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Tricyclic Antidepressants (TCA's)

- General:
  - Introduced 1958 by Professor Kuhn in Switzerland.
  - Adult evidence of safety and efficacy; evidence of relative safety (with cardiovascular risks) but negative efficacy for the treatment of pediatric depression; not recommended for the treatment of depression in children and adolescents due to lack of evidence of efficacy in these age groups.
  - Evidence in ADHD
    - Of 33 studies (21 controlled and 12 open, with desipramine and imipramine being the two most well-studied agents in this category) evaluating TCA's in 1,139 children/adolescents and 78 adults, 91% demonstrated positive effects of ADHD symptoms. Nine of the studies demonstrated enduring positive effects for up to two years.
    - More consistently treat behavioral than attentional symptoms. Most efficacious in those with co-morbid ADHD and depression/anxiety and in those with co-morbid ADHD and tic disorders. May take 4-6 weeks for positive effects.
    - In 13 studies, TCA's tended to perform at the same level or slightly worse than stimulants (in 3 studies, the TCA's outperformed stimulants)
- Pharmacology
  - For pediatric ADHD, TCA's (except for nortriptyline) dosed as follows: initiated at 1 mg/kg/day and titrated at 1 mg/kg/week to maximum of 5 mg/kg/day; usually divided twice-a-day; nortriptyline started at lower dose with max 2 mg/kg/day.
  - Function by blocking norepinephrine reuptake and (via pre-synaptic alpha-2 receptor binding) increasing release of norepinephrine; binds to post-synaptic beta-adrenergic receptors leading to downregulation of these receptors. Also bind to pre-synaptic serotonin-1 autoreceptor which blocks serotonin reuptake and blocks breakdown of serotonin; also binds to post-synaptic serotonin-2 receptors. Finally, these effects may lead to increased activation of the cAMP cascade (with downregulation of c-fos transcription and up-regulation of cAMP response element-binding (CREB) protein and brain-derived neutrotrophic factor (BDNF)). This, in turn, may lead to neurogenesis of neurons affected by depression in the hippocampus and prefrontal cortex and may protect neurons from damaged caused by stress and anxiety/depression.
  - Relative long half-life of 12 hours
- Include:
  - Amitriptyline (Elavil)
    - 150-300 mg/d
    - therapeutic level (AMI+metab) 80-200 ng/ml.
    - more likely to aggravate seizures
  - Clomipramine **(Anafranil**)
    - FDA-approved for OCD
    - most serotonergic
    - 100-250 mg/d
    - 25, 50, and 75 mg caps
    - seizure risk 1.5%; risk increases with dose such that 300 mg/d has risk of 7/1000
    - substrate of 2D6, 1A2 so can be increased by Prozac, Paxil, Wellbutrin, Cymbalta and Luvox (→ more CMI, less dm-CMI; this leads to more SRU inhibition which can be useful in OCD and depression)
    - 1A2→ desmethyl-clomipramine (active)→ NRU inhibition → increased norepinephrine
    - half-life 17-28 hours
    - side effects, in decreasing order of incidence
      - Dry mouth
      - Somnolence
      - Dizziness
      - Fatigue
      - Tremor
      - Headache
      - Constipation
      - Poor appetite
      - Abdominal pain
      - Upset stomach
      - Insomnia
      - Hypomania
      - seizure risk 1.5%
  - Desipramine (**Norpramin**)
    - FDA-approved for depression
    - May help neuropathic pain, anxiety, insomnia, bed wetting, ADHD, tics
    - mostly noradrenergic.
    - Dosing
      - 100-200 mg/day (occ up to 300 mg/d) in adults
      - 1-5 mg/kg/day in children; in pediatric ADHD: 3.5-5 mg/kg/day; max in adolescents 150 mg/day
      - 50-150 mg/day for chronic pain in adults

