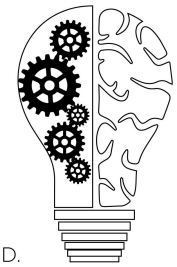
Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



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There are no conflicts of interest for this episode.

In today's episode of the podcast, we'll be continuing our deep dive into duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI). In part two of this two-part series, we'll be covering the approved indications and off-label uses of duloxetine.

Indications for duloxetine:

Duloxetine was initially FDA approved for treatment of major depressive disorder (MDD). Later, it was FDA approved for neuropathic pain related to diabetes. It is now also approved for generalized anxiety disorder (GAD) and various pain syndromes.

How is response to treatment measured?

Hamilton Depression Rating Scale (abbreviated as HDRS or HAM-D) was developed as a research tool. There are 3 versions of the HAM-D. The 17-item version is the original and is used in most research studies today. There are 21-item and 24-item versions of the HAM-D, as well. On the 17-item HAM-D, a score between 8 and 16 is considered mild depression, between 16 and 23 is moderate depression, and over 24 is considered severe depression.

Comparing duloxetine and paroxetine in treating major depressive disorder

Let's discuss a study that compares duloxetine and paroxetine in treatment of major depressive disorder (Goldstein et al., 2004). The study was a randomized, double-blind, evaluation that compared duloxetine at 40 mg/day, duloxetine 80 mg/day, paroxetine 20 mg/day, as well as a placebo group. Improvement was assessed according to the 17-item HAM-D.

- Duloxetine 80 mg group: superior to placebo in that HAM-D score decreased by 3.62 points (95% CI 1.38, 5.86; P =0.002), and remission rate of 57%
- Duloxetine 40 mg group: superior to placebo in that HAM-D score decreased by 2.4 points (95% CI 0.19, 4.66; P=0.034)

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

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- Paroxetine 20 mg group: not superior to placebo. HAM-D score decreased by 1.51 points, (95% CI -0.55, 3.56; P=0.150), and remission rate of 36%

Conclusion: Duloxetine 80 mg was superior to placebo for most measures including overall pain severity. Duloxetine was also superior to paroxetine in terms of depression symptoms.

Consider the 3.62 point change on the HAM-D for the duloxetine 80 mg group. Is this clinically significant? It really depends on the nature of these studies as well as the average severity of the depression being studied. This study HAM-D scores starting at around 17-18, which is in the low moderate range before the study began, so we can expect the effect size to be lower. A change of 3.6 points lower the person into mild depression. Later in this article we will show what happens as the severity of depression increases and how that changes the effect size.

Do clinicians and patients perceive improvement and recovery differently?

Historically, clinicians perceive psychotropic medications as being more effective than the patients perceive them to be. A placebo study (Rief et al., 2009) demonstrated that clinician response rate for placebo was higher as well. 45% of clinicians reported improvement in depressive symptoms following administration of placebo, whereas only 26% of patients reported improvement. This could be explained by what patients and clinicians are seeking. For example, patients are seeking a return to a state of wellness, whereas clinicians are looking for any sign of clinical improvement.

Severity of depression and effect size

Besides remission rate, another clinically significant measure is effect size, which comments on the magnitude of impact. Effect size of 0.3 or less is small, 0.4-0.6 is moderate, and greater than 0.6 is a good effect size.

One study explored severity of depression and effect size (Khan et al., 2005). They found that the effect size for low-moderate depression was 0.50, high-moderate was 0.54, moderate-severe group was 0.77 and the severe group was 1.09. With severe depression

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

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(HAM-D score >29), antidepressants make a big difference. There is less room for improvement in a patient with milder depression, compared to someone with severe depression. If a drug has a positive effect, the effect is larger in a person who is more ill.

If you look at the change in HAM-D with the antidepressant:

- Change in low-moderate group was 10.6
- Change in high-moderate group was 12.4
- Change in moderate-severe group was 15
- Change in severe group was 16.5

When considering placebo vs. antidepressant effect, for the severe group there is a difference of roughly 8.3, but the overall response to antidepressant is 16.5 in this category. This is a very significant decrease in depressive symptoms. It is fair to say that antidepressants (in particular SNRIs when used in treating severe depression) have immensely alleviated suffering in many individuals.

In this study, placebos decreased HAM-D score across the board around 8, even for the severe group. This could be due to increased interaction with clinicians due to research protocol. For example, patients involved in research studies get a lot of clinical attention and psychosocial support. They are not living alone with their depression. Additionally, some people will spontaneously recover whether or not they are treated.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

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Below is table 2 from Khan et al., 2005:

Table 2
Pre-treatment and change in Hamilton Depression Rating Scale (HAM-D) for 329 patients with low moderate, high moderate, moderately severe, and severe depression participating in 15 randomized placebo-controlled, double blind trials

	Placebo	Antidepressant	*t*-Test	Effect size
Mean pre-treatment total HAM-D score ± SD	25.0 ± 3.2	24.5 ± 3.4	$t = 1.6$, df = 329, p = ns	na
Low moderate[a]	21.1 ± 1.1	20.8 ± 1.6	$t = 1.0$, df = 91, p = ns	na
High moderate[b]	24.1 ± 0.8	24.0 ± 0.8	$t = 0.6$, df = 107, p = ns,	na
Moderately severe[c]	26.9 ± 0.9	26.8 ± 0.8	$t = 0.6$, df = 82, p = ns	na
Severe[d]	30.4 ± 1.2	30.2 ± 1.9	$t = -0.4$, df = 43, p = ns	na
Mean change in total HAM-D score at final LOCF ± SD	−8.2 ± 7.4	−13.0 ± 7.5	$t = 5.8$, df = 327, $p = 0.000$	0.65
Low moderate	−6.9 ± 7.2	−10.6 ± 6.4	$t = 2.5$, df = 90, $p = 0.013$	0.51
High moderate	−8.5 ± 7.2	−12.4 ± 6.6	$t = 3.0$, df = 107, $p = 0.004$	0.54
Moderately severe	−9.1 ± 7.7	−15.0 ± 8.0	$t = 3.4$, df = 81, $p = 0.001$	0.77
Severe	−8.2 ± 7.6	−16.5 ± 9.3	$t = 3.3$, df = 43, $p = 0.002$	1.09

[a] Low moderate ($13 \geqslant$ HAMD $\leqslant 22$).
[b] High moderate ($23 \leqslant$ HAM-D $\leqslant 25$).
[c] Moderately severe ($26 \leqslant$ HAM-D $\leqslant 28$).
[d] Severe ($29 \geqslant$ HAM-D $\leqslant 35$).

What is the best medication to treat depression? How do clinicians choose which antidepressant to prescribe?

There is not an easy way to pick a single drug that will work best for every patient. Probably the most effective antidepressant molecules are the monoamine oxidase inhibitors (MAOis). However, MAOis are seldom used due to their side-effect profile. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are second most effective, and appear to be more effective than selective serotonin reuptake inhibitors (SSRIs).

However, SSRIs account for about 70% of all antidepressant prescriptions. This is because they are generally safe medications.

When selecting antidepressant pharmacotherapy, clinicians consider other comorbidities. For example, for a patient diagnosed with both depression and chronic pain, duloxetine might help with both conditions.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Generalized anxiety disorder (GAD) and effectiveness of duloxetine

GAD is characterized by anxiety and worry. It is an overactivation of the fear circuit involving the frontal cortex, thalamus, and amygdala. Serotonin directly inhibits activity of the amygdala, which is why SSRIs are often effective for GAD. Duloxetine and the other SNRIs go one step beyond that and increase norepinephrine, which subsequently downregulates alpha-1 and beta-1 noradrenergic receptors, which decreases activity in that circuit.

An important clinical note when starting SNRI for GAD is that oftentimes a patient's anxiety symptoms initially get worse. This is because the downregulation of postsynaptic receptors lags behind the initial increase in norepinephrine. Patients should expect it to take between 2-6 weeks before their anxiety levels get to a new baseline.

Aside from an initial increase in anxiety when starting SSRIs and SNRIs, both of these medications can trigger manic symptoms, as well. Additionally, any medication that increases serotonin (including SSRIs and SNRIs) can cause akathisia. This is because serotonin binds to 5HT2A receptors in the nigrostriatal pathway and decreases dopamine release. In vulnerable individuals, this can induce akathisia. In elderly individuals, serotonergic medications can result in dyskinetic symptoms.

In a meta-analysis by Bandelow et al., (2015) comparing the efficacy of pharmacological, psychological and combined treatments for the three main anxiety disorders (panic disorder, generalized anxiety disorder and social phobia), pharmacotherapy was associated with a statistically significant higher average pre–post effect size as compared to psychotherapy [2.02 (1.90–2.15) vs. 1.22 (1.14–1.30) respectively] and SNRIs had a greater effect size as compared to SSRIs (2.25 vs. 2.09 respectively).

Pharmacological treatment is more immediately robust, but the effects of cognitive behavioral therapy (CBT) tend to be longer lasting. When an individual stops a medication, the symptoms may return to the initial baseline, but in someone who has done CBT, they may have better symptom control even in the absence of medications. Psychotherapy, exercise, and other non-pharmacologic means of reducing anxiety are all very important tools in symptom management.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

In a systematic review and meta-analysis by Jakubovski et al., (2019) comparing the efficacy of SNRIs and SSRIs for anxiety disorders, longitudinal meta-analysis failed to demonstrate a significant difference in efficacy between SSRIs and SNRIs for the treatment of anxiety disorders in adults. Jakubovski et al., (2019) found that higher doses of SSRIs were shown to be marginally more effective than lower doses for treating anxiety disorders, whereas higher doses of SNRIs were not. However, higher doses of SSRIs and SNRIs in treating anxiety were also associated with reduced tolerability due to the increased risk of side-effects.

