Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

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In today's episode of the podcast, we will be doing a deep dive into duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI). In part one of this two-part series, we will cover the history of SNRIs as well as mechanisms of action, cytochrome P450 issues, side effects, and contraindications to consider when prescribing duloxetine and this class of medications.

The History of SNRIs

The first generation of antidepressants were the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which were introduced in the 1950s (López-Muñoz & Alamo, 2009). While these medications were a tremendous boon to the field of psychiatry by finally providing a pharmacological treatment modality for depression and broadening the field's neurobiological understanding of depression through the monoamine hypothesis, they were also quite problematic due to their pharmacological properties and side effects (Hillhouse & Porter, 2015; Hirschfeld, 2000; López-Muñoz & Alamo, 2009). For example, the TCAs have a narrow therapeutic index, as the median lethal dose (LD50) for TCAs is only 6-8x the therapeutic dosage. Ingesting 10-20 mg/kg can cause fatal toxicity (Benowitz, 2012). MAOIs can also precipitate a hypertensive crisis in combination with dietary tyramine, which is also referred to as the "cheese effect" but can also be attributed to the consumption of cured meats and fermented products with concurrent MAOI usage (Yamada & Yasuhara, 2004).

The second generation of antidepressants was developed to more specifically target certain neurotransmitters and include medication classes such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). The first SSRI introduced was fluoxetine in the late 1980s (López-Muñoz & Alamo, 2009). One major benefit to SSRIs as compared to the first generation antidepressants was that SSRIs were much safer and more difficult to overdose on. However, while SSRIs were as effective as the older antidepressants in mild or moderate depression, they were perceived to not be as effective as the first generation antidepressants in treating severe depression (Barbey & Roose, 1998; Schatzberg, 1996). While our most recent understanding is that SSRIs are as effective in

treating severe depression as well as non-severe depression, that perception led to the development of other antidepressants, such as SNRIs, as focus shifted from solely pushing on one neurotransmitter (i.e. serotonin) to recruiting other neurotransmitters (i.e. norepinephrine and dopamine) involved in mood regulation (Hieronymus et al., 2019; Hillhouse & Porter, 2015).

The first SNRI to be approved was venlafaxine in 1993 for MDD (Hillhouse & Porter, 2015; Sansone & Sansone, 2014). The immediate release (IR) form that was dosed twice a day was approved for MDD in 1993. In 1997, the extended release (XR) form, dosed only once a day, was also approved for MDD (Hillhouse & Porter, 2015; Sansone & Sansone, 2014). Other indications that have since been added include generalized anxiety disorder, social anxiety disorder (social phobia), and panic disorder. Venlafaxine has also shown efficacy in treating various pain conditions such as diabetic peripheral neuropathy and vasomotor symptoms associated with perimenopause, although it is not FDA-approved for such use (Grothe et al., 2004; North American Menopause Society, 2015; Sansone & Sansone, 2014; Thase, 2006). Sibutramine was approved in 1997 as a treatment for obesity, but was removed from the market in the U.S. in 2010 due to its increased risk of cardiovascular events (i.e. myocardial infarction and stroke) (James et al., 2010; Padwal & Majumdar, 2007). Duloxetine was approved in 2004 for MDD and was the first drug in the U.S. to be approved for diabetic peripheral neuropathy (Eli Lilly and Company, 2004; Sansone & Sansone, 2014). Duloxetine was later approved for generalized anxiety disorder (GAD), fibromyalgia and chronic musculoskeletal pain. Because of this, it holds the most FDA-approved indications out of all the SNRIs (Eli Lilly and Company, 2004; Sansone & Sansone, 2014). Duloxetine is also approved for stress urinary incontinence in Europe, although it is not approved for such use in the U.S. (Maund et al., 2017; Sansone & Sansone, 2014). Desvenlafaxine, a metabolite of venlafaxine, was approved in 2008 for the treatment of MDD (Liebowitz et al., 2008). Milnacipran was approved in 2009 for fibromyalgia in the US; however, it has not been approved in the U.S. for MDD even though it is approved for MDD in many other countries (Gendreau et al., 2005; Sumpton & Moulin, 2014). Levomilnacipran, the levo-enantiomer of milnacipran, is the most recent addition to the SNRIs and was approved in 2013 for MDD (Wagner et al., 2018).

