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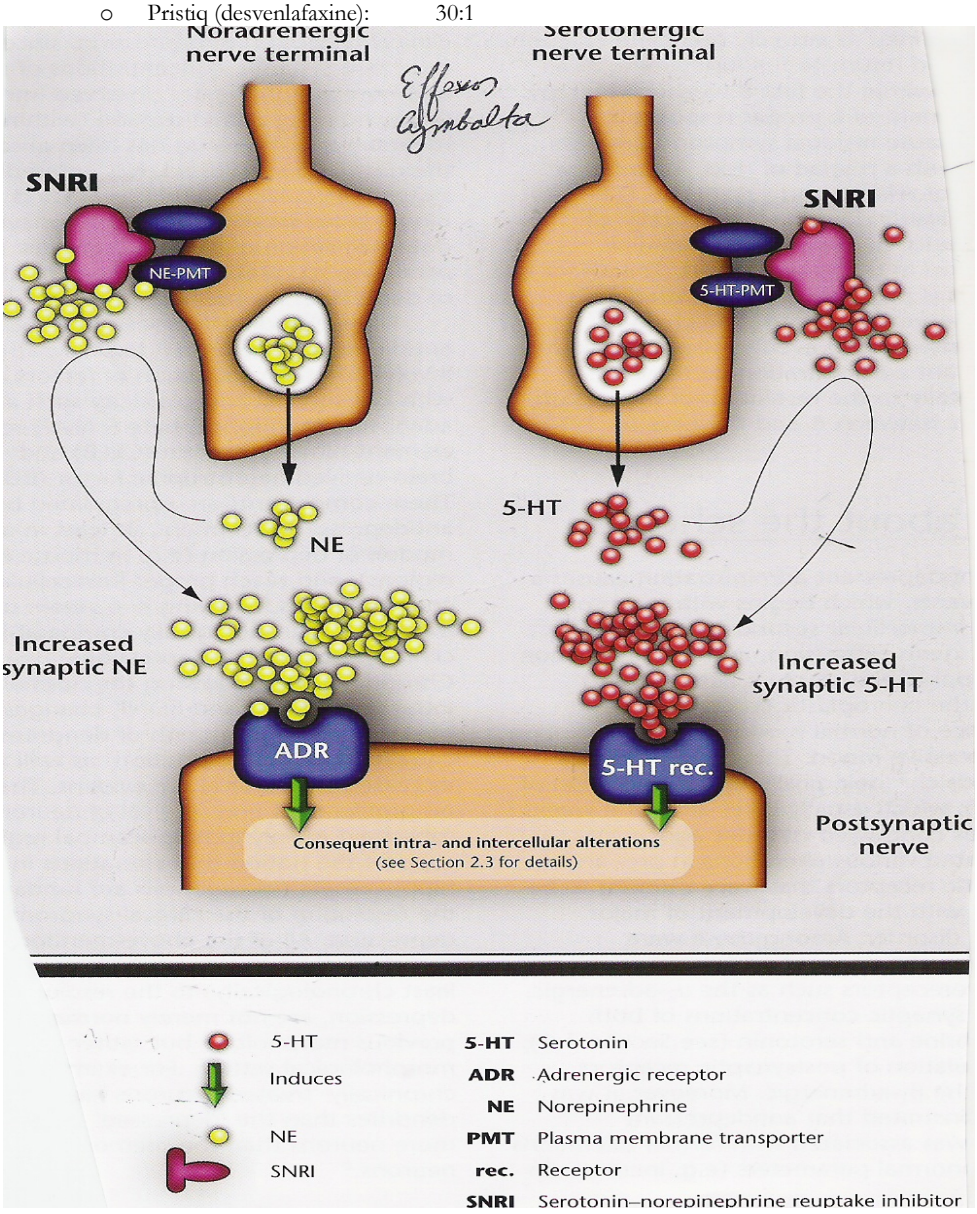
Serotonin Norepinephrine Reuptake Inhibitors (SNRI's)