The SNRIs directly increase serotonin and norepinephrine and so they essentially reach a "ceiling effect" earlier than SSRIs. The concentration effect curve for most drugs is a sigmoid shape and as the dose increases, the effect increases until you reach a point where it begins to flatten. That "flattening" occurs earlier (at a lower dose) for the SNRIs than for the SSRIs which is why once you reach that ceiling and the curve is now flat, increasing the concentration of the drug does not produce any further effect.

Neuropathic pain and effectiveness of duloxetine

The ability of SNRIs to increase both serotonin and norepinephrine also leads to their usefulness in treating various pain syndromes. SNRIs increase serotonergic and noradrenergic neuron activity in the descending inhibitory spinal pathway of the dorsal horn (Lee & Chen, 2010). SNRIs inhibit dorsal horn neurons, suppresses excessive nociceptive input and decreases pain transmission to the brain (Lee & Chen, 2010). SNRIs are also involved in modulating the ascending pain pathways through direct inhibition by noradrenergic input in the brain stem, which is helpful in treating neuropathic pain (Marks et al., 2009).

SNRIs decrease substance P in the dorsal horn, thereby inhibiting the ascending pain signal. Substance P is the neurotransmitter that transmits pain signals between the incoming nerve fiber and the neuron body in the dorsal horn which gives rise to the ascending pain signal. SNRIs also inhibit ascending pain pathways in the brainstem via its noradrenergic component. This is why SNRIs are more effective for treating pain than SSRIs.

Generally speaking, the more noradrenergic the SNRI, the better it is for pain control. With levomilnacipran with most noradrenergic effects: Levomilnacipran > Desvenlafaxine = Duloxetine > Venlafaxine.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Fibromyalgia and effectiveness of duloxetine

Fibromyalgia can be thought of as a pain disorder or a psychosomatic disorder, depending on whether it is viewed from the standpoint of rheumatology/pain or psychiatry respectively (Clauw et al., 2014; Wolfe et al., 2014).

The pharmacotherapy for fibromyalgia is aimed towards either decreasing levels of neurotransmitters that facilitate pain (e.g., glutamate) or increasing levels of inhibitory neurotransmitters that will decrease pain (e.g., serotonin, norepinephrine, GABA) (Clauw et al., 2014). Among the different medications and medication classes with level 1A evidence for efficacy in treating fibromyalgia (e.g., amitriptyline and cyclobenzaprine among TCAs, pregabalin and gabapentin among gabapentinoids, γ-hydroxybutyrate), SNRIs like duloxetine and milnacipran distinguish themselves by also treating comorbid MDD and/or anxiety disorders with a more favorable side-effect profile as compared to the TCAs (Clauw et al., 2014). Lifetime prevalence of any psychiatric disorder in patients with fibromyalgia is around 80% (Epstein et al., 1999; Malt et al., 2000). Patients with fibromyalgia have a lifetime prevalence of mood disorders (mainly MDD) between 20-86%, and 13-48% of patients with fibromyalgia also carry a concurrent diagnosis of MDD (Borchers & Gershwin, 2015). Patients with fibromyalgia have a lifetime prevalence of anxiety disorders around 35%, and 27% of patients with fibromyalgia also carry a concurrent diagnosis of an anxiety disorder.

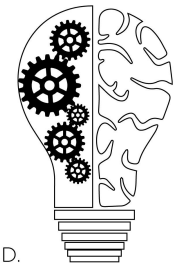
Duloxetine is commonly prescribed for fibromyalgia, as are nortriptyline and amitriptyline, although these have more side effects. Pregabalin is helpful for some patients, but sedation is a common side effect.

Chronic musculoskeletal pain and effectiveness of duloxetine

Chronic musculoskeletal pain is extremely prevalent in the adult population with chronic lower back pain and osteoarthritis of any joint, occuring in >50% of adults in the United States above the age of 60 years (Smith et al., 2012). If people can get stronger they will have less pain, but medications such as duloxetine can be helpful in this journey, as well. It is very rare for patients with chronic pain to be on monotherapy. Pain specialists incorporate duloxetine as an adjunct to other treatment modalities such as physical therapy, massage, topical capsaicin or direct local anesthetics, as well as exercise.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



In a large cross-sectional, internet-based survey with 27,035 respondents, the prevalence (weighted to be representative of the U.S. population) of self-reported chronic pain lasting at least 6 months was found to be 30.7%, while the weighted prevalence of primary chronic lower back pain and primary osteoarthritis was found to be 8.1% and 3.9%, respectively (Johannes et al., 2010). In addition, the association between pain and depression has long been known, and approximately 21% of adults with osteoarthritis are diagnosed with concomitant pain and depression (Bair et al., 2003; Osani & Bannuru, 2019).

Obsessive-compulsive disorder (OCD) and effectiveness of duloxetine

Duloxetine is a desirable medication for OCD over other noradrenergic medications, such as milnacipran and levomilnacipran, due to its added serotonergic effect. Patients who are not responding well to higher doses of SSRIs may benefit from duloxetine's noradrenergic effect, compared to other noradrenergic medications such as anafranil (Mowla et al. 2016). Anafranil is very serotonergic, but since it is a TCA (tricyclic antidepressant) it is metabolized to its own secondary amine. Anafranil has noradrenergic component as well as antihistaminic component. Like many of the tricyclics, anafranil is a dirty drug, and its therapeutic index is very narrow.

First-line treatment for OCD involves psychotherapeutic intervention (e.g., CBT) and antidepressants (i.e., SSRIs, clomipramine), which have less of an effect size as compared to psychotherapy, but are often used in conjunction with psychotherapy, especially in cases of severe OCD (Hirschtritt et al., 2017; Skapinakis et al., 2016). Considering that about 25%-30% of patients do not respond sufficiently to psychotherapy or SSRIs, augmentation with other medications (e.g., antipsychotics) or alternative therapies should be considered in treatment-nonresponsive OCD (as defined by less than a 25-35% improvement in OCD severity or less than "much improved" on the CGI scale) (Hirschtritt et al., 2017; Sansone & Sansone, 2011). Duloxetine can be effective as a second-line alternative to SSRIs in treatment-resistant OCD or in patients with other pertinent comorbidities, considering that it shares the same mechanism as clomipramine, which also inhibits both serotonin and norepinephrine reuptake, while also having less side effects and being more tolerable (Dell'Osso et al., 2006).

The evidence for the usage of duloxetine in OCD is encapsulated by a few case reports, one open-label trial and one double-blind randomized control trial. In their case report, Blay and

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

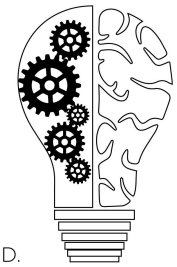
Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Black et al., (2007) described the difficulties of a 38-year-old man with a history of OCD for 8 years in finding the right pharmacotherapy. The patient was initially started on 75 mg/day of clomipramine, which was effective but resulted in sexual dysfunction after 1 month of treatment. The patient was also unable to tolerate 60 mg/day of paroxetine due to severe headaches and sexual dysfunction. 30 mg/day of mirtazapine was started to address his sexual side effects and the patient was able to function for the next 4 years until he experienced an exacerbation in his symptoms. He was switched to 20 mg/day of escitalopram, which improved his symptoms initially; however, his symptoms continued to worsen over the next year. Finally, the patient was switched to 60 mg/day of duloxetine from escitalopram, which was increased to 120 mg/day after 4 weeks of no improvement. The patient had significant improvement in his symptoms after 1 month and reported no side effects or intrusive obsessional thoughts at the 1 year follow-up appointment. In their case series, Dell'Osso et al., (2008) treated 4 OCD patients with comorbid mood or anxiety disorders with up to 120 mg/day of duloxetine after partial or no response to therapeutic doses of SSRIs for at least 12 weeks. After 12 weeks, 3 out of the 4 patients showed improvement as shown by ≥35% reduction in their Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores.

