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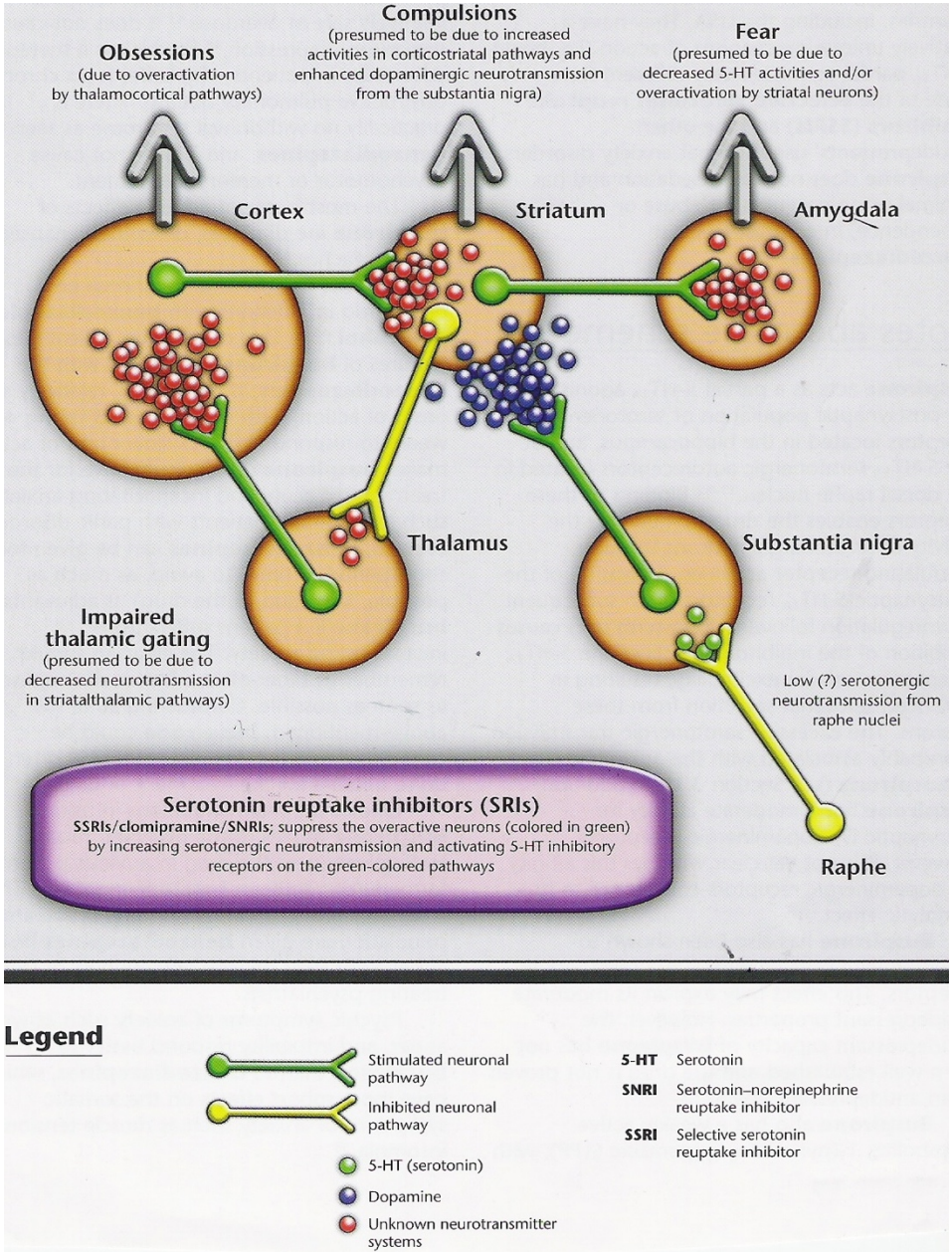
Obsessive Compulsive Disorder:Treatment