- General
  - SNRI's have evidence of higher response rate and quicker onset of efficacy compared to SSRI's in adult depression and some anxiety disorders
    - Papakostas et al, 2007, meta-analysis of more than 93 trials in more than 17,000 patients:
      - Response rate for SNRI's 64% vs. 59% for SSRI's
      - None of the SNRI's appeared better than other SNRI's
      - More than ¾'s of the studies were funded by the manufacturer
    - 2007 evidence supports a higher rate of remission (50%) compared to SSRI's (as a group and individually).
    - Annals of Internal Medicine, 2005: 88% of comparative efficacy studies demonstrate no statistically significant difference in any outcome measure (though exact doses are critical to interpret this here)
    - Of clients who are work-impaired, nearly twice as many clients reach full work functionality compared to those on SSRI's
    - Meta-analysis of 15 studies with 2971 patients demonstrate remission rates of Remeron (which is functionally an SNRI) vs. SSRI's
      - 43% for Remeron (and was more rapidly effective)
      - 38% for SSRIs
  - May better treat symptoms of pain and also fibromyalgia
  - Ratio of serotonin-to-norepinephrine reuptake inhibition:
    - Fetzima (levomilnacipran): 1:2
    - Cymbalta (duloxetine) 10:1
    - Effexor (venlafaxine) XR: 30:1 (ratio decreases with dose)
    - Pristiq (desvenlafaxine): 30:1



- **Effexor (venlafaxine)/Effexor XR**
  - General
    - FDA-approved for depression, generalized anxiety disorder, social anxiety disorder, panic disorder.
    - Released in 1994; available in XR form 1998. Half-life is 5 hours for venlafaxine and 11 hours for it's major metabolite O-desmethylvenlafaxine.
    - At doses under 150 mg, Effexor XR acts primarily like an SSRI. At doses 150 mg and higher (likely 250 mg and higher), Effexor XR inhibits norepinephrine reuptake in addition to serotonin reuptake. May lead to down regulation of beta-adrenergic receptor-coupled cAMP.
    - Metabolized by **2D6** and 3A4
      - 2D6 is critical for metabolism of venlafaxine (Effexor) to desvenlafaxine (Pristiq)
      - one way to determine if one is a slow 2D6 metabolizer is to get blood levels of venlafaxine and desvenlafaxine. If venlafaxine is 20-25% and desvenlafaxine is 75-80%, then the person is a normal ("extensive") metabolizer. If the ratio is reversed so that there is more venlafaxine and less desvenlafaxine, then that indicates the person is a slow 2D6 metabolizer.
  - Evidence
    - May be effective in neuropathic pain, fibromyalgia, other chronic pain conditions, and ADHD.
    - Adults
      - Depression
        - There is clear evidence that Effexor is safe and efficacious in the treatment of depression in adults. FDA-approved for depression in adults.
        - May be more effective in adult depression than SSRI's (in adults), in terms of rapidity of response as well as remission, though 2005 evidence suggests otherwise.
        - Kocsis et al, 2007 (PREVENT study): initial random assignment to Effexor XR 75-300 mg/day or Prozac 20-60 mg/day for 10 weeks; responders then received 6 months continuation treatment; those who remained responders were enrolled in a 12-month maintenance trial where they would either receive Effexor XR (average dose 224.7 mg/day) or placebo during those 12 months; Prozac responders continued Prozac for those 12 months; results:
          - Cumulative probability of recurrence through 12 months for Effexor XR 23.1% vs. 42% for placebo
          - Side effects:
            - Headache 25% vs. 24% placebo
            - Dry mouth 15% vs. 11% placebo
            - Insomnia 14% vs. 12% placebo
            - Sweating 14% vs. 12% placebo
            - Weight gain 12% vs. 7% placebo
            - Dizziness 11% vs. 21% placebo (was this latter # from discontinuation syndrome?)
            - Nausea 11% vs. 10% placebo
            - Abnormal ejaculation/orgasm 16% vs. 11% placebo
            - Lassitude 11% vs. 10% placebo
            - Libido decreased 10% vs. 8% placebo
            - Constipation 9% vs. 6% placebo
            - Nervousness 5% vs. 10% placebo
            - Somnolence 5% vs. 8% placebo
            - Stomach upset/abdominal pain 9% vs. 10% placebo
            - Diarrhea 3% vs. 7% placebo
            - Nerve tingling 2% vs. 10% placebo
        - Kennedy et al, 2007: 16 weeks of Effexor XR vs. CBT for adult depression, 24 patients
          - CBT: 58% response; response correlated with a reciprocal modulation of cortical-limbic connectivity
          - Effexor XR: 75% response; response correlated with engagement of cortical and striatal regions
          - Reduced metabolism in several prefrontal cortical areas prior to treatment was associated with response to either treatment
        - Effexor XR vs. Zoloft in RCT, DB, active-control, in adult MDD
          - Response: 65-70% Effexor XR vs. 55-59%
          - Remission: 49-50% Effexor XR vs. 38-48% Zoloft
        - Davison et al, 2003: remission rates (after 12 weeks): 24.3% with Zoloft, 30.2% with Effexor XR, 19.6% with placebo
      - Anxiety
        - Fergusen et al, 2007: effective in relapse prevention in adults with panic disorder
        - Denys et al, 2003: efficacy in the treatment of OCD same as SSRI's
        - Generalized anxiety disorder
          - Increasing rates of remission from week 2 through 6 months (45% remission by 6 months vs. ~21% placebo)
        - Social Anxiety Disorder
          - Stein et al, 2005
          - Liebowitz et al, 2005
          - Rickels et al, 2004
    - Youth
      - Depression
        - Emslie et al, 2007: open-label study, 86 children aged 7-12 and 13-17 with major depression for up to 6 months
          - 55% response by 6 months (which included 10% of those who did not respond by 1 month)
          - 45% remission