In their case report, Yeh et al., (2009) describe a 30-year-old man with a 10 year history of OCD comorbid with MDD. The patient first received CBT and 250 mg/day of fluvoxamine for over 12 weeks; however, he had no significant improvement in his symptoms. The patient went on to try the following antidepressants in succession for durations up to 16 weeks: 100 mg/day of fluoxetine, 200 mg/day of fluoxetine, 80 mg/day of paroxetine and 337.5 mg/day of venlafaxine. Several augmentative antipsychotics were trialed, including 6 mg/day of risperidone, 15 mg/day of olanzapine, 400 mg/day of quetiapine, and 120 mg/day of ziprasidone. While the patient's depressive symptoms improve, none of these pharmacotherapies could significantly improve his obsessive-compulsive symptoms. Since the best response was with 337.5 mg/day of venlafaxine with 6 mg/day of risperidone (22% decrease in Y-BOCS score from 36 to 28), the patient was started on 30 mg/day of duloxetine and was titrated to 120 mg/day within a month. At the end of the first month of treatment, Y-BOCS score decreased to 26. Dosage was increased to 180 mg/day and after 12 weeks of treatment, the patient achieved full remission with Y-BOCS score of 6. A temporary decrease in the dose to 120 mg/day caused his obsessive-compulsive symptoms to relapse and the patient resumed the 180 mg/day dosage. The patient did not experience any recurrence of symptoms or any side effects after another year of treatment at 180 mg/day. In a case report by Safer and Arnow, (2012), 180 mg/day of duloxetine was able to successfully treat an 18-year-old woman with severe MDD and comorbid anorexia nervosa binge-purging type and OCD, after 40 mg of citalopram was unable to bring remission of her symptoms.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



In a 17-week open-label trial by Dougherty et al., (2015), 20 patients with OCD were initiated on 30 mg/day of duloxetine, which was increased to 120 mg/day by week 4, if effective and tolerated, in order to assess its efficacy and safety in treating OCD. The primary outcome measures were the Y-BOCS in measuring OCD symptom severity and the Clinical Global Improvement (CGI) Scale. The secondary outcome measure was the Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q) to assess quality of life, and the tertiary outcome measures were the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) to assess depressive and anxiety symptoms, respectively. 11 of the 20 study participants were female with mean age of 29.9 (range= 18-55) and mean age of onset of OCD at 15.35 (range= 5-50). 8 participants were lost due to follow up and discontinuation of medications. DUL at the dose range of 60 to 120 mg/day in the completer analysis showed statistical significant reduction in Y-BOCS total score (mean ± SD = 28.33 ± 4.66 at baseline, 18.5 ± 7.98 at endpoint; $P < 0.001$) and CGI score (mean ± SD = 4.00 ± 0 at baseline, 2.17 ± 0.72 at endpoint; $P < 0.001$). The Intention-To-Treat Analysis also showed similar results in Y-BOCS (mean ± SD = 27.45 ± 4.08 at baseline, 20.45 ± 7.57 at endpoint; $P < 0.001$) and CGI score (mean ± SD = 4.00 ± 0 at baseline, 2.17 ± 0.923 at endpoint; $P < 0.001$). The five participants out of 20 discontinued the study because of adverse events. The most common unwanted effects were nausea (50% of subjects), fatigue (41.2%), sexual dysfunction (23.1%), and headache (11.1%); no serious adverse events occurred.

The 8-week randomized controlled, double-blind study of 46 patients assessed the efficacy of adjunct DUL or sertraline in patients with resistant OCD treated with SSRIs or fluvoxamine. Prior to trial, patients had failed an average of 2.2 SSRI trials and failed to respond to at least 12 weeks of treatments with an adequate dose of an SSRI reflected by Y-BOCS score of 18 or greater. DUL (dose range = 20–60 mg/day; mean dosage = 44.4 mg/day; n = 24) or sertraline (dose range = 50–200 mg/day; mean dose = 123.8 mg/day; n = 22). The primary outcome measure was the Y-BOCS; the efficacy index of CGI was used at the end of the study. At endpoint, both DUL and sertraline were effective in reducing OCD symptoms, as assessed by Y-BOCS mean total score reduction (33.0% for DUL and 34.5% for sertraline from baseline) without significant difference ($P = 0.861$). Six patients in the DUL group and five patients in the sertraline group dropped out because of unwanted side effects; the most common were gastrointestinal disturbances, followed by headache and sexual disturbances (Mowla et al., 2016).

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Attention Deficit Hyperactivity Disorder (ADHD) and duloxetine

First-line pharmacotherapy for ADHD is stimulant medications (such as amphetamines or methylphenidates). There are non-stimulant treatments for ADHD such as atomoxetine, guanfacine, and clonidine. Due to its noradrenergic effects, duloxetine could potentially benefit individuals living with ADHD although it would not be a first-line treatment. Duloxetine may be a good second-line choice for individuals with ADHD who are unable to tolerate first-line treatments, or if they have comorbid depression/anxiety symptoms.

In one 6-week randomized, placebo-controlled pilot study, 30 adult participants with ADHD were treated with either placebo or duloxetine 60 mg daily. 24 participants completed the trial, 6 participants from the duloxetine group were dropped out due to medication adverse effects. The duloxetine group showed lower score on CGI-severity at week 6 (3.00 vs 4.07 for placebo), greater improvement on CGI-improvement (2.89 vs 4.00), and greater decreases on five of eight subscales of the Conners' Adult ADHD Rating Scale (CAARS) (Bilodeau et al., 2014).

In another study, seventeen adolescents with ADHD participated in an open-label study on duloxetine's efficacy in ADHD treatment. Duloxetine was given 30 mg/day for the first week and 60 mg/day from week 2 to the end of the study. Conners' Parent Rating Scale-Revised (CPRS-R) was used as the primary measure. Four participants discontinued the trial due to noncompliance (1 participant) and adverse drug reactions, including manic symptoms, hyperhidrosis, and GI symptoms. Overall, duloxetine was well tolerated; the most commonly reported adverse effects among the comcompleter group were decreased appetite (46%) and dry mouth. None of the completers required dosage reduction due to the side effects. By the end of week 6, there was a statistically significant decrease in the mean CPRS-R raw score, as well as in all four subscales of CPRS-R (oppositionality, inattention, hyperactivity, and ADHD index) as described in the following table (Gharaei et al., 2011).

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

DAVID PUDER, M.D.
PSYCHIATRY & PSYCHOTHERAPY

158 J. MAHMOUDI-GHARAEI *ET AL.*

Table 3. Treatment efficacy measured by CPRS-R

		Baseline (mean ± SD)	Week 2 (mean ± SD)	p^a	Week 4 (mean ± SD)	p^b	Week 6 (mean ± SD)	p^c	F	p^d	Effect Size
Oppositionality	Raw	11.84 ± 0.91	10.53 ± 1.36	0.978	8.92 ± 1.44	0.045	8.92 ± 1.30	0.010	6.63	0.001	0.35
	T score	72.00 ± 2.54	68.07 ± 3.64	0.776	63.69 ± 3.87	0.038	63.92 ± 3.50	0.008	7.01	0.001	0.36
Inattention	Raw	13.69 ± 0.95	11.46 ± 1.28	0.458	10.00 ± 1.59	0.133	10.84 ± 1.51	0.268	3.14	0.037	0.20
	T score	69.30 ± 2.03	65.07 ± 2.72	0.630	61.76 ± 3.26	0.136	63.61 ± 3.10	0.296	3.13	0.037	0.20
Hyperactivity	Raw	9.84 ± 1.71	7.92 ± 1.50	0.069	5.76 ± 1.52	0.005	7.15 ± 1.71	0.080	7.92	<0.001	0.39
	T score	75.38 ± 4.59	70.53 ± 4.60	0.572	59.69 ± 6.07	0.008	67.30 ± 5.00	0.110	8.06	<0.001	0.40
ADHD index	Raw	26.53 ± 1.72	21.61 ± 2.34	0.193	19.23 ± 2.75	0.029	20.46 ± 2.69	0.092	5.19	0.004	0.30
	T score	71.61 ± 1.84	66.00 ± 2.70	0.211	63.00 ± 3.08	0.031	64.69 ± 3.09	0.127	4.99	0.005	0.29

SD, standard deviation; ADHD, attention deficit/hyperactivity disorder; CPRS-R, Conner's parent rating scale-revised, ANOVA, analysis of variance.
[a]*p*-values are given for the comparison of mean scores between baseline and week 2.
[b]*p*-values are given for the comparison of mean scores between baseline and week 4.
[c]*p*-values are given for the comparison of mean scores between baseline and week 6.
[d]*p*-values are given for the comparison of end point changes from baseline using within-subjects effects of repeated measure ANOVA.

Binge eating disorder and duloxetine

Duloxetine is used as a second-line agent in treatment of binge eating disorder. First-line agents for binge eating disorder are SSRIs, but if people cannot tolerate SSRIs, duloxetine is a worthwhile consideration.

Binge eating disorder (BED) is defined as recurrent episodes of eating an amount of food that is definitively larger than most people would eat in a similar situation. The binge eating episode is associated with a sense of lack of control over eating during the episode. These episodes occur, on average, at least 1 day a week for 3 months (American Psychiatric Association, 2013). Although recent studies have shown alterations of dopamine function as an important contributor to BED, it is hypothesized that serotonergic and noradrenergic systems are also involved (Kessler et al., 2016).

Interpersonal psychotherapy and guided self-help based on cognitive behavior therapy are first-line treatment options for most patients with BED. There have also been studies supporting the pharmacotherapy of SSRIs and lisdexamfetamine (Reas & Grilo, 2008).

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Although there is limited evidence supporting the usage of duloxetine in other eating disorders, there have been studies that revealed effectiveness in treating binge eating disorder. In one 12-week, double-blinded, placebo-controlled trial, 40 patients diagnosed with binge eating disorder and comorbid current depressive disorder received duloxetine (N=20) or placebo (N=20). The outcome measure was weekly binge eating day frequency. Results showed that duloxetine (mean 78.7 mg/day) was superior to placebo in reducing frequency of binge eating days (p=0.04), binge eating episodes (p = 0.02), weight (p=0.04), Clinical Global Impression Score (p= 0.02), and depressive disorders (p=0.01) (Guerdjikova et al., 2012).

A separate 12-week, preliminary, and open-trial study evaluated the efficacy of flexible doses of duloxetine (60-120mg/day) in a sample of 45 obese patients. From the sample, 22 patients satisfied criteria for binge eating disorder and 23 patients were characterized with subthreshold binge eating with high eating impulsivity. 31 patients who completed the course of duloxetine reported a significant reduction in their Binge Eating Scale (BES) score, number of binges, weight, BMI, Beck Depression Inventory (BDI) score, and Clinical Global Impression Scale scores. 14 subjects dropped out for reasons unrelated to side effects. DUL was generally tolerated with most frequent side effects being nausea and insomnia (Leombruni et al., 2009).

