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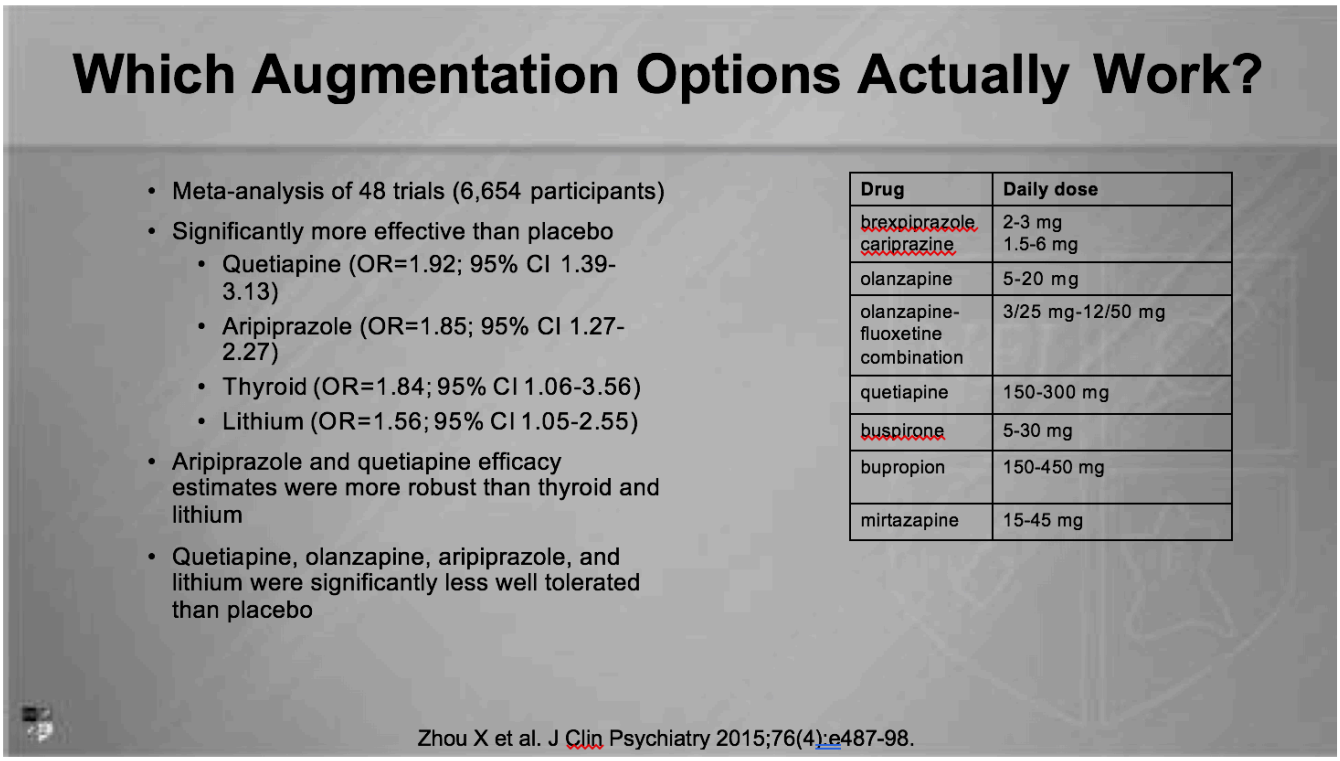
Other Treatments and Strategies to Treat Psychiatric Conditions and Residual Symptoms: Optimizing Efficacy

- General
  - Residual symptoms are present in 30-50% of patients in remission (Blier and Briley, 2011)
  - Common residual symptoms associated with depression
    - Sleep dysregulation
    - Mental apathy
    - Physical fatigue
    - Daytime somnolence
    - Cognitive impairment
  - Causes of residual symptoms
    - Partially or inadequately treated symptoms of depression
    - Side effects of antidepressants
  - Evaluating residual symptoms of depression
    - Was the medication trial adequate in dose and duration
    - Adherence
    - Correct diagnosis (r/o bipolar depression/depression with psychotic features)
    - Other co-morbid diagnoses
    - Other medical co-morbid diagnoses
- Algorithm for treatment of depression and anxiety
  - Begin with single antidepressant (+/- short-term benzodiazepine to treat anxiety during the titration period of the antidepressant)
  - Slow titration up to minimal effective dose (could take 0-15 days)
  - Observe over 4 weeks from the first date of minimal effective dose
  - If partial positive response, wait 2-4 more weeks, then, if no further improvement, consider increase dose of same antidepressant
  - If the increased dose (after 2-4 weeks) does not improve response, decrease dose back down and consider adding an adjuvant or second antidepressant
  - If no response, then reassess diagnosis/diagnoses and consider change to another antidepressant within same class and repeat above
  - Cipriani, et al, 2018
    - Systematic review and network analysis of 522 trials (116,477 participants)
    - Comparison of 21 antidepressants for the acute management of major depression in adults
    - Response rates for antidepressants > placebo at 8 weeks
      - Amitriptyline: highest odds ratio (2.13)
      - Reboxetine: lowest odds ratio (1.37)
    - Head-to-head comparisons (194 studies; 34,196 participants)
      - Higher response rates
        - Agomelatine
        - Amitriptyline
        - Lexapro
        - Remeron
        - Paxil
        - Effexor
        - Zoloft
        - Trintellix
      - More tolerable meds
        - Agomelatine
        - Celexa
        - Lexapro
        - Prozac
        - Zoloft
        - Trintellix
  - Thase, ASCP Fall Conference, 2017
    - Should one switch to a different med or add an adjunctive med?
      - STAR-D did not answer the question
      - STAR-D did suggest that adjunctive strategies are better for PARTIAL responders and switching is better for NON-responders
      - The case for switching
        - If first med is poorly tolerated
        - Second drug can be selected based on outcome from first
        - Can switch to a med with different mechanism of action
      - Should we switch within or across classes

        - Across-class switch was the standard until the mid-90's
        - Subsequent studies don't support this
        - A 2nd within-class trial now a widely accepted option for SSRIs and SNRIs
        - No consensus on a 3rd within-class trial
    - Data on switching
        - Remission rates after switching to (Baldomero et al, 2005)
            - Effexor XR 59.3%
            - Zoloft 52.7%
            - Prozac 52%
            - Celexa 52%
            - Paxil 51.6%
            - Remeron 44.8%
        - STAR-D level 2 results; remission rates after switching to
            - Effexor XR 25%
            - Wellbutrin XL 25.5%
            - Zoloft 26.6%
            - Vs combo therapy
                - Celexa plus Wellbutrin XL 39%
                - Celexa plus Buspar 33%
        - SSRI NON-response → Effexor XR vs. (different) SSRI (Baldomoro et al, Poirer and Boyer, Rush et al)
            - Effexor XR better for response and remission
- The preponderance of evidence suggests that switching to Effexor in this circumstance is more effective than switching within class or to Wellbutrin
- If no response with second antidepressant in same class, then reassess diagnosis/diagnoses and consider trying antidepressant in a second class and repeat above
- If continued lack of response, consider change to a third antidepressant in another class, and/or further combination treatment (with one or more antidepressants and one or more adjuvants)
- In melancholic depression, remission rates:
    - Tricyclic antidepressant: 60-70% remission rates
    - SSRI 40-55% remissions rates
- In atypical depression:
    - Early onset/chronic
        - Monoamine oxidase inhibitors 76.5% response rate
        - Tricyclic antidepressants 42.9% response rate
        - Placebo 22% response rate
    - Late onset/non-chronic
        - Monoamine oxidase inhibitors 81.3% response rate
        - Tricyclic antidepressants 81% response rate
        - Placebo 31.3% response rate
- Recurrent depression
    - Lithium
        - In melancholic type 57% response rate
        - In non-melancholic type 25% response rate
- Combine with individual, group, or family therapy whenever possible to improve response



- Medication Treatment Algorithms for Major Depression, Youth
  - Youth with no additional diagnosis of ADHD
    - Monotherapy
      - Prozac is first-line
      - Celexa
      - Zoloft
    - Alternate monotherapy
      - Prozac
      - Celexa
      - Zoloft
      - Lexapro
      - Paxil, in adolescents
    - If partial response: augmentation
      - Lithium
      - Wellbutrin
      - Remeron
      - (Buspar)
    - If partial or no response: alternate monotherapy
      - Effexor
      - Wellbutrin
      - Remeron
      - Cymbalta
      - (Nefazodone)
    - If partial or no response:
      - Alternate monotherapy
      - Augmentation/combination treatment with Eff, Wellb, Remeron, Cymbalta, or Serzone
        - Lithium
        - Wellbutrin
        - Remeron
        - Cymbalta
        - Serzone
  - Youth with co-morbid ADHD
    - If depression more severe, use above algorithm
    - If depressive symptoms improve without improvement in ADHD symptoms, begin ADHD algorithm and add it to treatment for depression
    - If neither depression not ADHD symptoms improve, continue with depression algorithm
    - If ADHD more severe, use ADHD algorithm
    - If ADHD symptoms improve without improvement in depression, begin depression algorithm and add it to treatment of ADHD

        - If ADHD and/or depression worsens, discontinue ADHD algorithm and begin depression algorithm
- Youth, maintenance visits
    - At least weekly visits with patient or family/contact members for first 4 weeks
    - At least every-other visits with patient of family/contact members for the next 4 weeks
    - Then a meeting one month later (12 weeks after beginning medication)
    - Then, depending on clinical factors, every 12 weeks thereafter, though every 4-8 weeks is preferred
    - When discontinuing medications, dose should be tapered by 25% per week or as slow as practical with available dose forms
    - If antipsychotic medication is necessary, consider taper of medications 2-3 months AFTER REMISSION of psychotic symptoms
- SSRI + TCA
    - **Prozac + Desipramine (started at same time)**
        - 1 study, 39 patients (Nelson, 2004)
        - Combo > Mono
- Remeron
    - **Remeron + SSRI**
        - 1 study, 26 patients (Carpenter, 2002)
        - Combo > Mono
    - **Remeron + Paxil (started at same time)**
        - 1 study, 63 patients (Blier, 2009)
        - Combo > Mono
    - Remeron + Prozac vs. Remeron + Effexor vs. Remeron + Wellbutrin (started at same time)
        - 1 study, 444 patients (Blier, 2010)
        - Combo = Mono
    - Remeron + SSRI or SNRI (British Medical Journal, 2018) in treatment resistant depression over 12 weeks
        - Numerically but not statistically superior
- Wellbutrin + SSRIs
    - Wellbutrin + SSRI (started at same time)
        - 1 study, 445 patients (Rush, 2011)
        - Combo = Mono
    - **Wellbutrin + Celexa**
        - 1 study, 61 patients (Carpenter, 2002)
        - Combo > Mono
    - More details
        - See STAR-D
        - Treats sexual side effects of SSRI's
        - Treats sleepiness and fatigue side effects of SSRI's
        - See separate packet on Wellbutrin
- Stimulants
    - **Methylphenidate + Celexa**
        - 1 acceleration study, 16 patients (Lavretsky et al, 2006)
            - Combo > Mono
            - methylphenidate (average dose 15 mg/day) vs. placebo added to Celexa (average dose 30 mg/day)
            - 81% response rate vs. 46% with placebo
    - Stimulants
        - 3 augmentation studies in treatment resistant patients
            - Negative
        - 1 small augmentation study, 16 patients
            - Positive
        - Parker et al: Concerta helped but wasn't statistically significant; response rate 40% with Concerta vs. 23.3% placebo
    - Vyvanse
        - ?More helpful
        - Thase, ACSP 2017
        - Failed to show efficacy in controlled studies of treatment-resistant depression
        - May have secondary benefits (e.g., executive functioning/energy/cognitive functioning (Madhoo et al, 2013)
        - Trivedi et al, 2013
            - Non-responders to Celexa 20 mg/day (after 4 weeks): placebo vs. Vyvanse 20-50 mg/day
            - Numerically but not statistically significant improvement
- T3
    - **T3 + TCA's**
        - 6 acceleration studies, 125 patients
            - T3 accelerated response
        - 4 augmentation studies, 75 patients (one higher quality positive study, meta-analysis negative)
            - Mixed results