        - Elsewhere it is noted that "two acute venlafaxine studies (Emslie et al, 2007) in children and adolescents with major depressive disorder have been negative"
    - 2 studies (APA, 2004; not clear if these are separate from the UK studies below):
        - In one (161 youth): 50% response vs. 41% with placebo.
        - In other (193 youth): 67% response vs. 61% with placebo.
    - 2 multicenter, double-blind, placebo-controlled studies with 266 youths with depression; both ***negative***—data from the United Kingdom demonstrates Effexor "did not demonstrate efficacy in depressive illness (in children) and showed an increase in the rate of harmful outcomes including hostility, suicidal ideation, and self-harm."
- Anxiety
    - March et al, 2007: 285 youth aged 8-17 years, social anxiety disorder, 37.5-225 mg/day; 16 weeks
        - 56% much improved to very much improved with Effexor vs. 37% placebo
        - ~1/3 discontinued treatment due to lack of efficacy
        - 3 youth on Effexor reported suicidal ideation, but no suicidal behaviors were reported
        - 1 youth experienced time-limited hypomania that did not require discontinuation of Effexor
        - 6 youth were activated
    - Rynn et al, 2007: 2 RCT, DB, 59 sites in 2000 and 2001, children aged 6-17 yo, GAD:
        - 69% response rate with Effexor
        - 48% with placebo

- Side effects/risks
    - Headache 28-38% (46% in kids) vs. 19% in placebo
    - Insomnia 22.5% at 150 mg and 8-13.6% at 375 mg; (10% in kids) vs. 13% in placebo
    - Abdominal pain 19% in kids
    - Sexual side effects 18% (BUT 65% when formally assessed)
    - Nervousness or Anxiety 15-32% (13% in kids) vs. 8-18% in placebo
    - Drowsiness OR fatigue 14-37% (8% in kids) vs. 1% in placebo
    - Dizziness 10-18% vs. 18% in placebo
    - Nausea/vomiting 9-45% vs. 14% in placebo
    - Tremor 9% vs. 2% in placebo
    - Diarrhea 8-10% (6% in kids) vs. 6% in placebo
    - Sweating 8-13% vs. 1% in placebo
    - Lassitude 8% (13% in kids)
    - Weight loss 6% in kids
    - 5% risk of hypertension at doses less than 200 mg; 13% risk in doses over 300 mg. The average increase is 5-7 mm Hg. Less problematic with Effexor XR.
    - Agitation 5% in kids
    - Constipation 4-9% vs. 0% in placebo
    - Dry mouth 2-18% vs. 0% in placebo
    - Depression <1-2% vs. 6% in placebo
    - Reduced appetite 0-10% vs. 2% in placebo
    - Syncope (fainting) has also occurred
    - Severe rash 0.8% vs. 2.3% in other antidepressants
    - Significant elevations in liver enzymes 0.8% vs. 3.1% in other antidepressants
    - Seizure 0.4% vs. 1.5% in other antidepressants
    - Suicide 0.4% vs. 0.8% in other antidepressants
    - Mania in 0.4%
    - Pregnancy
        - One study: no increased risk of major malformations, ?increased risk of spontaneous abortions (?depression vs. treatment?); 4.5-11% risk of spontaneous abortion in general population
        - 2 case reports of neonatal in utero seizures—not clear if related