Posttraumatic Stress Disorder (PTSD) and duloxetine

Duloxetine can be useful in PTSD due to its substantial serotonergic component. Two SSRIs (sertraline and paroxetine) are currently FDA approved for the treatment of PTSD. Duloxetine could be considered as a second-line choice in situations where SSRIs are not effective. Duloxetine should be used with caution in individuals living with PTSD, as it is inherently a hyper noradrenergic state. It is important to gradually uptitrate duloxetine in this situation so that a downregulation of postsynaptic noradrenergic receptors can be achieved that would not occur with SSRIs.

Posttraumatic stress disorder (PTSD) is a maladaptation to a traumatic experience that is characterized by symptoms of frequent and intrusive re-experiencing of the traumatic stressor, hyperarousal and avoidance behavior (Steckler & Risbrough, 2012). Many neural circuits and neurochemical systems have been implicated in PTSD, including the serotonergic system (Steckler & Risbrough, 2012). Among the pharmacological treatments for PTSD, SSRIs have

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

been shown to decrease symptoms of re-experiencing, hyperarousal and avoidance and are first-line due to their safety and efficacy (Lancaster et al., 2016).

While not as extensively studied as SSRIs, SNRIs such as duloxetine have been shown to be efficacious in treating the symptoms of PTSD. In a 12-week, open-label trial, 20 male veterans were treated with a mean dose of 81 mg/day of duloxetine (initiated on 30 mg/day and increased to 120 mg/day by week 8 if ineffective and tolerated) in order to assess its efficacy and tolerability in treating military veterans with PTSD (Villarreal et al., 2010). The primary efficacy variable was the total Clinician Administered PTSD Scale (CAPS) score (all subjects had a CAPS score of at least 60 at baseline) and secondary efficacy variables included the CAPS symptom cluster subscores, Hamilton Depression Rating Scale (HAM-D or HDRS), Clinical Global Impressions Scale-Severity of Illness (CGI-S), Davidson Trauma Scale (DTS), and Pittsburgh Sleep Quality Inventory (PSQI) (Villarreal et al., 2010). Significant improvement, most of which was observed by week 2 of treatment, was seen in PTSD symptoms, depressive symptoms, and sleep. 45% of the respondents (9/20) were responders, as defined by a >20% improvement on total CAPS score, with one subject achieving remission of PTSD symptoms (total CAPS score <20). Five subjects were unable to complete the study with three withdrawing due to side effects (1 to tachycardia, 1 to emesis and vertigo, 1 to restlessness), 1 due to personal reasons and 1 due to emerging paranoia despite improvements in PTSD symptoms.

In another 8-week open-label study by Walderhaug et al., (2010), 21 treatment refractory male veterans were given between 60 mg/day to 120 mg/day of duloxetine to evaluate the efficacy and tolerability of duloxetine in treating PTSD and comorbid MDD. The primary outcome measure was the PTSD Checklist (PCL-C) and secondary outcome measures included the Hamilton Anxiety Scale (HAM-A), the Montgomery Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression of Severity Scale (CGI-S). There was a significant improvement in every outcome measure, showing the efficacy of duloxetine in treating PTSD symptoms, anxiety and depression. 42% (8/20) of the patients were responders as defined by $\geq$30% decrease in PCL-C score from baseline to week 8. 21% (4/2) met remission criteria as defined by $\geq$30% decrease on the PCL-C, in addition to a total HAM-A score of $\leq$10 by the end of the 8-week trial. The most common adverse event was increased dream activity without nightmares with other adverse events being mild and transient. One patient withdrew consent from the study, but not due to adverse events.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Vasomotor symptoms and duloxetine

Duloxetine (among other SSRIs and SNRIs) has been shown to be an effective non-hormonal therapy option for vasomotor symptoms in perimenopausal women, with or without depression, although it is not FDA approved for such use (Hall et al., 2011). Vasomotor symptoms, such as hot flashes and nocturnal hot flashes (i.e., night sweats), can occur in 60-90% of women during the perimenopausal period, leading to significant physical discomfort and impairment as well as emotional distress (Hall et al., 2011; Thurston & Joffe, 2011). As a result, antidepressants are an effective therapy that can treat the psychiatric consequence of vasomotor symptoms, such as depression and/or relapse. (Clayton & Ninan, 2010; Frey et al., 2008; Worsley et al., 2017). Antidepressants are also useful in treating vasomotor symptoms without depression as both serotonin and norepinephrine are involved in thermoregulation (Hall et al., 2011). One central mechanism involves norepinephrine acting on the hypothalamus to cause vasodilation and heat loss while one peripheral mechanism involves serotonin indirectly causing peripheral vasodilation through nitric oxide (Hall et al., 2011).

In one 8-week open-label trial by Joffe et al., (2007), 20 postmenopausal women with major depressive disorder and vasomotor symptoms who were not responsive to placebo for 2 weeks were put on a flexible dosing of duloxetine (60 - 120 mg/day) to measure improvement in depressive symptoms (as measured by their Montgomery-Asberg Depression Rating Scale (MADRS) score) as well as changes in vasomotor symptoms (as measured by their Greene Climacteric Scale (GCS) score), sleep quality, anxiety and pain. The 14 women who completed the trial had significant improvement in their depressive symptoms as shown by a decrease in mean MADRS score from 19 to 5.5, with 80% of the patients also achieving remission with MADRS scores < 10. The participants also showed significant improvement in their vasomotor symptoms, with 64.3% of them having a GCS VMS subscore <2 after 8 weeks of treatment with duloxetine, as well as significant improvement in sleep quality, pain and anxiety.

In another open-label study that followed up on the results of Joffe et al., (2007) by Freeman et al., (2013), 19 peri- and postmenopausal women received 8 weeks of duloxetine (30 mg the first week followed by 60 mg the following 7 weeks) after a one week placebo lead-in in order to further measure the efficacy of duloxetine on major depressive disorder (as measured by the Hamilton Rating Scale for Depression (HAM-D)), daytime and nighttime VMS (as measured by daily diaries, GCS score and the Hot Flash-Related Daily Interference Scale (HFRDIS)), as well as anxiety (as measured by the Generalized Anxiety Disorder scale (GAD-7)). Of the 16 participants able to be evaluated, there was a significant decrease in their median HAM-D score (15 to 6.5), with a 56.3% response rate (≥50% decrease in HAM-D score)

and remission rate (HAM-D score ≤7). With regards to VMS symptoms, there was a significant decrease in the frequency and severity of total and daytime hot flashes according to the daily diaries, median GCS scores (21 to 10) and median HFRDIS scores (42.5 to 11.5); however, there was not a significant change in the frequency and severity of nighttime hot flashes. Finally, there was a significant decrease in anxiety, with median GAD-7 scores falling from 8.5 to 2.5.

Urinary incontinence and duloxetine

Duloxetine has been shown to be an effective and safe pharmacologic treatment for stress urinary incontinence and overactive bladder. Although it is not FDA approved for stress urinary incontinence (SUI) in the United States, duloxetine is approved for SUI in Europe (Maund et al., 2017). Through its inhibition of serotonin and norepinephrine reuptake, duloxetine suppresses parasympathetic activity while enhancing sympathetic and somatic activity in the lower urinary tract (Jost & Marsalek, 2004; Thor & Katofiasc, 1995). This results in an increase in bladder capacity and urethral sphincter contractility, which improves stress urinary incontinence (Jost & Marsalek, 2004; Thor & Katofiasc, 1995).

Duloxetine has demonstrated in many clinical trials to be effective in significantly decreasing the frequency of urinary incontinence episodes by approximately 50%-60%, compared to placebo (approximately 30-40%), leading to a significant improvement in quality of life that was previously hampered by involuntary urinary leakage (Dmochowski et al., 2003; Mariappan et al., 2005; Millard et al., 2004; Norton et al., 2002; van Kerrebroeck et al., 2004).

In a recent systematic review of the usage of duloxetine in men with postprostatectomy stress urinary incontinence, duloxetine resulted in a mean dry rate of 58%, improvement in pad number of 61%, and mean improvement in 1-h pad weight of 68% at short-term follow-up of 1-9 months. However, adverse events with duloxetine were relatively high, leading to discontinuation in 38% of patients (Kotecha et al., 2020.

In a systematic review and meta-analysis of the role of duloxetine in stress urinary incontinence, duloxetine resulted in a significant decrease in significant incontinence episode frequency (defined as ≥ 50% reduction in incontinent episodes) at 52.5%, compared to placebo at 33.7%. The numbers of cured patients were slightly higher in the duloxetine group than the placebo (10.8% vs 7.8% overall). Similarly to the previous systematic review, over 62.7% of duloxetine participants reported adverse effects including nausea, constipation, fatigue, insomnia and

dizziness; however, 45.3% of patients with placebo also reported side effects. Overall, 17.3% of duloxetine participants discontinued, with nausea as the most common cause (Li et al., 2013).

