**
thus, for aggressively suicidal pts. may need to consider ECT

**metabolism** of antidepressants varies widely across Ss
**large individual differences** (x1 to x40)
usually have to individually tailor dose levels
about 80% of original dose is metabolized by liver

½ **lives of different drugs vary widely** (from 5 to 126 hours), but most are long enough to only need to dose once a day

some of these drugs have a "**therapeutic window**"
a certain range of drug (per unit of blood) is "just right", and produces a good antidepressant effect
either above or below this range drug has less/no benefit

once pt. is symptom-free, pt. is **maintained** on that drug at that dose level (usually do not need to change) **for 6 months**; at that point can consider tapering off drug & see what happens (i.e. does depression reoccur?)

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3. **<u>Pharmacological Effects</u>**

**block presynaptic reuptake of NE & 5HT** (blocks transporter protein)
underlies antidepressant effects
may also block **DA** presynaptic transporter protein…
may also increase amount of NE released from presynaptic membrane
may lead to RS down regulation…?
**blocks post-synaptic histamine RSs** --- SEs (see below)
**blocks post-synaptic muscarinic ACh RSs** --- SEs (see below)
some newer drugs (e.g. trazodone/Desyrel) have fewer antiACh effects and fewer cardiovascular effects

note: antidepressants taken by NCs --- no effect on mood, may see SEs when taken by depressed Ss --- increased activity, alertness, appetite, and better sleep, plus improved mood

note: **no abuse potential** (in depressed Ss or in NCs)
assume no effect on reward/focus system of CNS, no euphoria

4. **<u>Side-Effects</u>**

**most frequent and most severe are cardiovascular**
from effects on PNS, antiACh effects most likely
tachycardia (rapid, irregular EKG), arrhythmias, heart failure & sudden death
**esp. with amitriptyline (Elavil)**

can also produce "**orthostatic hypotension**" as well

**other antiACh SEs**:

| | | |
|---|---|---|
| psychomotor slowing | loss of concentration | muscle weakness |
| dry mouth (no saliva) | fatigue | headaches |
| tremors | dizziness | blurred vision |
| constipation (GI motility slowed) | increased urinary/fecal retention | |

**esp. bad with amitriptyline (Elavil), imipramine (Tofranil)**

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4. **Side-Effects** (cont.)

**tolerance does develop to antiACh effects**, so may want to start at lower doses & gradually increase dose as tolerance develops

can also take AChE-blocking drugs along with antiACh antidepressants:
e.g. physostigmine or pyridostigmine
however, these antiAChE drugs also have their own SEs: slowed heart rate, bronchoconstriction, hypotension…there is no free lunch!:(

**more toxic SEs/OD** (sign that dose is too high):
delirium reduced reflexes seizures
dilated pupils with sluggish pupillary responses to light
raised pulse rate lowered core body temp respiratory arrest
cardiovascular collapse

5. **Dependence/Withdrawal**

do not cause addiction, but do have **mild dependence** (withdrawal Sxs):
general malaise, aches, vomiting, anxiety, restlessness
avoid withdrawal Sxs by **tapering off** more slowly over a week or so, even over just a few days vs. sudden D/C

6. **Drug Interactions**

**can get exaggerated antiACh effects** when heterocyclic antidepressants are combined with:
ETOH BZDs antiparkinson drugs (DA agonists)
all neuroleptics glutethimide (Doriden)

the following drugs cause **liver enzyme induction** & **will decrease the effectiveness of any antidepressant taken with them**:
ETOH lithium barbiturates
chloral hydrate propranolol (Inderal)
smoking oral contraceptives

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7. **Phenothiazine-like SEs**

phenothiazine drugs are used to treat psychosis, & block DA RSs
some heterocyclics have SEs very similar to phenothiazine SEs:
**tremors, jaundice, photosensitivity, & sedation**

e.g. amitriptyline (Elavil) is very sedating (used as a **sleeping pill**)
amoxapine (Asendin) primary effect is DA RS blockage
SEs include: tardive dyskinesia, EPSEs, & above effects

8. **Miscellaneous SEs**

| | | |
|---|---|---|
| anorexia | insomnia | nausea & vomiting |
| acid reflux | paradoxical depression & anxiety | |
| mania | psychotic Sxs | |

9. **Pregnancy**

TCAs seem safer than most drugs in first trimester
do cross placenta, but seem safe for fetus

10. **Miscellaneous**

these antidepressants have antiACh effects --- should have SEs of **impaired concentration, confusion, & reduced memory**…and they do
esp. true for **amitriptyline** (Elavil), **doxepin** (Adapin, Sinequan)

very young and very elderly Ss are much more susceptible to these antiACh effects, esp. to **memory deficits**

very elderly Ss are much more susceptible to antiACh **constipation** effects (may become impacted)…which means just what you think it means!
which can be fatal if not treated
add a stool softener or use an antidepressant with **less antiACh effect**
e.g. **desipramine** (Norpramine)
**nortriptyline** (Pamelor, Aventil)
**clomipramine** (Anafranil)