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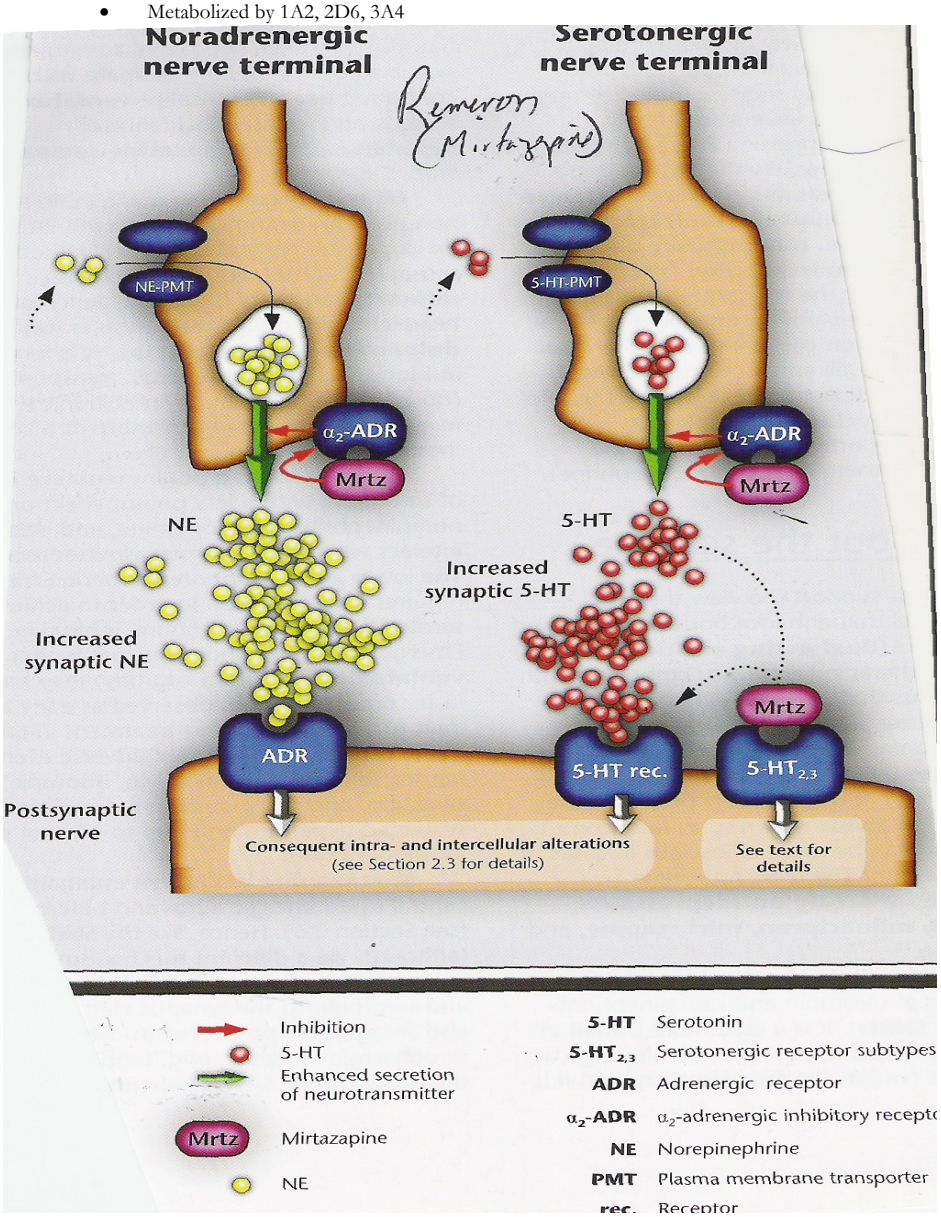
Anxiety and Depression Treatments: MTZ, Traz, NFD, Busp, Others