In addition to treating SUI, duloxetine has also shown effectiveness in treating overactive bladder by decreasing urinary urgency and frequency (Steers et al., 2007; Wang et al., 2015; Yoshimura & Chancellor, 2002). In a 12-week, randomized, placebo-controlled, double-blinded clinical trial by Steers et al., (2007), 306 women were either assigned to placebo or duloxetine (started at 80 mg/day for 4 weeks, but increased to 120 mg/day for 8 weeks). The primary outcome measure was measured as the difference in mean number of voiding episodes per day from baseline to endpoint of treatment. Secondary outcome measures included the change from baseline to endpoint of treatment in the number of urinary incontinent episodes per day, in the Incontinence Quality of Life questionnaire (I-QOL) score and in the mean daytime voiding interval (VI). Duloxetine was shown to have significant improvement over placebo in reducing the mean number of daily voiding episodes and urinary incontinence episodes, as well as in increasing the mean daytime voiding interval (48.2% of patients treated with duloxetine vs. 21.3% of patients on placebo had voiding intervals ≥2 hours, p <0.001) and showing improvements in the “avoidance and limiting behavior” and “psychosocial impact” subscales of the I-QOL. Treatment emergent adverse events (TEAEs) were significantly more commonly reported by patients taking duloxetine as compared to the patients on placebo (79.1% vs 55.6% respectively, p < 0.001) with the most common TEAEs due to duloxetine being nausea (31%) dry mouth (16%), dizziness (14%), constipation (14%) insomnia (13%), and fatigue (11%). Most of the aforementioned TEAEs due to duloxetine were reported within the first 4 weeks of taking duloxetine 80 mg/day.

Premenstrual dysphoric disorder (PMDD) and duloxetine

Duloxetine may be effective in treating PMDD in those who have regular menstrual cycles. A patient can start taking duloxetine a few days before menses and discontinue 1-2 days after the onset of menses. As there is a decline in serotonin levels and uptake in the late luteal phase of the menstrual cycle, duloxetine can benefit the symptoms of PMDD quite quickly, with symptoms improving overnight, as compared to taking weeks to show effect in treating MDD (Parry et al., 2001; Steiner & Pearlstein, 2000). For patients with irregular menstrual cycles, daily dosing throughout the month is recommended.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Premenstrual dysphoric disorder (PMDD) (formerly late luteal phase dysphoric disorder in the DSM-III) is characterized by at least 5 symptoms including depressed mood, anxiety, affective lability, changes in sleep, appetite, concentration, energy and various physical symptoms (e.g., breast tenderness) that occur by the final week before menses and remit in the week post-menses (Jarvis et al., 2008). Although the pathophysiology behind PMDD is not concretely defined, the current understanding is that progesterone produced by the corpus luteum crosses the blood-brain barrier, is metabolized in the brain and stimulates the GABAergic system, causing changes in affect, mood, and cognition (Rapkin & Akopians, 2012; Walsh et al., 2015). Progesterone also increases monoamine oxidase (MAO), which degrades serotonin and ultimately results in decreased mood due to decreased levels of serotonin (Rapkin & Akopians, 2012; Walsh et al., 2015). Considering the pathophysiology behind PMDD, it makes sense that serotonergic agents (i.e., SSRIs and SNRIs) are efficacious in treating PMDD. Fluoxetine, sertraline, and paroxetine are FDA-approved for PMDD (Jarvis et al., 2008; Rapkin & Lewis, 2013). Among SNRIs, venlafaxine and duloxetine have both been shown to be efficacious in treating PMDD (Cohen et al., 2004; Freeman et al., 2001; Mazza et al., 2008; Ramos et al., 2009).

Although there is limited evidence supporting the usage of duloxetine in treating PMDD, the two studies that have looked at the efficacy and tolerability of duloxetine in treating PMDD have had positive results (Muscatello et al., 2019). In an open-label study by Mazza et al., (2008), 55 women were treated with 60 mg/day of duloxetine over two menstrual cycles. The primary outcome measure was a visual analog scale (VAS) recording the severity of 11 mood symptoms, as well as other outcome measures, such as the Zung Self-rating Scale for Depression, the Hamilton Depression Rating Scale (HDRS aka HAM-D), the Hamilton Anxiety Rating Scale (HARS) and the Clinical Global Impressions Scale (CGI-S) (Mazza et al., 2008). Out of the 50 women who completed the trial, 38 (78%) had a >50% decrease in daily depression and anxiety symptoms and most patients had a marked improvement in the four core symptoms (irritability, tension, affective lability, and depressed mood) of PMDD by the end of the first treatment cycle (Mazza et al., 2008).

In a single-blind trial by Ramos et al., (2009), 20 women with PMDD were treated with 60 mg/day of duloxetine for three menstrual cycles. The primary measure of treatment efficacy was the difference in the mean total luteal phase Daily Record of Severity of Problems (DRSP) scores from baseline to endpoint of treatment after 3 menstrual cycles, while secondary measures of treatment efficacy included subitems of DRSP, HDRS aka HAM-D, Sheehan Disability Scale (SDS), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the proportion of responders (defined as a >50% reduction from baseline DRSP scores), and the

proportion of responders defined as a CGI-I item score of 1 (very much improved) or 2 (much improved) at endpoint (Ramos et al., 2009). The results supported the findings of Mazza et al., (2008) that Duloxetine was efficacious in treating PMDD, as the difference in mean total DRSP scores from baseline to endpoint was a 52.62% reduction in premenstrual symptoms, with 84% of the total decrease in DRSP score from all three menstrual cycles happening by the end of the first treatment cycle (Ramos et al., 2009). Also, 65% of the intention-to-treat population (13/20 women) had a >50% reduction in their baseline premenstrual symptoms and 70% of the same population were significantly improved with CGI-I scores of ≤2 (Ramos et al., 2009).

Migraine prophylaxis and duloxetine

Duloxetine can be considered as second-line migraine prophylaxis in patients with comorbid depression that did not respond to conventional migraine prophylaxis due to its greater tolerability, as compared to TCAs and its increased noradrenergic activity, as compared to venlafaxine and the SSRIs (Burch et al., 2019; Galletti et al., 2009). Many neurology protocols suggest that if someone is having more than 2-3 migraines a month, it is worthwhile to consider migraine prophylaxis rather than resort to abortive treatments (i.e., triptans) every time. Take the patient's input into consideration, as they know how disabling their symptoms are.

Migraines are a debilitating type of headache characterized by recurring episodes of unilateral headaches that are often accompanied by nausea, vomiting and increased sensitivity to light and sound and, in certain cases, may be preceded by an "aura", which include visual and/or sensory disturbances (Galletti et al., 2009). Migraines are quite common, affecting 12% of the general population, and are often comorbid with a variety of psychiatric disorders, such as mood disorders (particularly MDD), anxiety disorders (particularly panic and phobia), personality disorders, PTSD, substance abuse, and increased risk for suicidality (Burch et al., 2019; Buse et al., 2013; Dresler et al., 2019; Minen et al., 2016; Radat & Swendsen, 2005). Among the various theories and mechanisms behind the pathophysiology of migraines, the serotonin system is one of the better-studied systems implicated in both migraines and other psychiatric disorders (e.g. depression, anxiety) Dresler et al., 2019; Galletti et al., 2009; Ressler et al., 2000). Migraines, like depression, can be considered a disorder of low brain serotonin activity and patients with migraines have chronically decreased levels of interictal serotonin, which can lead to activation of the trigemino-vascular nociceptive pathway and predispose the patient to a migraine attack (Dresler et al., 2019; Galletti et al., 2009). While amitriptyline has the best evidence supporting its efficacy in migraine prevention among antidepressants and is the 2nd

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

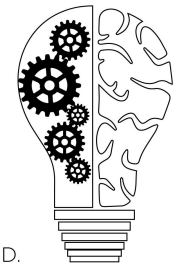
Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

most commonly prescribed medication for migraine prophylaxis behind topiramate, other antidepressants such as SSRIs (fluoxetine has been the most studied) and SNRIs (venlafaxine has been the most studied) have shown some efficacy in migraine prophylaxis, albeit with poorer evidence (Burch et al., 2019; Galletti et al., 2009).

Although there have not been many studies, duloxetine has been shown to be efficacious to varying degrees in its use in migraine prophylaxis. In an open-label retrospective study by Taylor et al., (2007), 65 patients were put on 30 mg/day to 90 mg/day of duloxetine for at least 2 months to evaluate its efficacy in migraine prevention. 17% of the patients had anxiety without depression, 3% had depression without anxiety and 38% of the patients had both anxiety and depression. After 2 months of treatment, there was a statistically significant mean reduction in total headache days reported in a 28-day period of 3.70. 22% of the entire patient sample had a 50% responder rate (at least a 50% reduction in headache days per month). Among the patients with anxiety with or without depression, duloxetine showed greater efficacy, with a statistically significant mean reduction in total headache days reported in a 28-day period of 4.28. The patients in this anxiety subgroup also had a greater responder rate (25%) as compared to patients without anxiety (17%) and the entire patient sample (22%).

In an 8-week open-label trial by Volpe et al., (2008), 30 patients with MDD and concurrent chronic headaches (migraines, tension headaches or both) received 60 mg/day of duloxetine for 8 weeks to evaluate the efficacy and tolerability of duloxetine for this comorbidity. The primary outcome measures were Montgomery-Asberg Depression Rating Scale (MADRS) scores and visual analog pain scale (VAS) scores. Secondary outcome measures were the number of headaches days/weeks and scores on the brief version of the World Health Organization Quality of Life scale (WHOQoL-BREF). There was a statistically significant decrease in mean MADRS scores (29.5 +/- 5.2 to 8.9 +/- 8.7 points) and VAS scores (5.8 +/- 1.9 to 1.9 +/- 2.5 points) by the end of the treatment, and significant improvements were seen for both headaches and depressive symptoms after the first week of treatment. The response rate was 66.7% (20/30) as defined by a >50% reduction in MADRS scores and >40% in VAS scores. Quality of life was also improved with increased mean WHOQoL-BREF scores (18.8 +/- 21.9 points) and decreased headache days/weeks (5.2 +/- 2.0 to 2.9 +/- 2.5 days/week). Two subjects discontinued participation due to side effects and 3 subjects discontinued due to nonadherence.

