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Serotonin-Specific Reuptake Inhibitors (SSRI's)

- General
  - Women before the age of 40 tend to respond better to SSRI's than men. After the age of 40, women tend to respond better to medications or medication combinations that increase norepinephrine
  - Obese men tend to respond much less to SSRI's than men who are not obese
  - Men tend to respond better to medications or medication combinations that increase norepinephrine, compared to women before the age of 40
  - Consider supplement with B6 (not mega-doses; discuss amount with psychiatrist)
  - **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**
  - **Likely optimal/maximal doses for SSRI's/SNRI's in youth per research studies; keep in mind, in individual cases, these maximal doses may be exceeded**
    - **Prozac up to 40 mg/day (TADS, 2004)**
    - **Fluvoxamine 100-150 mg/day (RUPP, 2001)**
    - **Zoloft 100-150 mg/day (CAMS, 2009)**
    - **Paxil 40-50 mg/day (Geller, 2004)**
    - **Cymbalta 60-120 mg/day (PDR)**
  - **Benefit/Risk of suicidality (see separate handout as well)**
    - **% difference between response rates of SSRI's and placebo**
      - **11% in depression**
      - **20% in OCD**
      - **37% in non-OCD anxiety**
    - **Numbers needed to treat (NNT) to show benefit of med (above placebo); the smaller the number the better**
      - **10 in depression (overall; the number drops to 3 if you include only NIH studies)**
      - **5 in OCD**
      - **3 in non-OCD anxiety**
    - **% difference between suicidality in those on SSRI's vs. placebo**
      - **1-2% overall (0.7 - >2%, depending on the med)**
      - **0.9% for depression**
      - **0.5% for OCD**
      - **0.7% for non-OCD anxiety**
    - **Numbers needed to harm (NNH) to show risk of suicidality from med (above placebo risk); the higher the number the better**
      - **50-143 overall**
      - **~100 in depression**
      - **~200 in OCD**
      - **~140 in non-OCD anxiety**
  - **It's important to note that placebo rates are higher in youth patients than adults patients, as it's impossible to not directly or indirectly address/provide psychosocial support for children/families in placebo conditions vc**
- **Systematic review and meta-analysis of SSRI's/SNRI's in youth depressive disorders, anxiety disorders, OCD, and PTSD (Locher et al, 2017)**
  - **36 studies examined**
    - **17 for depressive disorders**
    - **10 for anxiety disorders**
    - **8 for OCD**
    - **1 for PTSD**
  - 6,778 participants
  - SSRI's and SNRI's more effective than placebo (the higher the number, the better, as it measures how much more efficacious a medication is than placebo)
    - **Overall effect size** **0.32**
    - Anxiety do's 0.56
      - **Anxiety do's, SSRI's only** **0.71**
      - Anxiety do's, SNRI's only 0.41
    - Depressive do's 0.20
      - **Depressive do's, SSRI's only** **0.21**
      - Depressive do's, SNRI's only 0.16
    - **OCD, SSRI's only** **0.39**
    - **PTSD, SSRI's only** **0.16**

- There was a significantly larger placebo response in youth depression studies than in anxiety studies
- **More below, but meta-analysis of 27 trials of pediatric major depression in terms of risk of suicidal ideation and/or suicide attempts:**
  - **Antidepressants** **3%**
  - **Placebo** **2%**
- Side effects
  - Treatment-emergent side effects — 1.07X risk with SSRI's/SNRI's compared to placebo
    - **SSRI vs. placebo** **1.07X**
    - SNRI vs. placebo 1.07X
    - **Depressive disorders**
      - **SSRI vs. placebo** **1.06X**
      - SNRI vs. placebo 1.12X
      - Combined vs. placebo 1.06X
    - **Anxiety disorders**
      - **SSRI vs. placebo** **1.23X**
      - SNRI vs. placebo 1.06X
      - Combined vs. placebo 1.08X
    - **OCD**
      - **SSRI vs. placebo** **1.08X**
    - **PTSD**
      - **SSRI vs. placebo** **1.00X**
  - Severe adverse events — 1.76X risk with SSRI's/SNRI's compared to placebo
    - **SSRI vs. placebo** **1.84X**
    - SNRI vs. placebo 1.56X
    - **Depressive disorders**
      - **SSRI vs. placebo** **1.40X**
      - SNRI vs. placebo 2.95X
      - Combined vs. placebo 1.66X
    - **Anxiety disorders**
      - **SSRI vs. placebo** **3.45X**
      - SNRI vs. placebo 0.78X
      - Combined vs. placebo 1.38X
    - **OCD**
      - **SSRI vs. placebo** **3.59X**
    - **PTSD**
      - **SSRI vs. placebo** **2.31X**
  - Discontinuation due to adverse effects — 1.79X with SSRI's/SNRI's compared to placebo

- Youth depression
  - Meta-analysis by Bridge et al, 2017
    - Antidepressants with response rate of 61%
    - Placebo with response rate of 50% (!)
  - FDA-approved meds
    - Prozac in 8-17 yo, based on 3 trials
    - Lexapro in 12-17 yo, based on 1 trial
  - Other controlled pediatric depression studies

Controlled Pediatric Depression Trials

(K. Wagner, MGH Pediatric Psychopharmacology, 2016, 2018)

	Medication	Ages	Number
Positive	Citalopram	7-17	1
	Sertraline	6-17	2
Negative	Citalopram	13-19	1
	Escitalopram	6-17	1
	Paroxetine	7-17 12-18 13-18	3
	Mirtazapine	7-18 7-18	2
	Nefazodone	7-17 12-17	2
	Venlafaxine	7-17 7-17	2

  - Cipriani et al, 2016; antidepressants in youth depression
    - Only Prozac better than placebo
    - In pair-wise meta-analyses, Lexapro and Zoloft better than placebo

- In dichotomous response, Prozac, Lexapro (almost), Cymbalta, and Serzone more effective than placebo
- Imipramine, Effexor, and Cymbalta d/c'd due to side effects more than placebo
- Effexor associated more with increased risk suicidal events

- Meta-analysis of 13 studies, 3004 youth with depression, looking at Prozac, Paxil, Lexapro, Celexa, Zoloft; Varigonda et al, 2015
  - No difference between the 5 SSRI's
    - But Prozac has stronger benefit in Bridge et al, 2007 and Cipriani et al, 2016
  - No difference of age, number of sites, or maximum dose
    - But, less effective in younger kids (except for Prozac) in Bridge et al, 2007
    - But, higher dose associated with more improvement in Heiligenstein et al, 2006 and Sakolsky et al, 2011
  - **Ultimate response evidence within 2 weeks**
    - **Also seen in Tao et al**
    - **Also seen in Emslie 2010**
  - Lower response rates than adults
    - **Not so much if one controls for severity of depression**
  - Slow improvement through at least 10 weeks
- Differences between youth depression remitters and non-remitters, Tao et al, 2009 and Emslie et al, 2010
  - Less symptom reduction overall
  - Slower symptom reduction
  - Symptom reduction plateaus around 8-9 weeks (vs. slow improvement in remitters through at least 24 weeks)
- **Treatment of SSRI-Resistant Depression in Adolescents Trial**
  - **Looked at**
    - **different SSRI**
    - **different SSRI+CBT**
    - **switch to Effexor XR**
    - **switch to Effexor XR+CBT**
  - **Response rates**
    - **diff SSRI 47%**
    - **Effexor XR 48%**
    - **no CBT 42%**
    - **+ CBT 55%**
- **Summary of Treatment for Adolescent Depression Study (TADS)**
  - **Response rates at 12 weeks**
    - **Prozac+CBT 73%**
    - **Prozac 62%**
    - **CBT 48%**
    - **Placebo 35%**
  - **Response rates at 18 weeks**
    - **Prozac+CBT 85%**
    - **Prozac 69%**
    - **CBT 65%**
  - **Response rates at 36 weeks**
    - **Prozac+CBT 86%**
    - **Prozac 81%**
    - **CBT 81%**
- **Standard for depression treatment in youth**
  - **Start with SSRI**
    - **Prozac**
    - **Lexapro**
  - **If fails,**
    - **try another SSRI (if no response)**
      - **If used Prozac, try Lexapro (in adolescent)**
      - **If used Lexapro, try Prozac**
      - **Celexa**
      - **Zoloft**
    - **Consider augmentation (if partial response)**
      - **Abilify**
      - **Lithium**
      - **Wellbutrin XL**
  - **If fails, try different class of antidepressant**
    - **Wellbutrin XL (limited evidence)**
    - **Effexor XR**
    - **Cymbalta (conflicting evidence)**
    - **Pristiq (conflicting evidence)**
  - **If fails, consider**
    - **Trintellix**
    - **Viibryd**
    - **Levomilnacipran**
- Fournier, JAMA, 2009; meta-analysis of 6 randomized controlled drug trials of 718 patients, examining Paxil and imipramine, and NO OTHER antidepressants; studies lasted only 6-8 weeks; medication benefits were only statistically significant in very severe depression
- **Cheung et al, 2008: maintenance treatment for adolescent depression**
  - **Maintained response (without recurrence) at 52 weeks**
    - **Zoloft 38%**

        - **Placebo 0%**
    - Meta-analysis of Antidepressant Trials for Depression in Youth; Tsapakis et al, 2008; note: NNT less than 10 indicate likely/reasonable efficacy; it indicates the number of patients that need to be treated for a benefit to occur that is connected to the drug and not to random changes)
        - NNT 8 for adolescents (which demonstrates moderate efficacy)
        - NNT 21 for children (which demonstrates lack of efficacy)
    - Bridge et al, 2007; meta-analysis of antidepressants in pediatric trials; note: NNT less than 10 indicate likely/reasonable efficacy; and the higher the NNH, the lower the risk (it signifies the number of patients that need to be treated with the drug before a particular side effect, in this case suicidality, might occur that is connected to the drug and not the illness)
        - Major depression NNT 10 (range 7-15) NNH 112
        - OCD NNT 6 (range 4-8) NNH 200
        - Non-OCD anxiety disorders NNT 3 (range 2-5) NNH 143
    - Meta-analysis, Bridge, 2007
        - Antidepressants 61% response rate vs. 50% with placebo
    - Prozac FDA-approved for depression in kids aged 8-17
    - Lexapro FDA-approved for depression in kids aged 12-17
    - Zoloft has fairly good (pooled) evidence as well for depression
    - TORDIA (Treatment of Resistant Depression in Adolescents) study suggest 40% of depressed adolescents who do not respond to one SSRI will respond to a second SSRI (with or without CBT)
    - Celexa
        - One positive study in kids 7-17
        - One negative study in kids 13-18
    - Negative studies
        - Paxil
        - Effexor XR
        - Remeron
        - Serzone
- Youth anxiety
    - Prozac, Zoloft, and fluvoxamine FDA-approved for OCD
    - Efficacy of SSRI's in youth is greater in the treatment of anxiety disorders than depression
    - Meta-analysis of 9 studies (1673 kids) of antidepressants in pediatric anxiety, Strawn et al, 2014
        - All studies and overall effect size favors med over placebo
        - Risk of activation 1.86 fold increase overall (0.98-3.53 range; values >1 indicate risk)
        - Risk of suicidality 1.30 fold increase overall (0.53-3.16 range; values > 1 indicate risk)
        - Meds studied
            - Prozac
                - Beidel et al, 2007
                - Birmahar et al, 2003
            - Zoloft
                - Walkup et al, 2008
                - Rynn et al, 2001
            - Fluvoxamine
                - Rupp, 2003
            - Paxil
                - Wagner et al, 2004
            - Effexor
                - March et al, 2007
                - Rynn et al, 2007
            - Cymbalta
                - Strawn et al, 2013
    - Child/Adolescent Anxiety Multimodal Study (CAMS): Evaluating Safety (Rynn et al, 2015)
        - Kids aged 7-17 with various anxiety disorders
        - Sertraline vs. CBT vs. combined treatment vs. placebo
        - No suicide attempts in any of the children (in any arm) in study
        - Rates of total physical adverse events were greater with sertraline compared to CBT
            - Insomnia
            - Fatigue
            - Sedation
            - Restlessness/fidgeting
        - Rates of specific physical adverse events were greater with sertraline compare to CBT and combined treatment
        - Rates of total psychiatric adverse events were greater in all children across all arms and decreased over time, with no significant differences between treatment groups
        - Results support safety and tolerability of sertraline in the treatment of anxiety in youth
    - CAMS and Child/Adolescent Anxiety Multimodal Extended Long-Term Treatment Study (CAMELS): year 1 results
        - ½ of sample (46%) in remission (52% of initial responders in remission)
        - Relapse rates high
        - Acute treatment type unrelated to long-term outcomes
        - Predictors of remission
            - Male
            - Higher SES
            - Lower baselines anxiety
            - Not having an externalizing disorder at baseline like ADHD or ODD

        - Better family functioning
        - Fewer negative life events
- SSRI's decrease risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression (Bartels et al, 2018)
    - Depression itself is associated with increased risk of Alzheimer's disease
    - SSRI's decrease amyloid-beta generation and plaque load
    - 775 currently non-depressed participants with mild cognitive impairment (MCI)
    - In MCI patients with a history of depression
        - Long-term SSRI treatment (>4 years) was significantly associated with a delayed progression to Alzheimer's disease by approximately 3 years, compared with short-term SSRI treatment, treatment with other antidepressants, or no treatment and compared with MCI patients without a history of depression
        - No differences in CSF biomarker levels were observed between the treatment groups