Alpha-2 Receptor Antagonists

- **Include**
  - **Remeron/Remeron Soltabs**
    - General
      - Marketed in US in 1996.
      - Blocks central presynaptic alpha2-adrenergic receptors leading to increased release of norepinephrine/serotonin and consequent stimulation of alpha1-adrenergic receptors on serotonergic cells (with further increase release of serotonin). Also blocks serotonin-2a, 2c, 3 receptors and histamine-1 receptors.
      - 15, 30 and 45 mg tabs. Dissolving wafer (Remeron SolTabs) also available.
      - Peak in 2 hours; half-life is 20-40 hours
      - Metabolized by 1A2, 2D6, 3A4



    - Evidence
      - Evidence of safety and efficacy from several thousand adult patients with depression and FDA-approved for such.
      - Meta-analysis of studies including almost 3,000 patients demonstrated faster onset of action of antidepressant and anti-anxiety effects (both within 2 weeks) and remission and greater rate of remission (Thase).
      - Useful also for atypical depression and seasonal depression.
      - Mixed evidence of benefit in treating sexual side effects of SSRI's.

- Pediatric depression:
  - Cheung et al, 2005: two multicenter, double-blind, placebo-controlled of 259 youths with depression; both ***negative:*** first study reported response of 60% vs. placebo response of 57%, and the second reported a response of 54% vs. placebo response of 42%.
  - There is reported to be a large multi-site study funded by the pharmaceutical company of Remeron in the treatment of pediatric depression that was negative and not reported.
- Pediatric anxiety
  - Posey et al, 2001; open-label use of Remeron in kids with autism spectrum disorder, 26 subjects, 3.8-23.5 years (average age 10), average dose 30 mg
    - Effective for sleep, irritability, and hyperactivityf

- Side effects:
  - Drop-outs 16%
  - Sleepiness, sedation 36-50%, although this is more evident at lower doses (so recommendation is to start at 30 mg in adults); 10% stop Remeron due to this.
  - Increased appetite 11-20%
    - 10% report weight gain vs. 1% on placebo
    - 7.5% report weight gain of at least 7%
    - H2 blockers may decrease risk of weight gain.
    - Song, et al 2014; retrospective, observational study of Remeron in patients receiving naturalistic treatment for diabetes
      - BMI increase ~1 point in patients on Remeron vs. 0.3 points on placebo
      - More pronounced increase in BMI with Remeron in those initially overweight
      - Glucose/insulin control did not differ significantly
      - Lipids did not differ significantly
  - Cholesterol increase 15%; 6% have a significant increase in triglycerides.
  - Sexual side effects 4-12% (BUT 24% with formal assessment)
  - Dry mouth 10%-25% vs. 16% placebo
  - Constipation 6%
  - Elevated liver enzymes in 2% (similar to SSRI's, though data suggests 1.4-fold more than other antidepressants and 1.6-fold more than placebo)
  - Switch to mania 0.25%
  - Agranulocytosis 0.1% (2/2796, one of which had a rare autoimmune disorder prior to use of Remeron; later data—7 cases per more than 2 million exposures)
  - Neutropenia ~0.1%
  - Seizure 0.04% (1/2796), not different from placebo
  - Pregnancy
    - Spontaneous miscarriage rate:
      - 19% with Remeron (in Djulus et al, 2006)
      - 17% with other antidepressant groups
      - 11% baseline
      - not statistically significant—could be risk associated with depression itself
    - Increased risk of pre-term birth
    - No increased risk of major malformations

- **Mianserin**—more noradrenergic than serotonergic
- **Yohimbine—**the alpha-1 properties limit it's utility