In a 5 visit, prospective, open-label study by Young et al., (2013), 22 completers (plus 5 subjects who took at least 1 dose of duloxetine) were put on 60 mg/day to 120 mg/day (mean dose of 110 mg/day) of duloxetine to evaluate the efficacy and safety of duloxetine in nondepressed patients with migraines. The primary outcomes were average number of migraine days,



frequency of migraine attacks, migraine duration, average headache severity, maximum headache severity, and level of functioning. By 3 months of treatment, subjects had a statistically significant decrease in migraine days (9.2 ± 2.7 headache days per month at baseline to 4.5 ± 3.4 headache days per month) and migraine attacks (6.4 ± 2.4 at baseline to 3.2 ± 2.3) with most of the improvements showing within 2 months of treatment. 52% of the subjects also had ≥50% improvement in headache days. There was not a statistically significant improvement in migraine duration, average headache severity, and maximum headache severity by 3 months of treatment. Two subjects discontinued treatment due to adverse events, two were lost to follow up, and one chose not to continue in the study.

In an 8-week, double-blinded, randomized control trial by Kisler et al., (2019), 55 participants with migraines received either 60 mg/day duloxetine (27 participants) or placebo (28 participants) to assess whether psychophysical pain measures could predict the efficacy of duloxetine in migraine prevention. Treatment outcome measures included changes in attack frequency, number of days with migraine, pain levels and a self-reported estimate of migraine improvement. By the end of the study, the duloxetine group reported statistically greater migraine improvement (52.3% ± 30.4%) vs the placebo group (26.0% ± 27.3%) with a significant decrease in the number of migraine attacks, days and depression. Interestingly, patients with greater pretreatment pain sensitivity showed greater migraine improvement on duloxetine, but not on placebo.

Borderline personality disorder and duloxetine

Borderline Personality Disorder (BPD) is characterized by emotional dysregulation, impulsivity, risk-taking behavior, irritability, feelings of emptiness, self-injury, and fear of abandonment, as well as unstable interpersonal relationships (Brüne et al., 2016). The pathophysiology of borderline personality disorder has not been fully elucidated, but the cause is currently understood to be a combination of genetic predisposition with early childhood environmental factors and neurobiological dysfunction (Chapman et al., 2020). One study showed evidence that polymorphism in the 5-HT(1A) gene C -1019G was associated with structural changes in the limbic system of BPD patients (Zetzsche et al., 2008).

Currently, first-line treatment for BPD is psychotherapy, specifically, dialectical behavioral therapy (DBT). Although there has been growing evidence for effective psychological treatments for BPD, pharmacologic treatments for BPD remain less well-studied. To date, no medication

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

has been approved by the FDA for BPD (Choi-Kain et al., 2017). However, The American Psychiatric Association (APA) guidelines recommend a symptom-targeted approach when using medications to treat specific BPD symptoms; their recommendations include the use of SSRIs for symptoms of affective dysregulation and impulsivity in BPD. Nevertheless, these guidelines had been contested by multiple meta-analyses that showed lacking evidence in SSRIs improving any symptoms of BPD (Lieb et al., 2010; Choi-Kain et al., 2017).

A 12-week open-label trial including a sample of 18 BPD patients showed that 60 mg/day of duloxetine significantly improved symptoms, such as impulsivity (P=0.028), outbursts of anger (P=0.0005), and affective instability (P=0.001) (Bellino et al., 2010).

SNRIs may be similar or more efficacious than SSRIs in treating symptoms of BPD. SNRIs may be a worthwhile consideration in BPD patients with prominent dysphoria. However, Dr. Cummings suggests that clinicians have recently been treating BPD symptoms with mood stabilizers rather than SSRIs due to the reconceptualization of the disorder, now thought of as an affective dyscontrol disorder (Ingenhoven et al., 2009).

Premature ejaculation and duloxetine

There is not a universally accepted definition of premature ejaculation due to the wide variability in ejaculatory time among men (Waldinger et al., 2007). The pathogenesis of premature ejaculation has classically been divided into psychogenic (e.g., anxiety) and biogenic factors (e.g., diabetes, prostatitis) (El-Hamd et al., 2019). Currently, several oral therapies have demonstrated improvement in intravaginal ejaculatory latency time such as phosphodiesterase-5 inhibitors, alpha-1 adrenergic agonists, tramadol, and SSRIs (Serefoglu et al., 2013). Serotonergic agents (especially paroxetine) are thought to be effective for premature ejaculation, as they postpone ejaculation through increased serotonin synaptic transmission (Waldinger et al., 1998; Waldinger & Olivier, 2004; Waldinger et al., 2007).

A comparative study of 80 patients with lifelong PE showed that there was no significant difference in intravaginal ejaculatory latency times between those treated with duloxetine 40 mg/day (117% increase from baseline to treatment) and paroxetine 20 mg/day (126% increase from baseline to treatment) (Ozcan et al., 2015).

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

SSRIs can be overly effective and cause delay in ejaculation, as well as anorgasmia and erectile dysfunction. SNRIs' noradrenergic component can offset its serotonin response, which may correct intravaginal ejaculatory latency time in patients with PE without causing sexual dysfunction (Meston & Frohlich, 2000).

Clinical pearls and key takeaways

- SNRIs are much safer and equally effective in many contexts as compared to TCAs.
- The primary indication for SNRIs is depression. SNRIs are more effective than SSRIs in treating moderate to severe depression. If a patient was not responsive to an adequate trial of an SSRI, it is worth considering the use of a SNRI as a second treatment.
- Consider using rating scales (e.g., HAM-D) periodically in patients, as that will give you a more concrete measure of what the patient's current status is and how much they have improved. Beyond the score itself, the results of the rating scale will allow physicians and patients alike to hone into the individual components of the illness (i.e., anxiety, insomnia).

References

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Archives of internal medicine*, *163*(20), 2433-2445.

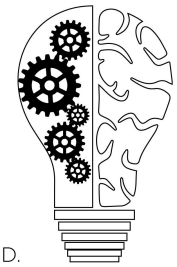
Bandelow, B., Reitt, M., Röver, C., Michaelis, S., Görlich, Y., & Wedekind, D. (2015). Efficacy of treatments for anxiety disorders: a meta-analysis. *International Clinical Psychopharmacology*, *30*(4), 183-192.

Bellino, S., Paradiso, E., Bozzatello, P., & Bogetto, F. (2010). Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder: a pilot study. *Journal of psychopharmacology*, *24*(3), 333-339.

Bilodeau, Mathieu et al. "Duloxetine in adults with ADHD: a randomized, placebo-controlled pilot study." *Journal of attention disorders* vol. 18,2 (2014): 169-75. doi:10.1177/1087054712443157

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



Blay, S. L., & Black, D. W. (2007). A case of obsessive-compulsive disorder responding to duloxetine. *Primary care companion to the Journal of clinical psychiatry*, *9*(3), 234.

Borchers, A. T., & Gershwin, M. E. (2015). Fibromyalgia: a critical and comprehensive review. *Clinical reviews in allergy & immunology*, *49*(2), 100-151.

Burch, R. C., Buse, D. C., & Lipton, R. B. (2019). Migraine: epidemiology, burden, and comorbidity. *Neurologic clinics*, *37*(4), 631-649.

Brüne, M. (2016). Borderline Personality DisorderWhy 'fast and furious'?. *Evolution, medicine, and public health*, *2016*(1), 52-66.

Chapman J, Jamil RT, Fleisher C. Borderline Personality Disorder. [Updated 2020 Nov 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430883/

Choi-Kain, L. W., Finch, E. F., Masland, S. R., Jenkins, J. A., & Unruh, B. T. (2017). What works in the treatment of borderline personality disorder. *Current behavioral neuroscience reports*, *4*(1), 21-30.

Clauw, D. J. (2014). Fibromyalgia: a clinical review. *Jama*, *311*(15), 1547-1555.

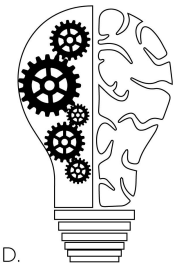
Clayton, A. H., & Ninan, P. T. (2010). Depression or menopause? Presentation and management of major depressive disorder in perimenopausal and postmenopausal women. *Primary care companion to the Journal of clinical psychiatry*, *12*(1).

Cohen, L. S., Soares, C. N., Lyster, A., Cassano, P., Brandes, M., & Leblanc, G. A. (2004). Efficacy and tolerability of premenstrual use of venlafaxine (flexible dose) in the treatment of premenstrual dysphoric disorder. *Journal of clinical psychopharmacology*, *24*(5), 540-543.

Dell'Osso, B., Nestadt, G., Allen, A., & Hollander, E. (2006). Serotonin-norepinephrine reuptake inhibitors in the treatment of obsessive-compulsive disorder: A critical review. *The Journal of clinical psychiatry*, *67*(4), 600-610.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



Dell'Osso, B., Mundo, E., Marazziti, D., & Altamura, A. C. (2008). Switching from serotonin reuptake inhibitors to duloxetine in patients with resistant obsessive compulsive disorder: a case series. *Journal of Psychopharmacology*, *22*(2), 210-213.