- **Prozac/Sarafem** (fluoxetine)
  - General
    - introduced 1988.
    - some inhibition of norepinephrine reuptake which may contribute to activating side effects. ?decreases dopamine?
    - therapeutic range 20-80+ mg/D; FDA max: 80 mg/D; in children, start with 5-10 mg
    - peak level in 6-8 hours
    - half life 1-4 days (and 7-15 days for active metabolite); half lives increase in duration with repeated administration due to inhibition of own metabolism
    - Metabolized by 2D6, 3A4
    - Inhibits 2D6, 3A4—raises Strattera
    - 10, 20, 40 mg caps, 90 mg weekly cap, 10, 20, 40 mg generic tablets and capsules; 20 mg/5 ml solution (120 ml bottle)
  - FDA-approval
    - **Depression in children 7 and older as of January, 2003**
    - Depression in adults
    - Dysthymia
    - OCD in youth (age 7 and older) and adults
    - Bulimia nervosa
    - Panic disorder
    - Pre-menstrual dysphoric disorder
    - Bipolar depression (in combination with Zyprexa)
  - Evidence in adults
    - Multiple trials demonstrating safety and efficacy in adults in anxiety and depression
      - Prevention of relapse and recurrence in responders to cognitive therapy (extended cognitive therapy vs. Prozac vs. placebo)
        - Extended cognitive therapy was more effective than placebo
        - Prozac was more effective than placebo
      - Maintenance study in depression, 11 months, 20% recurrence rate vs. 40% placebo
      - Maintenance study in depression, 12 months, 26% recurrence rate vs. 57% placebo
    - PTSD (Connor et al, 1999; Martenyi et al, 2002, van der Kolk et al 1994l Martenyi et al, 2002; off label)
    - Social Anxiety Disorder (data mixed)
      - Davidson et al, 2004
      - Clark et al, 2003
      - Kobak et al, 2002
    - Panic disorder: naturalistic study of 200 patients assigned to either Celexa, Prozac, fluvoxamine or Paxil for 12 months
      - Retention rates (the % of patients who remained in the study for all 12 months)
        - Paxil 76%
        - Celexa 68%
        - Fluvoxamine 60%
        - Prozac 50%
      - Weeks 4 and 8, Paxil and Celexa associated with less symptoms than fluvoxamine and Prozac
      - Months 3, 6, 9, and 12, no differences in relapse rates for any of the medications
      - Weight gain occurred to the same degree in all four
      - Sexual side effects occurred to the same degree in all four except fluvoxamine had a bit less at the 12 month point
  - Evidence in children demonstrating safety and efficacy:
    - Anxiety
      - Beidel, 2007: 140 youth with social phobia aged 7-26 in RCT, DB, placebo-controlled trial of Prozac vs. social effectiveness therapy for children (SET-C) vs. placebo; 12 weeks; Prozac dose up to 40 mg
        - SET-C
          1. 78% response rate
          2. 56% no longer met diagnostic criteria for social phobia
          3. Improvement begins at week 8 and continues past 12 weeks
        - Prozac
          1. 39% response rate
          2. 30% no longer met diagnostic criteria for social phobia
          3. Improvement occurred only from week four to week 8
        - Placebo
          1. 6% response rate
          2. 6% no longer met diagnostic criteria for social phobia
      - Birmaher et al, 2003: RCT, DB, 12 weeks, separation or generalized or social anxiety disorder;
        - 61% response with Prozac
        - 35% with placebo
      - Clark, 2005: open-lane, 1-year extension to controlled trial of 7-17 yo's with anxiety; safe and effective.
      - Birmaher, 2003: 7-17 yo, 74 youth, safe and effective vs. placebo in generalized anxiety disorder and social phobia but not in separation anxiety disorder
      - Fairbanks et al, 1997: Prozac in 16 youth (aged 9-18) with mixed anxiety disorders: 40-60% response rate.
      - 1997: 56% response vs. 33% with placebo.
      - Birmaher et al, 1994: Prozac (average dose 25.7 mg), 21 youth with anxiety disorders resistant to psychotherapy and other psychopharmacologic treatment, 10-week: 81% improvement

- Black and Uhde, 1994: 6-7 yo's with selective mutism plus social phobia or avoidant disorder, 15 youth, safe and effective vs placebo
- Data on OCD in a separate handout

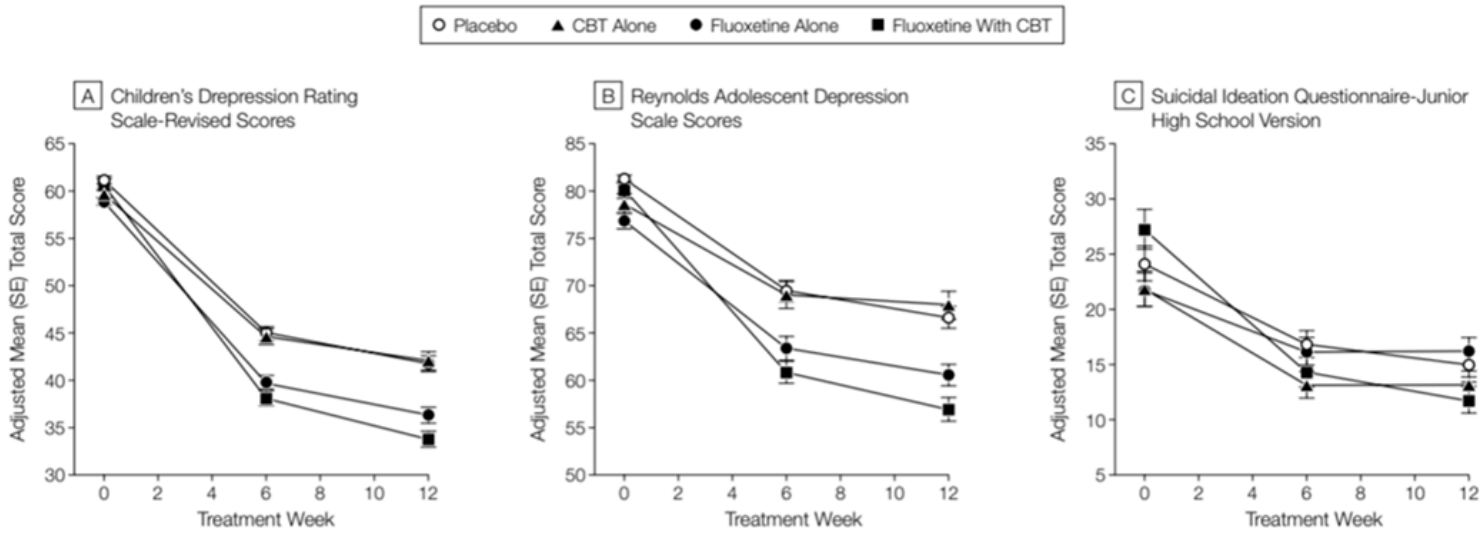
- Depression

Key Point: Algorithm for MDD Treatment

(Texas Consensus Panel; Hughes et al; JAACAP; 2007; 46 (6); 667-686 and K. Wagner, MGH Psychopharm; March 2014)

- **Stage 0:** Diagnostic assessment and monitoring; high placebo response rates should be kept in mind.
- Minimum 8 weeks each medication.
- **Stage 1**: Monotherapy: SSRI: fluoxetine, escitalopram
- **Stage 2**: Alternative SSRI (citalopram, sertraline)
- **Stage 2a:** Augmentation for partial responders: (lithium, bupropion, aripiprazole)
- **Stage 3**: Monotherapy Different Class: (bupropion, venlafaxine, duloxetine)
- **Stage 4**: Reassess or Maintenance or newer antidepressant (vilazodone, desvenlafaxine)
- *Patients require 6-12 months of acute treatment; some patient may need maintenance of one year or more to avoid recurrences.*

- Emslie et al, 2006, 2004, 2002, 1997: RCT, DB, placebo-controlled, children and adolescents with depression, responders to 12 weeks of Prozac treatment were then randomized to either Prozac or placebo for the next 6 months: Prozac was safe and effective in reducing chance of relapse.
- Tao et al, 2006: 12 weeks of open-label treatment of depression with Prozac in 168 youth aged 7-18: all depressive symptoms had significant improvement
  - 39.7% reduction in symptom scale scores by week 2
  - 59.6% reduction in symptom scale scores by week 4
  - 65.5% remission rate by week 12
- ***Treatment Study of Adolescent Depression Study 2005, 2007,*** multicenter, RCT, double-blind, placebo-controlled, 12 –weeks, 439 randomized patients, 359 of which remained in their designated treatment arms for 12 weeks
  - Treatment arms:
    - Prozac AND CBT together
    - Prozac ALONE
    - Cognitive behavior therapy (CBT) ALONE
    - Placebo
  - Quick summary
    - Response rates at 12/18/36 weeks:
      - **Prozac AND** CBT: 73%/85%/86%
      - **Prozac ALONE**: 62%/69%/81%
      - CBT: 48%/65%/81%
      - Placebo (12 weeks) 35%



CBT indicates cognitive-behavioral therapy. Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random coefficient model.

- Fuller Results:
  - **<u>Prozac AND</u>** CBT
    - Response rates
      1. Response rate, general
         - 73% at 12 weeks
         - 85% at 18 weeks
         - 86% at 36 weeks
      2. Response rate relative to placebo:
         - superior to placebo on 15 of 16 endpoints
         - faster onset of benefit
         - sooner time to stable response
         - 3-fold increased chance of sustained early response; more effective in improving functioning and quality of life on all endpoints
      3. Response rate relative to CBT alone:
         - superior on 14 of 16 end points
         - 3-fold increased chance of sustained early response (per psychotherapist ratings)
      4. Response rate relative to Prozac alone:
         - superior on 8 of 16 endpoints
         - sooner time to stable response
         - 1.5-fold increased chance of sustained early response
    - Remission rates
      1. Remission rate general
         - 37% at 12 weeks
      2. Relative to Prozac alone:
         - 2.1-fold increased chance of remission
         - 1.7-fold increased chance of no longer meeting criteria for depression
      3. Relative to CBT alone:
         - 3.3-fold increased chance of remission
         - 4.3-fold increased chance of no longer meeting criteria for depression
      4. Relative to placebo:
         - 3-fold increased chance of remission
         - 4.1-fold increased chance of no longer meeting criteria for depression
    - Worsening:
      1. 0% globally
      2. 2.8% if more lenient criteria used
      3. 1.9% if look at 1 point or more deterioration on the CDR-S scale
    - Suicidality ½ as much as Prozac alone
      1. Absolute benefit increase relative to placebo is 37%; relative to placebo 2%
      2. The benefit to risk ratio is 16.7
  - **<u>Prozac ALONE</u>**
    - Response rates
      1. Response rate, general
         - 62% at 12 weeks

        - 69% at 18 weeks
        - 81% at 36 weeks
    2. Relative to CBT:
        - superior on 8 of 14 endpoints
        - more effective in treating functioning and quality of life on one measure
    3. Relative to placebo:
        - superior to placebo on 7 of 16 endpoints
        - faster onset of benefit
        - sooner time to stable response
        - 2-fold increased chance of sustained early response
        - more effective in treating functioning and quality of life on one measure
- Remission rates
    1. Remission rate, general
        - 23% at 12 weeks
    2. Relative to CBT alone:
        - 1.6-fold increased chance of remission
        - 2.5-fold increased chance of no longer meeting criteria for depression
    3. Relative to placebo:
        - 1.5-fold increased chance of remission
        - 2.4-fold increased chance of no longer meeting criteria for depression
- Worsening:
    1. 1.8% globally
    2. 3.7% if more lenient criteria used
    3. 6.4% if look at 1 point or more deterioration on the CDR-S scale
- Absolute benefit increase relative to placebo is 27%
- Absolute risk increase relative to placebo is 4.7%
- The benefit to risk ratio is 5.3

- **<u>CBT ALONE</u>**
    - Response rate
        1. Response rates, general
            - 48% at 12 weeks
            - 65% at 18 weeks
            - 81% at 36 weeks
        2. Similar to placebo rate of response rate of 35%
    - Remission rates
        1. Remission rates, general
            - 16%
        2. Relative to placebo
            - 0.9-fold increased chance of remission
            - 1-fold increase chance of no longer meeting criteria for depression
    - Worsening:
        1. 0% worsened globally
        2. 9.9% if more lenient criteria used
        3. 5.4% if look at 1 point or more deterioration on the CDR-S scale
    - Suicidality ½ as much as Prozac alone
- **<u>Placebo</u>**
    - Response rate 34.8%
    - Remission rate 17%
    - Worsening:
        1. 1.8% worsened globally
        2. 7.1% if more lenient criteria used
        3. 5.4% if look at 1 point or more deterioration on the CDR-S scale
- Suicidality (also see below)
    - ***<u>29%</u>*** of the depressed young patients reported having clinically significant suicidal thoughts at baseline ***<u>(BEFORE MEDICATIONS)</u>***, even though youth who were the most suicidal were excluded from the study (due to clinical and ethical need to treat openly).
    - ***<u>10%</u>*** of the depressed young patients reported having clinically significant suicidal thoughts ***<u>at week 12</u>*** ***<u>OF TREATMENT</u>***
    - Still, suicidal events were twice as likely in patients treated with Prozac alone than Prozac AND CBT or CBT alone—this might indicate that CBT (or therapy in general) might mitigate against suicidality
    - Breakdown (NB: there were no youth with preparatory suicidal behavior nor any deaths):
        1. **<u>Prozac AND CBT</u>**: 1.9% suicide attempts; 0.9% self-injurious behavior; 2.8% suicidal ideation; **4.7-5.6**% **total** suicide-related events

(primary and sensitivity analysis)
2. **Prozac alone:** 1.8% suicide attempts; 0% self-injurious behavior; 7.3 suicidal ideation; **9.2% total** suicide-related events (primary and sensitivity analysis)
3. **CBT alone:** 0.9% suicide attempts; 0% self-injurious behavior; 3.6% suicidal ideation; **4.5% total** suicide-related events (primary and sensitivity analysis)
4. **Placebo:** 0% suicide attempts; 0% self-injurious behavior; 2.7% suicidal ideation; **2.7% total** suicide-related events (primary and sensitivity analysis)

- Long-term outcome following TADS
  - 47% experienced recurrence of depression
  - Multiple psychiatric co-morbidities
- Emslie, 2004: 32-week relapse prevention study of child and adolescent depression
- Emslie, 2002: depression; 52% response vs. 37% with placebo.
- Emslie, 2001: depression; treated with 20-60 mg Prozac for 19 weeks, responders randomized to Prozac or placebo for 32 weeks; relapse rates twice as high and time to relapse twice as fast for placebo vs. Prozac

- Autism spectrum disorder
  - Helps with repetitive behaviors in adults (not kids)
  - ACTN 2009; 14-week, double blind, placebo-controlled, 158 subjects, 5-17 yo
    - Not effective for repetitive behaviors
  - Hollander et al, 2005; crossover study, Prozac vs. placebo, 45 subjects, 5-11 yo, 5-15 mg/day
    - Prozac > placebo for compulsivity
    - No difference in side effects

- Side Effects
  - Early worsening of depression (via HAM-D) 30.4%; may be associated with decreased likelihood of achieving remission
  - Sexual dysfunction 15% when not assessed; 58% when formally assessed
  - Anxiety/agitation 10-26%
    - TADS: agitation spectrum 0.93-1.84% vs. 0-1.78% in placebo
    - TADS: anxiety 0-1.84% vs. 0-0.91%
    - Autism: 62% v. 77% placebo
  - Drowsiness OR fatigue OR lassitude 11.5-25%
    - TADS: 0.9-2.8% vs. 0% in placebo
    - Autism: 18% v. 11% placebo
  - Nausea 11-23%
  - Decreased appetite 11%; autism: 15% v. 11% placebo
  - Dry mouth 10%
  - Tremor 10%
  - Insomnia 6.7-20%
    - TADS study: 2.8-4.7% vs. 0.9% in placebo
    - Autism: 36% v. 47% placebo
  - Constipation 5%
  - Headache 4.8-21%
  - Hyperprolactinemia 4% in men and 22% in women
  - Sweating 4-8%
  - Dizziness 3-10%
  - Irritability in TADS: 1.86-3.67% vs. 0-0.89% in placebo
  - Vomiting in TADS: 1.8-3.7% vs. 1.8% in placebo
  - Mania spectrum in TADS: 0.93-3.67% vs. 0-0.89% in placebo
  - Upper abdominal pain in TADS: 0.9-5.5% vs. 0.90-1.8% in placebo