        - Dosing instructions:
            - Start with 25 mg/pm
            - Increase by 25 mg every 3-7 days
    - therapeutic level 150-300 ng/ml; in children 150-250
    - Pharmacokinetics
        - half-life 24 hours
        - 2D6, 1A2 substrate so can be increased by Prozac, Paxil, Wellbutrin, Cymbalta and Luvox
    - active metabolite of imipramine
    - 10, 25, 50, 75, 100, 150 mg tabs
- Doxepin **(Sinequan**)
    - FDA-approved for "psychoneurotic patient with depression and/or anxiety, deprn and/or anxiety associated with alcoholism, depn or anxiety associated with organic disease, psychotic depressive disorders with associated anxiety, involutional depression, manic-depressive disorder"
    - Also helps skin conditions (topically), insomnia, chronic pain
    - 75-150 (up to 300 mg/d)
    - half life 8-24 hours
    - substrate for 2D6
    - therapeutic level (doxepin+metab) 120-250 ng/ml
- Imipramine/imipramine pamoate **(Tofranil/Tofranil PM**)
    - 50-150 (up to 300 mg/d) in adults
    - 1-5 mg/kg/day in children; 0.3-1 mg/kg/day for bed wetting
    - therapeutic level (IMI+DMI) is less than or equal to 150-250 ng/ml
    - 75, 100, 125, 150 mf caps; 10, 25, 50 mg tabs
    - Substrate for 2D6, 1A2 (→ desipramine with half-life of 24 hours)
    - side effects
        - dry mouth 50-60% vs. 20% placebo
        - drowsiness OR fatigue (25-30%)
        - constipation 25-40%
        - nervousness (20%)
        - dizziness (18%)
        - sweating (15%)
        - sexual side effects (15%)
        - insomnia (8%)
        - nausea (3.5%)
        - headache (2%)
        - seizure risk 0.2-0.5%
- Nortriptyline **(Pamelor/Aventyl**)
    - 50-150 mg/d in adults; 0.5-2 mg/kg/day in children
    - therapeutic level between 50-150 ng/ml
    - more noradrenergic.
    - 10, 25, 50, 75 mg caps; 10 mg/5 ml liquid
    - Substrate for 2D6
    - Amitriptyline→nortriptyline by 1A2
    - Half-life 36 hours
- Protriptyline **(Vivactil/Triptil**)
    - FDA-approved for depression
    - Not as sedating as other TCA's but more anticholinergic
    - 15-40 mg/d (max 60 mg/d)
    - Substrate for 2D6
    - Half-life 74 hours
    - therapeutic level 75-250 ng/ml.
- Trimipramine maleate **(Surmontil**)
    - FDA-approved for depression and the treatment of enuresis (wetting) in children 6 years and older
    - 50-150 mg/d (max 300 mg/d)
    - 25, 50, 100 mg caps
    - Substrate for 2D6, 2C19, 2C9
    - Half-life 7-23 hours
    - therapeutic level unknown
- Amoxapine **(Ascendin**)
    - 150-400 mg/d
    - therapeutic level unknown
- Maprotiline **(Ludiomil**)
    - FDA-approved for depression
    - 50-15- mg/day (max 225 mg/d)
    - therapeutic level 150-250 ng/ml

        - Substrate for 2D6
        - Half-life 51 hours
        - Peak level 8-24 hours
        - risk of seizures, especially above 200 mg/day
    - **D**othiepin **(Prothiaden**)
        - serotonin and norepinephrine reuptake inhibitor
        - similar to amitryptyline
        - 75-150 mg/day (max 300 mg/d)
        - 25 mg cap, 75 mg tab
        - half life 14-40 hours
        - Substrate for 2D6
    - Lofepramine **(Deprimyl/Gamanil**)
        - norepinephrine reuptake inhibitor
        - 140-210 mg/d (max dose 280 for inpatients)
        - Substrate for 2D6 (→ desipramine)
        - Half-life 1.5-6 hours (but desip is ~24 hours)
        - major metabolite is desipramine
        - 70 mg scored tab; 70 mg/5 cc liquid
    - Tianeptine **(Coaxil/Stablon**)
        - tricyclic and serotonin reuptake enhancer
        - 25-50 mg/day, divided in 2-3 doses
        - 12.5 mg tab
        - not metabolized by P450 enzymes
        - half-life is 3 hours.
        - side effects
            - headache
            - dizziness
            - insomnia
            - nausea
            - sedation
            - dry mouth
            - constipation
            - blurred vision,
            - rare liver dysfunction
            - fast heart rate
            - ?risk of seizures
- Side effects and risks, in general
    - Sedation, dry mouth, weight gain, constipation, sexual side effects
    - Can use pilocarpine for mouth, bethanechol 10-50 tid-qid; fluids, NaCl 1-3 g, fludrocortisones 0.1-0.3 mg/d
    - Cardiovascular risk—must be monitored by blood levels and ECG's.
        - TCA's are associated with mostly minor, asymptomatic but statistically significant increases in heart rate and ECG measures of cardiac conduction times (more dangerous in those with preexisting block); may help those with some ventricular arrhythmias; careful monitoring is critical in those taking anti-arrhythmic medications
        - Orthostatic hypotension in 5-10%, up to 32% in patients with conduction disturbances and up to 50% in patients with left ventricular performancel less with NTP; increases risk of hip fracture 2-3 fold
        - Law and Schachar (1999) reported sudden unexplained death in four children with ADHD treated with desipramine; the causal link remains uncertain.
        - More than eight cases of sudden death have been reported since then.
        - A recent study look at records from 1983-2002; the risk of fatality in youth is 4-10 times higher with desipramine than with the other TCA's.
        - Risk of sudden death in children in perspective:
            - motor vehicle accident: 70 cases/million/year
            - desipramine: 8 cases/million/year
            - suicide (all causes): 7.4 cases/million/year
            - unknown cause: 4.2 cases/million/year
    - Weight gain 1.3-2.9 pound/month
    - Confusion risk with age
        - 10-29 yo: 0%
        - 30-39: 4%
        - 40-49: 25%
        - 50-59: 33%
        - 60-69: 43%
        - 70-79: 50%
    - Drop-outs due to side effects: 26-32%
    - Fine resting tremor

- Seizures <0.1%
- No abuse potential
- Sudden discontinuation of TCA's can lead to increased side effects