Norepinephrine-Specific Reuptake Inhibitors

Include

- **Reboxetine (Edronax/Norebox in Europe)**
  - General
    - Introduced in Europe in 1997
    - 3A4 metabolism
    - Inhibits 2D6 and 3A4 at high doses
    - Half-life is 13 hours.
    - Directly modulates locus coeruleus.
    - Starting dose in adults is 4 mg twice-a-day (then observe for 3-4 weeks and increase if necessary to max of 10 mg/day).
    - In elderly patients, start at 2 mg twice-a-day and increase to max 6 mg/day.
  - Evidence
    - Taner et al, 2007: RCT, 8 wks, 43 patients, fluoxetine as comparator, treatment of atypical depression, equally effective, less well tolerated than fluoxetine;
    - Eight randomized multinational studies on 2,613 adult patients with major depressive disorder with positive results. Superior to Prozac in improving social functioning and significantly better than Prozac in reducing symptoms of severe depression and melancholic depression. Prevents relapse/recurrence over 1 year of use.
    - Some American studies did not find evidence of efficacy. Currently under FDA review.

- Side effects
  - Less likely than SSRI's to cause nausea, diarrhea, somnolence and sexual side effects
  - In Taner 2007 study, more likely than fluoxetine to cause dry mouth, sweating, headache, urinary retention, and painful ejaculation
  - Include
    - dry mouth 27% (vs. 15% in placebo)
    - constipation 18% (vs. 9% in placebo)
    - headache 14.4% (vs. 13.9% in placebo)
    - sweating 12.1% (vs. 7.7% in placebo)
    - insomnia 12% (vs. 7% in placebo)
    - urinary hesitancy, retention
    - low blood pressure
    - 3% risk of hypertension
    - insomnia
    - dizziness 10.2% (vs. 5.7% in placebo)
    - anxiety
    - agitation

- **Strattera**—atomoxetine; no clear evidence of efficacy in the treatment of depression as of yet; some evidence of lack of efficacy in depression. FDA-approved for ADHD.
- **Viloxazine**—under investigation
- **1555U88**—under investigation

Serotonin-2a,c receptor antagonists

General

- Block post-synaptic serotonin-2a and -2c receptors (nefazodone > trazodone) leading to a paradoxical down regulation of serotonin-2 receptors as well as serotonin-1a receptor stimulation
- also mild serotonin (and, for nefazodone, norepinephrine) reuptake inhibition.
- An important metabolite, mCPP, is an activator of the serotonin-2c receptor and can exacerbate anxiety.

Include

- **Trazodone**
  - General
    - FDA-approved for depression
    - Made in the mid-1960's; released in US in 1981 (FDA-approval in 1991); first serotonergic agent released in the U.S.
    - Dose range 150-600 mg (25-200 mg for the treatment of insomnia). The most effective dose range may be 150-300 mg with doses above or below that range being less effective.
    - Optimal dosing is 2-3 times-a-day if taken at doses above 200 mg/day.
    - Peak within 2 hours; half-life is biphasic: 3-6 hours and then 5-9 hours.
    - 3A4 substrate
    - 2011: repackaged as a once daily extended release trazodone called Oleptro (150 mg tabs, 300 mg tabs)
  - Evidence
    - Evidence of relative safety and efficacy in adult depression from > 24 double-blind, placebo-controlled studies; inadequate evidence of safety and efficacy in children.
      - Evidence of efficacy of low-dose trazodone (50-150 mg) in general anxiety and generalized anxiety disorder comparable to chlordiazepoxide, diazepam, and imipramine.
      - Effective as a sleep agent at doses of 25-100 mg/PM; not addictive.
    - Side effects
      - sleepiness
      - dry mouth 15%
      - orthostatic hypotension and dizziness/fainting upon standing; usually lasts 4-6 hours after dose administration
      - constipation 8%
      - blurred vision 6%
      - urinary hesitancy 1%
      - priapism
        - prolonged and painful erection that can lead to permanent impotence occurs in 1 per 6,000 male patients
        - usually at doses <150 mg/day, usually in first month
        - over 200 cases of priapism (not all of which have been dangerous) have been reported in men and at least one case of clitoral priapism in women
      - nausea
      - swelling
      - headache
      - incoordination
      - tremor
      - cardiac rhythm: can exacerbate preexisting myocardial irritability, possibly precipitating ventricular tachycardia, cardiac conduction delay, or slow heart rate
      - rash