- **Pristiq** (desvenlafaxine extended release)
  - Metabolite of Effexor; being investigated
  - Two eight week RCTs, double-blind, placebo-controlled, 461 patients: effective and well-tolerated in depression (and ?pain)
  - Two industry-sponsored studies also positive
  - FDA approvable letter received on 1/22/07
  - 50-100 mg/day
  - Metabolized by **UGT 1A1**
  - Evidence
    - Youth
      - 2017, Prozac 20 mg/day vs. Pristiq 25 vs. 35 vs. 50 mg/day
        - Similar efficacy; people improved, but this was considered a failed study
      - 2015 Pfizer study
        - 340 youth, 7-17 yo
        - Pristiq=Prozac=Placebo
  - Side effects:
    - Nausea or vomiting 42-55% v. 14% placebo
    - Somnolence 24-30% v. 10% placebo
    - Insomnia 21-35% v. 10% placebo
    - Dry mouth 20-29% v. 12% placebo
    - Dizziness 18-22% v. 7% placebo
    - Nervousness 18-22% v. 5% placebo
    - Sweating 12-24% v. 4% placebo
    - Reduced appetite 12-16% v. 3% placebo
    - Constipation 10-16% v. 3% placebo
    - Lassitude 8-13% v. 6% placebo
    - Abnormal vision 6-8% v. 2% placebo
    - Abnormal ejaculation/orgasm 5-22% v. 1% placebo
    - Tremor 3-11% v. 1% placebo
    - Erectile dysfunction 3-5% v. 1% placebo
    - Blood pressure increases
    - Weight loss (minor)
  - Metabolism does not involve the P450 system

Desvenlafaxine Versus Placebo in a Fluoxetine-Referenced Study of Children and Adolescents with Major Depressive Disorder
Karen L Weihs, William Murphy, Richat Abbas, Deborah Chiles, Richard D England, Sara Ramaker, Dalia B Wajsbrot
Journal of Child and Adolescent Psychopharmacology 2017 November 30

OBJECTIVES: To evaluate the short-term efficacy and safety of desvenlafaxine (25-50mg/d) compared with placebo in children and adolescents with major depressive disorder (MDD).

METHODS: Outpatient children (7-11 years) and adolescents (12-17 years) who met DSM-IV-TR criteria for MDD and had screening and baseline Children's Depression Rating Scale-Revised (CDRS-R) total scores >40 were randomly assigned to 8-week treatment with placebo, desvenlafaxine (25, 35, or 50mg/d based on baseline weight), or fluoxetine (20mg/d). The primary efficacy endpoint was change from baseline in CDRS-R total score at week 8, analyzed using a mixed-effects model for repeated measures. Secondary efficacy endpoints included week 8 Clinical Global Impressions-Severity, Clinical Global Impressions-Improvement (CGI-I), and response (CGI-I ≤ 2). Safety assessments included adverse events, physical and vital sign measurements, laboratory evaluations, electrocardiogram, and the Columbia-Suicide Severity Rating Scale.

RESULTS: The safety population included 339 patients (children, n=130; adolescents, n=209). The primary endpoint, change from baseline in CDRS-R total score at week 8, did not statistically separate from placebo, for either desvenlafaxine (adjusted mean [standard error] change, -22.6 [1.17]) or fluoxetine (-24.8 [1.17]; placebo, -23.1 [1.18]). Week 8 CGI-I response rates were significantly greater for fluoxetine (78.2%; p=0.017) than for placebo (62.6%); desvenlafaxine (68.7%) did not differ from placebo. Other secondary outcomes were consistent with those obtained with CDRS-R. Rates of treatment-emergent adverse events were comparable among treatment groups (desvenlafaxine, 60.0%; placebo, 70.5%; and fluoxetine, 64.3%).

CONCLUSION: Desvenlafaxine did not demonstrate efficacy for treating MDD in children and adolescents in this trial. Because neither desvenlafaxine nor the reference medication, fluoxetine, demonstrated a statistically significant difference from placebo on the primary endpoint, this was considered a failed trial and no efficacy conclusions can be drawn. Desvenlafaxine 25-50mg/d was generally safe and well tolerated in children and adolescents in this study.