        - 4 augmentation studies in treatment resistant depression
            - Positive in two studies, negative in two studies
    - T3+ SSRIs
        - 4 acceleration studies, 44 patients
            - No acceleration, no enhancement
        - 1 augmentation study, 18 patients
            - Negative
        - 1 augmentation study in treatment resistant depression (SSRIs, Effexor, moclobemide)
            - Negative
    - T3 + Celexa
        - 1 augmentation study, 73 patients, open-label (STAR-D); 25% remission
    - More detail
        - At least 25 mostly positive studies
        - Helpful with energy and weight
        - Use with caution if history of coronary artery disease, high blood pressure, arrhythmia
        - If leads to suppression of TSH below normal, could lead to some degree of bone demineralization
        - T3 (e.g., Cytomel); might be more effective than T4 in unipolar depression
        - one study showed T3 in combo with Zoloft did better in the presence of a genetic mutation that makes conversion of T4→T3 harder (Cooper-Kazaz et al, 2009)
        - Start at 12.5-25 mcg/day
        - Increase by 12.5-25 mcg each week to 50 mcg/day max
        - An adequate trial is 1-4 weeks
        - Response rate 59% vs. 19% placebo
        - Peak in 2 hours
        - Half-life 1.5 days
        - Inconsistent efficacy in those with completely normal/optimal thyroid functioning
        - Especially helpful in women
        - Increases metabolic rates, cardiac output, oxygen consumption, body temperature, blood volume, growth and development at the cellular level
        - Evidence
            - Overall all evidence based on numbers of small studies, often with poor quality
            - Cooper-Kazaz et al, 2007: RCT, DB, placebo-controlled study of Zoloft 100 mg combined with Cytomel 40-50 mcg vs. Zoloft combined with placebo for adult depression:
                - Response rates: 70% for Zoloft plus Cytomel vs. 50% for Zoloft plus placebo
                - Remission rates: 58% for Zoloft plus Cytomel vs. 38% for Zoloft plus placebo
            - STAR-D: T3 augmentation equally effective as lithium augmentation
            - Int J Neuropsychopharmacol., 2007: safe and effective
            - Lerer, 2006: 25-50 mcg safe and effective in augmenting Zoloft treatment of depression
            - Abraham et al, 2006: further support for positive augmentation of SSRI treatment of depression.
            - Appelhoff et al, 2004: addition of T3 (25 mcg/day vs. 50 mcg/day vs. placebo) to Paxil 30 mg/day in 113 patients with depression; response rates 46% in all three treatment arms; no difference in effect by gender; more adverse effects with T3 than placebo
            - Altshuler et al, 2001: meta-analysis of six studies combining T3 with tricyclic antidepressants (TCAs): T3 accelerated the response of TCAs in 5 of 6 studies
            - Frye et al, 2000: effective in bipolar depression
            - RCT, DB, placebo-controlled study of Paxil plus Cytomel vs. Paxil plus placebo—no difference except more adverse effects with Cytomel
            - Agid and Lerer: T3 effective in 10 of 25 patients nonresponsive to SSRIs
            - Aronson et al: aggregated 8 studies (4 of which were RCT, DB), including 292 patients with treatment-resistant depression—Cytomel was added to ongoing antidepressant treatment; overall 23.2% absolute improvement in response rate (though the analysis showed the improvement was not statistically significant when only the RCT's were considered.
            - Altshuler et al: looked at 6 RCT, DB trials: Cytomel accelerated response from tricyclic antidepressants in 5 of the 6 studies
        - Biggest risks: arrhythmias, bone demineralization (depression is also a risk factor for osteoporosis)
        - Use cautiously if have angina, high blood pressure, cardiac disease, pregnancy, or if on TCA's, anticoagulants, and sympathomimetics
        - Decreases the effects of digitalis drugs, insulin, hypoglycemics, liothyronine, and estrogens
        - Side effects:
            - Insomnia
            - Tremor

- Headache
- Nausea
- Diarrhea
- Increased/decreased appetite
- Heat intolerance

- T4 (e.g., Synthroid)
  - May be better than T3 for rapid cycling bipolar disorder, but not at all clear
- T3+T4 together

- High dose thyroid (HDT) supplementation (T3>50 mcg or T4>200 mcg) for bipolar depression/rapid cycling bipolar disorder
  - Key points
    - Does not inherently create hyperthyroidism, despite some risk of doing so
    - No evidence that it causes osteoporosis, despite some concern that it might (see below)
    - Does not carry significant cardiovascular risks, despite some risk of atrial fibrillation
    - Data backing up its safety and efficacy
      - Bauer et al, 2015 (and demonstrated normalization of brain function in neuroimaging studies)
      - Kelly and Lieberman, 2009
      - Bauer et al 2005 (and demonstrated normalization of brain function in neuroimaging studies)
      - Bauer et al, 2003
      - Bauer et al, 2002
      - Bauer and Whybrow, 1990
    - Recommended by published treatment guidelines since 2000
      - Expert Consensus Guideline Series Medication Treatment of Bipolar Disorder
      - The American Psychiatric Association Bipolar Treatment Guidelines
      - Canadian Bipolar Treatment Guidelines (2013)
      - The Texas Algorithm Project Bipolar Guidelines (Yatham et al, 2013; Hirshfeld, 2010; Crismon et al, 2007; Sachs et al, 2000)
  - Bipolar I depression/rapid cycling
    - Goal is to bring T3 into high normal range and TSH into low normal range
    - If that is tolerable and symptom relief is not enough, one can bring T3 even higher and TSH even lower
    - Start with 12.5-25 mcg/day T3
    - Increase by 12.5-25 mcg/week until initial benefit is seen (which is usually between 50-125 mcg/day)
    - If no benefit is seen at 125 mcg/day and it remains tolerable, one can consider increasing it about that dose
    - Some meds, such as carbamazepine and oxcarbazepine, increase the metabolism of T3 or T4, so higher doses may be required
    - If need/want to discontinue T3
      - If 50 mcg/day or less, can stop it abruptly
      - If > 50 mcg/day, taper by 12.5-25 mcg every 1-2 weeks
  - Side effects of high dose thyroid (HDT) treatment
    - Anxiety
      - HDT can decrease anxiety, though there is some risk it could increase anxiety
      - Keep in mind, anxiety can increase with undertreated bipolar disorder as well
      - Minimizing caffeine helpful
      - Sometimes a dose decrease is helpful with this; sometimes a dose increase is
    - Increased resting heart rate
      - It's best to keep the heart rate below 100
      - Minimizing caffeine helpful
      - Can divide the dose to help with increased heart rate
      - Can use a low dose of a beta blocker (propranolol or atenolol)
      - If heart rate remains high related to HDT, dose can be decreased
      - Atrial fibrillation (AF)
        - This is urgent, but not always emergent
        - There is a 22.7% lifetime risk for AF in the general population (unrelated to HDT)
        - There isn't direct evidence that HDT causes AF
        - Stopping caffeine is often enough to stop AF
        - Adding a beta-blocker may stop AF
        - A dose reduction in HDT may stop AF
        - Known risk factors for AF include:
          - Hypertension
          - Valvular disease

- Cardiomyopathy
- Diabetes
- Thyroid disease (as separate from HDT)
- Previous hypothyroidism or hyperthyroidism
- Pneumonia
- Obesity
- Sleep apnea
- Alcohol use
- Tobacco use
- Caffeine use

- Feeling too warm or hot
  - One can divide the dose or decrease it
- Mild joint pain
  - Usually only at higher doses
  - Usually early on with dose increases
- Severe joint pain
  - 1 in 200
  - In hands and feet, usually
  - Can occur at low doses
  - Usually need to be stopped
- Thyrotoxicity/thyroid storms
  - There has never been a case of thyroid storm with HDT
  - Most cases of thyroid storm are associated with surgical manipulation of the thyroid gland, causing it to release it's (two week) stores of thyroid hormone all at once
  - Since HDT leads to a decrease in endogenous thyroid hormone, HDT may even decrease the risk of thyroid storm
  - Symptoms of thyrotoxicity or thyroid storm include
    - Palpitations/faster than normal heart rate
    - Increased appetite, but normal or reduced weight
    - Anxiety
    - Irritability
    - Tremor
    - Sweating
    - Changes in menstrual patterns
    - Feeling too hot
    - More frequent bowel movements
    - Fatigue
    - Muscle weakness
    - Difficulty sleeping
    - Skin thinning
    - Fine and brittle hair
  - Some of the symptoms overlap with bipolar disorder
- Tremor
  - In hands, but sometimes in thigh or calf muscles
  - Dividing or decreasing the dose can help
  - Low dose propranolol or atenolol can help
- Extreme physical exhaustion after hard physical workout
- Hair loss
  - < 2% of women
  - On the whole, not more prevalent than in the absence of HDT
  - Not the same as male pattern baldness
  - Can ease up over time
  - Selenium can help
- Thyroid poop out
  - ~50-60% will need escalations in thyroid dose over time
- Osteopenia/osteoporosis
  - Rates in the general population
    - 50% of Caucasian women in the US by age 60; the rate is fairly high in Asian women as well
    - Percentages are lower for other races
    - It's not uncommon in women under age 50
  - Risk factors

- Age
- Race
- Family history of osteoporosis
- Small body frame
- Immobility (including the hypersomnia and are reduced activity of those suffering from depression)
- Hyperparathyroidism
- History of hyperthyroidism past or present (and the link here may be more the autoimmune component than the higher than normal endogenous thyroid hormones
- Low calcium intake
- Low vitamin D levels
- Eating disorders past or present
- Previous gastrointestinal surgery
- History of extended use of steroids
- Early menopause
- Past or present alcohol abuse or dependence
- Past or present tobacco use

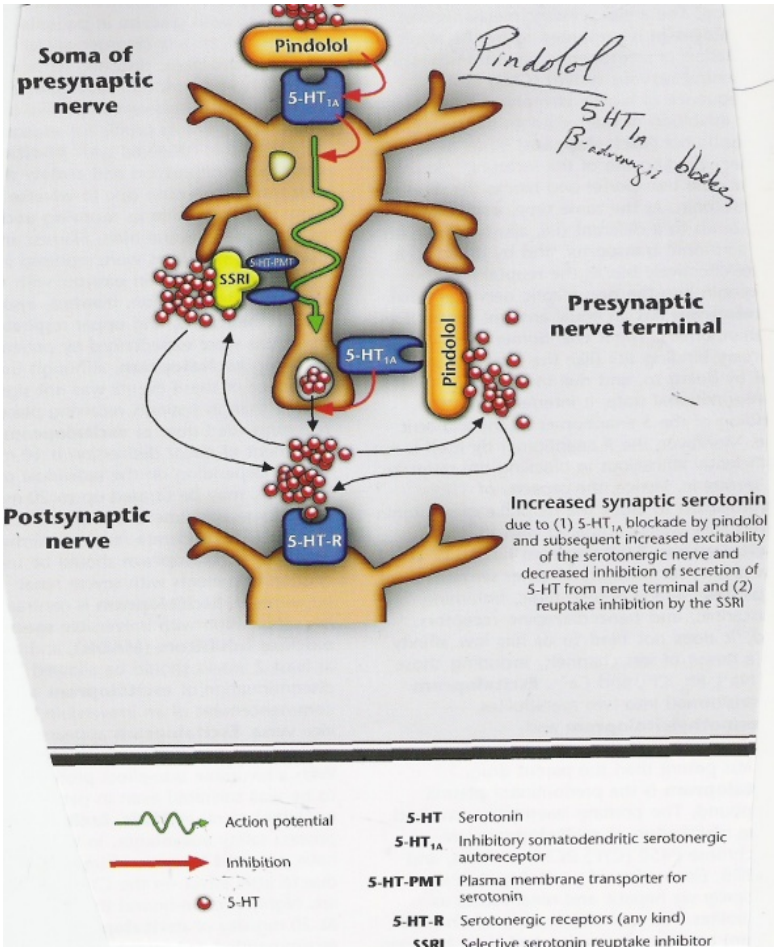
- The rate of both in women receiving HDT is within the rate in the general population
- There is no evidence that specifically suggests exogenous thyroid treatment itself increases the risk of osteopenia/osteoporosis, but there is theoretical risk

- Lithium
  - **Lithium + TCA's**
    - 5 acceleration studies, 231 patients
      - Trend toward Combo > Mono in meta-analysis
    - 9 studies of lithium augmentation; 236 patients
      - Combo > Mono; OR 2.46
  - **Lithium + SSRI's**
    - 3 RCT's (one positive, two negative), 74
      - Combo > Mono; OR 2.87, but wide interval: 1.06-7.77
    - 1 study in treatment resistant depression (STAR-D)
      - Remission rate 12.2%
  - More details
    - Used for augmentation for over 25+ years in over 60 trials; mostly with tricyclic antidepressants; mostly levels of 0.4-0.8; mostly positive, but mostly small studies, often uncontrolled
    - Allow 6 weeks for response
    - May also be used as monotherapy, especially in recurrent depression
    - Recently shown to be comparable in efficacy to adjunctive Seroquel or Abilify (Zhou et al, 2015)
    - Meta-analysis from Crossley and Bauer, 2007:
      - Five "acceleration" studies (231 subjects) where tricyclic antidepressants were started with lithium vs. without: lithium demonstrated a trend towards significant benefit
      - Ten "augmentation" studies (269 subjects) where lithium (vs. placebo) was added to various antidepressants: lithium statistically more effective than placebo
    - 45% (12.5-62.5%) response rate on lithium and 18% (0-25%) response rate on placebo
    - Overall, 3-fold increased chance of response
    - 28-36% had recurrence on lithium and 70-75% had recurrence on placebo
    - 8 studies demonstrated superiority of lithium to placebo but 5 did not demonstrate statistically significant differences
    - Meta-analysis, 2007: data from 7 studies on recurrent depression
      - 88.5% reduction in the risk of suicidal acts
      - Completed suicide rates were 0.33% with lithium treatment and 2.22% without
  - Response rates in recurrent depression
    - In melancholic type 57%
    - In non-melancholic type 25%
    - 39-69% reduction in the frequency of recurrences
    - 78% reduction in the duration of relapses
    - More compelling data for the combination of lithium and TCA's vs lithium and SSRI's
    - Most often takes 3 weeks, but can occur within 1 week
    - Doses of 900-1200 are common, following blood levels closely, aiming for blood levels of 0.4-0.8 mEg/L with max 1.0)
    - Lithium as monotherapy in unipolar depression
    - Efficacy comparable to tricyclic antidepressants