Dmochowski, R. R., Miklos, J. R., Norton, P. A., Zinner, N. R., Yalcin, I., Bump, R. C., & Duloxetine Urinary Incontinence Study Group. (2003). Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. The Journal of urology, 170(4 Part 1), 1259-1263.

Dougherty, D. D., Corse, A. K., Chou, T., Duffy, A., Arulpragasam, A. R., Deckersbach, T., ... & Keuthen, N. J. (2015). Open-label study of duloxetine for the treatment of obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology*, *18*(2).

Dresler, T., Caratozzolo, S., Guldolf, K., Huhn, J. I., Loiacono, C., Niiberg-Pikksööt, T., ... & Serafini, G. (2019). Understanding the nature of psychiatric comorbidity in migraine: a systematic review focused on interactions and treatment implications. *The journal of headache and pain*, *20*(1), 51.

El-Hamd, M. A., Saleh, R., & Majzoub, A. (2019). Premature ejaculation: an update on definition and pathophysiology. *Asian journal of andrology*, *21*(5), 425.

Epstein, S. A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., ... & Zisook, S. (1999). Psychiatric disorders in patients with fibromyalgia: a multicenter investigation. *Psychosomatics*, *40*(1), 57-63.

Freeman, E. W., Rickels, K., Yonkers, K. A., Kunz, N. R., McPherson, M., & Upton, G. V. (2001). Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstetrics & Gynecology*, *98*(5), 737-744.

Freeman, M. P., Hirschberg, A. M., Wang, B., Petrillo, L. F., Connors, S., Regan, S., ... & Cohen, L. S. (2013). Duloxetine for major depressive disorder and daytime and nighttime hot flashes associated with the menopausal transition. *Maturitas*, *75*(2), 170-174.

Frey, B. N., Lord, C., & Soares, C. N. (2008). Depression during menopausal transition: a review of treatment strategies and pathophysiological correlates. *Menopause international*, *14*(3), 123-128.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Galletti, F., Cupini, L. M., Corbelli, I., Calabresi, P., & Sarchielli, P. (2009). Pathophysiological basis of migraine prophylaxis. *Progress in neurobiology*, *89*(2), 176-192.

Goldstein, D. J., Lu, Y., Detke, M. J., Wiltse, C., Mallinckrodt, C., & Demitrack, M. A. (2004). Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *Journal of clinical psychopharmacology*, *24*(4), 389-399.

Guerdjikova AI, McElroy SL, Winstanley EL, Nelson EB, Mori N, McCoy J, Keck PE Jr, Hudson JI. Duloxetine in the treatment of binge eating disorder with depressive disorders: a placebo-controlled trial. Int J Eat Disord. 2012 Mar;45(2):281-9. doi: 10.1002/eat.20946. Epub 2011 Jul 8. PMID: 21744377.

Hall, E., Frey, B. N., & Soares, C. N. (2011). Non-hormonal treatment strategies for vasomotor symptoms. *Drugs*, *71*(3), 287-304.

Hirschtritt, M. E., Bloch, M. H., & Mathews, C. A. (2017). Obsessive-compulsive disorder: advances in diagnosis and treatment. *Jama*, *317*(13), 1358-1367.

Ingenhoven, T., Lafay, P., Rinne, T., Passchier, J., & Duivenvoorden, H. (2009). Effectiveness of pharmacotherapy for severe personality disorders: meta-analyses of randomized controlled trials. *The Journal of clinical psychiatry*, *71*(1), 14-25.

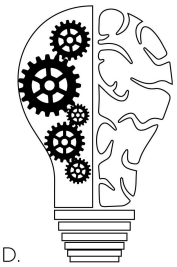
Jakubovski, E., Johnson, J. A., Nasir, M., Müller-Vahl, K., & Bloch, M. H. (2019). Systematic review and meta-analysis: Dose–response curve of SSRIs and SNRIs in anxiety disorders. *Depression and anxiety*, *36*(3), 198-212.

Jarvis, C. I., Lynch, A. M., & Morin, A. K. (2008). Management strategies for premenstrual syndrome/premenstrual dysphoric disorder. *Annals of Pharmacotherapy*, *42*(7-8), 967-978.

Joffe, H., Soares, C. N., Petrillo, L. F., Viguera, A. C., Somley, B. L., Koch, J. K., & Cohen, L. S. (2007). Treatment of depression and menopause-related symptoms with the serotonin-norepinephrine reuptake inhibitor duloxetine. *The Journal of clinical psychiatry*, *68*(6), 943-950.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The prevalence of chronic pain in United States adults: results of an Internet-based survey. *The Journal of Pain*, *11*(11), 1230-1239.

Jost, W., & Marsalek, P. (2004). Duloxetine: mechanism of action at the lower urinary tract and Onuf's nucleus. Clinical autonomic research : official journal of the Clinical Autonomic Research Society, 14(4), 220–227. https://doi.org/10.1007/s10286-004-0197-8

Kessler RM, Hutson PH, Herman BK, Potenza MN. The neurobiological basis of binge-eating disorder. Neurosci Biobehav Rev. 2016 Apr;63:223-38. doi: 10.1016/j.neubiorev.2016.01.013. Epub 2016 Feb 2. PMID: 26850211.

Khan, A., Brodhead, A. E., Kolts, R. L., & Brown, W. A. (2005). Severity of depressive symptoms and response to antidepressants and placebo in antidepressant trials. Journal of Psychiatric Research, 39(2), 145-150.

Kisler, L. B., Weissman-Fogel, I., Coghill, R. C., Sprecher, E., Yarnitsky, D., & Granovsky, Y. (2019). Individualization of Migraine Prevention: A Randomized Controlled Trial of Psychophysical-based Prediction of Duloxetine Efficacy. *The Clinical journal of pain*, *35*(9), 753–765.

Kotecha, P., Sahai, A., & Malde, S. (2020). Use of Duloxetine for Postprostatectomy Stress Urinary Incontinence: A Systematic Review. *European Urology Focus*.

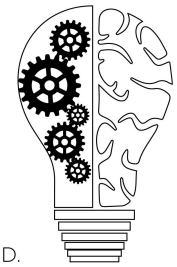
Lancaster, C. L., Teeters, J. B., Gros, D. F., & Back, S. E. (2016). Posttraumatic stress disorder: overview of evidence-based assessment and treatment. *Journal of clinical medicine*, *5*(11), 105.

Lee, Y. C., & Chen, P. P. (2010). A review of SSRIs and SNRIs in neuropathic pain. *Expert opinion on pharmacotherapy*, *11*(17), 2813-2825.

Leombruni P, Lavagnino L, Gastaldi F, Vasile A, Fassino S. Duloxetine in obese binge eater outpatients: preliminary results from a 12-week open trial. Hum Psychopharmacol. 2009 Aug;24(6):483-8. doi: 10.1002/hup.1040. PMID: 19536908.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



Li, J., Yang, L., Pu, C., Tang, Y., Yun, H., & Han, P. (2013). The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *International urology and nephrology*, *45*(3), 679-686.

Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br J Psychiatry. 2010 Jan;196(1):4-12. doi: 10.1192/bjp.bp.108.062984. PMID: 20044651.

Mahmoudi-Gharaei, Javad et al. "Duloxetine in the treatment of adolescents with attention deficit/hyperactivity disorder: an open-label study." *Human psychopharmacology* vol. 26,2 (2011): 155-60. doi:10.1002/hup.1188

Malt, E. A., Berle, J. E., Olafsson, S., Lund, A., & Ursin, H. (2000). Fibromyalgia is associated with panic disorder and functional dyspepsia with mood disorders: a study of women with random sample population controls. *Journal of psychosomatic research*, *49*(5), 285-289.

Mariappan, P., Alhasso, A. A., Grant, A., & N'Dow, J. M. (2005). Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. *Cochrane Database of Systematic Reviews*, (3).

Marks, D. M., Shah, M. J., Patkar, A. A., Masand, P. S., Park, G. Y., & Pae, C. U. (2009). Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. *Current neuropharmacology*, *7*(4), 331-336.

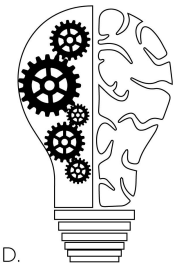
Maund, E., Guski, L. S., & Gøtzsche, P. C. (2017). Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 189(5), E194–E203. https://doi.org/10.1503/cmaj.151104

Mazza, M., Harnic, D., Catalano, V., Janiri, L., & Bria, P. (2008). Duloxetine for premenstrual dysphoric disorder: a pilot study. *Expert opinion on pharmacotherapy*, *9*(4), 517-521.

Meston, C. M., & Frohlich, P. F. (2000). The neurobiology of sexual function. *Archives of General Psychiatry*, *57*(11), 1012-1030.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



Millard, R. J., Moore, K., Rencken, R., Yalcin, I., Bump, R. C., & Duloxetine UI Study Group. (2004). Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. *BJU international*, *93*(3), 311-318.

Minen, M. T., De Dhaem, O. B., Van Diest, A. K., Powers, S., Schwedt, T. J., Lipton, R., & Silbersweig, D. (2016). Migraine and its psychiatric comorbidities. *Journal of Neurology, Neurosurgery & Psychiatry*, *87*(7), 741-749.