Pharmacokinetics and Tolerability of Single-Ascending Doses of Desvenlafaxine Administered to Children and Adolescents with Major Depressive Disorder
Robert L Findling, James Groark, Karen A Tourian, Sara A Ramaker, Deborah Chiles, Lingfeng Yang, Alice I Nichols
Journal of Child and Adolescent Psychopharmacology 2016 July 18

OBJECTIVE: To investigate the safety and pharmacokinetic profile of ascending doses of desvenlafaxine in children and adolescents with major depressive disorder. Assessment of the effect of desvenlafaxine on depression symptoms was exploratory.

METHODS: The 8-week, open-label study included an initial 3.5-day inpatient period followed by a 7.5-week outpatient period. Children (7-11 years) received a single desvenlafaxine dose of 10, 25, 50, or 100mg on day 1; adolescents (12-17 years) received desvenlafaxine 25, 50, 100, or 200mg/day. Plasma and urine samples were collected over the initial 72-hour inpatient period. Evaluations included treatment-emergent adverse events (TEAEs), physical examinations (including Tanner Staging), vital signs, laboratory assessments, 12-lead electrocardiogram, Columbia-Suicide Severity Rating Scale, and the Children's Depression Rating Scale-Revised (CDRS-R).
RESULTS: In all, 29 children and 30 adolescents took at least one dose of desvenlafaxine and were included in the safety population (children: 10mg, n=6; 25mg, n=7; 50mg, n=9; 100mg, n=7; adolescents: 25mg, n=7; 50mg, n=7; 100mg, n=8; 200mg, n=8). Total area under the drug concentration-time curve from 0 to infinity (AUC) appeared to increase linearly with increasing dose. Mean (standard deviation [SD]) AUC ranged from 628 (346) ng/mL (desvenlafaxine 10mg) to 6732 (3031) ng/mL (100mg) in children and from 1123 (361) ng/mL (25mg) to 11,730 (3113) ng/mL (200mg) in adolescents. During the combined inpatient and outpatient period, 16/29 (55%) children and 21/30 (70%) adolescents reported at least one TEAE. One serious adverse event (suicidal behavior) was reported. Mean (SD) change from baseline in CDRS-R total scores at week 8 was -19.00 (9.87) for children and -21.57 (11.50) for adolescents.
CONCLUSIONS: Desvenlafaxine AUC values increased linearly with dose; body weight alone provided an adequate prediction for dose-normalized AUC. Desvenlafaxine was generally safe and well tolerated in children and adolescents for treatment up to 8 weeks.