- Buspar
  - Buspar + Prozac
    - 1 acceleration study, 120 patients
    - Combo < Mono
  - Buspar + AD
    - 3 augmentation studies
      - Negative
  - General
    - Modulates serotonin
    - Effective in generalized anxiety disorder (when used on it's own) and augmentation for depression
    - 25-50 mg, 60 mg max
    - Peak in 1 hour
    - Half life 2-3 hours
    - May help depression if combined with melatonin (one study, 2009)
    - 1998 study in kids with autism spectrum disorder and anxiety; 8 weeks, 22 subjects, 6-16; helpful and tolerable
  - Side effects:
    - Dizziness—eases over time
    - Insomnia
    - Nervousness
    - Nausea, vomiting—eases over time
    - Thirst
    - Tiredness, reduced alertness—eases over time
- Atypical Antipsychotics
  - General
    - See separate handouts on individual medications
    - May be partially related to the ability to block 5HT2a,c receptors
    - Papakostas et al, 2007: meta-analysis of 10 clinical trials of SGA augmentation of antidepressant treatments involving 1500 patients with treatment-resistant major depression
      - Response rate: 57.2% with SGA augmentation vs 35.4% placebo
      - Remission rate: 47.4% with SGA augmentation vs. 22.3% placebo
      - Minimal data in this analysis on Abilify and Geodon
  - Seroquel/Seroquel XR
    - Seroquel + AD
      - 1 study, 114 patients
      - Combo = Mono
    - **Seroquel + SSRIs**
      - 5 studies, 1028 patients; (Khullar 2005, Mattingly 2006, McIntyre 2006, Earley 2007, El-Khalill 2008)
      - Combo > Mono; OR 1.61
    - Seroquel monotherapy
      - 6 studies; overall positive
      - 3 studies looking at efficacy in generalized anxiety disorder; overall positive
  - Zyprexa
    - **Zyprexa + SSRIs**
      - 5 studies, 1000 patients; (Shelton 2001, Shelton II 2005, Corya 2006, Thase 2007, Thase II 2007)
      - Combo > Mono; OR 1.39
  - Risperdal
    - **Risperdal + SSRIs**
      - 3 studies, 386 patients (Mahmoud 2007, Kelner 2009, Reeves 2008)
      - Combo > Mono; 1.83 OR
  - Abilify
    - **Abilify + SSRIs**
      - 3 studies, 1065 patients (Berman 2007, Marcus 2008, Berman 2008)
      - Combo > Mono; OR 2.07
  - Rexulti
    - 1-3 mg
    - doses above 1 mg have increased risk of akithisia
  - Latuda
    - Efficacy in bipolar depression
    - Some efficacy in MDD with mixed features
      - Loebel et al, 2014
  - Cariprazine
    - Durgam et al, AJP

- Provigil
  - Suggestive, but may relate to treatment of energy problems only
  - 43 patients with atypical depression were treated for 12-weeks in an open-label trial, followed by a 12 week randomized controlled trial; Provigil was efficacious and tolerated in the open portion of the study (the results from the second portion of the study are not yet available)
  - case report (Vorspan, 2005) of mania associated with therapeutic dose of modafinil.
- MAOI's
  - 30-60% response rates in TCA era
  - More effective in:
    - Atypical depression (Columbia)
    - Anergic depression (Pittsburgh)
    - Bipolar depression
  - Poor showing for tranylcypromine in STAR-D, likely due inability to tolerate minimally effective doses
- ECT
  - Most effective treatment for treatment-resistant depression (50-60% response rate)
  - 90% effective in uncomplicated depression
  - qaz
  - Bilateral vs. ultrahigh energy unilateral
  - Treatment of choice for delusional and melancholic cases of treatment-resistant depression
  - Li+TCA is as effective as maintenance ECT for preventing relapse
    - 0.7 cumulative probability of remaining well 24 weeks with Li+ TCA
    - 0.4 for NTP+placebo
    - <0.2 for placebo
  - Also helpful for bipolar depression
- TMS
  - Better tolerated and safer than ECT
  - Efficacy less effective than ECT
  - Vagal nerve stimulation
    - Studied in very treatment-resistant patients who had suffered for 18-25 years or more
    - Response rates:
      - Pilot study of 59 patients
        - 44% after 1 year
        - 42% after 2 years
      - Study of 212 patients
        - 27% after 1 year
    - Remission rates
      - Pilot study of 59 patients
        - 27% after 1 year
        - 22% after 2 years
      - Study of 212 patients
        - 16% after 1 year
- Pindolol
  - May accelerate benefit weeks 1-4 only (10 studies)
  - 2 augmentation studies showed no benefit
- Lamictal
  - 2 augmentation studies negative
- Folic acid
  - **Folic acid + AD**
    - 1 study, 127 patients
    - Combo > Mono in women but not men
- SAMe
  - **SAMe + SSRI** (s/p failed 6-weeks of SSRI treatment)
    - 1 trial, 73 patients
    - Combo > Mono
- L-methylfolate (LMF)
  - **LMF + SSRI** (s/p failed 8 weeks of SSRI treatment)
    - 2 trials (one at 7.5 mg/day with 148 patients and one at 15 mg/day with 75 patients)
    - Combo > Mono at 15 mg/day only
- **Omega-3 fatty acids**
  - 16 trials in depression, both monotherapy and adjunctive, unipolar and bipolar
  - 8 adjunctive trials in unipolar patients
  - Treatment resistance was suggested in trials but not established
  - Effective forms (by retrospective analysis
    - EPA/DHA > 60%
    - EPA doses 1000-2000 mg/day

- This group of options relatively equivalent
  - Switching from one antidepressant to another within the same class or to another class: 40-60% response rate (not in STAR-D)
  - Dual action antidepressants (e.g., Effexor XR, Cymbalta, Remeron)
    - Effexor XR with 42% remission rate vs. 20% with Paxil in treatment-resistant depression
  - MAOI or High dose MAOI: 50% response rate
  - TCA
  - SSRI and TCA combination
  - Buspar augmentation similar to Wellbutrin augmentation
  - Lithium augmentation similar to thyroid augmentation
  - MAOI and stimulants
    - Must be done with great care
    - Feighner et al: 13 patients, open-label, safe and effective
    - Fawcett et al: retrospective, naturalistic study, 32 patients
      - 78% with good response (breakdown: 53.8% very much improved; the rest, good improvement)
      - 3 cases of mania
  - Estrogen in postmenopausal women
  - SSRI and Wellbutrin
  - SSRI and Remeron
    - 60% response rate
    - British Medical Journal, 2018: Remeron vs. placebo added to SSRI or SNRI over 12 weeks: numerically but not statistically superior
- MAOI and TCA together
  - Done with extreme caution
  - AMI plus isocarboxazid started together at the same time
  - Less effective than ECT
- This group of options with less evidence of relative efficacy
  - Benzodiazepines (sometimes used at the start of SSRI treatment to prevent or minimize an increase in anxiety from the initiation of SSRI's)
  - Strattera—80 mg/day helpful in Carpenter, 2005 but not helpful in Michelson et al, 2007
  - Pindolol/beta blockers
    - Contraindicated if client has asthma
    - Mixed evidence; mostly negative
    - Propanolol
      - Used in the treatment of moderate anxiety and agitation in doses of 10-30 mg daily
      - Peak plasma level is reached within 1-1.5 hours
      - Half-life is 3-5 hours; metabolite half-life is 5-7 hours
      - Take without food
      - Metabolized via 1A2, 2D6, 2C19
      - Side effects
        - Slowed heart rate
        - Dizziness
        - Nausea/vomiting, fatigue
        - Constipation
        - Use in caution in cardiovascular disease, sinus node dysfunction, chronic bronchitis, or emphysema
        - Contraindicated in patients with Raynaud's syndrome, asthma, or 2nd and 3rd degree heart block
    - Pindolol
      - 5HT1a receptor blocking properties
      - start at 2.5 mg twice-a-day and then increase to 5 mg twice-a-day in the second week
      - common dose range 5-30 mg twice-a-day



- Second generation (atypical) antipsychotic (SGA) mood stabilizer medications:
- Anti-epileptic drugs (AED's)/mood stabilizers
  - Lamictal
    - Decreases glutamate release which may reverse the increased glutamatergic activity from the prefrontal cortex to the amygdala, hippocampus, and dorsal raphe nucleus which results from chronic stress; the increased glutamatergic activity is toxic to these brain areas and also lead to decreased production of serotonin which then reduces the efficacy of SSRI's.
    - Mostly negative data in unipolar depression
  - Depakote
  - Tegretol/Trileptal
  - Neurontin
  - Topamax
  - Lanicemine
    - NMDA-blocker
    - Demonstrated efficacy in a 3-wk, multicenter, US phase II study, 152 patients.
    - No psychotomimetic effects
- Dopamine agonists
  - Amantadine
    - Uses:
      - Antiviral (influenza) medication
      - Treatment for Parkinson's disease
      - Treatment of sexual side effects from SSRI's
      - Prevention/minimization of weight gain from psychiatric medications
        - Hoffman, et al, 2012: not as effective as metformin for preventing weight gain from Zyprexa
      - Osmolex ER tablets
        - For drug-induced extrapyramidal reactions in adults
        - For Parkinson's disease
        - Initial dose 129 mg tab once in the AM
        - Dose can be increased to max dose of 322 mg once daily in the AM
        - Extended release tabs: 129 mg, 193 mg, 258 mg
        - In moderate to severe kidney disease:
          - Moderate: 1 dose every 48 hrs, increase dose every 3 weeks
          - Severe: 1 dose every 96 hrs, increase dose every 4 weeks

        - End-stage: contraindicated
- Mechanism
    - Dopamine reuptake inhibition
    - Indirect agonist effects on dopamine neurons
    - Weak, non-competitive NMDA antagonist
    - Some anticholinergic properties
    - Neuroprotective properties
- Pharmacodynamics
    - Time to peak 3.3 hours (range 1-4 hours)
    - Half-life 16-17 hours (range 10-31 hours)
    - Cleared by kidneys
- Warnings and precautions
    - Falling asleep during activities of daily living
    - Somnolence
    - Suicidality
    - Depression
    - Hallucinations/psychotic behavior
    - Dizziness
    - Orthostatic hypotension
    - Withdrawal-emergent hyperpyrexia and confusion (if tapered abruptly)
    - Impulse control/compulsive behaviors
- Side effects from pooled studies (in Parkinson's disease and rx of extrapyramidal side effects) of immediate release amantadine
    - 5-10% frequency
        - nausea
        - dizziness
        - insomnia
    - 1-5% frequency (note some of these side effects are much more likely in patients with Parkinson's disease)
        - depression OR anxiety OR irritability
        - hallucinations OR confusion
        - decreased appetite
        - dry mouth
        - constipation
        - balance problems
        - headache
        - somnolence
        - diarrhea
    - 0.1-1%
        - Congestive heart failure
        - Psychosis
        - Urinary retention
        - Dyspnea
        - Skin rash
        - Vomiting
        - Weakness
        - Slurred speech
        - Euphoria
        - Thinking abnormality
        - Amnesia
        - Hyperkinesia
        - Hypertension
        - Decreased libido
        - Visual disturbance
        - Corneal opacity or punctate subepithelial opacity
        - Corneal edema
        - Decreased visual acuity
        - Sensitivity to light
        - Optic nerve palsy
    - Less than 0.1%
        - Convulsion
        - Leukopenia
        - Neutropenia
        - Eczematoid dermatitis
        - Oculogyric episodes

- Suicidal attempt
- Suicide
- Suicidal ideation

- Mirapex (pramepexole) up to 1 mg/day
  - Helps with restless legs
  - Helps with bipolar depression
  - May augment SSRI's in unipolar depression
  - Side effects (in patients with Parkinson's disease) include
    - Movement disorder 21.1% vs. 11.4% placebo (more prevalent in Parkinson's disease)
    - **Dizziness 17.4% vs. 11.4% placebo**
    - **Hallucinations 16.5% vs. 0 in placebo** (likely more prevalent in Parkinson's disease)
    - **Insomnia 13.8% vs. 0 in placebo**
    - **Somnolence 12.8% vs. 2.9% placebo**
    - **Constipation 11.9% vs. 2.9% placebo**
    - **Nausea 11.9% vs. 5.7% placebo**
    - Headache 11.9% vs. 14.3% placebo
    - Lassitude 9.2% vs. 17.1% placebo
    - Confusion 7.3% vs. 0 in placebo (likely more prevalent in Parkinson's disease
    - Swelling 6.4% vs. 2.9% placebo
- Ropirinole
  - Helps with restless legs
  - Augmentation for resistant MDD
    - Stanford-Duke study
      - Doses up to 12 mg/day
      - Average dose 8 mg/day
      - Nausea, somnolence, insomnia most common side effects
- Bromocriptine 7.5-52.5 mg/day
- Pergolide 1-2 mg/day
- Carbergoline (Dostinex)
- Dihydresidene (DAR-100a)
  - Highly selective D1 agonist
  - Crosses blood-brain barrier
  - Avoids side effects associated with non-selective (e.g., D1 and D2) dopamine agonists which act primarily through D2 receptor (like psychosis, nausea, impulsivity)
  - Improves cognitive functioning in schizotypal personality disorder
- Rotigotine
  - Neupro patch
  - FDA-approved for Parkinson's disease
  - 15 RCT, DB, placebo-controlled trials of over 1154 patients with Parkinson's
  - Dosing for patch in Parkinson's: 2 mg/24 hours; increase to 4 mg/24 hours after 1 week; max 6 mg/24 hours
  - Adverse effects:
    - Dizziness
    - Nausea/vomiting
    - Drowsiness/sleep attacks
    - Insomnia
    - Postural hypotension
    - Hallucinations

- L-methylfolate
  - Safe and improves efficacy of antidepressants in depression, especially if one carries copies of the genetic mutations (C677T or A1298C) of the enzyme that metabolizes folic acid (MTHFR) to the form (l-methylfolate) that is able to cross the blood-brain barrier
  - 7.5-15 mg/day; more efficacy with 15 mg/day
  - Increases production of dopamine, norepinephrine, and serotonin
  - The MTHFR gene test looks for mutations of the gene that codes for the enzyme methylenetetrahydrofolate reductase (MTHFR) or dihydrofolate reductase; MTHFR breaks down folic acid into the form tetrahydrofolic acid, also known as l-methylfolate; l-methylfolate is able to cross from the blood into the brain. There is a normal MTHFR gene and and two abnormal variants. Each individual inherits one copy of the gene from their mother, one from their father. So one can have any one of the following combinations of gene copies: a) two normal copies, b) 1 normal copy plus one (or the other) of the two abnormal variants as the other copy, c) two of one (or the other) abnormal variant copies, d) one abnormal variant copy of one type and the other abnormal variant of the other type, and e) both abnormal mutations contained on one copy and a normal copy. In any case, if one tests positive for the abnormal genes, there is a product I may recommend called Deplin (l-methylfolate). Deplin is a "medicinal supplement" FDA-approved for augmentation of antidepressants. It's simply the end product of the folic acid metabolism that is reduced in folks with the above mutations. By taking l-methylfolate directly, you circumvent the need for the enzyme. Since l-methylfolate is, among other things, critical to the synthesis of the three important brain neurotransmitters (serotonin, norepinephrine, and dopamine) involved in anxiety,

mood, and attention, the levels of those neurotransmitters should increase with proper amounts of l-methylfolate. This may allow for improved treatment of psychiatric conditions and/or a reduction in the doses of standard psychopharmacologic treatments.