The Mechanisms of Action of SNRIs

SNRIs are “dual-action” serotonergic-noradrenergic agents and work by inhibiting serotonin transporters (SERT) and norepinephrine transporters (NET) throughout the brain. This increases the concentration of these two neurotransmitters in the synaptic cleft (Stahl, 2013). Although they are SNRIs, venlafaxine, desvenlafaxine, and duloxetine have weak dopamine reuptake inhibition (Sansone & Sansone, 2014). Interestingly, SNRIs boost dopamine levels in

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

the prefrontal cortex (PFC) not through the inhibition of dopamine transporters (DATs), but through the inhibition of NETs (Stahl, 2013). Due to the scarcity of DATs in the PFC, NETs in the PFC have greater affinity for dopamine than norepinephrine and inhibiting NETs in the PFC increases both levels of synaptic norepinephrine and dopamine (Stahl, 2013).

While all SNRIs inhibit the reuptake of serotonin (5-HT) and norepinephrine (NE), the SNRIs have varying selectivity in their reuptake inhibition (Auclair et al., 2013; Deecher et al., 2006; Sansone & Sansone, 2014; Stahl et al., 2005) .

- Venlafaxine has a 5-HT:NE reuptake inhibition ratio of 30:1.
- Desvenlafaxine has a 5-HT:NE reuptake inhibition ratio of 10:1.
- Duloxetine has a 5-HT:NE reuptake inhibition ratio of 10:1.
- Milnacipran has a 5-HT:NE reuptake inhibition ratio of 1:1.
- Levomilnacipran has a 5-HT:NE reuptake inhibition ratio of 1:2, which makes it unique among SNRIs in that it is more noradrenergic than serotonergic.

As compared to older antidepressants, SNRIs are much less prone to causing adverse side effects due to their lack of additional muscarinic, histaminic, alpha-1 adrenergic receptor affinities (Lambert & Bourin, 2002). Per Dr. Cummings, besides looking out for rare adverse effects, paying attention to a patient's pulse and blood pressure during titration is the greatest clinical concern, especially in patients prone to hypertension. Thus, titrate up slowly to mitigate against tachycardia and hypertension.

The cytochrome P450s of SNRIs

Many of the SNRIs, like numerous other psychotropic medications, interact with the CYP450 system as substrates and/or inhibitors. Venlafaxine is metabolized by various CYP450 enzymes including 2D6, 2C19, 3A4 and 2C9, but is metabolized to its major active metabolite *O*-desmethylvenlafaxine (aka desvenlafaxine) by 2D6 (Ereshefsky & Dugan, 2000; Lambert & Bourin, 2002; McAlpine et al., 2007; Zhou, 2009). While 2D6 is not in short supply in most of the population, there are a great deal of genetic polymorphisms that can result in no 2D6 activity or decreased 2D6 activity (Zanger & Schwab, 2013). Certain genetic polymorphisms that result in decreased 2D6 metabolism are more prominent in specific populations such as the *CYP2D6*4* allele in Caucasians, *CYP2D6*10* allele in Asians and the *CYP2D6*17* allele in Africans (Zanger & Schwab, 2013).