- **Celexa** (citalopram)
  - General
    - Introduced in 1998.
  - Pharmacodynamics
    - With Paxil and Lexapro, one of the most potent of the SSRI's; may increase dopamine levels.
    - Therapeutic range 10-60 mg/D; FDA max: 60 mg/D
      - NB: new recommended FDA-max (2011) is 40 mg/day due to risk of ECG abnormalities on higher doses (namely QT interval prolongation)
    - In children, start 5-10 mg;
    - Half-life 23-45 hours; peak level in 4-6 hours
    - Metabolized by **2C19**; this is important in that poor metabolizers of 2C19 will have higher blood levels of citalopram, which can cause QTc prolongation (as such, 20 mg is max in 2C19 poor metabolizers)
    - Weak inhibitor of 2D6 (could increase levels of Strattera, codeine, and some beta blockers)
    - 10, 20, 40 mg scored tabs; 10 mg/5 ml solution (240 ml bottle); comes generic
  - FDA-approval
    - Depression in adults
    - Dysthymia
  - Evidence of safety and evidenced in adults
    - Multiple trials demonstrating safety and efficacy in adults
    - Maintenance study, 12-18 months, 18% recurrence rate vs. 45% placebo
    - Maintenance study, 11 months, 32% recurrence rate vs. 67% placebo
    - Social Anxiety Disorder (Celexa/Lexapro)
      - Kasper et al, 2005
      - Furmark et al, 2005
      - Lader et al, 2004
    - Panic disorder: naturalistic study of 200 patients assigned to either Celexa, Prozac, fluvoxamine or Paxil for 12 months
      - Retention rates (the % of patients who remained in the study for all 12 months)
        - Paxil 76%
        - Celexa 68%
        - Fluvoxamine 60%
        - Prozac 50%
      - Weeks 4 and 8, Paxil and Celexa associated with less symptoms than fluvoxamine and Prozac
      - Months 3, 6, 9, and 12, no differences in relapse rates for any of the medications
      - Weight gain occurred to the same degree in all four
      - Sexual side effects occurred to the same degree in all four except fluvoxamine had a bit less at the 12 month point
  - Evidence of safety and efficacy in children:
    - NB: recent concerns about QTc prolongation and the risk of arrhythmias with doses of Celexa above 40 mg/day have been reinvestigated (Zivin et al, 2013) and found that there does not appear to be such a risk. 618,450 patients on various doses of Celexa were assessed and compared to 365,898 patients on various doses of Zoloft and neither medicine at any dose was associated with arrhythmias, cardiovascular problems, or mortality. If anything, the risk with Celexa was lower at doses above 40 mg/day vs. doses below 40 mg/day.
    - Depression
      - Shirazi, 2005: 30 children with depression aged 8-17 were treated in an open trial with Celexa 10-40 mg for six weeks. 91.7% had a moderate to large improvement in symptoms. However, 5 of the 30 patients unexpectedly developed mania.
      - Wagner, 2004: randomized, placebo-controlled eight-week study of Celexa for the treatment of major depression in children and adolescents supported the safety and efficacy of Celexa.
      - Wagner, 2001, 174 outpatient children with depression, ages 7-17; 8 week, double-blind, placebo-controlled study, 20-40 mg Celexa (average 23 mg); safe and efficacious (in terms of response and remission).
    - Anxiety
      - Seedat, et al, 2002
        - 24 youth with PTSD
        - Effective and well-tolerated
      - Courturier and Nicolson examined retrospectively the use of Celexa in 17 children with Asperger's syndrome
        - it appeared safe and efficacious (but only in treating anxiety and aggression).
      - Unpublished European, double-blind randomized controlled trial in youths with depression
        - ***negative*** (but with mix of inpatients and outpatients, methodological flaws and high dropout rates).
      - Data on OCD in separate handout
    - Autism spectrum disorder
      - King et al, 2009
        - 149 youth, 6-12 yo, with repetitive behavior, 12 week, double-blind, placebo-controlled, 10-25 mg/day
        - Celexa = placebo
        - Side effects
          1. Increased energy

2. Impulsivity
3. Decreased concentration
4. Hyperactivity
5. Stereotypy
6. Diarrhea
7. Insomnia
8. Dry skin/itchiness

- Side effects
  - Insomnia 15%
  - Sweating 11%
  - Drowsiness OR fatigue 10-18%
  - Sexual side effects 8% but 65% when formally assessed
  - Tremor 8%
  - Nausea 7-21%
  - Dry mouth 6-20%
  - Anxiety/nervousness 6%
  - Decreased appetite 4%
  - Diarrhea 3-8%

High-Dose Citalopram and Escitalopram and the Risk of Out-of-Hospital Death

Wayne A Ray, Cecilia P Chung, Katherine T Murray, Kathi Hall, C Michael Stein

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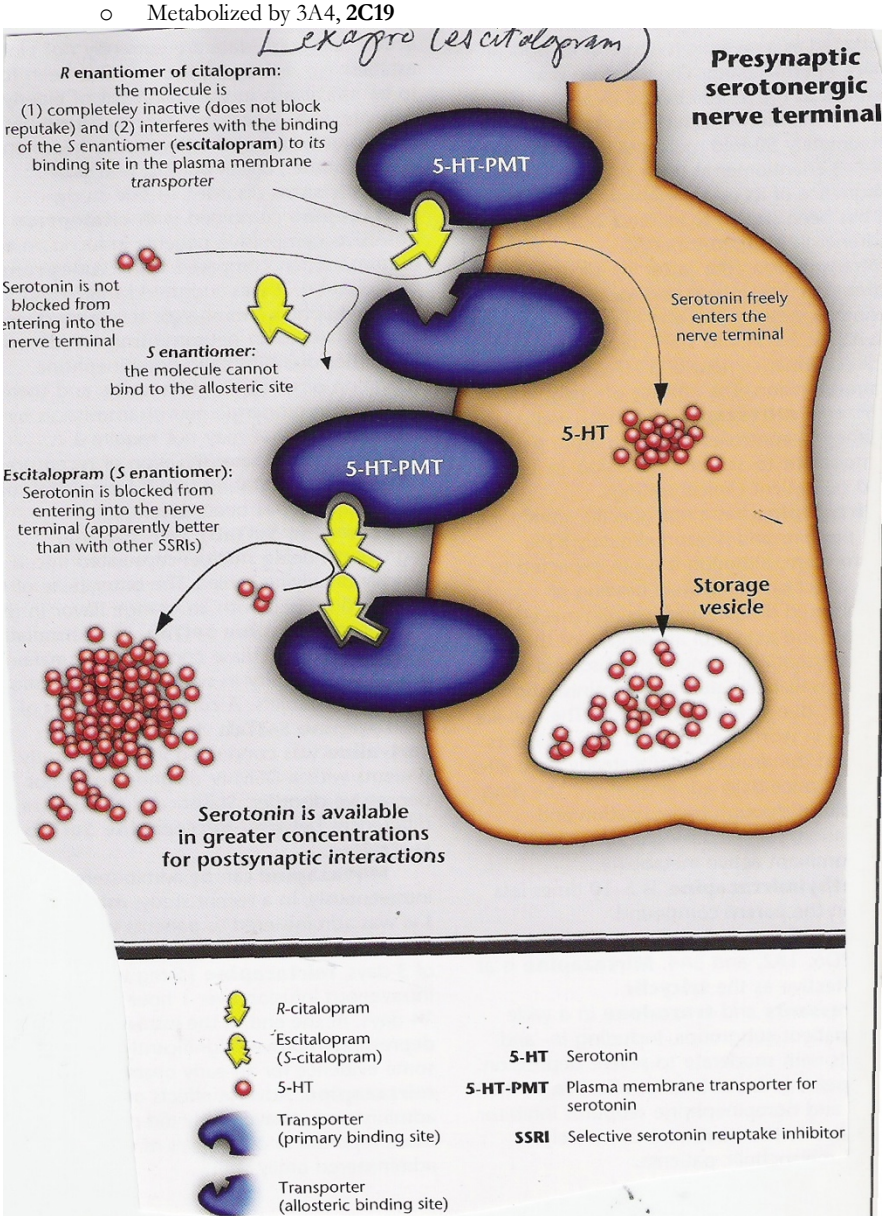
OBJECTIVE: Studies demonstrating that higher doses of citalopram (> 40 mg) and escitalopram (> 20 mg) prolong the corrected QT interval prompted regulatory agency warnings, which are controversial, given the absence of confirmatory clinical outcome studies. We compared the risk of potential arrhythmia-related deaths for high doses of these selective serotonin reuptake inhibitors (SSRIs) to that for equivalent doses of fluoxetine, paroxetine, and sertraline.

METHODS: The Tennessee Medicaid retrospective cohort study included 54,220 persons 30-74 years of age without cancer or other life-threatening illness who were prescribed high-dose SSRIs from 1998 through 2011. The mean age was 47 years, and 76% were female. Demographic characteristics and comorbidity for individual SSRIs were comparable. Because arrhythmia-related deaths are typically sudden and occur outside the hospital, we analyzed out-of-hospital sudden unexpected death as well as sudden cardiac deaths, a more specific indicator of proarrhythmic effects.

RESULTS: The adjusted risk of sudden unexpected death for citalopram did not differ significantly from that for the other SSRIs. The respective hazard ratios (HRs) for citalopram versus escitalopram, fluoxetine, paroxetine, and sertraline were 0.84 (95% CI, 0.40-1.75), 1.24 (95% CI, 0.75-2.05), 0.75 (95% CI, 0.45-1.24), and 1.53 (95% CI, 0.91-2.55). There were no significant differences for sudden cardiac death or all study deaths, nor were there significant differences among high-risk patients (≥ 60 years of age, upper quartile baseline cardiovascular risk). Escitalopram users had no significantly increased risk for any study end point.

CONCLUSIONS: We found no evidence that risk of sudden unexpected death, sudden cardiac death, or total mortality for high-dose citalopram and escitalopram differed significantly from that for comparable doses of fluoxetine, paroxetine, and sertraline.

- **Lexapro/Cipralex** (escitalopram)
  - General
    - The most potent SSRI
    - The s-isomer of Celexa; start 2.5-5 mg; range—2.5-10 mg (?higher); half-life ~32-35 hours, 17-19 hours in children; peak level in 5 hours
    - FDA-approved for
      - Depression, youth (aged 12 and older) and adults
      - Generalized anxiety disorder;
      - May soon by FDA-approved for the treatment of panic disorder.
    - 5, 10, 20 mg tabs; oral solution 5 mg/5 ml (240 ml bottle)
    - Half-life 27-32 hours
    - Metabolized by 3A4, **2C19**



  - Evidence of safety and efficacy in adult depression and anxiety
    - Depression
      - Multiple studies demonstrating safety and efficacy
      - Maintenance study, Kornstein et al, 2006, 12 months, RCT, DB, placebo-controlled, 10-20 mg/d, 139 patients: safe and effective
        - ~25% relapse rate for Lexapro after 1 year
        - ~67% relapse rate for placebo after 1 year
      - Maintenance study, 9 months, recurrence rate 26% vs. 40% placebo.
      - Meta-analysis of 1,262 adult patients with depression (2003), Lexapro was found to be superior to Celexa.
    - Anxiety
      - Robert et al, 2006: open-label study in adult PTSD demonstrated safety and efficacy
      - Davidson, 2005: generalized anxiety disorder, 6 month open-label extension of three 8-week studies, 75-92% response rate
      - Data on OCD in separate handout
      - Social Anxiety Disorder (Celexa/Lexapro)

- Kasper et al, 2005
- Furmark et al, 2005
- Lader et al, 2004

- Evidence of safety and efficacy in pediatric depression
  - Depression
    - Findling et al, 2013; controlled long-term trial of Lexapro vs. placebo in adolescent major depression
      - Remission at 8 weeks: 40% for Lexapro and 35% for placebo
      - Remission at 24 weeks: 50% for Lexapro and 36% for placebo
    - Wagner, 2006: 164 youth aged 6-17 with major depression, 8 weeks, 10-20 mg Lexapro/day; not significantly effective (but some evidence in 12-17 yo group); headache and abdominal pain in >10%; discontinuation rates 1.5% for Celexa and placebo; "suicidal events" in one Lexapro-treated youth and two placebo-treated youths.
    - AACAP, 2004: 164 youth, 6-17 yo, 63% response vs. 53% with placebo.
    - The company that makes Lexapro withheld data from two studies demonstrating lack of efficacy of Lexapro in the treatment of pediatric depression (6/04). Multicenter, double-blind, placebo-controlled trial of 264 youths with major depression was ***negative*** (this might be one of the two studies withheld)***.***
    - A small, open-label trial of 24 pediatric patients with depression was conducted over 8 weeks (mean dose 15 mg/day): positive effect with mild adverse effects such as headache, sleepiness, and stomach ache.
- Side effects
  - Sweating 16%
  - Flu-like symptoms 16% vs. 2% on placebo
  - Headache 11-25.5% vs. 6% placebo
  - Sexual side effects 10-24%
  - Dry mouth 11.2%
  - Nausea 8-24%
  - Weight gain 8%
  - Drowsiness OR fatigue 7-24%
  - Insomnia 5-14.8%
  - Diarrhea 3-16%
  - Dizziness 3% vs. 17-20% on placebo
  - Constipation 2%