- rare seizures
- rare mania

- **Nefazodone (Serzone)**
  - General
    - FDA-approved for depression
    - Made by Bristol-Myers Squibb (BMS) in 1980's; made available in the US in 1995.
    - Half-life: 3 hours
    - Active metabolites: 3, 18-33 hours
    - 300-600 mg/day
    - 50, 100, 150, 200, 250 mg tabs
  - Evidence
    - Evidence of relative safety and efficacy in adult depression from > 8 double-blind studies.
      - One particular study in severely and melancholically depressed inpatients: 54% response rate vs. 18% placebo.
    - May alleviate anxiety in adults with depression at doses < 250 mg/day. May be effective in PTSD. Less sedation than trazodone, but may improve sleep architecture.
      - RCT study in the treatment of social phobia: negative
    - 2 multicenter trials in youths with depression—negative; one study reported response of 65% vs placebo response of 40%.
    - Side effects
      - dizziness (23%)
      - dry mouth (12%)
      - visual trailers in 12% of patients taking Serzone.
      - nausea (11%); stomach upset
      - drowsiness OR fatigue (11-15%)
      - sexual side effects (5% BUT 8% when formally assessed)
      - constipation (6%)
      - headache (3%)
      - insomnia (2%)
      - increased appetite
      - agitation
      - confusion
      - memory impairment
      - balance problems
      - tingling in extremities
      - increased cough
      - rare postural hypotension
      - liver damage
        - in 1999, an isolated report at one center of three patients on Serzone who sustained liver failure
          - they were women b/w 16-57 yo who were treated with 200-400 mg of Serzone for an average of several months
          - at least one was using another medication at the same time.
        - through 2002, there have been 109 reported cases of severe liver damage associated with approximately 8.3 million patients using the medication
          - 16 of the 109 had liver damage that progressed to liver transplant or death.
        - Venkatesh, 2003: found that the rate of abnormal liver function tests (while taking Serzone) was 3.9%.
        - it is estimated that the risk of severe liver damage is 1/250,000-300,000 which, while very small, is 3-4 times the background rate for severe liver damage. For this reason, BMS no longer markets brand name Serzone.
        - the highest estimated risk of serious liver failure (1/150,000 patient years (the number of years that the number of patients on nefazodone were on it)
        - this 1/150,000 risk is far less than the risk of dying in an auto accident (50,000/year in the USA out of 300,000,000 people, or 1/6000, or 25x higher!
      - seizure risk 0.04%
- **YM992**—similar to Serzone
  - **MDL**-100907—selective serotonin-2a receptor antagonist under investigation for treatment in schizophrenia.
  - **SR46349**—selective serotonin-2a receptor antagonist under investigation for treatment in schizophrenia.
  - **Flibanserin**—also with serotonin-1a agonism
  - **Adatanserin**— also with serotonin-1a agonism
  - **BMS181,101**—also with serotonin-1a agonism

Serotonin-1a partial agonists

- **Buspar**—buspirone, comes in generic
  - Not efficacious in depression, but effective in augmenting antidepressants
  - Effective in generalized anxiety disorder
  - 25-60 mg/day split 2-3 times-a-day
  - Peak level within 1 hour