- Long-term efficacy, safety, and tolerability of L-methylfolate calcium 15 mg as adjunctive therapy with selective serotonin reuptake inhibitors: a 12-month, open-label study following a placebo-controlled acute study
  - John M Zajecka, Maurizio Fava, Richard C Shelton, Lori W Barrentine, Page Young, George I Papakostas
  - *Journal of Clinical Psychiatry 2016, 77 (5): 654-60*
  - **OBJECTIVE:** To evaluate remission and recovery, safety, and tolerability for up to 12 months of open-label adjunctive L-methylfolate calcium 15 mg.
  - **METHOD:** Subjects in this analysis were adult outpatients (18-65 years) enrolled from 2 acute, double-blind, placebo-controlled trials comparing adjunctive L-methylfolate and placebo for DSM-IV major depressive disorder (MDD) with an inadequate response to monotherapy selective serotonin reuptake inhibitor (SSRI). Subjects who completed the acute trial were offered to enroll in a 12-month, open-label treatment phase with L-methylfolate and continued SSRI treatment, with scheduled visits for efficacy, safety, and tolerability every 12 weeks. Subjects were enrolled between September 2006 and February 2010. Efficacy outcomes included predefined criteria for response, remission, recovery, relapse, and recurrence. Subjects treated with adjunctive L-methylfolate 15 mg were included in the efficacy analysis.
  - **RESULTS:** Of 68 subjects who met criteria for the 12-month open-label phase, 38% (n = 26) achieved full recovery, and none experienced a recurrence of MDD. For subjects entering the open-label phase in remission (n = 11), 91% (n = 10) achieved full recovery with L-methylfolate 15 mg, and none experienced a relapse or recurrence. Among 57 subjects who entered the open-label phase as nonremitted, 61% (n = 35) achieved remission. Of subjects who entered the open-label phase with a response without remission (n = 4), 50% (n = 2) had full recovery, and of subjects entering the open-label phase with no response (n = 53), 26% (n = 14) met recovery criteria.
  - **CONCLUSIONS:** Adjunctive L-methylfolate 15 mg/d may be an early option in patients who fail to adequately respond to antidepressant monotherapy, with preliminary evidence demonstrating sustained remission and sustained recovery.
- Correlation of clinical response with homocysteine reduction during therapy with reduced B vitamins in patients with MDD who are positive for MTHFR C677T or A1298C polymorphism: a randomized, double-blind, placebo-controlled study
  - Arnold W Mech, Andrew Farah
  - *Journal of Clinical Psychiatry 2016, 77 (5): 668-71*
  - **OBJECTIVE:** This study was designed to evaluate the efficacy and safety of reduced B vitamins as monotherapy in adults with major depressive disorder (MDD) who were also positive for at least 1 methylenetetrahydrofolate reductase (MTHFR) polymorphism associated with depression and further test the hypothesis that reduced (metabolized) B vitamins will lower homocysteine in a majority of clinically responding patients.
  - **METHODS:** 330 adult patients with MDD (DSM-5) and positive for either MTHFR C677T or A1298C polymorphism were enrolled in a trial conducted between August 1, 2014, and April 3, 2015. 160 patients received placebo, while 170 received a capsule containing a combination of reduced B vitamins. Plasma homocysteine levels were measured at baseline and week 8. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to evaluate efficacy for MDD.
  - **RESULTS:** 159 of 170 vitamin-treated patients and 123 of 160 placebo-treated patients were completers. Of the active treatment group, 131 (82.4%) showed a reduction in homocysteine (for a mean in this subgroup of 25%, $P < .001$), while 28 (17.6%) showed no significant change. Placebo patients demonstrated a small elevation in homocysteine. Active-treatment patients demonstrated, on average, a 12-point reduction on the MADRS by week 8, and 42% achieved full remission ($P < .001$). No side effect was significantly different between groups. No patients experienced mania.
  - **CONCLUSIONS:** A combination of reduced B vitamins and micronutrients, when used in the treatment of MDD in patients with MTHFR polymorphism, resulted in a separation from placebo by week 2, and 42% of the treatment arm achieved remission by week 8. Further, clinical improvement correlated with a significant reduction in homocysteine levels in a majority of responders. These results support the homocysteine theory of depression and the safety and therapeutic benefit of reduced B vitamins as monotherapy for MDD, particularly in patients with MTHFR polymorphism.

- Voltage dependent NMDA antagonists/glutamatergic meds
  - Memantine
    - General
      - Moderate affinity
      - Rapid antidepressant effects without causing psychosis in animal models (such as can occur with the similar medication ketamine)
      - FDA-approved for the treatment of Alzheimer disease
      - Open study, ADHD, adults, 10 mg bid, over 12 weeks: +
      - Open study, major depression, Clinical Neuropharmacology, 2007
        - Dose at 5 mg/day with weekly increases to 20 mg/day and max of 40 mg/day
        - Benefits noted at week 1; continued improved til plateau at 8 weeks
        - 75% response rate (1 left the study but had improved)
        - Side effects

        - Sleepiness
        - Dizziness
        - Insomnia
        - Headache
        - Anxiety
        - Amnesia
        - Flu-like symptoms
        - No clinically significant changes in labs, vital signs, or ECG's
    - Open study, treatment of cognitive, behavioral, and memory dysfunction in pervasive developmental disorders, Owley et al, 2006; youth aged 3-12, 8 wks, 0.4 mg/kg:
        - Minor benefits
    - Safety and Efficacy of Memantine in Children with Autism: Randomized, Placebo-Controlled Study and Open-Label Extension
        - Michael G Aman, Robert L Findling, Antonio Y Hardan, Robert L Hendren, Raun D Melmed, Ola Kehinde-Nelson, Hai-An Hsu, Joel M Trugman, Robert H Palmer, Stephen M Graham, Allyson T Gage, James L Perhach, Ephraim Katz
        - *Journal of Child and Adolescent Psychopharmacology 2016 March 15*
        - **OBJECTIVE:** Abnormal glutamatergic neurotransmission is implicated in the pathophysiology of autism spectrum disorder (ASD). In this study, the safety, tolerability, and efficacy of the glutamatergic N-methyl-d-aspartate (NMDA) receptor antagonist memantine (once-daily extended-release [ER]) were investigated in children with autism in a randomized, placebo-controlled, 12 week trial and a 48 week open-label extension.
        - **METHODS:** A total of 121 children 6-12 years of age with Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR)-defined autistic disorder were randomized (1:1) to placebo or memantine ER for 12 weeks; 104 children entered the subsequent extension trial. Maximum memantine doses were determined by body weight and ranged from 3 to 15 mg/day.
        - **RESULTS:** There was one serious adverse event (SAE) (affective disorder, with memantine) in the 12 week study and one SAE (lobar pneumonia) in the 48 week extension; both were deemed unrelated to treatment. Other AEs were considered mild or moderate and most were deemed not related to treatment. No clinically significant changes occurred in clinical laboratory values, vital signs, or electrocardiogram (ECG). There was no significant between-group difference on the primary efficacy outcome of caregiver/parent ratings on the Social Responsiveness Scale (SRS), although an improvement over baseline at Week 12 was observed in both groups. A trend for improvement at the end of the 48 week extension was observed. No improvements in the active group were observed on any of the secondary end-points, with one communication measure showing significant worsening with memantine compared with placebo ($p = 0.02$) after 12 weeks.
        - **CONCLUSIONS:** This trial did not demonstrate clinical efficacy of memantine ER in autism; however, the tolerability and safety data were reassuring. Our results could inform future trial design in this population and may facilitate the investigation of memantine ER for other clinical applications.
- Lanicemine
    - Mixed results
- Taxoprodol
    - 60% response rate vs. 20% with placebo (Preskorn et al, 2008)
- MK-0657
- Rapastinil
    - Positive short term studies
- D-cycloserine (Seromycin)
    - Mixed results, small studies
- Adamantine
    - Rapid antidepressant effects without causing psychosis in animal models (such as can occur with the similar medication ketamine)
- Neramexane
    - Rapid antidepressant effects without causing psychosis in animal models (such as can occur with the similar medication ketamine)
- Minocycline
    - Properties
        - Neuroprotective
        - Blocks activation of microglia, preventing release of cytokines
        - Helps maintain normal glutamatergic neurotransmission
    - Lancet Psychiatry, 2018; adjunctive minocycline in the treatment of schizophrenia
        - No differences vs. placebo

- Minocycline as Adjunctive Treatment to Risperidone in Children with Autistic Disorder: A Randomized, Double-Blind Placebo-Controlled Trial Ali Ghaleiha, Rosa Alikhani, Mohammad-Reza Kazemi, Mohammad-Reza Mohammadi, Payam Mohammadinejad, Atefeh Zeinoddini, Mehdi Hamedi, Mona Shahriari, Zahra Keshavarzi, Shahin Akhondzadeh; *Journal of Child and Adolescent Psychopharmacology 2016 April 29*
    - **OBJECTIVE:** This is an investigation of minocycline efficacy and safety as an adjuvant to risperidone in management of children with autism.
    - **METHODS:** Forty-six children with diagnosis of autistic disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) criteria (American Psychiatric Association 2000) and a score of ≥12 on the Aberrant Behavior Checklist-Community (ABC-C) irritability subscale, who were already drug-free for at least 6 months participated in a randomized controlled trial and underwent 10 weeks of treatment with either minocycline (50 mg twice per day) or placebo in addition to risperidone titrated up to 2 mg/day (based on bodyweight). Patients were evaluated using ABC-C at baseline and at weeks 5 and 10.
    - **RESULTS:** General linear model repeated measures showed significant effect for time × treatment interaction on the irritability [$F(2, 88) = 3.94$, $p = 0.02$] and hyperactivity/noncompliance [$F(1.50, 66.05) = 7.92$, $p = 0.002$], but not for lethargy/social withdrawal [$F(1.61, 71.02) = 0.98$, $p = 0.36$], stereotypic behavior [$F(1.34, 58.80) = 1.55$, $p = 0.22$], and inappropriate speech subscale scores [$F(1.52, 66.88) = 1.15$, $p = 0.31$]. By week 10, 21 (91.3%) patients in the minocycline group and 15 (65.5%) patients in the placebo group achieved at least partial response ($p = 0.03$). Frequencies of adverse events were not significantly different between groups.
    - **CONCLUSIONS:** Minocycline seems to be a safe and effective adjuvant in management of patients with autistic disorder. Future studies with larger sample sizes, longer follow-ups, and inflammatory cytokine measurements are warranted to confirm these findings and provide insight into minocycline mechanism of action in autistic disorder.
- Liu et al, 2014; adjunctive minocycline (alongside Risperdal) for negative symptoms in schizophrenia
    - 92 patients, aged 18-40 (average age 27), within 5 years of diagnosis (average duration 2 years), on stable doses of Risperdal
    - 200 mg/day for 16 weeks
    - Results
        - Significantly greater reductions in negative symptoms than with placebo at weeks 8, 12, and 16
        - At week 16, patients with minocycline had an average 27-point decreases in symptoms scores vs. 13 with placebo
        - At week 16, 44% of patients with minocycline responded vs. 10% with placebo
        - Slightly larger improvement in attention with minocyline
- Riluzole
    - Indicated for patients with amyotrophic lateral sclerosis, may be effective for treatment resistant OCD, depression, and generalized anxiety disorder
    - Open label study (1/04) suggesting efficacy in clients with treatment-resistant depression.
    - Mechanism
        - Inhibits glutamate release
        - Inactivates sodium channels
        - Interferes with intracellular events that follow neutrotransmitter binding at excitatory amino acid receptors
        - Neuroprotective
        - Some anticonvulsant effects
    - Pharmacodynamics
        - 50 mg twice-a-day
        - High fat meal decreases absorption (decreases availability by ~20% and peak levels by ~45%)
        - Half-life 12 hours
        - 1A2 P450 metabolism
    - Side effects and risks
        - Lassitude (physically run down) in 15-20% vs. 12% placebo
        - **Abdominal pain** in 5-8% vs. 4% in placebo
        - **Nausea OR vomiting** in 16.2-24.5% vs. 12.2% placebo
        - **Dizziness** 5-13% vs. 2.5% placebo
        - **Vertigo** 1.9-4.5% vs. 0.9% placebo
        - **Tingling** around mouth 1.3-3.3% vs. 0% placebo
        - Decreased lung function in 10-16% vs. 9.4% placebo
        - Increased cough 2.1-3.7% vs. 1.6%
        - **Liver enzyme elevation**
        - Low white blood cell counts in 3 of 4,000 patients studied
- Acamprosate
    - Uses
        - Alcoholism

- Mechanism
  - Inhibits glutamate overactivity via reduction of release of glutamate from presynaptic nerve terminals and reducing the overactivation of postsynaptic NMDA receptors
  - Weak inhibitor of presynaptic GABAb receptors in the Nucleus Accumbens
- Dose
  - 333 mg tab; 1-2 tabs three times-a-day (less if kidney problems)
- Safety and tolerability
  - Side effects
    - Lassitude
    - Nausea
    - Itchiness
    - Flatulence
    - Diarrhea—decreases over time
    - Suicidal behaviors—1.4-2.4% with use up to 12 months vs. 0.5-0.8% placebo; no difference in completed suicides
  - Does not affect liver enzymes
  - Does not affect microsomal enzymes
  - Eliminated primarily by kidneys
  - Can be co-administered with benzodiazepines, hypnotics, non-opioid analgesics, anti-anxiety medications, Antabuse, and can be taken when alcohol is used