- **Cymbalta** (duloxetine).
  - General
    - Released in 2004 after a long delay due to re-analysis of safety data in the face of a completed suicide of a 19 y.o. woman (with no history of depression) taking duloxetine as part of clinical research.
    - Higher relative norepinephrine reuptake inhibition relative to Effexor. May lead to down regulation of beta-adrenergic receptor-coupled cAMP.
    - Doses between 60-120 mg/day; doses above 60 mg/day have shown some indirect evidence of more effectiveness in depression. Capsules: 20 mg, 30 mg, 60 mg
    - Peak 6 hours on an empty stomach, 6-10 hours if with food
    - Morning doses are cleared faster than evening doses (e.g., 60 mg/am may be equivalent to 40 mg/pm)
    - Half-life 12 hours (8-17 hours)
    - Metabolized by **2D6** and 1A2; Moderate inhibitor of P450 2D6 and, less so, 1A2
  - FDA-approved for
    - Depression
    - Generalized anxiety disorder
      - Adults
      - Youth
    - Diabetic peripheral neuropathic pain
  - May be helpful for stress urinary incontinence, fibromyalgia
  - Evidence
    - Emslie et al, 2014
      - Considered a failed trial, though it did work as well as Prozac (neither beat placebo)
      - Prozac 20 mg/d vs. Cymbalta 30 mg/day vs. 60 mg/day
        - Equal efficacy
      - Prozac 20-40 mg/day vs. Cymbalta 60-120 mg/day
        - Equal efficacy
    - Alaka et al, 2013: safe and effective in generalized anxiety disorder at a dose range of 30-120 mg/day
    - Koran et al, 2007: effective in dysthymia/double depression
    - 2007: 3 RCT's demonstrated efficacy in generalized anxiety disorder
    - Pooled data from six randomized, double-blind, placebo-controlled studies comparing over 700 clients on duloxetine, over 400 on SSRI's, and over 500 on placebo; duloxetine was safe and effective, perhaps more than SSRI's in moderate to severe depression (at least in terms of remission rates).
    - Two 9-week, double-blind, placebo-controlled studies on over 500 clients; safe and efficacious in both studies
    - Social Anxiety Disorder
      - Simon et al, 2010
    - Youth
      - Strawn et al, 2015: RCT study of youth generalized anxiety disorder
        - 135 kids on Cymbalta vs. 137 on placebo, random assignment for first 10 weeks, then open-label for 18 weeks
        - 30-120 mg/day
        - Cymbalta safe and superior in efficacy to placebo in 10 week portion of trial
          - Response rate: 59% vs. 42% placebo
          - Remission rate: 50% vs. 34% placebo
          - Functional remission rate: 37% vs. 24% placebo
        - Heart rate increased an average of 4.5 beats per minute compared to placebo
        - Weight decreased by 0.1 kg with Cymbalta versus an increase of 1.1 kg with placebo
        - Side effects that were statistically greater with Cymbalta than placebo:
          - Nausea
          - Vomiting
          - Decreased appetite
          - Oropharyngeal pain
          - Dizziness
          - Cough
          - Palpitations
        - No statistically significant differences between Cymbalta and placebo for
          - Suicidal ideation
            1. 5.9% of patients treated with Cymbalta vs. 5.2% treated with placebo experienced treatment-emergent suicidal ideation
          - Suicidal behavior
            1. No suicidal behaviors were reported during the 10 week phase
          - Nonsuicidal self-injurious behavior
            1. 1.5% of those treated with Cymbalta vs. 0.8% treated with placebo experienced treatment-emergent nonsuicidal self-injurious behavior
        - In extension treatment (18 weeks after the 10 week acute phase)
          - 2 patients experienced suicidal behaviors
          - 1 child experienced acute psychosis with suicidal ideation and suicidal behaviors upon transitioning from placebo to Cymbalta

- 1 teen with a history of suicidal behaviors experienced suicidal ideation and behaviors when he was noncompliant with Cymbalta during weeks 24 and 28
- Compared to lead-in baseline (after the 10 week acute phase),
    1. 2.9% of those initially randomized to Cymbalta (and kept on Cymbalta in extension phase) experienced suicidal ideation and 3.9% experienced nonsuicidal self-injurious behavior
    2. 2.9% of those initially randomized to placebo (and transitioned to Cymbalta in extension phase) experienced suicidal ideation and 4.8% experienced nonsuicidal self-injurious behavior

- Acute and longer-term safety results from a pooled analysis of duloxetine studies for the treatment of children and adolescents with major depressive disorder
  Graham J Emslie, Thomas G Wells, Apurva Prakash, Qi Zhang, Beth A Pangallo, Mark E Bangs, John S March
  Journal of Child and Adolescent Psychopharmacology 2015, 25 (4): 293-305
  OBJECTIVE: To assess acute and longer-term safety of duloxetine in the treatment of children and adolescents with major depressive disorder (MDD), a pooled analysis of data from two completed randomized, double-blind, multicenter, phase 3, placebo- and active-controlled trials was undertaken. In these studies, neither duloxetine (investigational drug) nor fluoxetine (active control) demonstrated a statistically significant improvement compared with placebo on the primary efficacy measure.
  METHODS: Patients ages 7-17 years with MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) received duloxetine (n=341), fluoxetine (n=234), or placebo (n=225) for 10 week acute and 26 week extended (duloxetine or fluoxetine only) treatments. Safety measures included treatment-emergent adverse events (TEAEs), the Columbia-Suicide Severity Rating Scale, vital signs, electrocardiograms, laboratory samples, and growth (height and weight) assessments.
  RESULTS: Significantly more patients discontinued because of adverse events during duloxetine (8.2%) treatment than during placebo (3.1%) treatment ($p \leq 0.05$). TEAEs in >10% of duloxetine-treated patients were headache and nausea. No completed suicides or deaths occurred. During acute treatment, 6.6% of duloxetine-, 8.0% of fluoxetine-, and 8.2% of placebo-treated patients had worsening suicidal ideation from baseline. Among patients initially randomized to duloxetine or fluoxetine who had suicidal ideation at study baseline, 81% of duloxetine- and 77% of fluoxetine-treated patients had improvements in suicidal ideation at end-point in the 36-week studies. Suicidal behavior occurred in two fluoxetine-treated patients and one placebo-treated patient during acute treatment, and in seven duloxetine-treated patients and one fluoxetine-treated patient during extended treatment. Duloxetine-treated patients had a mean pulse increase of ~3 beats per minute, and mean blood pressure (both systolic and diastolic) increases of <2.0mm Hg at week 36. Weight decrease (≥3.5%) during acute treatment occurred with statistically ($p \leq 0.05$) greater frequency for both the duloxetine (11.4%) and fluoxetine (11.5%) groups versus the placebo (5.5%) group; however, mean weight increase occurred for both duloxetine and fluoxetine groups during extended treatment.
  CONCLUSION: Results from this pooled analysis of two studies were consistent with the known safety and tolerability profile of duloxetine. Clinical Trial Registry Numbers: NCT00849901 and NCT00849693.
    - Two controlled 10 week trials in pediatric major depression, aged 7-17; Cymbalta (117 kids) vs. Prozac (117 kids) vs. placebo (103 kids) (Emslie, et al, 2014; Atkinson, et al, 2014)
        - Cymbalta = Prozac = placebo