Mowla, A., Boostani, S., & Dastgheib, S. A. (2016). Duloxetine augmentation in resistant obsessive-compulsive disorder: a double-blind controlled clinical trial. *Journal of clinical psychopharmacology*, *36*(6), 720-723.

Muscatello, M. R. A., Zoccali, R. A., Pandolfo, G., Mangano, P., Lorusso, S., Cedro, C., ... & Bruno, A. (2019). Duloxetine in psychiatric disorders: expansions beyond major depression and generalized anxiety disorder. *Frontiers in psychiatry*, *10*, 772.

Norton, P. A., Zinner, N. R., Yalcin, I., Bump, R. C., & Duloxetine Urinary Incontinence Study Group. (2002). Duloxetine versus placebo in the treatment of stress urinary incontinence. *American journal of obstetrics and gynecology*, *187*(1), 40-48.

Osani, M. C., & Bannuru, R. R. (2019). Efficacy and safety of duloxetine in osteoarthritis: a systematic review and meta-analysis. *The Korean journal of internal medicine*, *34*(5), 966.

Ozcan, L., Polat, E. C., Otunctemur, A., & Ozbek, E. (2015). Duloxetine, dual serotonin and norepinephrine reuptake inhibitor, versus paroxetine, selective serotonin reuptake inhibitor, in the treatment for premature ejaculation. *International urology and nephrology*, *47*(2), 283-287.

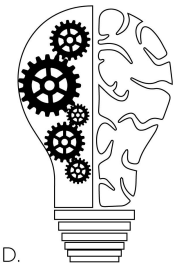
Parry, B. L. (2001). The role of central serotonergic dysfunction in the aetiology of premenstrual dysphoric disorder. *CNS drugs*, *15*(4), 277-285.

Radat, F., & Swendsen, J. (2005). Psychiatric comorbidity in migraine: a review. *Cephalalgia*, *25*(3), 165-178.

Ramos MG, Hara C, Rocha FL. Duloxetine treatment for women with premenstrual dysphoric disorder: a single-blind trial. *Int J Neuropsychopharmacol* (2009) 12:1081–8. doi: 10.1017/S1461145709000066

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



Rapkin, A. J., & Akopians, A. L. (2012). Pathophysiology of premenstrual syndrome and premenstrual dysphoric disorder. *Menopause international*, *18*(2), 52-59.

Rapkin, A. J., & Lewis, E. I. (2013). Treatment of premenstrual dysphoric disorder. *Women's Health*, *9*(6), 537-556.

Reas DL, Grilo CM. Review and meta-analysis of pharmacotherapy for binge-eating disorder. *Obesity (Silver Spring)*. 2008;16(9):2024-2038. doi:10.1038/oby.2008.333

Ressler, K. J., & Nemeroff, C. B. (2000). Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depression and anxiety*, *12*(S1), 2-19.

Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG . Meta-analysis of the placebo response in antidepressant trials. J Affect Disord 2009; 118: 1–8. https://www.karger.com/Article/FullText/506879

Safer, D. L., & Arnow, K. D. (2012). Suprathreshold duloxetine for treatment-resistant depression, anorexia nervosa binge-purging type, and obsessive-compulsive disorder: a case report. *Innovations in clinical neuroscience*, *9*(3), 13.

Sansone, R. A., & Sansone, L. A. (2011). SNRIs pharmacological alternatives for the treatment of obsessive compulsive disorder?. *Innovations in clinical neuroscience*, *8*(6), 10.1

Serefoglu, E. C., Saitz, T. R., Trost, L., & Hellstrom, W. J. (2013). Premature ejaculation: do we have effective therapy?. *Translational andrology and urology*, *2*(1), 45.

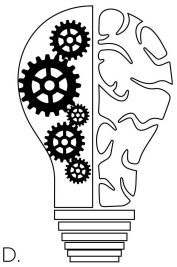
Steers, W. D., Herschorn, S., Kreder, K. J., Moore, K., Strohbehn, K., Yalcin, I., ... & Duloxetine OAB Study Group. (2007). Duloxetine compared with placebo for treating women with symptoms of overactive bladder. *BJU international*, *100*(2), 337-345.

Steiner, M., & Pearlstein, T. (2000). Premenstrual dysphoria and the serotonin system: pathophysiology and treatment. *Journal of Clinical Psychiatry*, *61*, 17-21.

Skapinakis, P., Caldwell, D. M., Hollingworth, W., Bryden, P., Fineberg, N. A., Salkovskis, P., ... & Lewis, G. (2016). Pharmacological and psychotherapeutic interventions for management of

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *The Lancet Psychiatry*, *3*(8), 730-739.

Smith, H. S., Smith, E. J., & Smith, B. R. (2012). Duloxetine in the management of chronic musculoskeletal pain. *Therapeutics and clinical risk management*, *8*, 267.

Wolfe, F., Walitt, B. T., Katz, R. S., & Häuser, W. (2014). Symptoms, the nature of fibromyalgia, and diagnostic and statistical manual 5 (DSM-5) defined mental illness in patients with rheumatoid arthritis and fibromyalgia. *PloS one*, *9*(2), e88740.

Steckler, T., & Risbrough, V. (2012). Pharmacological treatment of PTSD–established and new approaches. *Neuropharmacology*, *62*(2), 617-627.

Taylor, A. P., Adelman, J. U., & Freeman, M. C. (2007). Efficacy of duloxetine as a migraine preventive medication: possible predictors of response in a retrospective chart review. *Headache: The Journal of Head and Face Pain*, *47*(8), 1200-1203.

Thor, K. B., & Katofiasc, M. A. (1995). Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. The Journal of pharmacology and experimental therapeutics, 274(2), 1014–1024.

Thurston, R. C., & Joffe, H. (2011). Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. *Obstetrics and Gynecology Clinics*, *38*(3), 489-501.

van Kerrebroeck, P., Abrams, P., Lange, R., Slack, M., Wyndaele, J. J., Yalcin, I., ... & Duloxetine UI Study Group. (2004). Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. *BJOG: An International Journal of Obstetrics & Gynaecology*, *111*(3), 249-257.

Villarreal, G., Canive, J. M., Calais, L. A., Toney, G., & Smith, A. K. (2010). Duloxetine in military posttraumatic stress disorder. *Psychopharmacol Bull*, *43*(3), 26-34.

Volpe, F. M. (2008). An 8-week, open-label trial of duloxetine for comorbid major depressive disorder and chronic headache. *The Journal of clinical psychiatry*, *69*(9), 1449-1454.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.

Walderhaug, E., Kasserman, S., Aikins, D., Vojvoda, D., Nishimura, C., & Neumeister, A. (2010). Effects of duloxetine in treatment-refractory men with posttraumatic stress disorder. *Pharmacopsychiatry*, *43*(02), 45-49.

Waldinger, M. D., Berendsen, H. H., Blok, B. F., Olivier, B., & Holstege, G. (1998). Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behavioural brain research*, *92*(2), 111-118.

Waldinger, M. D., & Olivier, B. (2004). Utility of selective serotonin reuptake inhibitors in premature ejaculation. *Current opinion in investigational drugs (London, England: 2000)*, *5*(7), 743-747.

Waldinger, M. D. (2007). Premature ejaculation. *Drugs*, *67*(4), 547-568.

Walsh, S., Ismaili, E., Naheed, B., & O'Brien, S. (2015). Diagnosis, pathophysiology and management of premenstrual syndrome. *The Obstetrician & Gynaecologist*, *17*(2), 99-104.

Wang, S. M., Lee, H. K., Kweon, Y. S., Lee, C. T., & Lee, K. U. (2015). Overactive bladder successfully treated with duloxetine in a female adolescent. *Clinical Psychopharmacology and Neuroscience*, *13*(2), 212.

Worsley, R., Bell, R. J., Gartoulla, P., Robinson, P. J., & Davis, S. R. (2017). Moderate–severe vasomotor symptoms are associated with moderate–severe depressive symptoms. *Journal of Women's Health*, *26*(7), 712-718.

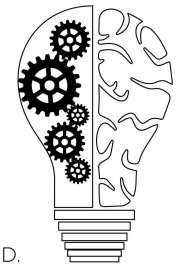
Yeh, Y. W., Chen, C. H., Kuo, S. C., Wang, S. C., Chen, C. K., & Feng, H. M. (2009). High-dose duloxetine for treatment-resistant obsessive-compulsive disorder: a case report with sustained full remission. *Clinical neuropharmacology*, *32*(3), 174-176.

Yoshimura, N., & Chancellor, M. B. (2002). Current and future pharmacological treatment for overactive bladder. *The Journal of urology*, *168*(5), 1897-1913.

Young, W. B., Bradley, K. C., Anjum, M. W., & Gebeline-Myers, C. (2013). Duloxetine prophylaxis for episodic migraine in persons without depression: a prospective study. *Headache: The Journal of Head and Face Pain*, *53*(9), 1430-1437.

Episode 112: Duloxetine and the SNRIs Deep Dive Part 2

Annabel Kuhn, M.D., Harrison Bae B.S., Amanda Shim B.S., Joseph Wong, M.D., Michael Cummings, M.D., David Puder, M.D.



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Zetzsche, T., Preuss, U. W., Bondy, B., Frodl, T., Zill, P., Schmitt, G., ... & Meisenzahl, E. M. (2008). 5-HT1A receptor gene C−1019 G polymorphism and amygdala volume in borderline personality disorder. *Genes, Brain and Behavior*, *7*(3), 306-313.