- **Zoloft** (sertraline)
  - General
    - Blocks dopamine reuptake (comparable to Ritalin and more than Wellbutrin); some sigma receptor blockade.
    - Therapeutic range 50-200+ mg/D
    - In children, start 12.5-25 mg
    - FDA max: 200 mg/D
    - Half-life 22-36 hours (and 62-104 hours for active metabolite)
    - Half-life in teens
      1. A single dose of 50 mg has a half life of 27 hours
      2. However, once 50 mg/day reaches steady state, half-life decreases to 15 hours
      3. And higher doses (once they reach steady state) have half-lives of 20 hours
    - Peak level in 6-8 hours.
    - 25, 50, 100 mg tabs; oral concentrate 20 mg/mL (60 ml bottle); comes generic
    - Metabolized by 2B6, 2C9, 2C19, 2D6, 3A4
    - inhibits 2D6, 3A4
  - FDA-approval
    - OCD in children 6 and older
    - Depression
    - Dysthymia
    - Panic disorder
    - OCD
    - Post-traumatic stress disorder
    - Social anxiety disorder
    - Pre-menstrual dysphoric disorder
  - Evidence of safety and efficacy in adults
    - Multiple studies demonstrating safety and efficacy in adults with anxiety or depression
    - Maintenance studies in depression
      - 18 months, 6% recurrence rate vs. 23% placebo
      - 24 months, 39% recurrence rate vs. 31% placebo (not effective in this study)
      - 4 months, 16% recurrence rate vs. 16% in patients on imipramine controls
    - Social Anxiety Disorder
      - Liebowitz et al, 2003
      - Van Ameringen et al, 2001
      - Katzelnick et al, 1995
    - PTSD
      - Stoddard et al, 2011: youth burn victims; efficacious per parent report, but not per child report
      - Robb et al, 2010: youth; not efficacious over 10 weeks
      - Cohen et al, 2007: added to TF-CBT in youth; not efficacious
      - Friedman et al, 2007: RCT, DB, not efficacious
      - Davison et al, 2003: remission rates (after 12 weeks): 24.3% with Zoloft, 30.2% with Effexor XR, 19.6% with placebo but Zoloft beat placebo in risk of relapse or deterioration after 6 months
      - Davidson et al, 2001
      - Brady et al, 2000
  - Evidence of safety and efficacy in youth
    - Depression
      - Cheung et al, 2008: maintenance treatment for adolescent depression; 12 weeks on Zoloft in acute phase (93 youth), with responders continuing in 24 weeks in continuation phase (51 youth), with responders continuing for 52 weeks with either Zoloft (13 youth) or placebo (9 youth)
        - 38% of those on Zoloft maintained response (lack of recurrence) at 52 weeks
        - 0% of those on placebo maintained response
      - Alderman et al, 2006: open-label study; safe and effective, but 49% withdrew after acute trial; of those that remained, only one complained of suicidal ideation
      - Melvin et al, 2006: 73 adolescents with depressive disorder; cognitive-behavioral therapy (CBT) vs. Zoloft (relatively low dose) vs. combination of CBT and Zoloft; all treatment groups improved and improvement was maintained at 6 mo follow-up; combination treatment was ***NOT*** superior; CBT was superior to Zoloft for acute treatment of mild-moderate depression.
      - Donnelly et al, 2006: 177 youth aged 6-11 and 199 youth aged 12-17 with major depressive disorder; 10-week placebo-controlled treatment followed by 24 week open-label Zoloft treatment—efficacy was not analyzed; Zoloft was associated with a faster time to first persistent response in adolescents but not in children.
      - Two (2003-2004) 10-week multicenter double blind, placebo-controlled, flexible-dose studies of Zoloft in the treatment of outpatient children (6-11 yo) and adolescents (12-17 yo) with major depressive disorder examined 376 subjects and demonstrated safety and efficacy in the treatment of pediatric major depressive disorder (one of the two studies is Donnelly, Ambrosini, Wagner, 2003, partially funded by Pfizer)
    - Anxiety
      - Child/adolescent anxiety multimodal study (CAMS); 488 youth, SoAD, GAD, SepAD; Zoloft vs. CBT vs. combination vs. placebo; 12 wks
        - Response rates
          1. Zoloft 56%
          2. CBT 59%
          3. Combo 81%

4. Placebo 24%

- Younger kids with anxiety do best with all treatments
- Zoloft well tolerated, but younger kids have more side effects
- Highest safe/tolerable dose reached was 120 mg/day

- PTSD
  - Stoddard, et al, 2011; PTSD in burned children, 26 kids, age 6-20; 24 weeks; very effective
  - Cohen, at al, 2007; not very helpful for PTSD
- GAD
  - Rynn (2002): 50 mg safe and effective for generalized anxiety disorder in 22 children
- Social anxiety disorder
  - Compton et al, 2001: open-label, social anxiety disorder: safe and effective
  - Mancini et al, 1999: case series social anxiety disorder: safe and effective
- OCD
  - Pediatric OCD Treatment Study (POTS), 2004; 112 kids, 7-17 yo, 3 sites, 12 weeks, CBT vs. Zoloft vs. combination vs. placebo
    1. Combo > Zoloft = CBT > placebo
    2. The more formal the CBT, the better the results of the CBT
  - Data on OCD in separate handout

- Side effects
  - Sexual side effects 8-30%
  - Nausea 14.3-30%
    - One study
      - 25 mg: 10% vs. 6% placebo
      - 50 mg: 21% vs. 6% placebo
  - Drowsiness OR fatigue 10%
  - Diarrhea 8.4-24%
  - Insomnia 7.6-20%
    - One study:
      - 25 mg: 14% vs. 9% placebo
      - 50 mg: 20% vs. 9% placebo
  - Dry mouth 7-15%
  - Tremor 5-11%
  - Sweating 5-8%
  - Anxiety/nervousness 4-10%
  - Dizziness 4-13%
  - Decreased appetite 3-11%
  - Constipation 2.1-8%
  - Headache 1.3-26%
    - One study
      - 25 mg: 13% vs. 8% placebo
      - 50 mg: 6% vs. 8% placebo

- **Fluvoxamine/Luvox CR**
  - General
    - Some blocking of the sigma opioid receptor which may bring added benefit.
    - Therapeutic range 100-300 mg/D (100-200 mg/D in children)
    - In children, start 25-50 mg; FDA max: 300 mg/D
    - Half-life 15-26 hours (elsewhere 15-19 hours); peak level in 2-8 hours.
    - Generic 25, 50, 100 mg tabs
    - Metabolized by **1A2**
    - FDA-approved for
      - Children 7 and older for the treatment of OCD and in adult OCD
      - Adult dysthymia
    - FDA-approved (as Luvox CR) for
      - Once daily treatment of social anxiety disorder
      - Obsessive compulsive disorder in adults
  - Evidence of safety and efficacy in adults
    - Multiple studies demonstrating safety and efficacy in adults
    - Maintenance study, 12 months, 13% recurrence rate vs. 35% placebo
    - Social anxiety disorder
      - Owen, 2008
      - Asakura et al, 2007
      - Davison et al, 2004
      - Stein et al, 1999
      - Van Vliet et al, 1994
    - Panic disorder: naturalistic study of 200 patients assigned to either Celexa, Prozac, fluvoxamine or Paxil for 12 months
      - Retention rates (the % of patients who remained in the study for all 12 months)
        - Paxil 76%
        - Celexa 68%
        - Fluvoxamine 60%
        - Prozac 50%
      - Weeks 4 and 8, Paxil and Celexa associated with less symptoms than fluvoxamine and Prozac
      - Months 3, 6, 9, and 12, no differences in relapse rates for any of the medications
      - Weight gain occurred to the same degree in all four
      - Sexual side effects occurred to the same degree in all four except fluvoxamine had a bit less at the 12 month point
  - Evidence of safety and efficacy in youth:
    - Depression
      - Gothelf, 2005: pilot study of treatment of depression and anxiety disorders in youth with cancer 15 youth; 100 mg/day; 8 week open trial; safe and effective
    - Anxiety
      - RUPP, 2001: 6-17 yo's, 128 youth, safe and effective vs. placebo in generalized anxiety disorder, social phobia, and separation anxiety disorder
        - 76% response rate on Luvox
        - 29% on placebo
        - 33/35 subjects maintained gains over one year
        - 10/14 Luvox failures responded to Prozac
        - Data on OCD in separate handout
    - Autism spectrum disorder
      - Helps adults (not kids) with repetitive behaviors
      - McDougle (unpublished); ~107 mg/day, 12 wk study, double-blind, placebo-controlled, 34 subjects, ~9.5 yo
        - 1/18 response vs. 0/16 with placebo
        - side effects
          1. insomnia
          2. motor hyperactivity
          3. agitation
          4. aggression
  - Side Effects
    - Sexual side effects
    - Nausea 26-40%
    - Drowsiness OR fatigue 22%
    - Headache 22%
    - Insomnia 11-21%
    - Diarrhea 11%
    - Dizziness 11%
    - Anxiety/nervousness 7-17%
    - Sweating 7%
    - Decreased appetite 6%
    - Tremor 5%
    - Dry mouth 4-14%
    - Constipation 2-10%

- **Paxil** (paroxetine hydrochloride)/**Paxil CR/Pexeva** (paroxetine mesylate)
  - General
    - With Celexa and Lexapro, one of the most potent SSRI
    - At doses of more than 40 mg/day, may block norepinephrine reuptake as much or more than Effexor. Anticholinergic side effects weak but significant.
    - Paxil CR, when compared to Paxil, may have less incidence of nausea, somnolence and sexual dysfunction.
    - Therapeutic range 10-60 mg/D; In children, start 5-10 mg; FDA max: 60 mg/D; half-life 20-24 hours; half life increases in duration with repeated administration due to inhibition of own metabolism; peak level in 2-8 hours.
    - 10, 20, 30, 40 mg Paxil and generic paroxetine tabs; 12.5, 25, and 37.5 mg Paxil CR tabs; oral solution 10 mg/5 ml (250 ml bottle)
    - When using Paxil CR, must use a dose 25% higher than the effective dose of Paxil.
    - FDA-approved for adult depression, dysthymia, panic disorder, social anxiety disorder, post-traumatic stress disorder, and generalized anxiety disorder. Recently FDA-approved for intermittent dosing for the treatment of premenstrual dysphoric disorder.
    - Metabolized by **2D6**
  - Evidence of safety and efficacy in adults:
    - Multiple studies demonstrating safety and efficacy in adults with depression or anxiety
    - Maintenance study, 24 months, 37% recurrence rate vs. 58% placebo for depression
    - Social anxiety disorder
      - Lepola et al, 2004
      - Liebowitz et al, 2002
      - Baldwin et al, 1999
      - Allgulander et al, 1999
      - Steine et al, 1998
    - PTSD:
      - Schneier et al, 2011: CBT plus Paxil more effective than CBT plus placebo
      - 12 week study, 551 patients, Marshall 2001; response rates: 57-63% for Paxil 20-40 mg vs. 37% with placebo; in another study by Marshall on dissociation in PTSD: response rates 67% for Paxil and 22.2% with placebo; in same (latter) study Paxil effective in treating interpersonal problems in chronic PTSD
      - Multiple other studies
    - Panic disorder: naturalistic study of 200 patients assigned to either Celexa, Prozac, fluvoxamine or Paxil for 12 months
      - Retention rates (the % of patients who remained in the study for all 12 months)
        - Paxil 76%
        - Celexa 68%
        - Fluvoxamine 60%
        - Prozac 50%
      - Weeks 4 and 8, Paxil and Celexa associated with less symptoms than fluvoxamine and Prozac
      - Months 3, 6, 9, and 12, no differences in relapse rates for any of the medications
      - Weight gain occurred to the same degree in all four
      - Sexual side effects occurred to the same degree in all four except fluvoxamine had a bit less at the 12 month point
  - Evidence of safety and efficacy in youth:
    - Depression
      - Keller et al, 2001: mild efficacy in depression
      - 3 multicenter studies (with a total of 767 youths) were all negative (Berard et al, 2006; Emslie et al, 2006. One (275 youth): 66% response vs. 48% with placebo.
      - Some positive open-label studies
      - **As of July, 2003, the FDA has withdrawn FDA approval of Paxil in the treatment of pediatric depression due to pooled data that demonstrated Paxil is not more effective than placebo in pediatric depression and that it is associated with increased suicidal thoughts and suicidal behaviors (though no actual deaths))**
    - Anxiety
      - Geller et al, 2004; 203 children 7-17, double blind, placebo-controlled
        - Paxil > placebo
        - Mild side effects
      - Wagner, 2004: 332 children 8-17 yo with social phobia; 16 week study
        - 78% response with Paxil
        - 38% response with placebo.
  - Side Effects
    - Sexual side effects 20% BUT 65% when formally assessed
    - Drowsiness OR fatigue OR lassitude 14-46%
    - Nausea 16.4-26%
    - Tremor 8-11%
    - Sweating 8-14%
    - Insomnia 7-24%
    - Dizziness 7-14%
    - Dry mouth 6-18%
    - Decreased appetite 6%
    - Constipation 5.2-16%
    - Anxiety/nervousness 4.9-14%

- Diarrhea 4-12%
- Headache 0.3-18%

- **Vilazodone (Viibryd)**
  - SSRI and serotonin 1a partial agonist (the latter not evident at 20 mg/day or less)
  - FDA-approved for depression in adults on 1/21/11
  - 20 mg may be the minimum effective dose; efficacy increases to 40 mg/day; doses above 40 mg/day poorly tolerated
  - Onset of efficacy not more rapid than SSRI's (or no evidence of that yet)
  - 10 mg, 20 mg, 40 mg tabs
  - Several early failed or negative trials
  - Two recent positive studies, positive, separated by one week
  - One pediatric depression study completed (not published)
  - Most common side effects:
    - Diarrhea (28% vs. 9% placebo)
    - Nausea/vomiting (28% vs. 6% placebo)
    - Insomnia (6% vs. 2% placebo)
    - Other side effects occurring in at least 2% and at least twice the rate of placebo:
      - gastroenteritis
      - paresthesia (tingling)
      - tremor
      - abnormal dreams
      - restlessness
      - sexual side effects
        - decreased libido
          1. 3.7% vs. 0.2% in placebo
        - abnormal orgasm
        - delayed ejaculation
        - erectile dysfunction
        - BUT:
          1. Two 8 week studies of vilazodone 40 mg/day vs. placebo showed no difference in sexual side effects
          2. 52-week open study showed improvements in sexual functioning over time
      - jitteriness
      - palpitations
      - increased appetite
  - Most common side effects leading to discontinuation:
    - Diarrhea
    - Nausea
    - Palpitations
    - Fatigue
  - Khan, 2012
    - >800 patients, pooled from two studies
    - Efficacy looked at in the first 8 weeks, safety and tolerability in the 52 week portion
    - Response rates and remission higher with vilazodone
    - Not associated with significant weight gain
  - Pharmacokinetics
    - peak levels in 4-5 hours if taken with food
    - half-life 25 hours
    - absorption much greater when taken with food
    - primarily metabolized by 3A4, less so by 2C19 and 2D6
    - no active metabolites
  - Pregnancy/breast feeding: no human data yet

Efficacy and safety of vilazodone in patients with generalized anxiety disorder: a randomized, double-blind, placebo-controlled, flexible-dose trial

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OBJECTIVE: To evaluate the efficacy, safety, and tolerability of vilazodone as an acute treatment for generalized anxiety disorder (GAD). Vilazodone is a selective serotonin reuptake inhibitor and 5-HT1A receptor partial agonist approved for the treatment of major depressive disorder in adults.

METHODS: This was a randomized, placebo-controlled, parallel-group, multicenter, flexible-dose study conducted from May 2013-March 2014. Adult patients (18-70 years, inclusive) who met DSM-IV-TR criteria for GAD were randomized (1:1) to placebo or vilazodone 20-40 mg/d for 8 weeks of double-blind treatment. Primary and secondary efficacy parameters were change from baseline to week 8 in the Hamilton Anxiety Rating Scale (HARS) total score and in the Sheehan Disability Scale (SDS) total score, respectively, analyzed using a mixed-effects model for repeated measures approach on a modified intent-to-treat population. Safety outcomes were summarized

descriptively.
RESULTS: Efficacy analyses were based on 400 patients (placebo = 200, vilazodone = 200); 76% completed the study (placebo = 81%, vilazodone = 71%). The least squares mean difference (95% CI) in total score change from baseline to week 8 was statistically significant for vilazodone versus placebo on the HARS (-2.20 [-3.72 to -0.68]; P = .0048) and on the SDS (-1.89 [-3.52 to -0.26]; P = .0236). Treatment-emergent adverse events reported in ≥ 5% of vilazodone patients and at least twice the rate of placebo were nausea, diarrhea, dizziness, fatigue, delayed ejaculation, and erectile dysfunction.
CONCLUSION: Statistically significant differences in favor of vilazodone 20-40 mg/d versus placebo were seen on all measures of anxiety and functional impairment in patients with GAD. Vilazodone was generally well tolerated, and no new safety concerns were noted.