- General
  - Response to cognitive behavioral therapy (CBT, utilizing exposure and ritual/response prevention (ERP) for 13-20 sessions or serotonin-specific reuptake inhibitors) SSRI/serotonin reuptake inhibitors (SRI) treatment often not enough
  - Response is often defined as 25-35% decrease in symptom scores
  - CBT (ERP +/- cognitive therapy +/- relaxation techniques)
    - Response rates 25-75% across 4 studies (with improvement in symptoms by 25-50%)
    - Recovery/remission rates 22-33%
    - 25% of patient's can't cooperate with ERP
    - Cognitive therapy vs. ERP:
      - Cognitive therapy: 42-53% reduction in symptoms
      - ERP: 41-44% reduction in symptoms
  - Medication treatment



- **FDA-approval for SSRI's in YOUTH**
  - **Major depression**
    - **Prozac** **12 yo and older**
    - **Lexapro** **12 yo and older**
  - **OCD**
    - **Prozac** **7 yo and older**
    - **Zoloft** **6 yo and older**
    - **Luvox** **8 yo and older**
    - **Clomipramine (this is a TCA)** **10 yo and older**
  - **Generalized anxiety disorder**
    - **Cymbalta** **7 yo and older**
  - Response rates of SSRI's
    - 52.5% across 9 studies
    - Up to 65% achieve a 20-40% reduction in OCD symptoms
  - Remission rates of SSRI's
    - 25% or less achieve remission (e.g., minimal symptoms)
  - Recent meta-analysis of 12 treatment studies in OCD with 1044 participants—Prozac, Paxil, Zoloft, fluvoxamine, Anafranil vs. Placebo
    - Highly significant difference between medications and placebo
    - Anafranil (clomipramine) superior to SSRI's
  - Generally requires high doses and long durations of treatment before response is attained
  - Response rates are lower and relapse rates higher compared to depression

- SSRI's
  - SSRI's comparably effective
    - FDA-approved options for OCD
      - Prozac (kids and adults)
      - Luvox (kids and adults)
      - Paxil (adults; also, efficacious in kid OCD)
      - Zoloft (adults and kids)
      - (Clomipramine (kids and adults))
    - Non-FDA approved options that are likely effective for kids
      - Celexa
      - Lexapro
  - With children and adults, all SSRI's appear equally effective
  - There is good evidence for the use of SSRIs in pediatric OCD (McClellan and Werry, 2003)
- Cognitive behavior therapy (involving exposure and response prevention) is critical
  - Equal or superior to SSRI treatment
  - Greatly improves the response and remission rates when combined with SSRI medication
  - More effective alongside SSRI's than is Risperdal (see below)

- Overall strategies for acute phase treatment
  - Mild, any age--> CBT (ERP) alone for 13-20 weekly sessions, then periodic 'booster' sessions thereafter with decreasing frequency over time
    - ALL studies report improvement in OCD with effect sizes greater than medications
    - Recommended first line treatment in mild-moderate OCD by the AACSP Practice Parameters Expert Consensus Guidelines
    - Theoretical basis of exposure and response prevention (ERP)
      - Exposure
        - --> anxiety provoking obsession
        - --> urge to ritualize
        - --> performance of compulsiom
        - --> relief of anxiety
        - --> (in time) new obsession
      - Prevention of performance of ritual compulsion -->anxiety not relieved
        - --> habituation
        - --> obsessions diminish
  - If CBT is inadequate and/or SRI treatment is more acceptable to patient, consider adding SSRI (fluvoxamine, Paxil, Zoloft, Prozac, Celexa, Lexapro)
    - 27 studies overall, >1100 youth, meta-analysis of which demonstrated efficacy (Geller et al, 2003)
    - Anafranil a bit more effective than SSRI's
    - SSRI's more tolerable and safer than Anafranil
    - Combination of CBT plus medication treatment usually more effective than either alone
  - Pediatric OCD Treatment Study (POTS, 2003); 5 yr outcome study, 3 sites, Zoloft vs. CBT vs. Zol+CBT vs. Placebo
    - Zol+CBT>CBT or Zoloft>placebo
  - Adequate drug trial
    - Adequate dosage; relatively high doses needed; general recommendations include:
      - Prozac 10-80 mg (average 25)
      - Zoloft 50-250 mg (average 178)
      - Fluvoxamine 50-300 mg (average 165)
      - Paxil 10-60 mg (average 32)
      - Celexa 10-60 mg
      - Lexapro 10-30 mg?
      - Anafranil 50-200 mg
      - Effexor XR 187.5-300 mg?
      - Remeron 45-90 mg?
      - Pristiq, Cymbalta?
      - Max doses may exceed range above
      - Systematic dose/response data not available for youth
    - Duration of medication treatment
      - 10-12 weeks at a therapeutic dose