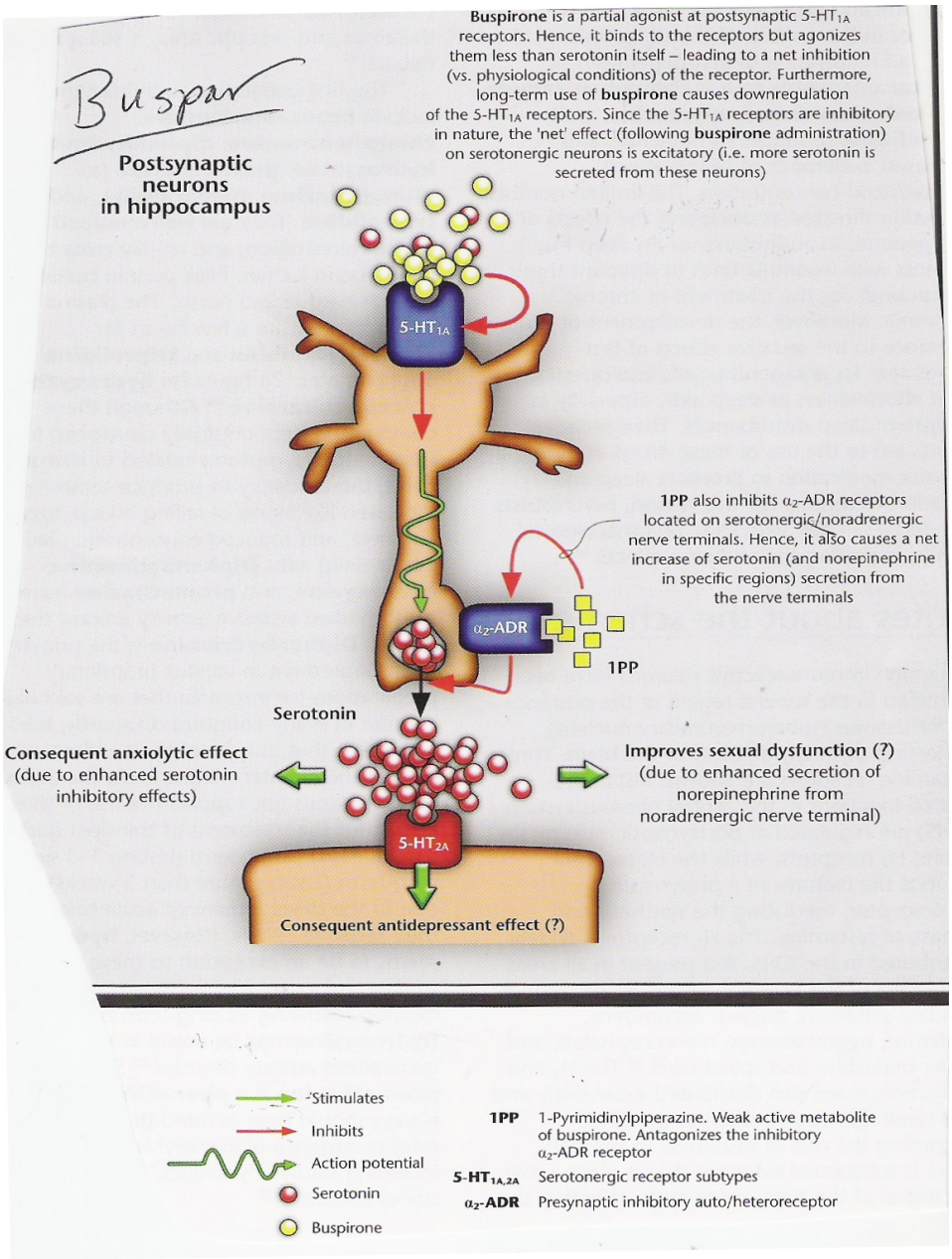
- Food may double the amount in the blood
- Half-life 2-3 hours, but active metabolite has half-life of 6 hours
- Side effects:
  - Nervousness or uneasiness 17%
  - Dizziness 12%—usually 30-60 minutes after dose administration; eases over time
  - Tiredness, reduced alertness 10%—eases over time
  - Headache 6%
  - Nausea, vomiting 6%—eases over time
  - Diarrhea 3%
  - Insomnia
  - Thirst
- Buspirone in Children and Adolescents with Anxiety: A Review and Bayesian Analysis of Abandoned Randomized Controlled Trials
  Jeffrey R Strawn, Jeffrey A Mills, Gary J Cornwall, Sarah A Mossman, Sara T Varney, Brooks R Keeshin, Paul E Croarkin
  Journal of Child and Adolescent Psychopharmacology 2017 August 28