- Side effects/risks
    - decreased appetite 41.7% in an open-label study
    - somnolence 29.2% in an open-label study
    - sweating 29.2% in an open-label study
    - dizziness 20.8% in an open-label study
    - nausea 20-38% vs. 7% placebo
    - dry mouth 15-20.8% (latter % from an open-label study) vs. 6% placebo
    - diarrhea 12%
    - fatigue/lassitude 11-41.7% (latter % from an open-label study)
    - insomnia 11-33.3% (latter % from an open-label study) vs. 6% placebo
    - constipation 11-29.2% (latter % from an open-label study) vs. 4% placebo
    - urinary hesitancy, retention
    - dose-related increase in blood pressure (0.5-2 mm Hg).
    - rate of completed suicide in ~7,200 patients studied was 0.085%, roughly the same as other antidepressants and as placebo
    - sexual side effects 33.3 in an open-label study but see below for data from RCT's

Adverse Event		Percentage of Patients Reporting Event			
		% Male Patients		% Female Patients	
		Cymbalta (N=378)	Placebo (N=247)	Cymbalta (N=761)	Placebo (N=530)
Orgasm abnormal [2]	4	1	2		0
Ejaculatory dysfunction [3]	3	1	NA		NA
Libido decreased	6	2	1		0
Erectile dysfunction	4	1	NA		NA
Ejaculation delayed	3	1	NA		NA

	Male Patients	Female Patients

	Cymbalta (n=175)	Placebo (n=83)	Cymbalta (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56 *	-1.07	-1.15	-1.07
Item 1--Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2--Arousal	0.01	-0.26	-0.21	-0.18
Item 3--Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4--Ease of reaching orgasm	0.40 **	-0.24	-0.09	-0.13
Item 5--Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

- increases liver nzyme ALT in 0.4-1.7% of patients; 3 cases of more severe liver problems (at least two of which were also associated with alcohol); 2 cases of more severe liver problems in patients taking placebo. 10/05: several postmarketing reports of liver inflammation, sometimes in those with pre-existing liver disorders.
- seizure in 1/1900 patients.

- **Savella (Milnacipran)**
  - General
    - Compared to SSRI's, higher incidence of headache, dry mouth, and dysuria.
    - Norepinephrine reuptake inhibition is more potent than serotonin reuptake inhibition.
    - May also be weak noncompetitive NMDA-receptor blocker at high doses
    - FDA-approved for the treatment of fibromyalgia; approved to treat depression in several European countries
    - Half-life 8 hours
    - Dose range 30-200 mg/day in twice-daily doses, aim for 100 mg/day.
    - 30-200 mg/day; max 300 mg/day
    - 15, 25, 50 mg caps (outside US)
  - Evidence
    - Asnis et al, 2013, randomized controlled study in depression
      - 40 mg, 80 mg, 120 mg, vs. placebo
      - all doses significantly effective, more efficacy with increasing dose
      - most common side effects
        - headache 15-20% vs. 11% placebo
        - nausea 10-20% vs. 2.3% placebo
        - constipation 10-13% vs. 4% placebo
        - dry mouth 6-15% vs. 9.7% placebo
        - increased heart rate 6-10% vs. 1.7% placebo
        - increased sweating 5-13% vs. 2.3% placebo
        - Erectile dysfunction 2.9-9.5% vs. 2.9% placebo
        - Ejaculatory delay 0-5.9% vs. 0% placebp
    - Two randomized double-blind placebo-controlled studies reportedly demonstrating efficacy in the treatment of adult depression