- Optimal duration of maintenance treatment unclear
- Recommendation is to maintain treatment for 6-12 months after response
- Relapses are frequent when discontinue medications (CBT can help here)
- When reducing or discontinuing medication treatment, taper slowly

- SSRI adverse effects (see other information packets for more details)
  - Headache
  - Tremor
  - Drowsiness
  - Insomnia
  - Nausea
  - Gastrointestinal complaints
  - Sexual problems
  - Disinhibition
  - Agitation
  - Hypomania/mania
  - Possible worsening of tics in co-morbid cases
  - Behavioral side effects
    - 25-50%
    - Can have later onset, around 4-6 weeks at times
    - Usually persistant
    - More common in younger youth
    - Dose related
    - May need mood stabilizer
  - Suicidality in SSRI treatment trials for OCD (see analysis in other information packet; below is very brief summary; no suicides occurred in any studies)
    - SSRI risk: 1% (0-2% range)
    - Placebo risk: 0.3% (-0.3-1% range)
    - Pooled risk difference: 0.5% (-1-2% range)
    - Risk from undertreatment cannot be ignored

- Fluvoxamine—FDA-approved age 8 or more
  - Dosing: target is 200 mg/day; maximum dose range 300-450 mg/day
  - RCT, DB; one long-term study
    - ERP vs. fluvoxamine vs. ERP+fluvoxamine; five year follow-up
      - Prevalence of OCD declined in all groups over 5 years (due to improved patients no longer meeting criteria for the disorder)
      - Clinical benefits were maintained throughout the 5 years
      - About half of patients who used fluvoxamine at the start of the study continued antidepressant use for five years
    - Youth
      - Riddle et al, 2001: multicenter, RCT, DB, 10 weeks; 120 youth; 42% response (defined as 25% or more reduction in symptoms) vs. 26% placebo; insomnia in ~30% of those on fluvoxamine vs. 9.5% placebo
- Zoloft—FDA-approved age 6 or more
  - Dosing: target is 200 mg/day; maximum dose range 200-400 mg/day
  - RCT, DB; effective in long-term open trials
  - Youth
    - Pediatric OCD Study Team, 2004: 12 weeks
      - Combination of CBT and Zoloft: 53.6% remission rate
      - CBT alone: 39.3% remission rate
      - Zoloft alone: 21.4% remission rate
      - Placebo: 3.6% remission rate
    - Wagner et al, 2003, one year remission rates

	Children	Adolescents
Full remission	53-66%	41-45%
Partial remission	22-28%	28-33%
Combined	75-94%	69-78%

    - March et al, 1998: RCT, DB, 12 weeks, 187 youth, positive
    - Cook et al: 137 youth 2 year open-label extension study of March 1998: remained effective

- Sertraline Treatment of Nonresponders to Extended Cognitive-Behavior Therapy in Pediatric Obsessive-Compulsive Disorder
  Gudmundur Skarphedinsson, Bernhard Weidle, Tord Ivarsson
  Journal of Child and Adolescent Psychopharmacology 2015, 25 (7): 574-9
  OBJECTIVE: The purpose of this study was to investigate the effect of sertraline (SRT) in children and adolescents with obsessive-compulsive disorder (OCD) who did not respond to two consecutive courses of cognitive-behavior therapy (CBT).
  METHODS: Observational study with 11 participants (males, n=6), 7-17 years of age with Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) primary OCD. All had received 14 plus 10 sessions of CBT over the course of 218-532 days (mean=342.2, SD=85.5). Outcome measures were mean reduction of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score and adequate clinical response (CY-BOCS<16). All participants received SRT (maximum dose 200mg/day). The study was a part of the Nordic Long-Term OCD Treatment Study (NordLOTS).
  RESULTS: Participants were treated with SRT over 72-300 days (mean=164.2, SD=68.3). The mean CY-BOCS score was reduced from 21.5 (SD=2.6) to 17.5 (SD=3.3). Only three participants obtained adequate clinical response (27.2%), and only two obtained >25% CY-BOCS total score reduction (close to 50%).
  CONCLUSIONS: A clinical response in approximately one third of the participants suggests that SRT treatment might be beneficial to a minority of patients who have consistently failed CBT.