In cases like these, patients cannot usually tolerate more than 75 mg of venlafaxine; however, you can put the patient who is a poor 2D6 metabolizer on desvenlafaxine and they can do just fine, as desvenlafaxine is the metabolite of venlafaxine. On the other hand, one should also

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

consider that desvenlafaxine is more expensive than venlafaxine. A more common scenario than having a genetic polymorphism that decreases 2D6 metabolism is taking venlafaxine concurrently with a potent 2D6 inhibitor (e.g. paroxetine, fluoxetine, bupropion) (Foley et al., 2006; Lam et al., 2002; Otton et al., 1993). One important clinical implication of using venlafaxine in patients with decreased 2D6 activity or 2D6 inhibition is that there is an increased risk for cardiovascular toxicity (Lessard et al., 1999). Therefore, before prescribing venlafaxine, make sure to go over their medications to avoid 2D6 inhibition.

Duloxetine is metabolized by both 2D6 and 1A2 and is also a moderately potent inhibitor of 2D6 (Frampton & Plosker, 2007; Lantz et al., 2003; Skinner et al., 2003). So one has to take into consideration using duloxetine in conjunction with other medications that inhibit 2D6 or are metabolized by 2D6, such as the SSRIs fluoxetine and paroxetine, which are also dually 2D6 inhibitors and substrates (Frampton & Plosker, 2007; Skinner et al., 2003). In addition to paying attention to 2D6 inhibitors, you need to look out for 1A2 inhibitors such as fluvoxamine (SSRI), cimetidine (H2 blocker), and ciprofloxacin and enoxacin (both fluoroquinolones) when using duloxetine (Eli Lilly and Company, 2004; Frampton & Plosker, 2007). 1A2 activity is also affected by a patient's sex and smoking status, which can impact duloxetine levels (Knadler et al., 2011). Women have less 1A2 activity compared to men and have higher duloxetine concentrations as compared to men (Knadler et al., 2011). Smoking increases 1A2 activity and results in decreased duloxetine concentrations in smokers as compared to non-smokers (Knadler et al., 2011). Knadler et al. (2011). Do note that it is not warranted to dose differently based on a patient's sex or smoking status. While sex and smoking status do play a role in duloxetine's pharmacokinetics on a broad population scale, there are more important factors that affect duloxetine's clearance on an individual basis. However, since duloxetine is metabolized by both 2D6 and 1A2, even if one pathway is inhibited, duloxetine levels may not be drastically increased as it still can be metabolized by the other pathway.

Per Dr. Cummings, there are two important aspects to polypharmacy:

1) Rational polypharmacy involves using different therapeutic mechanisms of action, which means not using two drugs that work on the same neurotransmitter via the same mechanism and produce the same therapeutic effect. The goal is to seek complimentary/additive mechanisms of action that may reinforce therapeutic effects without excessively increasing side-effect burden.
2) With the introduction of SSRIs, psychiatrists had to pay more attention to the CYP450 system. Understanding the metabolism of these medications will go a long way toward avoiding drug-drug interactions.

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

There are claims that genetic testing of a patient's CYP450 profile is able to give you nuance in what might be the best medication for an individual; however, per Dr. Puder's and Dr. Cumming's clinical experience, these recommendations are not too helpful. According to Dr. Cummings, a more practical method as compared to getting a genetic profile is to slowly titrate the desired medication up to steady state levels and measure a plasma concentration. This provides a precise measurement of the kinetics of the medication in question.

The Side Effects of Duloxetine

Duloxetine, like venlafaxine, inhibits serotonin and norepinephrine sequentially as the dosage increases (Sansone & Sansone, 2014). This results in the onset of serotonergic side effects (e.g., nausea, vomiting, insomnia, sexual dysfunction, diarrhea) before the noradrenergic side effects (e.g. dry mouth, sweating, constipation) (Montgomery, 2008; Sansone & Sansone, 2014; Stahl, 1998).