- **Fetzima (levomilnacipran SR)**
  - General
    - FDA-approved in July, 2013 for the treatment of MDD
    - More active enantiomer of milnacipran
    - Stronger affinity for norepinephrine reuptake than serotonin reuptake (twice as potent with norepinephrine reuptake); 10-fold more selective for norepinephrine reuptake than Cymbalta or Effexor
    - Not associated with weight gain
    - 80-120 mg/day, once daily dosing
    - 20 mg, 40 mg, 80 mg, 120 mg capsules
  - Positive efficacy in MDD in adults
    - Bakish et al, 2014
      - 1-week run-in, 8-week double-blind treatment, 1-week down taper, placebo-controlled,
      - 40 mg/day vs. 80 mg/day vs. placebo (557 patients)
      - Safe and effective at both doses
      - Most common side effects
        - Nausea
        - Dry mouth
        - Increased heart rate
        - Constipation
        - Dizziness
        - Increased sweating
        - Urinary hesitation
        - Erectile dysfunction
    - Sambunaris et al, 2014
      - 20-120 mg/day vs. placebo in adults with major depression, multicenter, RCT, double-blind, 1 week run-in, 8 week double-blind treatment, 2-week double-blind down taper period, 434 patients
      - Safe and effective
      - Most common side effects
        - Nausea
        - Dizziness
        - Constipation
        - Tachycardia
        - Urinary hesitation
        - Increased sweating
        - Insomnia
        - Vomiting
        - Increased blood pressure
        - Ejaculation disorder
    - Montgomery et al, 2014; secondary and post-hoc analyses on 2013 study below (same name)
      - More data of efficacy in symptomatic and functional impairment of major depression
    - Citrome et al, 2013
      - Review of 6 (5 short-term and 1 long-term) pivotal placebo-controlled registration trials
      - Efficacy and safety similar to other recently introduced antidepressants
      - Pooled NNT 10
      - No association with weight gain
      - No increase in suicidality vs. placebo
      - NNT nonsignificant in the 24-week relapse prevention study
        - 14% relapse rate with medicine
        - 20% relapse rate with placebo
      - Nausea in 17% with an NNH of 10
      - Ejaculation and erectile difficulties with NNH's of 23 and 20, respectively
    - Wesnes et al, 2013:
      - Safe and effective for depression; also improved attention deficits; dose range 40-120 mg/day; 429 patients studied
    - Montgomery et al, 2013: 75-100 mg, 553 patients, placebo-controlled, RCT, 10-week
      - Response rates: 56-59.1% vs. 39-42.2% placebo
      - Remission rates: 33-46.4% vs. 21-26% placebo
      - Side effects
        - Nausea 58% (though 17% in another study) vs. 31% placebo
        - Headache 61% vs. 51% placebo
        - Sweating 40% vs. 12% placebo
        - Dry mouth 23% vs. 14% placebo
        - Constipation 20% vs. 4% placebo
        - Diarrhea 17% vs. 8% placebo

        - Fast heart rate 19% vs. 3% placebo
        - Palpitations 18% vs. 7% placebo
        - Hypertension 16% vs. 6% placebo
    - Three other RCT, double blind, placeb-controlled studies supporting the efficacy
        - Lasted 8-10 weeks
        - Dose range 40-120 mg/day
        - NNT for pooled results for these three plus two above):
            - 10 for response
            - 16 for remission
        - In the 24-week relapse prevention study:
            - Relapse rate for placebo: 20%
            - Relapse rate for levomilnacipran: 14%
- Adolescent depression study is in progress
- Biggest side effects
    - Mild to moderate nausea
    - Constipation
    - Heart rate increase
    - Hyper sweating