- Prozac—FDA-approved age 14 or more; FDA-approved for depression age 7 or more
  - Dosing: target is 40-60 mg/day; maximum dose range 80-120 mg/day
  - 3 RCT, DB and 1 open-label study
  - Youth:
    - Geller et al, 2001: RCT, DB, 13 weeks, 103 youth; 49% response (defined by 40% or more reduction in symptoms) vs. 25% placebo
    - Liebowitz et al: RCT, DB, 43 youth; 16 weeks, no different from placebo

- Celexa
  - Dosing: target is 40-60 mg/day; maximum dose range 80-120 mg/day
  - Two open-label studies demonstrate efficacy
  - RCT demonstrates efficacy
  - Youth
    - No controlled studies in children
    - Thomson et al: 2 years, open-label

- Lexapro
  - Dosing: target is 20 mg/day; maximum dose range 40-60 mg/day
  - Galvao-de Almeida et al, 2007: open-label study; 11 patients, 30 mg/day, 12 weeks; 54.5% response rate
  - RCT demonstrates efficacy
    - 6-month, placebo-controlled relapse prevention study: relapse was 2.74 times greater with placebo than with Lexapro
  - Youth
    - no control studies in children

- Paxil
  - Dosing: target is 40-60 mg/day; maximum dose range 60-100 mg/day
  - 4 studies, one of which demonstrated reduction in amygdalar volume and one of which demonstrated caudate glutamatergic concentrations
  - Youth
    - Geller et al, 2004: RCT, DB, 32 weeks; very high placebo rates; no difference except less relapse
    - Geller et al: RCT, DB, 10 weeks; effective but not statistically
    - Wagner et al, 2001: effective

- Inadequate response or no response to CBT with SSRI:
  - If moderate (but inadequate response)
    - Augment with:
      - Clomipramine 10-50 mg/day (not alongside 2D6 inhibitors like Prozac); fluvoxamine plus clomipramine can be a helpful combination if carefully monitores
      - Second generation mood stabilizer antipsychotic (SGA) medications
        - Overall 3.31-fold increased chance of response
        - Takes 2-4 weeks for response; 40-50% will respond
        - (First generation antipsychotic medications are also effective)
        - Several open-label and RCT's supporting safety and efficacy of Abilify augmentation of SRI's in OCD (from 2005-2012), with one study suggesting Risperdal may be more effective

- Doses (general)
    - Risperdal 0.5-4 mg/day; avg 2.2 mg/day
    - Zyprexa 5-20 mg/day; avg 11.2 mg/day
    - Seroquel up to 300 mg/day
    - Abilify 15 mg/day
    - (Haldol (first generation) 2-10 mg/day)
- 9 trials in adults: 143 on SGA's (or 1 study with Haldol) and 135 on placebo
    - Risperdal
        - Simpson et al, 2013: Risperdal not more effective than CBT for augmenting SRI's in OCD
        - Erzegovesi et al, 2006: positive
        - McDougle et al, 2000: positive
        - 4 open-label studies; negative statistically (but 40% response rate) in Hollander et al, 2003a
    - Seroquel
        - Denys et al, 2004a: positive
        - Pallanti et al 2002a: positive
        - Positive in a single-blind study of Atmaca et al, 2002
        - Positive in 3 open-label studies
        - Negative in Fineberg et al, 2005 and Carey et al, 2005
        - Negative in one open-label study
    - Zyprexa
        - Bystritskly et al, 2004: positive
        - Another study: positive
        - Positive in 6 open-label studies
        - Negative in Shapira et al, 2004
- Abilify