- Ceftriaxone
- MK-801
- Ketamine
- Traxoprodil (CP 101,606); NR2B selective NMDA antagonist
- AZD6765; NR2B selective NMDA antagonist
- EVT101/103; NR2B selective NMDA antagonist
- Radiprodil (RGH 896); NR2B selective NMDA antagonist
- MK 0657; NR2B selective NMDA antagonist
- Zinc
- AP-7
- CGP37849
- CGP39551
- CPP, AP-5
- ACPC
- 5,7-chloro-kynurenic acid
- D-cycloserine
- Taleglumetad (LY 544344)
- Metabotropic glutamate type II receptor antagonist

- ACE inhibitors/Captopril
- Buprenorphine
- Revia (naltrexone)
  - Used in opioid addicton
  - Used in alcohol abuse
    - Less effective in older women, especially if also suffering from cocaine addiction. than in men
  - Used in self-injurious behaviors
- Mifepristone 600 mg/d (for 8 days) for psychotic depression—small study
- Scopolamine
  - Anticholinergic
  - Khajavi et al, 2012
    - Celexa plus scop vs. Celexa plus placebo
    - Response rate 65% vs. 30% with placebo
    - Remission rate 65% vs. 20% with placebo
    - Side effects:
      - dry mouth 50% vs. 20% placebo
      - blurred vision 40% vs. 15% placebo
      - dizziness 40% vs. 15% placebo
      - drowsiness 35% vs. 25% placebo
- Statins
  - May increase BDNF levels
    - Induce tissue-type plasminogen activator (TPA)
    - Inhibit plasminogen activator inhibitor-1, the major inhibitor of TPA (thus→increased TPA)
    - TPA-plasmin pathway critical for the cleavage of pro-BDNF (a BDNF precursor) to BDNF
  - Anti-inflammatory
  - Antioxidative
  - Lovastatin

        - Ghanizadeh et al, 2013
            - Anti-inflammatory
            - Superior to placebo when added to Prozac
    - Stafford, Berk, 2011
        - Prospective investigation of whether the use of statins was associated with a reduced risk of developing depression in individuals who had a cardiac event or intervention
        - Reduced risk by 69% at 3 months and 79% by 9 months
- Cefdinir for recent-onset pediatric neuropsychiatric disorders: a pilot randomized trial
    - Tanya K Murphy, E Carla Parker-Athill, Adam B Lewin, Eric A Storch, P Jane Mutch
    - *Journal of Child and Adolescent Psychopharmacology 2015, 25 (1): 57-64*
    - **OBJECTIVE:** Previous studies suggest that the unexplained sudden and severe onset of obsessive-compulsive disorder (OCD) and/or tics may be infection or immune precipitated. Beta lactam antibiotics may be neuroprotective beyond their antimicrobial efficacy. We examine the preliminary safety and efficacy of cefdinir in reducing obsessive-compulsive and/or tic severity in children with new-onset symptoms.
    - **METHOD:** Twenty subjects were randomized to receive placebo or cefdinir for 30 days for the treatment of recent-onset OCD and/or tics. The placebo group received a comparable inactive treatment matched for taste, color, and consistency. The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) and Yale Global Tic Severity Scale (YGTSS) were the primary outcome measures utilized.
    - **RESULTS:** Subjects receiving cefdinir saw notable improvements in tic symptoms, with 44.4% showing at least a 25% reduction in YGTSS (mean decrease=9.5) scores compared with 9.1% of the placebo group (mean decrease=0.13). Despite improvements, significant group differences were not observed for YGTSS (F [1, 13]=4.03, p=0.066) although there were moderate differences between group treatment effects (d=0.72). For OCD symptoms, subjects receiving cefdinir saw improvements in OCD symptoms, with 33.3% showing at least a 25% reduction in CY-BOCS scores (mean decrease=7.8) compared with 27.3% of the placebo group (mean decrease=4.7), but there were also no significant differences for CY-BOCS (F [1, 13]=0.385, p=0.546; d=0.24).
    - **CONCLUSIONS:** Subjects assigned to cefdinir exhibited notable, albeit nonstatistically significant, improvements in tic symptoms, compared with the placebo group. There were also some improvements in OCD symptoms, although these were not significant. Overall, cefdinir was well tolerated. Given these preliminary results, a fully powered study is warranted to explore the efficacy of cefdinir as a therapeutic tool for new-onset pediatric neuropsychiatric symptoms, particularly those that appear to be precipitated by infection.
- Medications for borderline personality disorder
    - SSRI's
    - Lithium
    - AED mood stabilizers
        - Depakote
        - Lamictal
        - Topamax
        - Tegretol/Equetro
        - Neurontin
    - Second generation antipsychotic mood stabilizers
        - Abilify (Nickel et al, 2006)
        - Saphris (Martin-Blanco et al, 2013)
        - Zyprexa (mixed results; Schulz et al, 2008; Zanarini et al, 2012; Shafti et al, 2010)
    - Omega-3 fatty acids
- Varenicline in Autism: Theory and Case Report of Clinical and Biochemical Changes
    - Mojdeh Mostafavi, Paul Hardy, L Eugene Arnold
    - *Journal of Child and Adolescent Psychopharmacology 2016 April 28*
    - **OBJECTIVE:** To explore the potential benefits of varenicline (CHANTIX(®)), a highly specific partial agonist of neuronal α4β2 nicotinic acetylcholine receptors (nAChR), for autistic symptoms, and present resulting biochemical changes in light of dopamine-related genotype.
    - **METHODS:** The clinical and biochemical changes exhibited by a 19-year-old severely autistic man following the use of low-dose varenicline in an ABA experiment of nature, and his genotype, were extracted from chart review. Clinical outcome was measured by the Ohio Autism Clinical Impression Scale and 12 relevant urine and saliva metabolites were measured by Neuroscience Laboratory.
    - **RESULTS:** With varenicline, this patient improved clinically and autonomic biochemical indicators in saliva and urine normalized, including dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), epinephrine, norepinephrine, taurine, and histamine levels. In addition, with varenicline, the dopamine D1 receptor (DRD1) antibody titer as well as the percent of baseline calmodulin-dependent protein kinase II (CaM KII) activity dropped significantly. When varenicline stopped, he deteriorated; when it was resumed, he again improved. Doses of 0.5, 1, and 2 mg daily were tried before settling on a dose of 1.5 mg daily. He has remained on varenicline for over a year with no noticeable side effects.
    - **CONCLUSION:** This report is, to the best of our knowledge, only the second to demonstrate positive effects of varenicline in autism, the first to show it in a severe case, and the first to show normalization of biochemical parameters related to genotype. As with the previous report, these encouraging results warrant further controlled research before clinical recommendations can be made.
- Sleep deprivation (no sleep or sleep deprivation to 4 hours or less in the FIRST HALF of night only); can repeat every 4-7 day

- Vitamins/minerals/nutrients—see separate handout
    - Folic acid (0.5-1 mg/day) or Leucovorin (follinic acid) 15-30 mg/day
    - Omega-3 fatty acids 1-2 grams/day
    - Chromium picolinate 400-600 micrograms/day
    - Zinc 50-200 mg/day for hair loss with 2-3 mg Copper per each 50 mg of Zinc
    - Selenium 200 mcg/day for hair loss.
- Kava kava extract (piper methysticum/WS(R)1490)
    - Used for years in folk medicine
    - Used in Polynesia as a ceremonial beverage to induce relaxation
    - Kava plant is indigenous to the islands of the South Pacific
    - Belongs to the pepper family
    - Kava lactones act as GABA agonists
    - May mildly block norepinephrine reuptake
    - 6 placebo-controlled, randomized trials with the extract demonstrated some efficacy
    - When taken orally, in extracts that contain 70% kavapyrones, relieves anxiety
    - Oral dose: 60-120 mg kavapyrones extracted from the Kava root
    - Side effects/ risks
        - gastrointestinal side effects
        - Headaches
        - Sedation
        - Unsteadiness
        - Motor incoordination
        - May worsen depression
        - Pellagra-like illess
            - Dry flaky skin
            - Reddened eyes
            - Discoloration of the hair
        - Liver toxicity
            - 30 known cases of liver toxicity in Switzerland and Germany; some persons required liver transplants
            - 60 known cases in the United States; at least 4 persons needed liver transplants
            - Banned in France in 2002
            - Withdrawn from the market in Switzerland and Germany due to cases of liver toxicity and lack of evidence of efficacy
    - **WARNING: AVOID USE OF KAVA; DO NOT USE WITHOUT NOTIFYING ALL HEALTHCARE PROFESSIONALS**

Relapse Prevention

- Once depression is in remission, data backs up continuing the medication for 12 months after the first episode of depression
  - Treating for 6 months or more leads to less relapse than treating for less than 6 months
  - Treating for 12 months or more leads to less relapse than treating for less than 12 months
  - After a second episode, it is recommended that one treat for 24 months
  - After a third episode, it is recommended that treat chronically
  - While proper treatment as above generally reduces the rates of relapse, more recent data suggests that on going treatment has less prophylactic benefit than we have thought:
    - Keller, et al, 2007
      - After Effexor XR or Prozac treated an episode into remission, ongoing use of either medication over 12 months was not more effective (statistically) than placebo pill at preventing relapse

"TREATMENT-RESISTANT" DEPRESSION (or treatment-resistant anxiety)

Findings of the 2007 STAR-D: study from 25 different sites on the treatment of early stage treatment-resistant depression:

1. STEP I; 4,041 patients of which 3671 were evaluated on **Celexa**, average dose 42 mg/day, max dose 60 mg/day, max length of trial 12 weeks, although data was followed through 13-14 weeks; 766 patients left the trial before the trial finished so that 1,475 patients finished the trial:
   a. **Response rate: 48.6%; average of 5.5 weeks to respond**
   b. **Remission rate: 36.8%**; **average of 6.3 weeks to remit**; roughly 60% of the responders (above) remitted
   c. **16.3% had intolerable side effects**
   d. 1,127 patients exited the study
   e. 1,475 patients moved to follow-up
2. If fail to remit in STEP I, then patients move to STEP II
   a. **SWITCH antidepressant**:
      i. **Medication results:**
         1. Response rates
            a. **Overall** response rates for switch **overall**; the percentage of patients meeting response criteria **at the particular week noted**:
               i. ~18% by 2 weeks
               ii. ~24% only by 4 weeks
               iii. ~23% only by 6 weeks
               iv. ~11% only by 8 weeks
               v. ~11% only by 10 weeks
               vi. ~5% only by 12 weeks
               vii. ~7% only by 13 or more weeks
            b. **Remission** rates; 33% overall by 13 or more weeks of medication treatment; differences not statistically significant
            c. **Agents**
               i. **Zoloft** (238 patients; max dose 200 mg/day): response rate is 26.7%; average time to response is 6.3 weeks; intolerable side effects 21%
               ii. **Wellbutrin** SR (239 patients; max dose 400 mg/day): response rate is 26.1%; average time to response is 5.5 weeks; intolerable side effects 27.2%
               iii. **Effexor** XR (250 patients; max dose 375 mg/day): response rate is 28.2%; average time to response is 6.5 weeks; intolerable side effects 21.2%
               iv. **Cognitive Therapy** (62 patients); response rate is 34.1%; the average time to response is 7.8 weeks
      ii. **Cognitive therapy (only);** 62 patients
         1. **Response** rates for cognitive therapy; the percentage of patients meeting response criteria **by the particular week noted**:
            a. 0% responded by 2 weeks
            b. ~2% responded (total) by 4 weeks
            c. ~17% responded (total) by 6 weeks
            d. ~27% responded (total) by 8 weeks
            e. ~36% responded (total) by 12 weeks
            f. ~60% responded (total) by 14 weeks
         2. **Remission rates:**26% overall with cognitive therapy; the percentage of patients meeting response criteria **at the particular week noted**:
            a. 12.5% (total) remitted at 2 weeks
            b. 12.5% (total) remitted at 4 weeks
            c. 25% (total) remitted at 6 weeks
            d. ~35% (total) remitted at 8 weeks
            e. ~38% (total) remitted at 12 weeks

f. ~62% (total) remitted at 14 weeks

b. **AUGMENTATION of Celexa with Wellbutrin** SR **OR Buspar OR cognitive therapy**
   i. **Remission rates**
      1. **Celexa PLUS Wellbutrin** SR; 279 patients; 29.7-39%, depending on assessment tool; greater symptom reduction than Buspar, fewer side effects; fewer drop-outs due to side effects
      2. **Celexa PLUS Buspar;** 286 patients; 30.1-32.9%, depending on assessment tool
         a. NB: Buspar has failed to beat placebo in at least one RCT DB study in the augmentation of antidepressants in treatment resistant depression
      3. **Celexa PLUS cognitive therapy;** 85 patients; ~26%
         a. Wellbutrin SR (15 patients)
         b. Effexor XR (16 patients)

c. Medication response rates increase faster than cognitive therapy's beginning at ~2 weeks
d. Medication remission rates increase faster than cognitive therapy's beginning at ~4 weeks
e. Medication response rates increase faster than cognitive therapy's beginning at ~2 weeks and more so at 9 weeks
f. Medication remission rates increase faster than cognitive therapy's beginning at ~9 weeks
g. Rates decreased by presence of general medical conditions and/or anxiety
h. Overall response rate in Level II 28.5%; average time to response 6.5 weeks
i. Overall remission rate in Level II 30.6%; average time to remit 5.4 weeks

3. Cumulative rates of Level I AND Level II
   a. Overall response rate
   b. Overall remission rate ~50%
   c. Intolerable side effects in 19.5%

When the above treatment approaches failed, the following strategies were employed:

4. ***If SWITCH to Wellbutrin SR, Zoloft or Effexor XR OR AUGMENTATION of Celexa with Wellbutrin SR or Buspar fails,*** then one of the two options
   a. Switch to:
      i. Nortriptyline (116 patients); ***remission rate*** 15-20%
      ii. Remeron (110 patients); ***remission rate*** 10-12%
   b. Augment agent with:
      i. Lithium (63 patients); dose up to 900 mg/day; ***remission rate*** 13.2-15.9%; double the drop-out rate compared to Cytomel
      ii. Cytomel (T3 thyroid hormone; 70 patients); dose up to 50 mcg/day; ***remission rate*** 24.7%
   c. If 'a' and 'b' fail, then change to:
      i. Tranylcypromine (55 patients); max dose 40 mg/day; ***remission rate*** 6.9%
      ii. Effexor XR PLUS Remeron (50 patients); max dose 60 mg/day Remeron and 375 mg/day Effexor XR; ***remission rate*** 13.7; less side effects then tranylcypromine
5. ***If cognitive therapy or Celexa PLUS cognitive therapy fails***, then
   a. Switch to
      i. Wellbutrin SR (15 patients)
      ii. Effexor XR (16 patients)
6. If cognitive therapy, Celexa PLUS cognitive therapy, and then switch to to Wellbutrin or Effexor XR, then
   a. Switch to:
      i. Nortriptyline (5 patients); ***remission rate***
      ii. Remeron (4 patients); ***remission rate***
   b. Augment agent with:
      i. Lithium (6 patients); dose up to 900 mg/day; ***remission rate***
      ii. Cytomel (T3 thyroid hormone; 3 patients); dose up to 50 mcg/day; ***remission rate***
   c. If 'a' and 'b' fail, then change to:
      i. Tranylcypromine (3 patients); max dose 40 mg/day; ***remission rate***
      ii. Effexor XR PLUS Remeron (1 patients); max dose 60 mg/day Remeron and 375 mg/day Effexor XR; ***remission rate***

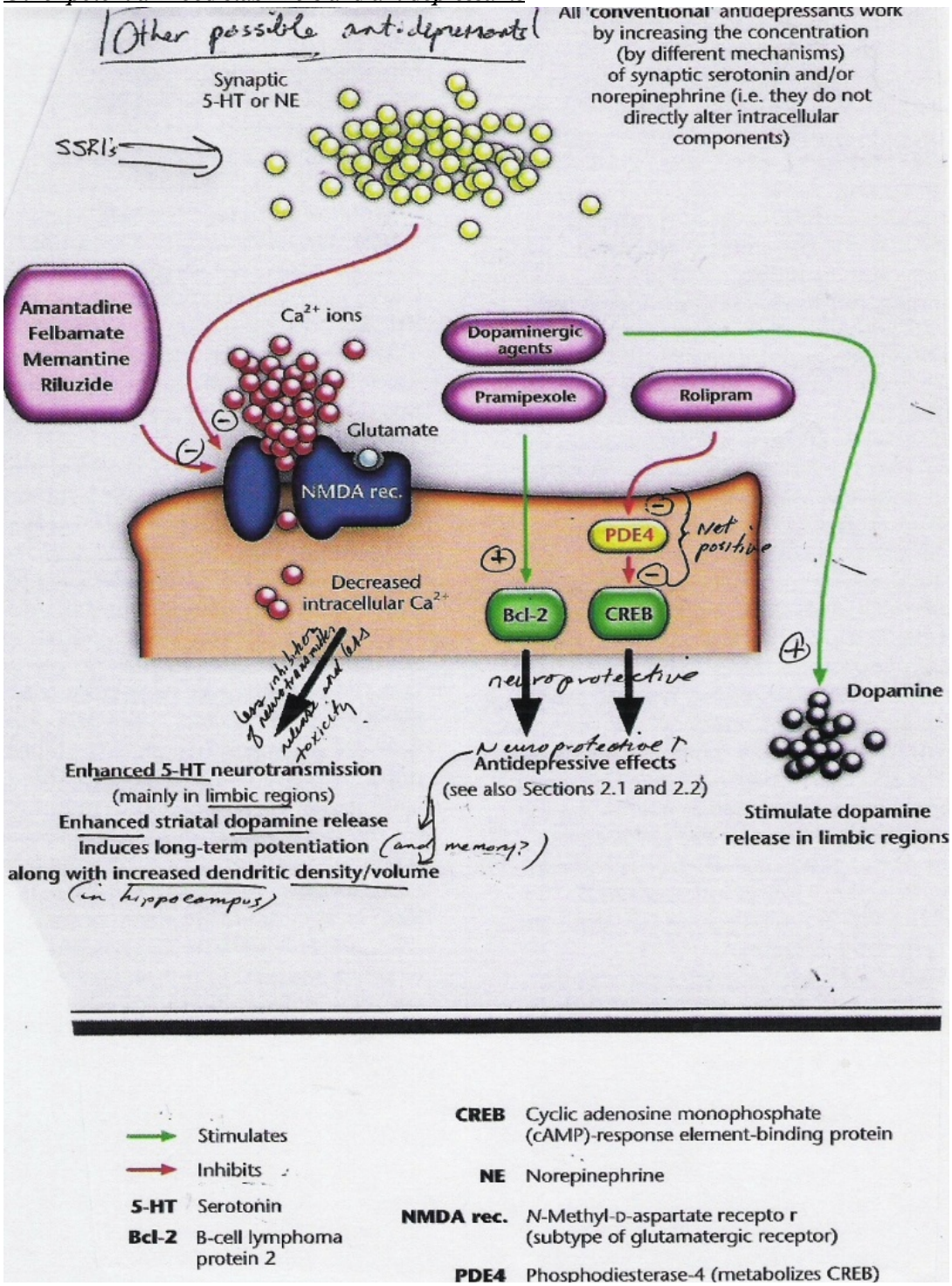
7. If fail to remit in Level II (either option), then move to Level IIIa or IIIb treatment:
   a. **Medication switch** from Celexa OR Zoloft OR Wellbutrin OR Effexor **to EITHER Remeron** (110 patients) **OR nortriptyline** (116 patients)
   b. **Augmentation of Zoloft OR Wellbutrin OR Effexor with lithium** (69 patients) **OR thyroid hormone** (T3; 73 patients) for up to 12 weeks
8. Follow-up; probability of relapse at 12 months
   a. End of Level I
      i. Remission rates
         1. ~52% if remitted by end of Level I
         2. ~73% if not remitted by end of Level I and no further treatment
   b. End of Level II

i. **Remission rates**
   1. ~70% if remitted by end of Level II
   2. ~80 if not remitted by end of Level II

c. End of Level III
   i. **Remission rates**
      1. ~70% if remitted by end of Level III
      2. ~85% if not remitted by end of Level III

d. End of Level IV
   i. **Remission rates**
      1. ~85% whether or not remitted by end of Level IV

Other potential mood stabilizers and antidepressants



- Allopurinol
  - Kraeplin was the first to associate manic symptoms with hyperuricemia, uric acid excretion, and gout
  - Allopurinol is a xanthine oxidase inhibitor approved for the treatment of gout

- Results from initial add-on studies with allopurinol in refractory mania were positive, though sample sizes were small
- 2012 4-week, randomized, placebo-controlled, double blind study. 180 subjects, comparing allopurinol 600 mg/d vs. dipyridamole 200 mg/d added on to lithium
  - Improvement seen over 21 days through day 28
  - Remission rates favored allopurinol
  - Decreased plasma uric acid levels were significantly positively associated with antimanic effects of allopurinol
  - Well-tolerated; most common adverse effects were dizziness and diarrhea

- Calcium Channel Blockers
  - General
    - Small, uncontrolled studies in bipolar disorder
    - Teratogenic risk much lower than with other mood stabilizers
    - Need to monitor blood pressure and get baseline ECG
    - Side effects
      - Common
        - Dizziness
        - Headache
        - Nausea
      - Rare
        - Malignant arrhythmias
        - Liver toxicity
        - Severe low blood pressure
        - Fainting
        - Tiredness
  - Nimotop (generic name is nimodipine)
    - Other mechanisms:
      - Also has anticonvulsant properties
      - Also blocks 5HT3 receptor function
      - Increases dopamine in the striatum
      - Decreases cocaine-induced hyperactivity
      - Little effect on the myocardium (heart)
      - Inhibition of calcium influx via L-type calcium channels
    - Pharmacodynamics
      - Peak in 1 hour
      - Half-life with two phases: 1-2 hours and 8-9 hours
      - Responders to Nimotop show cross-reactivity to the L-type calcium channel blocker israpidine but not verapamil
      - Penetrates blood-brain barrier better than Verapamil.
    - 30 mg caps
    - Evidence in adults
      - McDermut, 1995; Pazzaglia 1993, 1998: preliminary data in support of efficacy in patients with rapid- and ultradian-cycling bipolar disorder and patients with recurrent brief depressions
    - Start 30 mg tid then increase to range of 240-450 mg/day; might later be able to be switched to longer acting ones
  - Verapamil
    - Also, inhibits 5HT3 receptor function
    - Dosing
      - Starting dose 80 mg 2-3 times-a-day
      - Maximum dose 480 mg/day
    - Pharmacodynamics
      - Readily crosses the blood-brain barrier
      - Peak level in 1-2 hours
      - Half-life 3-7 hours; after repeated doses, 4-12 hours
    - Enhanced neurotoxicity when added to lithium and Tegretol
    - Evidence
      - several negative placebo-controlled studies
      - may be more effective in women
      - Wisner, 2002: 37 bipolar women, naturalistic study, effective for acute treatment of mania and for maintenance.
- Tamoxifen—a protein kinase C inhibitor, a mechanism of action shared by lithium, valproic acid, omega-3 fatty acids, and verapimil. Zarate et al, 2007, RCT, DB trial of 16 patients: effective.
- Inositol—small open study showed benefit in bipolar depression.
- L-690,300—IMPase inhibitor; does not readily cross blood-brain barrier
- L-690,488—readily crosses blood-brain barrier where it gets converted to L-690,330
- High dose thyroid hormone—initial reports of efficacy have failed to be replicated in larger studies
- Donepezil—may be efficacious (in a small study) but also induced mania
- RU486—glucocorticoid receptor blocker
  - Mixed data
- **Bitopertin**

- **Glycine transport inhibitor**
- **Enhances functioning of NMDA glutamate receptor**
- **May be especially helpful for negative symptoms of schizophrenia**
- **Umbricht et al, 2014:**
  - **Bitopertin (10 mg/day vs 30 vs 60) vs. placebo, added to standard antipsychotic therapy for 8 weeks**
  - **Associated with**
    - **Significant reduction in negative symptoms in the 10 mg/day and 30 mg/day groups**
    - **Significantly higher response rate in 10 mg/day group**
    - **Trend toward improved functioning in 10 mg/day group**
- Pomaglumetad Methionil
  - Metabotropic glutamate receptor agonist
  - Development halted in face of negative RCTs
- Other glutamate/NMDA-receptor blockers/modulators
- Famotidine
  - Meskanen et al, 2013: reduces symptom severity in severe, resistant schizophrenia
- Vyvanse
  - Lasser et al, 2013: pilot study reduced negative symptoms in a group of patients with schizophrenia whose positive symptoms were well controlled with antipsychotic medication
- Cariprazine
  - Oral antipsychotic medication
  - Ketter at al, 2013: efficacy in treating mania in bipolar I in an open-label, 16-week study of flexibly dosing
    - 402 patients
    - Dosing 3-12 mg/day; mean dose 6.2 mg/day
    - Major tolerability issues
      - Akathisia in 37%
      - Extrapyramidal muscle side effects in 7%
- Bexarotene
  - Retinoid X receptor agonist
  - Anti-tumor agent that might modulate numerous metabolic pathways involved in the pathogenesis of schizophrenia and/or schizoaffective disorder
  - 6-week, randomized, DB, placebo-controlled multicenter trial, added to ongoing antipsychotic treatment
  - Effective in reducing positive symptoms (reduced efficacy if also taking lipid-reducing medications)
  - Side effects
    - Transient increase in total cholesterol
    - Decrease in thyroxine levels
- Valdoxan (agomelatine)
  - Antidepressant and improves sleep qualities
  - Melatonin 1 and 2 agonist, 5HT2c antagonist
  - 50 mg/day > 25 mg/day
  - Approved in Europe
  - Two clinical trials (randomized, double blind, multiple countries, Zarecka et al, 2010, Stahl er al, 2010) demonstrated efficacy for major depression that was equivalent to Effexor XR with significantly
    - Overall: 304 patients on agomelatine 25-50 mg and 307 patients on Effexor XR 75-150 mg
      - 76.4% response rate and 73% remission rate (at 12 weeks) with agomelatine
      - 70.6% response rate and 67% remission rate (at 12 weeks) with Effexor XR
    - Side effects:
      - sexual side effects
        - 20% rate of sexual side effects with agomelatine
        - 40% with Effexor XR
      - gastrointestinal disorders—0.7%
      - elevated liver enzymes; time-limited, mild; worse with 50 mg than 25 mg
      - pooled analysis of three placebo-controlled studies demonstrated sexual side effects:
        - 3.2% (of 1,120 patients on agomelatine) with sexual dysfunction
        - 2.6% (of 998 patients on placebo) with sexual dysfunction
        - 10.8% (of 567 patients on SSRIs) with sexual dysfunction
- SR58611
  - beta-3 noradrenergic receptor agonist
  - under investigation
- Rolipram
  - blocks destruction of cAMP second messengers
- Lithium "mimetics"
  - under investigation.
- Serotonin 1d antagonists