- Nausea is the most common treatment-emergent adverse event (TEAE) reported by patients across all indications and dosages of duloxetine (Brunton et al., 2010). Fortunately, most cases of nausea are only mild to moderate in severity and occur early in treatment with significant decrease as time goes on (20% during the first week of treatment and <5% by the second week) (Brunton et al., 2010).
    - Nausea can be mitigated if duloxetine is taken with food or started at a lower dose and titrated up slowly.
        - In a randomized control study comparing the tolerability of different starting doses of duloxetine (30 mg qAM, 30 mg BID, and 60 mg qAM) taken with or without food, Whitmyer et al. (2007) found that the greatest significant benefit in reducing nausea was starting at a lower dose of 30 mg qAM regardless of taking it with or without food or taking the higher dosage of 60 mg qAM with food.
        - In an observational study that assessed the tolerability of duloxetine among women with stress incontinence in a nontrial situation, Duckett et al. (2007) found that significantly more women on the starting dose of 40 mg BID were unable to tolerate the medication due to nausea as compared to the women who started on 20 mg BID for two weeks before increasing to 40 mg BID.
        - Per Dr. Cummings, start at a lower dose like 20 mg or 30 mg and titrate up at intervals of not faster than once per week. This will decrease the amount of side effects like nausea.

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

- It takes 4-6 weeks to decrease anxiety, so a slower titration process can be afforded to see how the patient responds on a lower dose.
- Increasing the dosage too quickly can also result in the patient taking a higher dosage than necessary for a therapeutic effect.

- Sexual dysfunction is the most concerning side effect of antidepressants to patients, even if it may not be the most common side effect.
  - The three stages of normal sexual desire follow the order of desire (libido), arousal (excitement) and orgasm (Stahl, 2001). Antidepressants are well known to cause sexual dysfunction in the first three stages of sexual desire with decreased sexual libido, issues with arousal (i.e. erectile dysfunction in men and disruption in clitoral engorgement and lubrication in women), and issues with orgasm like anorgasmia or delayed ejaculation (Bitter et al., 2011; Serretti & Chiesa, 2009).
  - Sexual dysfunction due to antidepressant therapy is also known to affect men and women differently with regards to the sexual stages. In a comparative study of 3114 adult outpatients receiving antidepressant monotherapy (SSRI or SNRI), men were significantly more likely to experience dysfunction in the desire and orgasm stage whereas women were more likely to experience dysfunction in the arousal stage (Clayton et al., 2006). This stage-specific dysfunction was consistent across the different SSRIs and SNRIs studied (Clayton et al., 2006).
  - While serotonin has an overall effect of decreasing sexual desire and arousal, the response varies based on the specific receptor activity (i.e. stimulation of 5HT-2C contributes to erection, stimulation of 5HT-1A contributes to ejaculation, whereas stimulation of 5HT-2A and 5HT-3 leads to negative effects on sexual function) (Clayton et al., 2014; Stahl, 2001).
  - Thus, among the different antidepressants, SSRIs and SNRIs have the highest rates of sexual dysfunction (up to 80%) due to their serotonergic activity (Montejo et al., 2001; Montejo et al., 2019; Serretti & Chiesa, 2009). Among the SNRIs, venlafaxine has the highest risk of sexual side effects (70 - 80% prevalence) as it has greater serotonin reuptake inhibition as compared to its norepinephrine reuptake inhibition (Clayton et al., 2014; Serretti & Chiesa, 2009). Duloxetine, in comparison, has a more balanced serotonin and norepinephrine reuptake inhibition, which may explain its decreased risk for sexual dysfunction (25 - 45% incidence) as compared to venlafaxine and other SSRIs (Bitter et al., 2011; Clayton et al., 2007; Clayton et al., 2014; Delgado et al., 2005; Dueñas et al., 2011; Nelson et al., 2006). Levomilnacipran has the lowest risk (5 - 6%) of sexual

dysfunction (i.e. erectile dysfunction, ejaculation disorder) among the SNRIs due to it having the least amount of serotonin reuptake inhibition (Asnis & Henderson, 2015; Citrome, 2013; Deardorff & Grossberg, 2014).