A Promising Preliminary Study of Aripiprazole for Treatment-Resistant Childhood Obsessive-Compulsive Disorder
Eyup Sabri Ercan, Ulku Akyol Ardic, Elif Ercan, Deniz Yuce, Sibel Durak
Journal of Child and Adolescent Psychopharmacology 2015, 25 (7): 580-4
BACKGROUND: Obsessive-compulsive disorder (OCD) is a relatively frequent disease in childhood, which is generally treated with selective serotonin reuptake inhibitors (SSRIs) and/or clomipramine and cognitive behavioral therapy (CBT). However, nearly half of the cases are treatment resistant. Aripiprazole was shown to be beneficial in augmentation therapy in treatment-refractory OCD. This study evaluated its effectiveness as a single agent in these cases.
METHODS: Sixteen children (nine girls, seven boys), who were nonresponders to treatment with at least two types of SSRIs and CBT, were administered 12 weeks of aripiprazole treatment with a mean dose of 4.75mg/day (range: 2-7.5mg/day). Treatment outcomes were evaluated by the Childhood Yale-Brown Obsessive Compulsive Scale (CY-BOCS), and the Clinical Global Impressions-Severity and Improvement (CGI-S and CGI-I) scales.
RESULTS: Children with a mean age of 10.9±2.9 years had severe obsessive compulsive symptoms at baseline, and >80% of them had another comorbid psychiatric disease. Significant improvements in symptoms were achieved after 12 weeks of aripiprazole treatment, which were evaluated by significant decreases in symptom scores in the CY-BOCS, and improvements in CGI-I scores.
CONCLUSIONS: This very small study of aripiprazole, given to children with OCD resistant to at least 12 weeks treatment with at least two SSRIs and CBT, demonstrated striking improvement in CGI scores (all subsets, $p \leq 0.002$) for 13 of 16 children, and halved all CY-BOCS subscores after ~12 weeks of treatment.

- CBT (ERP)—improves remission rates when patients have inadequate response to medication treatment (Tenneij et al, 2005)
- Add cognitive therapy to ERP—little supporting evidence

- If little to no response:
    - Switch to a different SSRI—70% with mild or more improvement; 30% with no improvement
    - Switch to Anafranil (clomipramine)—FDA-approved age 10 or more
        - Dosing: target is 100-250 mg/day; maximum dose range is based on the blood level (the sum of plasma clomipramine and desmethylclomipramine levels 12 hours after the dose should be kept 500 ng/ml)
        - CYP2C19 poor metabolism (present in 13-23% of Asians and 2-5% of Caucasians) necessitates lower dosing and closer serum monitoring
        - Meta-analyses demonstrate greater efficacy compared to SSRI's

- 12-week study, RCT, comparing ERP, clomipramine, ERP plus clomipramine, and placebo:
  - Combination > ERP>>clomipramine alone>placebo
- Youth
  - Meta-analyses demonstrate greater efficacy compared to fluvoxamine, Zoloft, Prozac, and Paxil
  - DeVeaugh-Geiss et al, 1992
  - Leonard et al, 1989: superior to desipramine
  - Flament et al, 1985: superior to placebo
  - One other positive study
- Side effects
  - Dry mouth 25-39% vs. 11.5% placebo
  - Drowsiness or sedation or somnolence 52-79% vs. 19.1% placebo
  - Sexual side effects 22.2-38.7% vs. 3.8% placebo
  - Sweating 6.5-19.4% vs. 7.7% placebo
  - Tremor 10-17% vs. 0% placebo
  - Dizziness 13-17% vs. 11.5% placebo
  - Nausea 0-11.1% vs. 7.7% placebo
  - Headache 6.5-11.1% vs. 15.4% placebo
  - Constipation11.1-32.3% vs. 3.8% placebo
- Augment with second generation atypical antipsychotic (SGA) medications
- Switch to Effexor XR`
  - RCT demonstrates efficacy
  - Youth
    - No controlled studies in children
- Switch to Remeron
  - A small study with open-label phase followed by double-blind discontinuation supported the switch to Remeron 60 mg/day
- ?Switch to Cymbalta or Pristiq