- **Trintellix** (vortioxetine, formerly known as Brintellix)
  - General
    - FDA-approved for depression in adults on 9/3/13 after reviewing 6 global clinical trials and finding it to be more effective than placebo in alleviating depression and preventing relapse in more than 4700 participants aged 18-88.
    - Additional studies demonstrate efficacy with reduced side effects, such as sexual side effects, compared to other antidepressants.
    - Suicidality was not increased in patients aged 24-64 and was reduced in patients aged 65 and older.
    - Dose:
      - start at 5-10 mg/day
      - after 1 week, increase to 20 mg/day for depression if tolerated
      - dose range is 5-20 mg/day
  - Evidence
    - Depression
      - Findling et al, 2017; 48 youth 7-17 years old with depression and anxiety disorders; open-label
        - 5-20 mg/day
        - pharmacokinetics of Trintellix concentration proprational to dose
      - Boulenger et al, 2012
        - Maintenance study
        - 639 patients , 5 or 10 mg once daily dosing, initial 12-week open-label treatment phase; dose fixed during weeks 8-12
        - 396 patients who were in remissionat weeks 10 and 12 after open-label treatment were randomly assigned to continuation of a fixed dose at the final dose they responded to (about 75% of patients were on 10 mg/day) during the open-label phase or to placebo for 24-64 weeks
        - Patients on Brintellix experienced a statistically significantly longer time to have recurrence of depressive episodes than did patients on placebo
          - ~15% of those on Brintellix experienced a recurrence by 28 weeks
          - ~28% of those on placebo experienced a recurrence by 28 weeks
      - Alvarez, et al, 2011
        - Placebo and active treatment controlled short-term study in adults 18-65 with depression
      - Dragheim:
        - 501 European patients with major depressive disorder who responded inadequately to at least 6 weeks of monotherapy with citalopram, escitalopram, sertraline, paroxetine, venlafaxine, or duloxetine at approved doses.
        - The study participants, all of whom wanted to change their antidepressant because of inadequate response, were randomized to 12 weeks of double-blind treatment with flexibly dosed vortioxetine at 10-20 mg/day or agomelatine at 25-50 mg/day. Agomelatine is approved as an antidepressant in the European Union and elsewhere in the world, but not in the United States.
        - The primary study endpoint was the change in scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) between baseline and week 8. From a baseline MADRS total score of 29, the vortioxetine group improved by a mean of 2.2 more points than the agomelatine group, a statistically significant difference.
        - In addition, the vortioxetine-treated patients fared significantly better in terms of numerous secondary endpoints. They had a mean 1.9-point greater improvement than did the agomelatine group at 8 weeks in theHamilton Anxiety Rating Scale total score, a 0.3-point greater improvement on the Clinical Global Impression-Severity, and a 2.2-point bigger improvement on the Sheehan Disability Scale.
        - The week-8 response rate as reflected in at least a 50% improvement from baseline in MADRS score was 61.5% in the vortioxetine group and 47.3% with agomelatine.
        - Remission as defined by a MADRS score of 10 or less occurred in 40.5% of the vortioxetine group and 29.5% of the agomelatine group at week 8, and in 55.2% vs. 39.4%, respectively, at week 12 (P = .0002).
        - Study withdrawal because of adverse events occurred in 5.9% of the vortioxetine group, compared with 9.5% of patients on agomelatine.
        - Nausea, reported by 16% of patients on vortioxetine, was the only side effect more common in patients on that drug; however, less than 1% of subjects on vortioxetine left the study because of nausea.
        - Summary: The investigational antidepressant vortioxetine achieved a 55% remission rate in a large, double-blind study of patients with major depressive disorder switched to the drug after an inadequate response to one of a half-dozen approved selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors. "I think it's quite impressive to see a remission rate on the order of 55% in this difficult-to-treat population," Dr. Marianne Dragheim observed in presenting the study

findings at a meeting of the New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health. After all, in the landmark NIMH-sponsored sequential treatment alternatives to relieve depression, or STAR*D trial, in which citalopram nonresponders were switched to second-line treatment with sustained-release bupropion, extended-release venlafaxine, or sertraline, the mean remission rate after 12-14 weeks on the backup medication was just 31% (N. Engl. J. Med. 2006;354:1231-42), noted Dr. Dragheim of H. Lundbeck A/S, Valby, Denmark.

- Katona et al, 2012
  - Brintellix at 5 mg/day in elderly patients with depression
  - Compared to Cymbalta 60 mg/day or placebo
  - Brintellix and Cymbalta both significantly more effective than placebo
  - Response rates
    - Brintellix 53.2-61.6%, depending on criteria for response
    - Cymbalta 63.3-72.1%
    - Placebo 35.2-38%
  - Remission rates
    - Brintellix 29.2-33.8%, depending on criteria for remission
    - Cymbalta 34.7-46.9%
    - Placebo 19.3-20.7%
  - Depression scale scores dropped more with Cymbalta than with Brintellix, both more than placebo
  - Side effects
    - Nausea 21.8% Brintellix, 33.1% Cymbalta, 8.3% placebo
    - Headache 11.5% Brintellix, 11.9% Cymbalta, 17.2% placebo
    - Dizziness 9.0% Brintellix, 9.3% Cymbalta, 6.9% placebo
    - Fatigue 7.1% Brintellix, 10.6% Cymbalta, 3.4% placebo
    - Constipation 6.4% Brintellix, 13.9% Cymbalta, 4.1% placebo
    - Dry mouth 6.4% Brintellix, 21.9% Cymbalta, 4.8% placebo
    - Diarrhea 5.1% Brintellix, 9.3% Cymbalta, 6.9% placebo
    - Decreased appetite 4.5% Brintellix, 5.3% Cymbalta, 1.4% placebo
    - Increased sweating 3.8% Brintellix, 10.6% Cymbalta, 2.8% placebo
    - Sleepiness 2.6% Brintellix, 10.6% Cymbalta, 2.1% placebo
  - Withdrawal rate due to side effects
    - Brintellix 5.8%
    - Cymbalta 9.9%
    - Placebo 2.8%

- Anxiety
  - Anxiety symptoms in depression
    - Significant improvement vs. placebo in 5 placebo controlled short term studies
  - Generalized anxiety disorder
    - 3 US-based, 8-week studies with Brintellix 2.5-10 mg/day vs. placebo, >1500 patients
      - Not better than placebo
    - 1 non-US-based, 8-week, multinational study with Brintellix 5 mg/day vs. placebo, 301 patients
      - Significantly better than placebo
    - 1 non-US-based, multinational, relapse prevention study, 20-week open label Brintellix 5-10 mg/day followed by 24-56 week double-blind Brintellix 5-10 mg/day vs. placebo; 687 patients
      - Relapse rate 15% with Brintellix
      - Relapse rate 34% with placebo
- Cognitive function in depression
  - McIntyre et al, 2013
    - Effective
- Side effects overall (in pooled 6- to 8-week studies (with dose range 5-20 mg/day), over 4000 patients
  - Discontinuation due to adverse effects 5-8% vs. 4% placebo
  - Nausea (usually transient) 21-31% vs. 9% placebo
  - Sexual side effects, formally asked 22-34% vs. 20% placebo
    - Voluntarily reported only <1-2% vs. <1% placebo
  - Diarrhea 7-10% vs. 6% placebo
  - Dizziness 6-9% vs. 6% placebo
  - Dry mouth 6-8% vs. 6% placebo
  - Constipation 3-6% vs. 3% placebo
  - Vomiting 3-6% vs. 1% placebo
  - Flatulence 1-3% vs. 1% placebo
  - Itchiness 1-3% vs. 1% placebo

- Abnormal dreams <1-3% vs. 1% placebo
- Weight gain
  - 0 in short term studies vs. 0.1 kg placebo)
  - 0.4 kg in 6 month studies vs. 0.1 kg placebo

- Side effects
  - Discontinuation rates due to adverse effects
    - 4% with placebo
    - 5% with 5 mg
    - 6% with 10 mg
    - 8% with 15 mg
    - 8% with 20 mg
  - Nausea/vomiting 10% placebo vs. 24-38% with medicine
  - Diarrhea: 6% placebo vs. 7-10% with medicine
  - Dry mouth: 6% placebo vs. 6-8% with medicine
  - Constipation: 3% placebo vs. 3-6% with medicine
  - Flatulence: 1% placebo vs. 1-3% with medicine
  - Dizziness: 6% placebo vs. 6-9% with medicine
  - Abnormal dreams: 1% placebo vs. <1-3% with medicine
  - Pruritis: 1% placebo vs. 1-3% with medicine
  - Voluntarily reported sexual side effects:
    - Females: <1% placebo vs. 1-2% with medicine
    - Males: 2% placebo vs. 3-5% with medicine
  - Sexual side effects from form
    - Females: 20% placebo vs. 22-34% with medicine
      - 22% on 5 mg/day
      - 23% on 10 mg/day
      - 33% on 15 mg/day
      - 34% on 20 mg/day
    - Males: 14% placebo vs. 16-29% with medicine
      - 16% on 5 mg/day
      - 20% on 10 mg/day
      - 19% on 15 mg/day
      - 29% on 20 mg/day
  - Weight increase
    - Short term: 0.1 kg placebo vs. 0 kg with medicine
    - Long term: 0.1 kg placebo vs. 0.4 kg with medicine
- Pharmacology
  - It is an inhibitor of the 5-hydroxytryptamine (5-HT)/serotonin transporter (like SSRI's)
  - Blocks
    - 5-HT-1D
    - 5-HT3
    - 5-HT7
    - 5-HT10
  - 5-HT1A receptor agonist
  - 5-HT1B receptor partial agonist
  - Increase release of
    - Serotonin
    - Norepinephrine
    - Dopamine
    - Acetylcholine
    - Histamine
  - Comes in 5 mg, 10 mg, 20 mg tabs; can be broken but they're tear shaped
  - Mean terminal half life 66 hours; steady state reached in 2 weeks
  - Peak plasma level reached within 7-11 hour post-dose
  - No effect of food
  - Metabolized through *2D6, 3A4/5, 2C19, 2C9, 2A6, 2C8, 2B6; 2D6 is the primary enzyme; poor 2D6 metabolizers have approximately twice the plasma concentrations and max recommended dose in 2D6 poor metabolizers is 10 mg
  - Presence of mild to moderate liver or mild-severe/end stage kidney disease did not affect clearance of medicine
  - No dose adjustment for lithium, aspirin, warfarin is necessary
  - Unlikely to inhibit 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, and P-gp
  - No induction of 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 3A4/5

Efficacy of Vortioxetine on Cognitive Functioning in Working Patients With Major Depressive Disorder

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Journal of Clinical Psychiatry 2016 October 25

OBJECTIVE: This post hoc analysis investigates the effect of vortioxetine on cognitive functioning and depressive symptoms in working adults with major depressive disorder (MDD).

METHODS: Population data from FOCUS, a double-blind, randomized, placebo-controlled study investigating the efficacy of vortioxetine versus placebo on cognitive functioning and depression in patients with MDD, were used to analyze mean change from baseline scores for the Digit Symbol Substitution Test (DSST), Trail Making Test A/B (TMT-A/B), Stroop, and Perceived Deficits Questionnaire (PDQ). FOCUS, conducted from December 2011 through May 2013, included adult patients with recurrent MDD according to DSM-IV-TR criteria. Change in depression severity (Montgomery-Asberg Depression Rating Scale [MADRS] total score) was analyzed using data from 3 additional short-term placebo-controlled studies (2 of which included duloxetine) and 1 relapse prevention study. Analyses were done according to patients' working status at baseline and workplace position. All analyses were made versus placebo.

RESULTS: In FOCUS, the effect versus placebo on the DSST was 5.6 for 10 mg and 5.0 for 20 mg ($P < .001$ for both doses) in working patients; the effect was 4.0 ($P < .001$ for both doses) in total study population. The effect remained significant when adjusting for change in MADRS. In patients with "professional" positions, the effect was 9.2 for 10 mg ($P = .006$) and 9.0 for 20 mg ($P = .001$). A similar pattern of results was also observed for TMT-A/B, Stroop, PDQ, and MADRS total score. The efficacy of duloxetine was not different in working patients (MADRS).

CONCLUSIONS: The beneficial effects of vortioxetine on objective and subjective measures of cognitive functioning are greater in working patients with MDD; the observed benefits were independent of improvement in depressive symptoms.

Pharmacokinetics and Safety of Vortioxetine in Pediatric Patients

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OBJECTIVE: The primary objectives of this study were to evaluate the pharmacokinetics (PK) and tolerability of single and multiple doses of vortioxetine in children and adolescents with a depressive or anxiety disorder and to provide supportive information for appropriate dosing regimens for pediatric clinical trials.

METHODS: This prospective, open-label, multinational, multisite, multiple-dose trial enrolled 48 patients (children and adolescents; 1:1 ratio) divided into 8 cohorts (4 adolescent and 4 child), with each cohort including 6 patients. The cohorts in each age group were assigned to receive one of four dosing regimens: vortioxetine 5, 10, 15, or 20 mg q.d. for 14 days. The total treatment period lasted 14-20 days with patients in the higher dose cohorts uptitrated over 2-6 days. Plasma samples for PK analysis were obtained on the first and last days of dosing.

RESULTS: Among children and adolescents, respectively, 62% and 92% had depression and 58% and 33% had anxiety disorder. Comorbid attention-deficit/hyperactivity disorder (ADHD) was present in 50% of children and 38% of adolescents. After 14 days q.d. at the target dose, the PK of vortioxetine concentrations was generally proportional to the dose in both age groups. Exposure, as assessed by maximum plasma concentrations and area under the plasma concentration-time curve from time 0 to 24 hours, was 30%-40% lower in adolescents than in children. There was no significant relationship between sex, height, or ADHD diagnosis and PK parameters. Most adverse events were mild in severity and consistent with those seen in adults.

CONCLUSION: The results suggest that the dosages of vortioxetine evaluated (5-20 mg q.d.; approved for treatment in adults) and the uptitration schedule used are appropriate for pediatric efficacy and safety trials.

A 6-Month Open-Label Extension Study of Vortioxetine in Pediatric Patients with Depressive or Anxiety Disorders

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Journal of Child and Adolescent Psychopharmacology 2017 October 16

OBJECTIVES: In this 6-month open-label extension (OLE) of NCT01491035 (a 14-day, open-label, pharmacokinetic/safety lead-in study), the long-term safety and tolerability of vortioxetine (5-20 mg/day) were investigated in children and adolescents with a DSM-IV-TR™ diagnosis of depressive or anxiety disorder in the United States or Germany. The study also was designed to provide data to inform dose selection and titration in future pediatric studies with vortioxetine.