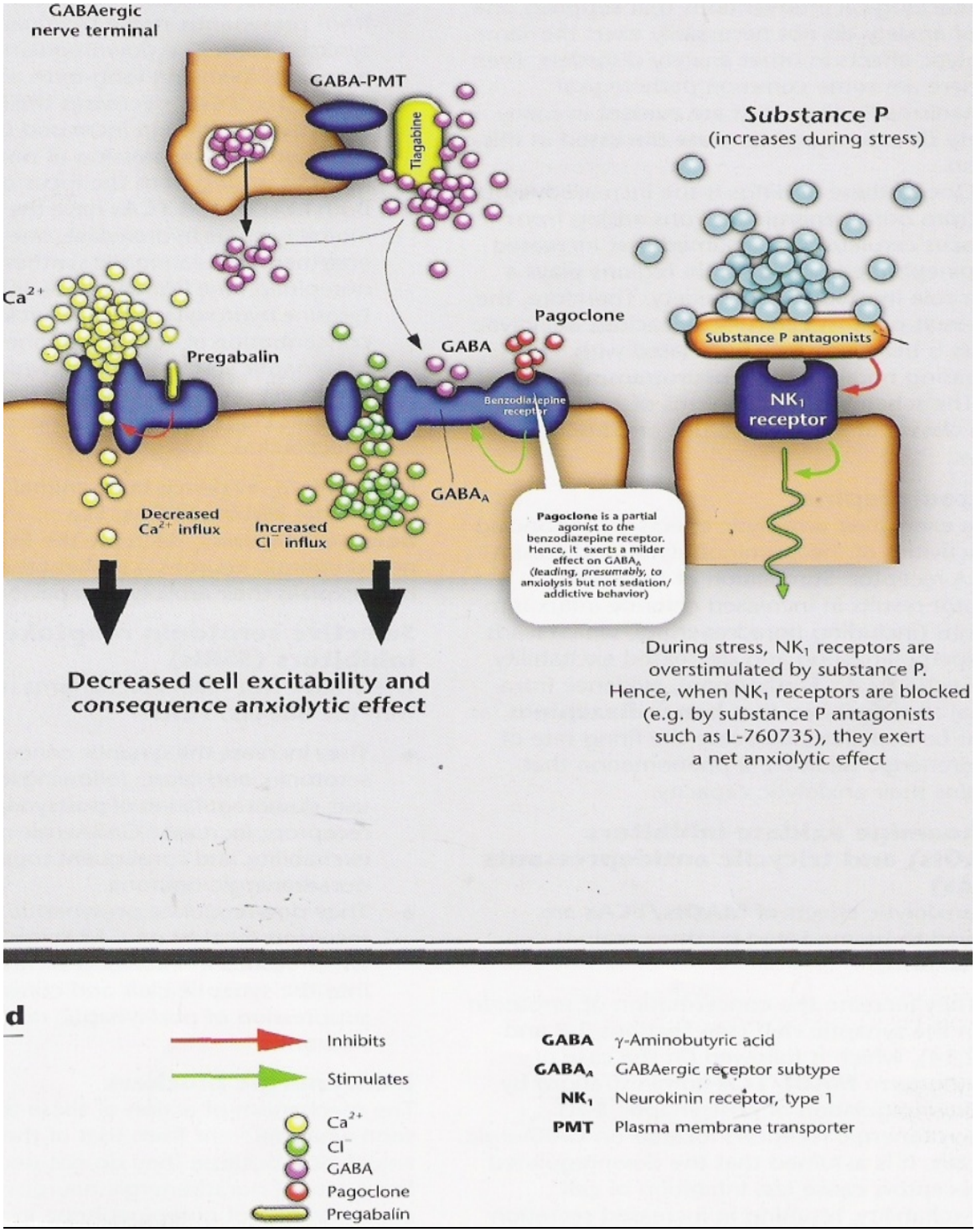
- CP-448,147 is under investigation
- **Serotonin 1a modulators**
- **Serotonin Reuptake Enhancers**
  - **Tianeptine**
    - appears to normalize abnormalities in the cortisol system and treat symptoms of depression
    - research is currently in progress.
- Noradrenergic modulators
  - SR 58611—noradrenergic beta-3 receptor agonist
- Norepinephrine Reuptake Inhibitors
  - Lofepromine
  - Viloxazine
- Norepinephrine-Dopamine Reuptake Inhibitors
  - minaprine—affinity for serotonin, dopamine, and muscarinic receptors; under investigation
  - bazinaprine—under investigation.
- Triple Reuptake Inhibitors (Serotonin-Norepinephrine-Dopamine)
  - Silbutramine
    - serotonin, norepinephrine, dopamine reuptake inhibitor and beta-3 adrenergic receptor agonist
    - approved for the treatment of obesity
    - side effects include dry mouth, constipation.
    - could theoretically have antidepressant effects.
  - Amitifadine
  - GSK 372475
  - BMS 820836
  - SEP 225289
  - Lu AA24530 (also has actions at 5HT2c, 3, and 2A and alpha 1a receptors)
  - PRCO25—S(6)>N(19)>D(100)
  - PRCO5O—N(0.4)>S(6)>D(120)
  - DOV 216303—S(14)>N(20)>D(78)
    - safe and well-tolerated in small samples of normal volunteers and depressed patients in single doses of 5-150 mg/day or multiple doses of 50, 75, or 100 mg for 10 days
    - at the highest dose—gastrointestinal side effects
    - multicenter comparison trial of 50 mg twice-a-day (36 patients) vs. Celexa 20 mg twice-a-day (31 patients) for 2 weeks—after 1 week, both treatments produced comparable reductions in symptoms
  - DOV 21947—S(99)>D(213)>N(262); also in development for restless legs syndrome
  - DOV 102677—D(222)>S(740)>N(1030); in development for ADHD, obesity, depression
- MIN-117
  - Possibly
    - faster onset of action
    - complete restoration of euthymia
    - beneficial effects on cognition
    - beneficial effects on sexual functioning
    - strong anti-anxiety effects
    - no prolongation of REM sleep latency
  - Actions
    - serotonin reuptake inhibition
    - 5HT1a activity
    - 5HT2a blocking
    - dopamine reuptake inhibition
    - alpha-1A and alpha-1B noradrenergic activity
    - → sustained release of serotonin and dopamine
    - t-1/2 ~60 hours
  - Data
    - MIN-117 at 2.5 or 0.5 mg/day vs. Paxil 20 mg/day vs. placebo for depression for 6 weeks; 84 pts
    - MIN-117 at 2.5 or 5 mg/day vs. placebo for depression; 324-patient
    - Preliminary data very strrong
- Netamiftide—under investigation; novel injectable pentapeptide
- Steroid/Immune modulators
  - Corticotropin Releasing Hormone 1 receptor (CRHR1) blockers
    - R121919
      - experimental compound may alleviate depression (Zobel, 2000) and anxiety
      - development cancelled liver damage; others are in development).
    - BMS 562086
    - ONO-2333Ms
    - SSR125543
  - Glucocorticoid receptor antagonists

- RU 486 (mefipristone)
  - Belanoff, 2001, for psychotic depression
  - Simpson, 2005: an 8-week open-label trial of a 6-day course for psychotic depression demonstrated positive efficacy during the first (but not last) 4 weeks.
  - Cognitive and mood improvements in bipolar depression (Young, 2004).
- CA-1073—at 600 mg/day for 7 days in psychotic depression; may be more helpful in psychosis than in depression.
- Org 34517
- Cortisol synthesis inhibition
  - Metyrapone
- Substance P/Neurokinin-1 (A/B) receptor antagonists
  - NK-1 receptor antagonists (under investigation):
    - MK-869 (Emand/Aprepitant)
      - MK-869 appeared to be as efficacious as Paxil in a 6 week trial with 213 patients, but MK-869 had a better side effect profile than Paxil; Kramer 1998); this has not been replicated.
      - Substance P infusion leads to depressive symptoms and also to increases in cortisol secretion; not commercially available.
    - Compound A
    - SR140333
    - L-760-735
    - L-733,060
    - CP-96,345
    - CP-122,721
  - NK-2 receptor antagonists
    - Saredutant (SR48968)
    - GR-159897
  - NK-3 receptor antagonists
    - SR142801
- Brexanolone injection for postpartum depression
  - Rapid and durable improvement (3 pivotal randomized trials (aka Hummingbird trials)
  - Side effects
    - dizziness
    - sleepiness
  - Action
    - proprietary IV formulation of allopregnanolone, a metabolite of progesterone
    - modulates GABA, binding to synaptic and extra-synaptic GABA A receptors, increasing their functioning
- Curcumin; MAOI
- Infliximab; TNF alpha antagonist
- Edivoxetine; norepinephrine reuptake inhibition
- Relidep; unknown mechanism; derived from chicken eggs
- Cimicoxib; COX-2 inhibition
- Phototherapy
  - Seldom sufficient if used alone in bipolar depression (Pjrek, 2004)
  - Treatment-emergent hypomania and rarely mania is risk (Chan, 1994)
- Dopamine serotonin stabilizer RP5063: A randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder

  Marc Cantillon, Arul Prakash, Ajay Alexander, Robert Ings, Dennis Sweitzer, Laxminarayan Bhat

  Schizophrenia Research 2017 February 16

  The study objectives were to evaluate the efficacy, safety, tolerability, and pharmacokinetics of RP5063 versus placebo. The study was conducted in adults with acute exacerbation of schizophrenia or schizoaffective disorder. This 28-day, multicenter, placebo-controlled, double-blind study randomized 234 subjects to RP5063 15, 30, or 50mg; aripiprazole; or placebo (3:3:3:1:2) once daily. The aripiprazole arm was included solely to show assay sensitivity and was not powered to show efficacy. The primary endpoint was change from baseline to Day 28/EOT (End-of-Treatment) in Positive and Negative Syndrome Scale (PANSS) total score; secondary endpoints included PANSS subscales, improvement ≥1 point on the Clinical Global Impressions-Severity (CGI-S), depression and cognition scales. The primary analysis of PANSS Total showed improvement by a mean (SE) of -20.23 (2.65), -15.42 (2.04), and -19.21 (2.39) in the RP5063 15, 30, and 50mg arms, versus -11.41 (3.45) in the placebo arm. The difference between treatment and placebo reached statistical significance for the 15mg ($p=0.021$) and 50mg ($p=0.016$) arms. Improvement with RP5063 was also seen for multiple secondary efficacy outcomes. Discontinuation for any reason was much lower for RP5063 (14%, 25%, 12%) versus placebo (26%) and aripiprazole (35%). The most common treatment-emergent adverse events (TEAE) in the RP5063 groups were insomnia and agitation. There were no significant changes in body weight, electrocardiogram, or incidence of orthostatic hypotension; there was a decrease in blood glucose, lipid profiles, and prolactin levels. In conclusion, the novel dopamine serotonin stabilizer, RP5063 is an efficacious and well-tolerated treatment for acute exacerbation of schizophrenia or schizoaffective disorder.



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Inhibits

Stimulates

Ca^{2+}

Cl^-

GABA

Pagoclone

Pregabalin

GABA γ-Aminobutyric acid

$GABA_A$ GABAergic receptor subtype

NK_1 Neurokinin receptor, type 1

PMT Plasma membrane transporter

Other potential antipsychotic medications

- Penfluridol
  - very long-acting; can be given orally once-a-week
  - available in Europe; failed to pass FDA's carcinogenicity screen
- Fluspirilene; similar to fluphenazne; long-acting injectable drug held in suspension by a chemical not approved by the FDA
- Flupentixol decanoate
  - clear antdepressant properties
  - on the market in Canada as 0.5 mg tab and long-acting injectable.
  - antidepressant dose is less than 3 mg/day; antipsychotic dose is more than 3 mg/day
- Pipotiazine palmitate; depot neuroleptic available in Europe
- Mazapertine**;** dopamine 2 antagonist and serotonin 1a antagonism
- Methotrimeprazine (levomepromazine**)**
  - widely used in Europe; available in US on in injectable form for pain
  - very sedating
  - analgesic effects
- Nemonapride**;** dopamine 2, 3, 4 antagonist and serotonin 1a agonist
- MDL-100,907—serotonin 2a antagonist; dropped due to lack of efficacy in schizophrenia
- Ritanserin; serotonin 2a, 2c antagonist; dropped due to lack of efficacy in schizophrenia
- Serotonin 6, 7 antagonists
- Dopamine 4 antagonists (generally disappointing results)
  - YM-43611
  - Nemonapride
  - Fanaserin
  - L-745,870
  - PNU-101,387G
  - NGD-94-4
  - LU-111,995
- Dopamine 3 antagonists
- Dopamine 1-like antagonists
- Sigma antagonists
  - BMY-14,802; sigma antagonist; not impressive
  - SR31742A
- OPC14523; sigma antagonist, serotonin 1a agonist, serotonin reuptake inhibitor
- Cannabinoid 1 receptor antagonist (e.g., SR141716A); may precipitate anxiety and panic
- Neurontensin antagonist (e.g., SR-142948)
- Alpha-7-nicotinic cholinergic agonists

Options for augmenting antipsychotics for the treatment of psychosis

- Raloxifene
  - 60-120 mg
  - Efficacy seen when added to antipsychotic medications in women
- Lithium, 300-900 mg/day; may not be as helpful as once thought
- Carbamazepine (Tegretol)
- Depakote
- Glycine; co-agonist at NMDA receptor; 0.8 g/kg/day
- d-serine
- d-cycloserine; 1-3 mg/kg/day effective in reducing social withdrawal in autism
- Sarcosine
  - naturally occurring amino acid
  - blocks glycine reuptake (which leads to more activation of NMDA glutamate neurotransmission)
  - May be an effective adjuvant at 2 grams/day.
  - Side effects included elevated heart rate.
- Muscarinic-1 agonists (e.g., desmethylclozapine)
- **Buspar, tandospirone**—serotonin-1a partial agonists
- Omega 3 fatty acids
- See information packet on depression.