- Continued inadequate response OR little to no response
  - SSRI plus a different SGA
  - Switch SSRI or SRI to a different agent
  - Augment SSRI with Anafranil (efficacy shown in combination with Celexa or Effexor)
  - Augment SSRI or SRI with:
    - First generation antipsychotic (FGA) medications
      - Haldol—2 mg/d, RCT, 65% response vs. 0% with placebo; more response in those with tics (McDougle et al, 1994)
      - Pimozide—6.5 mg/day (McDougle et al, 1990)
    - Neurontin 1200-2400 mg/day
    - Buspar—little supporting evidence, despite initial positive case reports
    - Pindolol—one small RCT (2.5 mg three times-a-day) positive, but one negative
    - Remeron 12.5-30 mg (add-on)
    - Inositol—three studies of 6 grams three times-a-day, one positive, another demonstrated no benefit, and the third demonstrated benefit in three of ten patients
    - Glutamate antagonist—little supporting evidence
      - Topamax—two positive case series
      - Lamictal
        - Arrojo-Romero et al 2013:
          - Two case reports of successful augmentation with Lamictal
        - Bruno et al, 2012
          - 16 wk, randomized, DB, placebo-controlled, add-on study, 100 mg vs. placebo
          - Safe and effective
        - one case series demonstrated efficacy (with doses up to 100 mg) in one of seven patients
      - Riluzole—glutamate antagonist; positive in open trial (which was methodologically flawed)

- Memantine—positive case reports
- D-cycloserine—partial NMDA agonist; enhances NMDA neurotransmission
    - Some evidence that medications which increase glutamate activity in at least some receptor subtypes may be helpful in OCD; agents that increase NMDA glutamatergic receptors, which are critical for learning and memory, enhance associative learning during exposure and response prevention (ERP) of CBT; more evidence in adults; pilot studies in kids ongoing
- Glutamatergic Agents as Add-On Medication for the Treatment of Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis
  Zacharias G Laoutidis, Georgia E Lekka, Kanellos T Kioulos
  Journal of Clinical Psychiatry 2016 October 25
  OBJECTIVE: The aim of the present study was to review the existing literature on clinical trials with glutamatergic agents in adults with obsessive-compulsive disorder (OCD) and to perform a meta-analysis to estimate the overall effect size.
  DATA SOURCES: We searched in MEDLINE, Embase, and the Cochrane Library for eligible studies, using the following search terms: (glutamate OR glutaminergic OR glutamatergic OR NMDA OR AMPA OR kainate) AND (obsessive-compulsive disorder OR obsessive OR compulsive OR OCD). A separate search was performed for generally known glutamatergic agents. The databases were searched for articles published by May 31, 2015.
  STUDY SELECTION: Eligible studies were double-blind, randomized controlled trials that tested the efficacy of add-on treatment with a glutamatergic agent in patients with OCD.
  DATA EXTRACTION: Data were extracted independently by 2 reviewers. We extracted dichotomous data (number of patients with response and remission) to estimate relative risk ratios (RRs), as well as continuous data (scores in Yale-Brown Obsessive Compulsive Scale and Clinical Global Impressions-Severity of Illness and -Improvement scales), which were used to estimate standardized mean differences. Effect sizes were estimated using a random-effects model.
  RESULTS: Eight randomized controlled trials were identified. The overall ratio for response was RR = 3.71 (95% CI, 2.35-5.83; P < .001). When limited to the studies with treatment-resistant patients, the effect size remained significant (RR = 4.30; 95% CI, 2.19-8.43; P < .001). Secondary outcomes, such as the standardized mean differences for continuous data, showed the statistically significant superiority (P < .001) of glutamatergic agents over placebo. The risk of dropouts was RR = 1.18 (95% CI, 0.83-1.69; P = .361) and the risk of dropouts due to adverse effects was RR = 3.04 (95% CI, 1.57-5.89; P = .001).
  CONCLUSIONS: Glutamatergic agents are effective as add-on treatment for OCD in general and especially for treatment-refractory OCD.
- N-acetylcysteine
- Fish oils
    - 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 (50mg twice per day) or placebo in addition to risperidone titrated up to 2mg/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.
    - 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.

