ANTIDEPRESSANTS: Heterocyclics (p.1)

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 1 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. Pharmacological Effects
   - 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. Side-Effects
   - 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)