METHODS: Safety evaluations included spontaneously reported adverse events (AEs), the Columbia Suicide Severity Rating Scale (C-SSRS), and the Pediatric Adverse Events Rating Scale (PAERS; clinician administered). Clinical effectiveness was determined by Clinical Global Impressions. Comorbid attention-deficit/hyperactivity disorder was permitted, including concomitant use of stimulant medication (US sites only).

RESULTS: Of the 47 patients who completed the lead-in period, 41 continued into the OLE. Most patients (n = 39 [95%]) continued their previous dose regimen. Twenty-one patients (51%) withdrew during the OLE; the most common primary reasons were administrative [n = 8], AEs [n = 4], and lack of efficacy [n = 3]. Thirty-five patients (85%) had ≥1 AE, 86% of which were mild or moderate in severity. Five patients (12%) reported a severe AE, none of which was considered related to study medication. The most common AEs (≥10%) were headache (27%), nausea (20%), dysmenorrhea (females; 19%), and vomiting (15%), with no relationship between AE intensity and age or dose. Five patients reported instances of suicidal ideation during the OLE, one of whom also reported this during the lead-in period. Two patients had nonsuicidal self-injurious behavior; one had a nonfatal suicide attempt. Throughout the study, there was a decrease over time in the incidence and intensity of AEs collected using the PAERS. Effectiveness assessment indicated a trend toward improvement based on numeric results.

CONCLUSION: This OLE confirms the findings from the lead-in study, which concluded that a dosing strategy of 5-20 mg/day is safe, well tolerated, and suitable for future clinical studies of vortioxetine in pediatric patients.

Additional Information on SSRI's

- The most common side effects are usually short-lived and mild; they include:
  - Nausea (more rarely: vomiting)—taking with meals might help
  - Constipation (more common with Paxil and Luvox)
  - Tiredness/lethargy (more common with Paxil and Luvox); taking at 8 pm may help
  - Too much energy (more common with Prozac, Zoloft); take in AM
  - Anxiety
  - Behavioral activation/disinhibition; can include agitation, aggression, irritability, restlessness, hyperactivity, behavioral disinhibition, and insomnia.
    - Occurs with any drug that alleviates negative mood, including alcohol, antihistamines, barbiturates, tricyclic antidepressants, Diamox, Dazamide, benzodiazepines, steroids, bromides, primidone, sulthiamine, stimulants.
    - Risk factors: children, elderly, physical illness, alcohol/recreational drugs, learning disorders, neurologic disorders, psychiatric disorders involving impulsivity
    - Rates of activation are low when systematically observed: 8% (range is 6-28% with SSRI's and 0-13% with placebo).
    - Rates of rebound (end of day) symptoms in 10-30% of children; 9% had to stop the medication due to this
    - No diagnostic significance in and of itself
    - Children are more likely to experience this than adolescents and adults
    - With some SSRI's, children may metabolize the parent compound faster than older youth and adults which may leave higher levels of active metabolites (with lower metabolism of these compounds) than in older folks
  - Insomnia, poor sleep
  - Nightmares or intense dreams
  - Tremor—propanolol 10 mg three times-a-day might help
  - ***Sexual side effects***
    - Antidepressants most associated with sexual side effects
      - SSRI's (but see below)
      - Effexor XR
        Tricyclic antidepressants
      - Oral MAOI's
    - Antidepressants with few negative effects on sexual functioning
      - Wellbutrin XL
      - Remeron
      - Nefazodone
      - Emsam
      - Reboxetine
      - Cymbalta
      - Pristiq
      - Viibryd
      - Trintellix
      - Agomelatine
    - Meta-analysis by Seretti et al, 2009; antidepressants listed from most commonly to least commonly to cause sexual side effects:
      - Most (each about the same amount)
        - Zoloft
        - Effexor XR
        - Celexa
      - Nearly the most (each about the same)
        - Paxil
        - Prozac
      - Next most likely (nearly the same)
        - Imipramine
        - Cymbalta
        - Lexapro
      - Fluvoxamine
      - Placebo (0)
      - Least (each about the same)
        - Wellbutrin XL
        - Nefazodone
        - Agomelatine
    - JCP, 2002+ other data; antidepressants in order of decreasing likelihood of sexual side effects:

	Incidence	OVERALL	IN THOSE WITHOUT OTHER PROBABLE CAUSES OF SEXUAL DYSFUNC.
Paxil	2-28%	43% (40-70%)	27% (19-33%)
Remeron	2-6%	41% (29-55%)	---
Effexor XR	12%	40% (37-68%)	30% (20-42%)
Zoloft	14%	40% (38-70%)	26% (20-34%)
Celexa	1-3%	38% (37-41%)	30% (22-41%)
Prozac	2-11%	37% (35-68%)	23% (18-30%)
Effexor IR	12%	34% (26-68%)	---
Serzone	1%	28% (7-35%)	---
Wellbutrin SR	1-3%	25% (21-29%)	8% (2-18%)
Wellbutrin IR	1-3%	22% (12-36%)	---
Lexapro	?10-24%?	?10-24%?	
PLACEBO	1-6%	??	??

    - Treatment of sexual side effects; discuss with your psychiatrist; some options include:

- Taking SSRI just before sleep
- SSRI holidays (must discuss with psychiatrist)
- Change from one SSRI to another
- Amantadine 50-100 mg/day (max 300 mg); main side effect is nausea
- Bromocriptine 2.5-5 mg/day
- Pramiprexole
- Ropirinole (Requip)
    - begin at 0.25/day (in PM) for 2 days
    - increase by 0.25-0.5 mg/day/week to target dose of 1 mg (max 4 mg/day)
    - greater affinity for the dopamine D3 receptor than the D2 receptor.
    - half-life 6 hours. 1A2 metabolism
    - tabs: 0.25, 0.5, 1, 2, 3, 4, 5 mg
    - side effects
        - 40-60% nausea (8-22% placebo)
        - 16% stomach upset or pain (8% placebo)
        - 12-40% sleepiness (6% placebo)
        - 12% fainting (1% placebo)
        - 11-40% dizziness (5-22% placebo)
        - 11-12% vomiting (2-7% placebo)
        - 8-11% fatigue (4% placebo)
        - 6% lassitude (1% placebo)
        - 4% less appetite (1% placebo)
- Wellbutrin 75-450 mg/day or 200 mg ½-4 hours prior to sex
- Stimulant medication (e.g., Ritalin, Concerta. Adderall)
- Buspar 7.5-30 mg/day (max 60 mg/day); mixed evidence
- PDE5 Inhibitors
    - Viagra (sildenafil)
        - 50-100 mg about 1 hour pre-sex
        - breakable tabs: 25 mg, 50 mg, 100 mg
        - high fat meal delays peak and decreases absorption by ~30%
        - duration of effect 6 hours; half-life 4 hours
        - may be effective for women as well as men
        - side effects
            - headache
            - flushing
            - stomach upset
            - nasal congestion
            - abnormal vision
            - diarrhea
            - overly prolonged and painful erection
    - Levitra (vardenafil)
        - starting dose is 5-10 mg taken ~60 minutes prior to sexual activity
        - 2.5, 5, 10, and 20 mg tabs
        - high fat meals reduces peak levels by 50%
        - duration of effect 6 hours; half-life 4 hours
        - side effects
            - headache
            - flushing
            - nasal congestion
            - stomach upset.
    - Cialis (tadalafil)
        - 5-10 mg 1-2 hours pre-sex
        - breakable tabs: 5, 10, and 20 mg tabs
        - duration of action 36 hours; half-life 17 hours
        - side effects
            - headache
            - stomach upset
            - back pain
            - muscle soreness
            - nasal congestion
            - flushing
            - prolonged and painful erection
- Trazodone
- Remeron; 7.5-30 mg ; some negative evidence
- Serzone
- Zyprexa; some positive evidence
- Cyproheptadine 2-4 mg ½ to 4 hours prior to sex; max is 12 mg/day; very sedating and may reverse therapeutic effects
- Yohimbine 5.4 mg three times-a-day or 5.4 mg ½-4 hours prior to sex; can cause anxiety
- Gingko biloba
    - Ancient folk remedy used for at least 4 thousand years in China
    - Ginkgo tree found in Asia
    - Mechanism of gonkgolide derivatives of the leaf:
        - May increase cerebral, cardiovascular, and genital bloodflow
        - Harvester of free radicals
        - Inhibits activity of platelet activating factor
    - Side effects/risks
        - Increased risk of bleeding
        - Allergic reaction
        - Confusion
        - Headache
        - Gastrointestinal upset

        - Dry mouth (more common with Paxil and Luvox)
        - Poor appetite and mild loss of weight
        - Mild weight gain (usually over many months)
        - Seizure risk overall 0.2%
    - Dosing
        - 60-240 mg/day for sexual side effects OR 60-120 mg ½-4 hours prior to sex
        - LeBars, 1997: 120 mg/day may retard progression of dementia; 120-360 mg used in Alzheimer's
        - Interaction with other medications
        - Some drug-drug interactions are dangerous (e.g., SSRIs and monoamine oxidase inhibitors)
- Abilify
    - Abilify augmentation of antidepressants in depression
        - Improved sexual functioning in women (vs. placebo), independent of improvement in depressive symptoms
        - No change in sexual functioning in men
- DHEA
- Discuss ***all*** medications and drugs (including over-the-counter, homeopathic, and herbal medications) you are taking or you are about to take with your psychiatrist to prevent drug-drug interactions

- The less common side effects, idiosyncratic reactions, and other possible reactions/effects (discuss with physician)
    - Yawning
    - Sweating; can treat with:
        - Terazosin (Hytrin) 1-2 mg/PM
        - Doxazosin (Cardura) 1-2 mf/PM
        - Hyosamine (Levsin) 1-2 mg/PM
        - Ditropan 5 mg twice-a-day
        - Beta-blocker
        - Aluminum chloride in anhydrous ethyl alcohol used locally
    - Hypomania or mania:
        - 0.9-6.25%
        - In bipolar disorder
        - 25% if used without mood stabilizers
        - 6% if used with mood stabilizers
    - Serotonin syndrome
        - altered consciousness
        - sweating
        - autonomic nervous system disturbances
        - high body temperature
        - movement abnormalities
        - muscle jerkiness
        - tremor
        - shivering
        - diarrhea
        - incoordination
        - agitation
    - Abnormal muscle movements, especially when taking other medications
        - Akathisia (muscle restlessness)
        - Jaw tightness/clenching/grinding; can treat with
            - Buspar 5-10 mg/PM
            - Valium/benzodiazepines
    - Increase risk of bleeding
        - Wang et al, 2014: risk of gastrointestinal bleeding when SSRI's are combined with NSAIDs is 3.44-fold higher; the risk when SSRI's are combined with low dose aspirin is 2.07-fold higher.
        - Decreased platelet aggregation (may improve cardiovascular function)
        - Increase risk of bleeding—1.5-3X increased risk (fuller range is 1.1-4.8X increased risk); the risk is higher if used with aspirin or NSAIDs
        - 2013 study demonstrated higher rates of post-op bleeding complications: University of California, San Francisco took a closer look at SSRI use before surgery and the rate of adverse events in a group of 530,416 patients over age 18 who had operations between January 2006 through December 2008 at 375 different U.S. hospitals.
    - Cardiovascular
        - Above
        - Wu et al, 2011; possible increased risk of cerebrovascular events with antidepressant use; this was associated with all antidepressants, though serotonergic meds perhaps more so; this may relate to platelet inhibition and increased risk of bleeding; it's not clear how real this risk is at this point (7/1/11)
        - Whang, 3/09; 63,469 women without baseline coronary heart disease; depression was associated with fatal coronary heart disease, and a measure of clinical depression including antidepressant use was associated with sudden cardiac death.
        - Women's Health Initiativel 136,293 postmenopausal women
            - SSRI's and TCA's were associated with increased risk of mortality;
            - SSRI's were associated with hemorrhagic and fatal stroke
                - SSRI risk 0.42% vs. 0.30% for those not taking an SSRI; this is a 45% increase in risk
                - No difference between SSRI's and TCA's
            - Not clear whether the risk was related to medication use or depression itself
        - Women's Ischemia Syndrome Evaluation, 2009; women with ischemic symptoms who had undergone clinically indicated angiography, followed over nearly 6 years
            - Combined use of antidepressants and anxiolytics predicted more cardiovascular events and mortality compared with women who did not use those medications, although use of either alone did not
            - Not clear whether the risk was related to medication use of depression itself
    - Syndrome of inappropriate anti-diuretic hormone secretion with risk of low sodium and subsequent seizures coma and death; symptoms

may include stomach upset, tiredness, headache, confusion
- Hair loss; can use:
  - Zinc, copper, selenium, omega-3 fatty acids
  - Selsun Blue shampoo
  - Minoxidol (Rogaine)
- May slow rate of weight and height increases in children and adolescents; however, this is unclear since there is evidence that children with anxiety disorders (in the absence of pharmacologic treatment) grow to be shorter (on average) than children without anxiety disorders; bone development may be slowed or affected by SSRI use (January, 2012); this is currently being further investigated
- May cause or worsen tinnitus (ear ringing) in the context of head or jaw movement
- May affect bone metabolism and risk of osteoporosis
  - SSRI's (and TCA's) have been linked to increase risk of fractures in adults; risk of fractures seems more related to risk of falls than reduced bone density
  - Theoretically this could affect growth in youth
  - Depression itself increases risk of decreased bone density, falls, and fractures
    - Depression is linked to changes in diet, weight loss, decreased physical activity, smoking, alcohol abuse, and decreased sun exposure
  - Clodagh et al, 2016
    - Depression itself increases the risk of osteoporosis
    - Prozac is protective of bone loss/osteoporosis
    - Celexa increases risk of osteoporosis by 2-fold (range 1.3-2.9), which is statistically significant
    - These antidepressants increase the risk to a degree that is not statistically significant
      - Remeron increases risk 2.3-fold
      - Tricyclic antidepressants increase risk 1.5-fold
      - Zoloft increases risk 1.4-fold
      - Lexapro increases risk 1.3-fold
    - These antidepressants are not linked to change in risk of osteoporosis
      - Paxil
      - Effexor XR
      - Cymbalta
- Weight gain
  - Prozac: 4.8-6.8% vs. 6.3% placebo
  - Celexa: 3.9% vs. 2.8% placebo
  - Zoloft: 4.2%
  - Paxil: 25.5%
- Liver issues
  - 2% risk elevated liver enzymes; case reports with Prozac, Paxil, Zoloft, Luvox, Celexa.
  - Case reports of liver and combined liver/kidney damage
  - Voican et al, 2014
    - Antidepressants of greatest risk
      - Iproniazid (an MAOI)
      - Nefazodone (Serzone)
      - Phenelzine (an MAOI)
      - Imipramine (a TCA)
      - Amitriptyline (a TCA)
      - Cymbalta (an SNRI)
      - Wellbutrin (a noradrenergic/dopaminergic antidepressant)
      - Trazodone
      - Tianeptine
      - Agomelatine
    - Antidepressants with least evidence of risk
      - Celexa
      - Lexapro
      - Paxil
      - Luvox (fluvoxamine)
- Reversible, dose-related syndrome of apathy, indifference, loss of initiative, and/or disinhibition (called amotivational syndrome)
- Suicidality—see separate handout
- Shah, 2011: antidepressants as a group (not solely SSRI's) may be linked to thicker carotid arteries
- Nursing home residents with dementia who use SSRIs have an increased risk of having a fall that causes injury compared with those who do not use SSRIs (Stretke et al, 2012)
  - The risk is dose-dependent, with those using average doses having 3 times the risk compared with nonusers.
- In animal studies (noting that there are lifelong brain changes in the hippocampi of some animals after exposure to stress in youth)
  - Persistent increase in serotonin transporter density in the frontal cortex after childhood exposure to SSRI's in rats
  - Fluoxetine in newborn mice led to behaviors later in development that mimicked anxiety and depression (in mice) (Ansorge et al, 2004)
  - Chronic administration of fluoxetine in young rats impaired dendritic growth and spine density in the hippocampus (Norrholm and Ouimet, 2000)