- Investigational agents of antineuronal antibody mediated OCD (PANDAS)
  - Plasma exchange (Nicholson, 2000)
  - IVIG (Perlmutter et al, 1999)
  - Prednisone is contraindicated
- Adderall—one positive trial
- Morphine—one small, double-blind crossover trial supported once-weekly morphine 30-45 mg/day
- Lithium—limited supporting evidence, despite initial positive case reports
- Guanfacine/clonidine—if tics also present
- Neurontin—failed, despite initial positive case reports
- St John's Wort—failed in a large RCT
- Switch to Dexedrine monotherapy—two positive small RCT single dose (30 mg) studies
- Switch to Tramadol monotherapy—positive case reports and case series
- Switch to ondansetron monotherapy—little supporting evidence
- Switch to MAOI monotherapy—little supporting evidence
- ?Trazodone
- Combination treatment; open-label studies

- If response still inadequate:
  - IV clomipramine
- If that fails, consider
  - ECT
  - Transcranial magnetic stimulation
  - Vagus nerve stimulation
  - Neurosurgery
  - Deep brain stimulation

From Stanford:

Pharmacological Treatments

The mechanism of action of the drugs effective in treating OCD (clomipramine, a non-selective serotonin reuptake inhibitor, and the selective serotonin reuptake inhibitors [SSRIs]: citalopram, fluoxetine, fluvoxamine, sertraline and paroxetine) has given rise to the hypothesis that deficient serotonin function is a key element in the pathophysiology of OCD. These drugs block serotonin reuptake by the pre-synaptic neuron, thereby increasing serotonin availability at post-synaptic receptors. The serotonin hypothesis is also supported by the observation that m-CPP (a metabolite of trazodone), which is a partial agonist at serotonin receptor types 1A, 1D and 2C, exacerbates OCD.

About 40% to 60% of patients will respond to clomipramine or to any particular SSRI, and one cannot predict which patient will respond to which drug. A trial of 10-12 weeks at the maximum comfortably tolerated dose is necessary to determine whether a given drug is producing a clinically meaningful response. Direct, controlled comparison studies have found fluvoxamine, paroxetine and sertraline equal in efficacy to clomipramine, the first drug that was demonstrated to be effective in treating OCD. Dr. Koran's clinical

practice is to push the patient in weekly increments to the maximum easily tolerated SSRI (or clomipramine) dose, since it is not possible to predict the dose that will prove effective for an individual patient. For fluvoxamine, he starts the patient at 50 mg/day (25 mg/day for patients who are "sensitive to drugs"), and increases the dose every 5 to 7 days by 50 mg/day to a maximum daily dose of 300 mg/day if possible. Over 10-12 weeks, symptoms decrease by about 40% to 50% or more in about 60% of patients. Disappearance of all symptoms rarely occurs. Benefit is usually noticeable after 6 weeks, but may take 8 weeks to begin. Non-responders to one SSRI may respond to another or to behavior therapy. Partial responders may benefit further from potentiating (augmenting) drugs or from adding behavior therapy (exposure and response prevention, or cognitive approaches). In addition, reports exist of cases successfully treated with buspirone (60 mg), clonazepam (6.5 mg), trazodone (plus tranylcypromine) and venlafaxine, but these drugs should not be used as single-agent therapy until other, better supported medications have been tried. Clozapine, carbamazepine, lithium, clonidine, stimulants, ECT, sleep deprivation, and bright light therapy are not effective.

Drug therapy should be continued indefinitely, since the available data suggest that patients' symptoms will return within one to two months after medications are stopped, even after two years of successful pharmacotherapy. A recent study suggests that 20% of patients who discontinue a successful drug will not respond when the drug is restarted. Available data suggest, but do not prove, that providing behavior therapy while the patient is taking medication may delay or prevent relapse when medication is discontinued. A number of drugs appear to act as potentiators or augmentors of SSRIs, although the data are limited, but controlled trials of potentiating strategies are sorely needed. OCD patients who have comorbid tics or schizotypal personality are unlikely respond to clomipramine or an SSRI alone, but usually will respond to combining one of these drugs with a modest dose of a neuroleptic such as haloperidol, pimozide or risperidone.

In patients who have not responded to an anti-OCD medication or whose response has been inadequate (about 40% of any large series of patients), the clinician can consider adding one of the following drugs: risperidone 0.5-6.0 mg/day; buspirone 60-90 mg/day; olanzapine 2.5-20 mg/day (weight gain is a problem); trazodone 150-600 mg/day; or, L-tryptophan 2 gm twice daily, plus pindolol 2.5 mg three times daily, plus niacinamide 500 mg daily. One starts with a small dose and increases the dose weekly to the likely therapeutic range, as necessary and as tolerated. Response should be evident within two weeks at a given dose, except for trazodone and the L-tryptophan combination, which may take four to six weeks to produce a substantial effect.