- In terms of antidepressants that are less likely to cause sexual dysfunction, mirtazapine can be an option (5 - 25% incidence) although it is associated with a risk of significant weight gain for some patients (Clayton et al., 2014; Fawcett & Barkin, 1998; Masand & Gupta, 2002; Montejo et al., 2001). If a patient is a SSRI responder, other options include vortioxetine or vilazodone, which as 5HT1A partial agonists, have drastically reduced risk of sexual dysfunction (<2% or not significantly distinguishable from rates in placebo) as compared to other antidepressants (Jacobsen et al., 2019; McIntyre, 2017; Wagner et al., 2018). However, the consideration with vortioxetine and vilazodone is that they are much more expensive as compared to other SSRIs/SNRIs.
- It is important to start a discussion with the patient about the potential of sexual dysfunction before starting antidepressant medication due to how prevalent this side effect is and how distressing it is to patients. Part of that discussion is getting a baseline for the patient's three stages of normal sexual desire and recording that information in the chart to compare against changes in sexual function after the medication is started.
- The risk of sexual dysfunction is dose-dependent, so you need to weigh the therapeutic benefit of the medication vs. the risk of side effects as you decide how quickly you want to titrate up.

- Other side effects of duloxetine that have been reported include (Bitter et al., 2011; Brunton et al., 2010; Carter & McCormack, 2009; Frampton & Plosker, 2007; Nelson et al., 2006):
  - Somnolence
  - Headache
  - Dizziness
  - Insomnia
  - Fatigue
  - Weakness
  - Tremor
  - Hyperhidrosis
  - Xerostomia
  - Sinusitis
  - Nasopharyngitis
  - Abdominal pain

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

- Anorexia
- Weight loss
- Vomiting
- Diarrhea
- Constipation
- Urinary retention

The Warnings, Precautions and Important Considerations of Duloxetine

- **Increased Risk for Suicidality**
  - Depression is listed by WHO as the fourth leading cause of death and disability worldwide (Reddy, 2010). An in-person interview study of 36,309 patients indicated that the 12-month and lifetime prevalences of MDD were 10.4% and 20.6% respectively in the United States (Hassin et al.,2018). Such high prevalence in the United States is a serious health risk to our population, as another interview study of 269 depressed patients indicated that 58% of them had experienced suicidal ideation and 15% of them had also attempted suicide during their current major depressive episodes (Sokero, 2006).
  - The first case published about suicidality secondary to SSRI/SNRI therapy was discussed in 1990, but only became generally recognized in the media in 2002 (Sharma et al., 2016). Since it would take a few weeks of antidepressant therapy before clinical improvement became apparent, it was thought that during the initial partial recovery phase, patients may regain their energy and desire, leading to increased suicidal ideation (Jick et al., 2004).
  - In 2004, the FDA issued a black box warning on antidepressants for increased risk of suicidality as a means to increase physician check-ins after the start of antidepressant therapy. However, the black box warning caused many physicians to be wary of prescribing antidepressants, which led to increased suicide rates in those with untreated depression as they were not being prescribed antidepressants (Friedman, 2014).
  - Nevertheless, clinical studies have shown that there is no significant difference in suicidality in adults on antidepressants, but has shown increased suicidality in adolescents and young adults who initiated SSRIs or SNRIs. In a systematic review and meta-analysis of 70 trials (n = 18,526 patients) by Sharma et al. (2016), there was no significant increase in suicidality (0.81, 95% confidence interval 0.51 to 1.28)) or mortality (odds ratio 1.28, 0.40 to 4.06) overall in adults during antidepressant treatment. However, the risk for suicidality was doubled in

children and adolescents during antidepressant treatment (odd ratio 2.39, 1.31 to 4.33) (Sharma et al. (2016).

- Dr. Cummings, therefore, emphasizes the importance of having a one-week follow-up appointment with the patient after prescribing SNRI/SSRI to monitor for signs of suicidality and any mood abnormalities.

- Areas with more suicides in the U.S. are areas with fewer psychiatrists and therapists (Tondo et al., 2006). The most common prescribers of antidepressants are not psychiatrists but rather primary care physicians (Barkil-Oteo, 2013). Only 39% of patients seeing a primary care provider were receiving therapeutic dose of antidepressants for MDD (compared to 48% for psychiatrists) (Simon et al., 1993).