Do Antidepressants Induce Psychosis in Children and Adolescents? A Naturalistic Study in Ambulatory Pediatric Population

Mariela Mosheva, Ehud Mekori, Shir Kantor, Yael Berg, Abraham Weizman, Doron Gothelf

Journal of Child and Adolescent Psychopharmacology 2016, 26 (5): 478-84

OBJECTIVE: The aim of the present study was to examine if selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) induce psychotic symptoms in children and adolescent outpatients. We secondarily aimed to assess the occurrence of adverse events

(AE), with particular interest in psychiatric adverse events (PAE), timing of their onset, and the effectiveness of antidepressants in children and adolescents.
METHODS: We retrospectively evaluated the computerized medical records of children and adolescents treated with antidepressants (SSRIs or SNRIs) for depressive disorders, anxiety disorders, and obsessive-compulsive disorders. AE and Clinical Global Impressions scores were recorded.
RESULTS: Sixty-nine children and adolescents aged 13.3±3.0 years were included. None of the patients treated presented with acute psychotic symptoms (delusions, hallucinations, and disorganized thinking or behavior). Duration of treatment extended over 13.4±11.8 months. PAE occurred in 39% of cases. Of these, 16% included suicidality (ideations or attempts), and 3% included nonpsychotic hypomanic symptoms. Significant clinical improvement was achieved in 41% of patients.
CONCLUSIONS: In contrast to the clinical impression of some clinicians, antidepressant treatment in pediatric ambulatory population was not associated with emergence of psychotic symptoms.

- SSRI Discontinuation Syndrome
    - When SSRIs are reduced significantly over a short period of time or stopped suddenly.
    - Worse with Paxil, Effexor.
    - Not dangerous
    - Highly uncomfortable like a bad flu
    - Usually begins 24-72 hours after the last dose of the SSRI and lasts 24-72 hours; however, at times, the syndrome can last on the order of weeks or months
    - Does not represent relapse
    - Symptoms may include: nausea, vomiting, diarrhea, anorexia, abdominal pain, malaise, aching muscles, headaches, runny nose, sweating, insomnia, nightmares, lethargy, imbalance, tremors, numbness, irritability, agitation, confusion, dizziness, visual disturbances, movement-induced exacerbation of symptoms
- Overdose: overall very safe in overdose, but can cause seizures, arrhythymias, decreased consciousness, and, at doses of 150 times the common daily therapeutic dose, death
- Pregnancy
    - Am J Obstet Gynecol. 2016 Dec;215(6):722-730. doi: 10.1016/j.ajog.2016.07.011. Epub 2016 Jul 16.

      Selective serotonin reuptake inhibitors for depression in pregnancy.

      Susser LC[1], Sansone SA[2], Hermann AD[3].

        - Perinatal depression is associated with a high risk of morbidity and mortality and may have long-term consequences on child development. The US Preventive Services Task Force has recently recognized the importance of identifying and treating women with depression in the perinatal period. However, screening and accessing appropriate treatment come with logistical challenges. In many areas, there may not be sufficient access to psychiatric care, and, until these resources develop, the burden may inadvertently fall on obstetricians. As a result, understanding the risks of perinatal depression in comparison with the risks of treatment is important. Many studies of selective serotonin reuptake inhibitors in pregnancy fail to control for underlying depressive illness, which can lead to misinterpretation of selective serotonin reuptake inhibitor risk by clinicians. This review discusses the risks and benefits of selective serotonin reuptake inhibitor treatment in pregnancy within the context of perinatal depression. Whereas selective serotonin reuptake inhibitors may be associated with certain risks, the absolute risks are low and may be outweighed by the risks of untreated depression for many women and their offspring.

        - Antidepressant Exposure During Pregnancy and Risk of Autism in the Offspring, 1: Meta-Review of Meta-Analyses

          Chittaranjan Andrade
          Journal of Clinical Psychiatry 2017 September 26
          There are no randomized controlled trials of antidepressant drugs to treat depression, or to prevent relapse into depression, during pregnancy; therefore, the safety of antidepressant drug exposure during pregnancy is based on evidence from case-control or cohort studies. Many of these observational studies, during the past decade, examined the risk of autism spectrum disorder (ASD) in exposed offspring. Different studies using different methods and examining different periods of antidepressant exposure before and during pregnancy obtained different results. Studies with adverse outcomes were highlighted in the mass media, whereas those with reassuring outcomes were mostly ignored. Meta-analyses were conducted to reconcile the findings of the different studies and determine the magnitude of the effect size. In the last year or so, at least 6 such meta-analyses examined the effects of antidepressant exposure during pregnancy on the risk of ASD in the offspring. The meta-analyses set different study selection criteria and employed different methods of analysis to address different objectives. The findings across meta-analyses have been reasonably consistent. Antidepressant exposure during pregnancy is associated with an increased risk of ASD in the offspring. The risk is decreased after adjusting for confounding variables and is mostly no longer statistically significant after adjusting for maternal mental illness. Additionally, antidepressant exposure is associated with an increased risk of ASD in the offspring even when exposure is limited to the preconception period, when the drugs cannot have a physiological effect on the fetus. These findings suggest that

maternal mental illness is an important determinant of the risk of ASD associated with antidepressant exposure during pregnancy.

- Pulmonary hypertension in newborns (PPHN)
  - Reviewing 6 studies examining the connection between prenatal use of SSRIs and persistent pulmonary hypertension of the newborn (PPHN), Occhiogross et al, 2012, found that 3 studies found no association and 3 found associations. Of the 3 studies finding an association, 2 looked at the same database, incorporating additional recent births. Examined altogether, the 6 studies found a rate of PPHN to be LOWER in those exposed prenatally to SSRI's than in the general population.
  - Chambers, 2006:
    - use of SSRI after 20th week associated with PPHN (odds ratio 6.1); risk calculated at 1%
    - use of SSRI before 20th week not associated with PPHN
  - Wichman, 2007:
    - evaluated records of 25,214 newborns, including 745 who had been treated with SSRI's
    - no association with PPHN
    - of those newborns with PPHN, none of moms had taken SSRI's
  - Kallen, 2008:
    - evaluated 831,324 infants, 506 of which diagnosed with PPHN
    - use of SSRI was associated with PPHN (risk ratio 2.01); risk calculated at 0.15% (1.5 per 1000)
  - Andrade, 2009:
    - retrospective study
    - no association between SSRI use and PPHN
    - 5 cases of PPHN observed, 2 among SSRI-exposed, 3 among non-SSRI-exposed
    - Among 1104 exposed to SSRIs in 3rd trimester, prevalence of PPHN 2.14/1000
    - Among 1104 not exposed to SSRIs in 3rd trimester, prevalence of PPHN 2.72/1000
- Neonatal distress syndrome (NDS)
- Prolonged Qtc
- Spontaneous abortion
- Congenital malformations
  - Baseline rate in the general overall population of birth defects is 3%
  - Note that some studies demonstrating an association between prenatal SSRI use and congenital anomalies have also shown an increase (up to 10-fold) rate of fetal alcohol syndrome and thus prenatal alcohol use which are associated with increased risk of congenital anomalies
  - Depressed pregnant women are more likely to use nicotine, illicit drugs, and alcohol and is less likely to seek prenatal care
  - Prenatal depression (separate from use of SSRI's) is associated with preeclampsia, low birth weight, low gestational age, premature birth, developmental delay, behavioral problems, and post-partum depression (which can adversely affect the infant's temperament, mother-infant interaction, and infant cognitive ability.
  - Louik et al, 2007, case control study with 9,849 infants with congenital malformations and 5,860 infants without congenital malformations:
    - No association found between SSRIs overall exposure and
      - Craniosynostosis
      - Omphalocoele
      - Overall congenital heart anomalies
    - Specific agents
      - Zoloft was associated with
        - 5.7-fold increased risk of omphalocoele
        - 2-fold increased risk of septal defects
        - Anal atresia
        - Limb-reduction defects
      - Paxil was associated with
        - 3.3-fold increased risk of right ventricular outflow tract obstruction defects; note that the baseline rate of this type of anomaly in the general overall population is 5.5/10,000 so that the increased rate with Paxil is roughly 0.15%
        - Neural tube defects
        - Club foot
        - Undescended testes
      - Non-SSRI antidepressants were associated with anal atresia
  - Alwan et al, 2007, case-control study looking at 9,622 with birth defects vs. 4,092 without birth defects
    - SSRI was found to be associated with a 2.4-fold to 2.8-fold increased risk of
      - Anencephaly
      - Craniosynostosis
      - Omphalocoele
    - None of the individual SSRI's were associated with overall risk of birth defects or combined totals of cardiac or non-cardiac defects
    - Paxil and Celexa were each associated with the combined group of anencephaly, craniosynostosis, and omphalocoele
  - Meta-analysis, Rahimiet al, 2006:
    - 9 studies looking at Celexa, Prozac, Paxil, Zoloft vs. general population
    - No association with increased risk of major malformations
    - No association with cardiovascular malformations
    - No association with minor malformations
    - However, increased risk of spontaneous abortions (but is this related to depression or treatment?)
  - King et al, 2006; looking prospectively at 19,691 cases
    - In general population the risk of major congenital malformation is 3-4%
    - In exposed cases the risk is 2.6%

- Risk of autism
  - risk doubles with SSRI treatment for the mother in the year prior to delivery
  - risk triples with SSRI treatment in the first trimester
  - not clear if this is a correlation or causal link
  - even if there was a causal link, it would explain only 2-3% of cases of autism, suggesting the vast majority (97-98%) have other causes

Selective Serotonin Reuptake Inhibitors Decrease Pancreatic Insulin Secretion in Older Adults and Increase the Risk of Insulin Dependence in Type 2 Diabetes Patients

Raymond Noordam, Nikkie Aarts, Robin P Peeters, Albert Hofman, Bruno H Stricker, Loes E Visser

Journal of Clinical Psychiatry 2016 August 2

OBJECTIVE: Selective serotonin reuptake inhibitors (SSRIs) may decrease insulin secretion, but evidence from population studies is scarce. We investigated the association between SSRIs and markers for glucose-insulin homeostasis in a nondiabetic older population. Furthermore, we studied the association between SSRI use and insulin dependence in a diabetic population of older adults.

METHODS: This study was embedded in the prospective population-based Rotterdam Study cohort (1991-2012). In nondiabetic participants, fasting glucose and insulin levels and the homeostasis model assessment for insulin sensitivity and secretion were compared between participants using SSRIs and participants using no antidepressant. In diabetic patients using oral glucose-lowering agents, the risk of insulin dependence, defined as the start of insulin treatment, was compared between participants using SSRIs and participants using no antidepressant.

RESULTS: In nondiabetic participants, SSRI users (n = 87) had, compared with participants using no antidepressants (n = 5,505), a significantly ($P < .05$) lower level of insulin (8.8 mU/L and 9.9 mU/L, respectively), a lower degree of insulin resistance (2.2% and 2.4%, respectively), and less insulin secretion (89.1% and 100.4%, respectively), but a similar glucose level. Furthermore, > 90 days of consecutive use of SSRIs in diabetic patients was associated with a 2.17 times higher risk (95% confidence interval, 1.02-4.60) of starting insulin treatment than that of participants using no antidepressants.

CONCLUSIONS: Use of SSRIs was associated with lower insulin secretion in nondiabetic participants and an increased risk of insulin dependence in type 2 diabetics in older adults. However, additional studies are required to confirm our results.

Antidepressant Exposure and Risk of Fracture Among Medicaid-Covered Youth

Barbara L Gracious, Cynthia A Fontanella, Gary S Phillips, Jeffrey A Bridge, Steven C Marcus, John V Campo

Journal of Clinical Psychiatry 2016, 77 (7): e950-6

OBJECTIVE: This study examines the association between antidepressant use and risk of fracture in depressed youth and assesses whether fracture incidence varies over the course of antidepressant treatment.

METHOD: A retrospective cohort analysis of Ohio Medicaid claims data was conducted for youth ages 6-17 years with a new episode of ICD-9-diagnosed depression from 2001-2009. The primary outcome variable was time to fracture. Fracture rates were compared between depressed youth treated with antidepressant medication and untreated depressed youth. Time categories of no use, past use, and current use were compared.

RESULTS: Of 50,673 depressed youths, 5,872 (11.6%) experienced a fracture. Of those who had a fracture, 2,228 (37.9%) were exposed to antidepressants, 80% of which were selective serotonin reuptake inhibitors. The adjusted hazard ratio (HR) was 3% higher in those currently prescribed antidepressants (HR = 1.03; 95% CI, 1.00-1.06; P = .03). The risk ratio (RR) for adjusted fracture rates per 10,000 persons was twice as high during the first 30 days of antidepressant use compared to the other time periods (RR = 2.0; 95% CI, 1.2-3.3; P = .007). The number of fractures for those with past antidepressant use did not differ from those with no history of antidepressant use.

CONCLUSIONS: Antidepressant use may be associated with a small but significant increase in fracture risk, particularly within the first 30 days of treatment. Findings underscore a need for additional prospective and mechanistic research. Prescribers should consider other risks for fracture in antidepressant-treated youth, particularly disability and the concomitant use of other medications that increase fracture risk.

Adherence to antidepressants is associated with lower mortality: a 4-year population-based cohort study

Amir Krivoy, Ran D Balicer, Becca Feldman, Moshe Hoshen, Gil Zalsman, Abraham Weizman, Gal Shoval

Journal of Clinical Psychiatry 2016, 77 (5): e566-72

OBJECTIVE: Despite the growing use of antidepressants and the potential grave consequences of inadequate treatment, little is known about the impact of adherence to antidepressant treatment on mortality in the general population. The objective of this study was to evaluate the association between adherence to antidepressants and all-cause mortality in a population-based cohort.