For severely anxious OCD patients, gabapentin 300-3600 mg/day or clonazepam 1-4 mg/day or lorazepam 1-4 mg/day are often helpful. No data support the practice of combining two SSRIs. However, European clinicians are combining clomipramine 50-150 mg with fluvoxamine (50-150 mg), fluoxetine (20-40 mg), sertraline (50-100 mg) or citalopram 40 mg/day and claiming success in many patients unresponsive to either drug alone. When clomipramine is combined with any SSRI other than citalopram, one must monitor blood levels of clomipramine and desmethylclomipramine to avoid cardiac and CNS toxicity. Aim for clomipramine levels of 225-350 ng/ml and combined clomipramine and desmethylclomipramine levels of < or = to 500 ng/ml in blood samples drawn about 12 hours after a dose; steady state takes two to three weeks to achieve. Note that Asian patients may require smaller doses of clomipramine than Caucasians. Unpleasant side effects such as sedation, sexual dysfunction, and weight gain (20-30 lbs.) can lead patients to discontinue clomipramine or SSRIs. Rare reports of akathisia, bleeding, easy bruising and dyskinesias exist. A variety of management strategies can be implemented. Anorgasmia or reduced libido may respond to bupropion 75-150 mg/day, buspirone 15-60 mg, amantadine 100-400 mg/day, methylphenidate 10-20 mg/day, dexedrine 5-10 mg/day or yohimbine 5.4-16.2 mg; additional drugs that may help anorgasmia include sildenafil, mirtazapine and nefazodone. Queasiness is usually transient (weeks) and can be minimized by lowering the dose and titrating up slowly. Diarrhea may respond to taking lactobacillus acidophilus capsules once or twice daily.

Early onset of response with selective serotonin reuptake inhibitors in obsessive-compulsive disorder: a meta-analysis

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OBJECTIVE: Selective serotonin reuptake inhibitors (SSRIs) are recommended as the first-line pharmacologic treatment for obsessive-compulsive disorder (OCD). SSRI response is thought to be delayed in OCD, even more so than in major depression. We conducted a meta-analysis to examine the trajectory of treatment response to SSRIs and how this trajectory is modulated by dosage.

DATA SOURCES: PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched on May 22, 2013, for randomized, placebo-controlled SSRI trials in OCD with the search terms "serotonin uptake in-

hibitors" [MeSH] OR "serotonin uptake inhibitors" [Pharmacologic Action] AND "obsessive-compulsive disorder" [MeSH]. There were no language limitations on the search.
STUDY SELECTION: Randomized, placebo-controlled trials that examined the efficacy of SSRIs in the treatment of adults with OCD and utilized the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) as an outcome were selected.
DATA EXTRACTION: We extracted weekly symptom data from randomized, placebo-controlled trials of SSRIs for the treatment of adults with OCD in order to characterize the trajectory of pharmacologic response. Our primary outcome was weighted mean difference on the Y-BOCS of SSRI treatment compared to placebo. We used the PROC MIXED procedure in SAS to examine 6 possible models of SSRI response. Interaction terms were utilized to examine the effect of dose, individual agent, and year of publication on SSRI response.
RESULTS: The meta-analysis included 17 trials of SSRIs including 3,276 subjects. A statistically significant benefit of SSRIs compared to placebo was seen within 2 weeks after the start of treatment (weighted mean difference = -0.91 [95% CI, -0.54 to -1.28], $P < .001$). A logarithmic response curve, indicating decreasing symptom improvement over time, provided the best fit for the trajectory of OCD symptom improvement. A significantly greater response was associated with using higher doses of SSRIs ($P < .0001$).
CONCLUSIONS: These results suggest that the greatest incremental treatment gains in OCD are seen early on in SSRI treatment. This is consistent with a previous meta-analysis examining time course of SSRI action in major depressive disorder and contrasts with the widely held belief that SSRI response in OCD is delayed.