Exceedingly Rare Side Effects:

- **Hepatotoxicity**
  - Per the prescription insert, duloxetine should not be prescribed in patients with substantial alcohol use, as the interaction could precipitate hepatic injury or chronic liver disease, as duloxetine could worsen preexisting liver disease (Eli Lilly and Company, 2004; Montgomery, 2008; Wernicke et al., 2008). However, it has been unclear whether duloxetine inflicts severe hepatic injury in practice.
  - A propensity score-matched cohort analysis of over 100,000 patients compared the incidence rate of hepatic injury in those treated with duloxetine to those treated with other SSRIs/SNRIs in individuals with pharmacologically untreated depression. Of the 30,844 patients treated with duloxetine, there were no cases of hepatic-related injury or liver failure. Studies indicated, however, that there was a clinically significant higher hepatic injury with unclear etiologies in those treated with duloxetine compared to venlafaxine. Nevertheless, this was concluded to be the result of chance, as the incidence rate of hepatic injury with unclear etiologies for the placebo group and duloxetine group was equivalent (Lin et al., 2015).

- **Eosinophilic Pneumonia**
  - Eosinophilic pneumonia are a heterogenous group of diseases characterized by an increase in eosinophils in lung tissue of bronchoalveolar lavage fluid. The etiologies of eosinophilic lung disease include parasitic infections, medications, toxins, autoimmune, inflammatory disease, and malignancies (Allen & Wart,

2018). It commonly presents with onset of cough, fever, dyspnea, and night sweats. If left untreated, acute eosinophilic pneumonia can progress to respiratory failure (Pahal et al., 2020).

- The pathophysiology of duloxetine's effect on eosinophilic pneumonia is unclear; however, a number of cases have been reported on its occurrence.
- For example, a case report discusses a 32-year-old man who presented with a two-month history of worsening fever, chills, and cough despite oral antibiotic therapy. Chest radiograph demonstrated migrating, peripheral upper lobe infiltrates with a CBC count demonstrating eosinophilia. Transbronchial biopsy confirmed the diagnosis of eosinophilic pneumonia. Upon cessation of duloxetine, the patient's radiographic abnormalities, symptoms, and eosinophilia were reversed (Espeleta et al., 2007).
- Dr. Cummings states that he has never seen a case of eosinophilic pneumonia secondary to duloxetine.

Other Side Effects To Watch For:

- **Orthostatic Hypotension and Syncope**
  - Orthostatic hypotension and syncope are important side effects to consider because they can lead to falls and fractures in the elderly, who may already have multiple risk factors (e.g. gait instability, polypharmacy) that make them more liable to fall (Lipsitz, 1989; Verhaeverbeke & Mets, 1997). This also needs to be taken into account with the fact that SNRIs can cause or exacerbate hyponatremia, which affects the elderly more, as they have a higher risk of developing low sodium as compared to other age groups (Filippatos et al., 2017).
  - The hypotensive effects of SNRIs are poorly studied; however, it is hypothesized to be due to SNRI's overstimulation of presynaptic α2-adrenergic receptors, resulting in reduced noradrenaline outflow (Rivasi et al., 2020). Additionally, other studies have implicated that serotonin may cause long-term decrease in blood pressure (Watts et al., 2012).
  - Although studies have not indicated a higher occurrence of orthostatic hypotension in patients taking duloxetine (Nelson et al., 2013), they have implicated that duloxetine may lower orthostatic blood pressure by a small but significant amount.

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

- For example, an eight-week randomized study of over 300 patients (median age 72 years) showed that there was significant difference in the change in orthostatic systolic blood pressure between patients taking 60mg/day duloxetine and placebo (-2.45 vs 0.93) (Raskin et al., 2008).