  OBJECTIVES: An increasing number of abandoned clinical trials have forestalled efforts to advance the evidence base for the treatment of mood and anxiety disorders in children and adolescents. With this in mind, we sought to present and validate a Bayesian approach for the reanalysis of summary data in abandoned clinical trials and to review and re-evaluate available pharmacokinetic, tolerability, and efficacy data from two large, randomized controlled trials of buspirone in pediatric patients with generalized anxiety disorder (GAD).

  METHODS: Prospective, randomized, parallel-group controlled trials of buspirone in pediatric patients with GAD as well as associated pharmacokinetic studies were identified and data were extracted. In addition to descriptive statistics, marginal posterior densities for each variable of interest were determined and a Monte Carlo pseudosample was generated with random draws obtained from the Student's t-distribution to assess, with inferential statistics, differences in variables of interest.

  RESULTS: Buspirone was evaluated in one flexibly dosed (N = 227) and one fixed-dose (N = 341) trial in children and adolescents aged 6-17 years with a primary diagnosis of GAD. With regard to improvement in the sum of the Columbia Schedule for Affective Disorders and Schizophrenia GAD items, buspirone did not separate from placebo in the fixed-dose trial at low (95% CI: -0.78 to 2.39, $p = 0.32$) or high dose (95% CI: -0.87 to 1.87, $p = 0.47$) nor did it separate from placebo in the flexibly dosed study (95% CI: -0.3 to 1.9, $p = 0.15$). Drop out as a result of a treatment-emergent adverse event was significantly greater in buspirone-treated patients compared to placebo ($p = 0.011$). Side effects were consistent with the known profile of buspirone with lightheadedness occurring more frequently in buspirone-treated patients ($p < 0.001$).

  CONCLUSIONS: Buspirone is well tolerated in pediatric patients with GAD, although two randomized controlled trials were underpowered to detect small effect sizes (Cohen's $d < 0.15$). Finally, Bayesian approaches may facilitate re-examination of data from abandoned clinical trials.



- **Gepirone-ER**
  - Efficacy
    - Studied over the last 20 years with established efficacy in generalized anxiety.
    - Keller, 2005: multicenter, RCT relapse prevention study, gepirone ER, over 40-44 weeks, 23% relapse rate with gepirone vs. 34.7% with placebo
    - Amsterdam et al 2004: immediate release form safe and effective for depression
    - Wilcox, 1996: effective in treating depression.
    - Feiger, 1996: as effective as imipramine in depression.
    - May be more effective in atypical depression (McGrath, 1994: 62% response with gepirone up to 120 mg/day versus 20% response to placebo; also, Quitkin and Gibertine, 2001).
    - On 9/04, deemed not approvable by the FDA
      - However, there are 2 reported RCTs, 8 wk duration, that are positive for depression—may be resubmitted.
  - More potent serotonin-1a agonist than Buspar.
  - Most effective dose range of extended-release formulation is 40-80 mg/day.
  - Side effects:
    - Nausea 15.7%
    - Dizziness 13.1%
    - Headache 12.9%
    - Insomnia 6.2%
    - Vertigo 6%
    - Lightheadednes
    - Tiredness
    - No significant sexual side effects. Weight neutral.

- Risk of seizure higher in those with seizure disorders, head injury, bulimia, anorexia, and with concurrent use of alcohol and drugs.

- **Ipsapirone**—no evidence of efficacy in the treatment of depression
- **Deramciclane**—under investigation.
- **Lesopitrone**—under investigation.
- **Sunepitrone**—under investigation.
- **Tandospirone**—under investigation.
- **Vilazodone**—also a serotonin reuptake inhibitor; may not be released
- Osemozotan (MN-305)—under investigation for generalized anxiety disorder
- **Flesinoxan—**under investigation.