METHODS: Data were extracted from the electronic medical record database of the largest health provider in Israel (53% of the nation's population) on a total of 251,745 patients aged 40 years and above who filled an antidepressant prescription at least once between 2008 and 2011. The main outcome measure was all-cause mortality during the study period. Adherence was measured as a continuous variable representing possession ratio (duration of filled antidepressant divided by duration of prescribed antidepressant). A polynomial model of proportional hazard Cox regression for multivariable survival analysis was used, adjusting for demographic and clinical variables that affect mortality.

RESULTS: The association between adherence and the hazard ratio (HR) for mortality follows a quadratic model in which the lowest HR (0.66 [95% CI, 0.64-0.69]) is at a level of 60% adherence in respect to nonadherence.

CONCLUSIONS: Adherence to antidepressants is significantly associated with a corresponding decrease in the risk of mortality, controlling for relevant covariates. Physicians from all disciplines should actively improve their patients' adherence to antidepressants since their persistent use is associated with increased survival.

Effectiveness of Antidepressant Medications for Symptoms of Irritability and Disruptive Behaviors in Children and Adolescents

Samuel Kim, Khrista Boylan

Journal of Child and Adolescent Psychopharmacology 2016 August 2

OBJECTIVES: Chronic irritability is a common presenting symptom in children and youth in both clinical settings (25%) and in the community (6%-8%). Treatment of irritability is relatively understudied. The purpose of this article is to synthesize evidence regarding the efficacy and safety of antidepressant medications for the treatment of irritability and related symptom dimensions in children and youth.

METHODS: Systematic review of the literature was conducted to identify studies (including youth aged 6-18) that assessed the effectiveness of antidepressant medications for the treatment of irritability or related behavioral phenotypes, including aggression or symptoms of. Studies of youth with developmental disabilities or autism spectrum disorders were excluded.

RESULTS: We identified 99 studies (three randomized trials) assessing the effect of antidepressants in improving irritability, aggression, or oppositional symptoms as secondary outcomes. Only two studies specifically measured the outcome of irritability. Eight of the 11 studies reported significant effects on aggression, oppositionality, or irritability with antidepressant exposure, although effect sizes in all, but two of these, studies were less than 0.25. These effects were significantly reduced, but remained significant in seven of these studies after controlling for changes in comorbid depression scores with treatment. The other three studies reported no change, an increase in frequency of self-harm or aggressive behaviors or benefit in only a subsample of youth who tolerated the antidepressants after 1 year of follow-up.

CONCLUSION: Antidepressant medication exposure appears to have a small effect on irritability and related symptoms in youth. Heterogeneity in the

study sample and absence of irritability being measured as a primary outcome across studies restrict the validity of the conclusions. Irritability is a debilitating outcome that needs specific attention in medication treatment studies.

Manic switches induced by antidepressants: an umbrella review comparing randomized controlled trials and observational studies
N Allain, C Leven, B Falissard, J-S Allain, J-M Batail, E Polard, F Montastruc, D Drapier, F Naudet
Acta Psychiatrica Scandinavica 2016 November 23
OBJECTIVE: We aimed to explore whether the prevalence of manic switch was underestimated in randomized controlled trials (RCTs) compared to observational studies (OSs).
METHOD: Meta-analyses and simple and systematic reviews were identified by two reviewers in a blinded, standardized manner. All relevant references were extracted to include RCTs and OSs that provided data about manic switch prevalence after antidepressant treatment for a major depressive episode. The primary outcome was manic switch prevalence in the different arms of each study. A meta-regression was conducted to quantify the impact of certain variables on manic switch prevalence.
RESULTS: A total of 57 papers (35 RCTs and 22 OSs) were included in the main analysis. RCTs underestimated the rate of manic switch [0.53 (0.32-0.87)]. Overestimated prevalence was related to imipraminics [1.85 (1.22-2.79)]; to serotonin-norepinephrine reuptake inhibitors [1.74 (1.06-2.86)]; and to other classes of drugs [1.58 (1.08-2.31)], compared to placebo treatment. The prevalence of manic switch was lower among adults than among children [0.2 (0.07-0.59)]; and higher [20.58 (8.41-50.31)] in case of bipolar disorder.
CONCLUSION: Our results highlight an underestimation of the rates of manic switch under antidepressants in RCTs compared to the rates observed in observational studies.

Long-Term Acute-Phase Treatment With Antidepressants, 8 Weeks and Beyond: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials
Jonathan Henssler, Mona Kurschus, Jeremy Franklin, Tom Bschor, Christopher Baethge
Journal of Clinical Psychiatry 2017 January 3
OBJECTIVE: In clinical practice, acute antidepressant treatment is often applied for several months until remission is achieved. However, data on treatment outcomes beyond 8 weeks are sparse and no systematic review exists to date. This study aims at assessing efficacy and tolerability of antidepressants compared to placebo in acute treatment at and beyond 8 weeks.
DATA SOURCES: MEDLINE, Embase, PsycINFO, and CENTRAL databases were systematically searched through March 2014 using generic terms for depressive and affective disorders combined with generic terms for individual drugs and placebo.
STUDY SELECTION: Double-blind, randomized, placebo-controlled studies of 8 weeks or more comparing antidepressant monotherapy to placebo in adult patients with acute depressive disorder.
DATA EXTRACTION: Data extraction and synthesis followed guidelines of the Cochrane Collaboration. All data were extracted independently by 2 reviewers. Primary outcome was standardized mean difference (SMD) between antidepressant and placebo; secondary outcomes were response, remission, and dropouts.
RESULTS: Of 6,043 articles screened, we selected 104 studies that met criteria and included 35,052 patients. Active treatment was statistically significantly superior to placebo, with consistent effect sizes (SMD [95% CL]) after 8, 12, 16, 20, and 24 weeks: 0.27 (0.24, 0.30), 0.34 (0.25, 0.43), 0.24 (0.09, 0.40), 0.31 (0.12, 0.51), and 0.34 (0.18, 0.50), respectively. Results remained stable across secondary outcomes and subgroup and sensitivity analyses.
CONCLUSIONS: Effect sizes of antidepressant monotherapy compared to placebo seem to be stable over 6 months. These results challenge the assumption that long-term antidepressant effects are due to the natural course of the disorder rather than to a pharmacologic effect.

Below is a summary of a study that I will be exploring (I have not seen the full article):

Risk of First Onset Stroke in SSRI-Exposed Adult Subjects: Survival Analysis and Examination of Age and Time Effects
Chin-Hong Chan, Hsiang-Hsiung Huang, Ching-Heng Lin, Yi-Chun Kuan, El-Wui Loh, Tsuo-Hung Lan
Journal of Clinical Psychiatry 2017 September 26
OBJECTIVE: Exposure to selective serotonin reuptake inhibitors (SSRIs) has been shown to increase the risk of stroke. In this study, we investigated age and time effects on the risk of first onset stroke in SSRI-exposed (SSRIEXP) adult subjects.
METHODS: We analyzed an 8-year cohort from the National Health Insurance Research Database, Taiwan. Patients were defined as SSRIEXP subjects if they received SSRI prescriptions for at least 2 consecutive months during January 1, 2001, to December 31, 2007. Otherwise, they were categorized as SSRI-nonexposed (SSRINONE) subjects. Stroke diagnosis was made according to ICD-9 codes 430-432 (hemorrhagic stroke) and 433-437 (ischemic stroke).
RESULTS: Kaplan-Meier survival analysis showed a greater probability of first onset stroke in SSRIEXP than SSRINONE subjects ($P < .001$). The higher incidence rates in SSRIEXP subjects persisted to the 3 year time point. Ischemic/hemorrhagic stroke cumulative incidence ratios were also higher during the first 3 years in SSRIEXP subjects. Analysis of adjusted hazard ratios indicated that younger SSRIEXP subjects were more likely to experience stroke, with a slight increase of risk in subjects older than 65 years. Stratified analysis of ischemic stroke and hemorrhagic stroke resulted in a similar hazard ratio trend.
CONCLUSIONS: Use of SSRIs independently increases the risk of stroke across age strata. The risk is higher in younger adult subjects, and the stroke is more likely to be ischemic than hemorrhagic. The underlying mechanisms of stroke may be related to cerebral microbleeding or an overcorrection of hemostasis function.

February 26, 2018

Association of Coprescription of Triptan Antimigraine Drugs and Selective Serotonin Reuptake Inhibitor or Selective Norepinephrine Reuptake Inhibitor Antidepressants With Serotonin Syndrome

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Author Affiliations Article Information
JAMA Neurol. Published online February 26, 2018. doi:10.1001/jamaneurol.2017.5144
Key Points
Questions What is the risk of serotonin syndrome associated with concomitant use of triptans and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants and how did the use of these drugs change after the 2006 US Food and Drug administration warning about this risk?

Findings In this data registry study of 47 968 patients prescribed triptans, the incidence of serotonin syndrome was 0 to 4 cases per 10 000 person-years of exposure to coprescription of triptans and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants. The proportion of patients who were coprescribed these drugs ranged from 21% to 29% and remained stable before and after the warning.

Meaning Serotonin syndrome was rare in patients who were coprescribed triptans and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants; those with coexisting affective disorders and migraine need not forgo management of one condition to treat the other.

Abstract

Importance In 2006, the US Food and Drug Administration (FDA) issued an advisory warning on the risk of serotonin syndrome with concomitant use of triptans and selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI) antidepressants, but the true risk of serotonin syndrome in these patients remains unknown.

Objective To assess the risk of serotonin syndrome with concomitant use of triptans and SSRI or SNRI antidepressants.

Design, Setting, and Participants This study used electronic health record data from the Partners Research Data Registry (RPDR) to identify patients who had received an *International Classification of Diseases, Ninth Revision* diagnosis compatible with serotonin syndrome who had been coprescribed triptans and SSRI or SNRI antidepressants in the Greater Boston, Massachusetts, area from January 1, 2001, through December 31, 2014 (14 years). Clinical information was extracted to determine whether the case met formal diagnostic criteria and had coprescription within a calendar year. Both conservative and broad case definitions were used to better characterize the spectrum of risk. Data analysis was performed from November 23, 2016, to July 15, 2017.

Main Outcomes and Measures Incidence of serotonin syndrome.

Results The RPDR search revealed 47 968 (±3) unique patients who were prescribed triptans during the 14-year period of the study. A total of 19 017 (±3) patients were coprescribed triptans and antidepressants during the study, with a total of 30 928 person-years of exposure. Serotonin syndrome was suspected in 17 patients. Only 2 patients were classified as having definite serotonin syndrome (incidence rate, 0.6 cases per 10 000 person-years of exposure; 95% CI, 0.0-1.5). Five patients were classified as having possible serotonin syndrome (incidence rate with these 5 cases added to the 2 definite cases, 2.3 cases per 10 000 person-years of exposure; 95% CI, 0.6-3.9). The proportion of patients with triptan prescriptions who were coprescribed an SSRI or SNRI antidepressant was relatively stable during the study, ranging from 21% to 29%.

Conclusions and Relevance The risk of serotonin syndrome associated with concomitant use of triptans and SSRIs or SNRIs was low. Coprescription of these drugs is common and did not decrease after the 2006 FDA advisory. Our results cast doubt on the validity of the FDA advisory and suggest that it should be reconsidered.

Introduction

In 2006, the US Food and Drug Administration (FDA) issued an advisory about the risk of serotonin syndrome associated with concomitant use of drugs from 2 widely prescribed medication classes: (1) selective serotonin reuptake inhibitor (SSRI) and selective norepinephrine reuptake inhibitor (SNRI) antidepressants and (2) triptan antimigraine drugs.[1] Cases of serotonin syndrome associated with triptan monotherapy have also been reported.[2] Serotonin syndrome is thought to result from elevated serotonin levels. It causes a constellation of features, including tachycardia, unstable blood pressure, hyperthermia, nausea, vomiting, and diarrhea. Severity varies, but it can be fatal.[3] The FDA advisory was based on a small number of case reports. Doubts exist about whether these cases actually met criteria for the disorder.[4,5] A position paper by the American Headache Society questioned the basis for the advisory and noted conflicting and insufficient information to discern the risk.[6]

Triptan antimigraine drugs and SSRI and SNRI antidepressants are widely prescribed. Depression and migraine are highly prevalent, long-lasting, disabling conditions that occur together at a frequency higher than expected by chance. In 2007 to 2008, triptans were prescribed for more than 5 million patients with migraine; other evidence suggests that 20% to 25% of triptan users are also prescribed SSRI or SNRI antidepressants.[7,8] One study suggested that the FDA advisory thus applies to an estimated 1.8% of the US population, with investigators remarking that "What remains missing from the literature is documentation as to the number of cases of serotonin syndrome due to the concomitant use of triptan, and SSRI or SNRI, and the resulting consequences."[8(p 199)]

Because there have been no population-based studies that link coprescription with the outcome of serotonin syndrome, the true risk remains unknown. Precise risk estimates would aid clinical decision making and would support or refute the validity of the FDA advisory. Meanwhile, the situation for physicians and patients is confusing. Pharmacy systems and other decision support systems routinely issue safety alerts when coprescription occurs. These alerts result in substantial disruption of clinical care.[9] For these reasons, we conducted a study to identify patients who were coprescribed these drugs and evaluate whether any had developed serotonin syndrome and to determine whether changes occurred in coprescription after the 2006 FDA advisory.

The Impact of Prolonged, Selective, Serotonin Reuptake Inhibitor Treatment on Serum Lipid and Glucose Levels in Children and Adolescents: A Preliminary Prospective Study

Lior Schapir, Abraham Weizman, Pavel Golubchik

Journal of Child and Adolescent Psychopharmacology 2018 June 6

OBJECTIVES: Treatment with selective serotonin reuptake inhibitors (SSRIs) is common and is considered safe and effective in the treatment of anxiety and depressive disorders in pediatric populations. SSRI administration, however, is associated with adverse metabolic effects. The aim of this preliminary study was to evaluate the possible influence of a 6-month SSRI treatment on metabolic parameters in children and adolescents with depressive and/or anxiety disorders.

METHODS: Metabolic parameters (glucose, cholesterol, triglycerides, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) were monitored in 22 children and adolescents (16 boys and 6 girls, aged 8-18 years) at baseline and after 6 months of SSRI treatment for depression and/or anxiety.

RESULTS: Six months of SSRI treatment did not affect serum glucose, cholesterol, or triglycerides significantly, but a tendency (p=0.06) toward elevation in serum LDL accompanied by a parallel reduction in HDL levels was detected.

CONCLUSION: It appears that the 6-month SSRI treatment is metabolically safe in children and adolescents and does not affect the glucose or lipid profile. Long-term large-scale studies in pediatric populations focusing on the possible impact of long-term SSRI treatment (>6 months) on metabolic parameters are warranted.