Options for treating negative/cognitive symptoms of psychosis or ?bipolar depression

- Summary for rx of neg/cog symptoms
  - Donepezil, galantamine, rivastagmine: negative studies
  - Nicotinic meds: negative studies
  - Glutamatergic: modest improvements
    - Glycine
    - D-Serine
    - D-cycloserine
    - Sarcosine
    - CX-516

        - RG 1678 (glycine reuptake inhibitor)
        - Lamictal
    - GABAergic: positive in small samples
        - Flumazenil
        - MK-0777
    - Noradrenergic: negative
    - Serotonergic: limited evidence of benefit
        - Tandospirone
        - Buspar
    - Antidepressants
        - Mixed to negative results
    - Famotidine
    - Dopaminergic
        - Tolcapone: safety issues
        - Amphetamine: long-term safety
    - Modafinil
        - Exacerbation of psychosis
    - Experimental
        - Methylphenidate/Vyvanse
        - L-dopa
        - Clozaril/Zyprexa/Abilify/Amisulpride
        - NSAIDS
        - Remeron
        - Anticonvulsants
        - Estrogen
        - Cannabinoid agonists
        - GlyT1 inhibitors
        - Dimesylate
- Levodopa
- Amphetamine, methylphenidate
- Amantadine
    - Antiviral (influenza) medication and treatment for Parkinson's disease
    - Mechanism
    - Direct and indirect effects on dopamine neurons
    - Weak, non-competitive NMDA antagonist
    - Some anticholinergic properties
    - Pharmacodynamics
        - Time to peak 3.3 hours
        - Half-life 16-17 hours
    - Side effects
        - 5-10% frequency
        - nausea
        - dizziness
        - insomnia
        - 1-5% frequency (note some of these side effects are much more likely in patients with Parkinson's disease)
            - depression OR anxiety OR irritability
            - hallucinations OR confusion
            - decreased appetite
            - dry mouth
            - constipation
            - balance problems
            - headache
            - somnolence
            - diarrhea
- Bromocriptine
- Selegiline 5 mg bid
- Low doses of standard antipyschotics can increase dopamine by blocking presynaptic dopamine autoreceptors
- SSRI's

Possible treatments for tardive dyskinesia

- gabapentin (Neurontin) 900-1800 mg.day
- benzodiazepines
    - clonazepam
- Tarvil branched-chain amino acids
    - Very little data
- Piracetam

- Mechanism
    - a powerful antioxidant
    - neuroprotective
    - neuronal metabolic and receptor enhancer
    - increases number of acetylcholine receptors
    - glutamate effects
    - potentiates potassium-induced release of glutamate in the hippocampus
    - structurally related to GABA
    - brain integrative agent
- Libov et al, 2007: 9-week, double-blind, crossover, placebo-controlled trial, 40 adults with TD; 4 weeks of 4800 mg/day vs. placebo and then cross over for 4 weeks; safe and effective
- IV use studied 20 years ago at 4000 mg/day—safe and effective
- Clinical reports of piracetam by mouth (at 800-24,000 mg/day) for TD
- Excreted unchanged in the urine
- Half-life is five hours; some accumulation in the brain over time
- No teratogenic effects

- Ginkgo biloba
- Amantadine
- Deutetrabenazine (SD-809)
    - Investigational treatment for tardive dyskinesia
    - Drug used in the treatment of choreiform movements associated with Huntington's disease
    - Tetrabenazine inhibits vesicular monoamine transporter 2 (VMAT-2), resulting in depletion of synaptic dopamine (but can also block dopamine and cause EPS, sedation, and other psychiatric side effects)
    - Deutetrabenazine is also a VMAT-2 inhibitor
    - NNT 6
    - No reports of depression, suicidal ideation, anxiety, insomnia, etc
- Valbenazine (NBI-98854)
    - Investigational treatment for tardive dyskinesia
    - Metabolized to (+)-alpha-dihydrotetrabenazine (the undesirable beta-tetrabenazine derivatives are not produced)
- Not recommended at this time (due to paucity of research or negative results)
    - Acetazolamide
    - Bromocriptine
    - Baclofen
    - Buspar
    - Diltiazem
    - Galantamine
    - Keppra
    - Vitamin E
    - Vitamin B6
    - Thiamine
    - Selegeline
    - Nifedipine
    - Yi-gan san
    - Biperiden discontinuation
    - Botilinum toxin type A
    - Alpha-methyldopa
    - Reserpine

Other

- Naltrexone: mu-receptor antagonist; side effects nausea and dysphoria; may cause reversible increases in liver enzymes at high doses
- Bethanecol (procholinergic), 25-50 mg 3-4 times-a-day for anticholinergic side *effects.*
- 4% pilocarpine drops for blurry vision from tricyclic antidepressants or diluted to 1% solution and swished in mouth for 30-60" for dry mouth from tricyclics
- Florinef for orthostatic hypotention with MAOI's (0.3 mg/d or more).
- Vitamin B6 100 mg/d for muscle pains and tingling in MAOI use.
- Nifedipine 10 mg qhour (usually 10 or 20 mg) and ER for hypertensive crisis with MAOI use.
- Prazosin for nightmares related to trauma/PTSD (2013)
    - May work through increased responsiveness to norepinephrine at CNS alpha-1 receptors
    - Improves sleep disturbance
    - Improves nightmares
    - Not sedating
    - No sexual dysfunction
    - No adverse metabolic effects
    - Maintaining adequate hydration important

- Chantix (varenicline)
    - Cigarette cessation
    - Case reports of exacerbation of psychosis/schizophrenia
        - Reanalysis of data (Mann and Gibbons, 2013) show Chantix does not appear to cause psychiatric events.
    - Cholinergic nicotinic agonist, especially at the presynaptic receptors (composed primarily of alpha2/beta 2 subunits) which cause the release of dopamine and other neurotransmitters
    - Binds also to serotonin 3 receptors which causes nausea
    - Max plasma level is 3-4 hours
    - Half-life is 24 hours
    - Does not interact with nicotine, Wellbutrin
    - Does not affect P450 liver enzymes
    - 0.5 mg pill, 1 mg pill
    - Dosing is 0.5 mg/day for 3 days, 0.5 mg twice-a-day for 4 days, then 1 mg twice-a-day for 12 weeks
    - No carcinogenic, not genotoxic, no impairment of fertility
    - Side effects:
        - Nausea 16-30% vs. 10% placebo
        - Insomnia 19% vs. 13% placebo
        - Headache 15-19% vs. 13% placebo
        - Abnormal dreams 12% vs. 5% placebo
        - Liver enzyme elevation
        - Weight increase
        - Poor concentration
        - Dizziness
        - Anxiety, depression, irritability, restlessness
        - Sweating, flushing
        - Hypertension
- Cytisine (acacia seed extract)
    - Nicotine partial agonist
    - Used in Europe
- Riminobant
    - CB1 antagonist
    - Nicotinic partial/full agonist
    - Experimental
- Alcohol Use Disorders
    - Naltrexone
        - 25-50 mg bid to tid
    - Acamprosate
        - 333-666 mg tid
    - Topamax
        - 100-300 mg/day
    - Ondansetron
        - 2-8 mg/day
    - Baclofen
        - 10-20 mg/day
    - Antabuse
- Marijuana
    - NAC 1200 mg bid
    - Buspar
    - Lofexidine/dronabinol
    - Neurontin
    - Topamax
    - Rimonabant
        - Experimental
        - CB1 antagonist
- Autism
    - Secretin
        - High strength of evidence for LACK of efficacy despite positive open studies and case series
    - Abilify
        - High strength of evidence of efficacy for irritability, hyperactivity/defiance
    - Risperdal
        - High strength of evidence of efficacy for irritability, hyperactivity/defiance
    - Haldol
    - Methylphenidate
        - Moderate strength of evidence of efficacy
        - 49% improved

        - 30% symptom reduction
        - 18% discontinued due to side effects such as worse irritability
    - Strattera
        - Harfterkamp, et al, 2012
            - 21% improved vs. 9% placebo
            - 1 patient stopped due to side effect (fatigue)
        - Handen, et al, 2015
            - 47-48% improved vs. 19% placebo or 29% placebo plus psychotherapy
            - Side effects: decreased appetite, dry mouth
    - Guanfacine
        - Insufficient strength of evidence of efficacy
        - Helpful for hyperactivity, but not for irritability
    - Clonidine
        - Insufficient strength of evidence of efficacy
        - Usually not helpful in severe cases
    - SSRI's
        - Insufficient strength of evidence of efficacy
        - King, et al, 2009 and JAMA 2013
            - Celexa not helpful overall or for repetitive behaviors
            - Slight improvement in irritability/agitation
            - Activation in 50%
        - No studies targeting anxiety or mood in children with autistic spectrum disorders
        - In adults with autism spectrum disorders
            - Hollander, et al, 2011
                - Prozac helpful
            - McDougle, et al, 1996
                - Fluvoxamine helpful
    - NAC
    - Propranolol?
    - Depakote?
    - Lithium?
    - Trileptal?
    - Klonopin? (watch for disinhibition)
    - Sleep problems
        - Behavioral
            - Bedtime ritual
            - Social story
        - Melatonin
        - Clonidine/guanfacine
        - Benadryl/hydroxyzine
        - Amitriptyline 5-25 mg
        - Doxepin 3-10 mg
        - Trazodone 25-100 mg
        - Neurontin 50-300 mg

Agomelatine as a Treatment for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents: A Double-Blind, Randomized Clinical Trial

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OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder. Due to lack of response to the medication and significant side effects of the treatment with stimulants, alternative medications should be considered. The aim of this study is to evaluate efficacy of agomelatine in treatment of ADHD.

METHODS: Fifty-four outpatients, children 6-15 years old, with diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria participated in a 6-week, parallel, double-blind, randomized clinical trial. Fifty patients completed 6 weeks of treatment with either ritalin (methylphenidate hydrochloride [MPH]) (20 mg/day in participants below 30 kg and 30 mg/day in patients with weight ≥30 kg) or agomelatine (15 mg/day in patients with weight ≥30 kg and 25 mg/day in patients with weight ≥45 kg). Participants were assessed using Parent and Teacher ADHD Rating Scale-IV at baseline and at weeks 3 and 6.

RESULTS: General linear model repeated measures showed no significant differences between the two groups on Parent and Teacher Rating Scale scores ($F = 1.13$, $df = 1.26$, $p = 0.305$, and $F = 0.95$, $df = 1.25$, $p = 0.353$, respectively). Changes in Teacher and Parent ADHD Rating Scale scores from baseline to the study end were not significantly different between the agomelatine group (9.28 ± 8.72 and 24.12 ± 7.04,

respectively) and the MPH group (6.64 ± 11.04 and 25.76 ± 7.82, respectively) (p = 0.46 and p = 0.44, respectively). There was a trend for less insomnia in the agomelatine group versus MPH-treated group (4% vs. 24%, p = 0.09).
CONCLUSIONS: A treatment course of 6 weeks with agomelatine demonstrated a favorable safety and efficacy profile in children and adolescents with ADHD. Nonetheless, larger controlled studies with longer treatment periods are necessary.

A Randomized, Double-Blind Placebo-Controlled Trial on Effectiveness and Safety of Celecoxib Adjunctive Therapy in Adolescents with Acute Bipolar Mania
Seyed Yaser Mousavi, Rasoul Khezri, Mohammad-Ali Karkhaneh-Yousefi, Payam Mohammadinejad, Faezeh Gholamian, Mohammad Reza Mohammadi, Atefeh Zeinoddini, Shahin Akhondzadeh
Journal of Child and Adolescent Psychopharmacology 2017 April 14
OBJECTIVE: Recent studies have focused on the role of inflammatory cascades as one of the possible etiologic factors of bipolar disorder. We hypothesize that celecoxib, through its anti-inflammatory properties, may have a therapeutic role in acute bipolar mania.
PATIENTS AND METHODS: Forty-two adolescent inpatients with the diagnosis of acute bipolar mania participated in a parallel, randomized, double-blind controlled trial, and 40 patients underwent an 8-week treatment with either celecoxib (100 mg twice daily) or placebo as an adjunctive treatment to lithium and risperidone. Patients were evaluated using Young Mania Rating Scale (YMRS) at baseline and weeks 2, 4, and 8. The primary outcome measure was to assess the efficacy of celecoxib compared with placebo in improving mania symptoms.
RESULT: General linear model repeated measures showed significant effect for time × treatment interaction on YMRS scores [F (2.54, 96.56) = 3.21, p = 0.03]. Significantly greater improvement was observed in YMRS scores in the celecoxib group compared with the placebo group from baseline YMRS score at week 8 (p = 0.04). Although a 35% greater response to treatment (considering a Clinical Global Impressions-Improvement score of ≤2, very much/much improved) was observed in the celecoxib group compared with the placebo group, the difference did not reach the statistical significance level (p = 0.09). No serious adverse event was reported.
CONCLUSIONS: Celecoxib may be an effective adjuvant therapy in treatment of manic episodes (without psychotic features) of adolescents with bipolar mood disorder. The mood-stabilizing role of this drug might be mediated through its action on inflammatory cascades.

Simvastatin as an Adjunctive Therapy to Risperidone in Treatment of Autism: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial
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OBJECTIVES: Providing novel treatments for autism has been a subject of long-standing research. Based on etiopathological findings, we aim at assessing potential therapeutic effects of statins, here simvastatin, on autism symptoms for the first time.
METHODS: In this randomized, double-blind, placebo-controlled, parallel-group 10-week clinical trial, 70 drug-free children aged 4 to 12 years old with diagnosis of autistic disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, who had an Aberrant Behavior Checklist-Community (ABC-C) scale irritability subscale score of ≥12, were equally randomized to receive either simvastatin (20-40 mg/day) or placebo as an adjunct to risperidone (1-2 mg/day) whereas administration of both drugs was started simultaneously from baseline. Patients with comorbid psychiatric disorders, active medical conditions, severe intellectual disability, seizure disorders, history of any treatments for autism in the past 6 months, or history of current anti-inflammatory drug consumption were excluded. Primary outcome was defined as the difference in mean change of the ABC-C scale irritability subscale score from baseline to the endpoint (www.irct.ir ; IRCT201602041556N86).
RESULTS: Significant differences in change of the ABC-C scale irritability (mean difference [95% confidence interval (CI)] = -3.45 [-5.37 to -1.54], p = 0.001; Cohen's d = 0.89) and hyperactivity/noncompliance (mean difference [95% CI] = -4.27 [-6.69 to -1.86], p = 0.001; Cohen's d = 0.87) subscales scores were detected between the two arms. No significant difference was detected in case of the other three subscales.
CONCLUSIONS: This study provides preliminary evidence for potential therapeutic effects of simvastatin in the treatment of autism that warrants further investigations.