- **Abnormal Bleeding**
  - It is thought that serotonin reuptake inhibitors increase the risk of abnormal bleeding by blocking the uptake of serotonin in platelets, thereby impairing platelet hemostatic response (Andrade et al., 2010).
  - However, studies have indicated mixed findings on duloxetine's effect on bleeding in vivo. For example, a recent meta-analysis indicated a significant increase in bleeding-related, treatment-emergent adverse events in those taking duloxetine 60 mg and 120 mg compared to the control group; it is worth mentioning that there was no significant difference in the bleeding incidences between the different dosages (Perahia et al., 2013).
  - On the other hand, one observational study of 350,000 patients indicated that there was no significant difference in incidences of upper GI bleeding between patients taking duloxetine and control group (Li et al., 2014).
  - Although rare, it is important to be aware of duloxetine's possibility for increased occurrence in abnormal bleeding and carefully review patients' medication regimen that may increase their chances for bleeding (i.e. anticoagulants, NSAIDs, antiplatelets).

- **Antidepressant Withdrawal Syndrome**
  - Antidepressant withdrawal syndrome (also referred to as antidepressant discontinuation syndrome) is defined by Haddad (2001) as:
    - Characteristic symptoms (i.e. flu-like symptoms, electric-shock-like symptoms, insomnia, nausea, etc.)
      - While the pathophysiology of withdrawal symptoms is still not fully understood, the best understood underlying mechanism is due to reduced serotonin levels as a result of decreasing levels of antidepressants Jha et al. (2018). This is supported by the quick resolution of withdrawal symptoms with reinitiation of the antidepressant or an increase in dosage. Other contributors that are thought to contribute to withdrawal symptoms include changes in glutamatergic and dopaminergic neurotransmission as well as involvement of the hypothalamic-pituitary-adrenal axis (Jha et al., 2018).

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

- Per Dr. Cummings, once SNRIs are discontinued, the ascending pain pathways that were once inhibited are now open. Since they haven't fully re-modulated, you have spontaneous firing of those neurons, which results in unpleasant "brain zaps" and "electric shocks."
    - A short duration that occurs soon after discontinuation of the medication or less commonly, in reduction in dosage
    - Shows rapid reversal on restarting the original medication
    - Is distinct from the condition the medication was prescribed for (e.g. depression)
    - Is not attributable to another cause
- Among SSRIs, discontinuation of paroxetine results in the greatest risk for withdrawal symptoms due to its short half-life (Jha et al., 2018). Among SNRIs, discontinuation of venlafaxine appears to result in the greatest risk for withdrawal symptoms (Fava et al., 2018). Among the randomized control trials and open trials that Fava et al. (2018) included in their systematic review, the rates of withdrawal symptoms from venlafaxine discontinuation ranged from 23% to 78%, from 17.2% to 55% for desvenlafaxine, from 6% to 55% for duloxetine, from 13% to 30% for milnacipran, and from 9% to 10% for levomilnacipran. The variability in withdrawal symptoms among SNRIs can be attributed to certain factors such as drug half-life (venlafaxine has a shorter half-life of 5 hours vs. duloxetine's longer half-life of 12 hours) and serotonin receptor receptivity (venlafaxine has a higher selectivity for the serotonin receptor vs. norepinephrine (30:1) vs duloxetine's (10:1) (Hou & Lai, 2014).
- A recent systematic review by Davies & Read (2019) found that the weighted average incidence rate of antidepressant rates was 56% (ranging from 27% to 86%) and 46% of those patients experiencing withdrawal symptoms described them as severe. A significant proportion of patients that experience withdrawal symptoms have symptoms for ≥2 weeks and some can even experience withdrawal symptoms for up to several months. These findings by Davies & Read (2019) suggest that withdrawal symptoms are not as mild nor as transient as commonly believed.
- In terms of tapering, Dr. Puder would even taper over a one-year period for patients that have been on these medications for years. At each appointment, he would make a small change and then wait six weeks to monitor symptom levels to know how to proceed. Also important during this time is engaging in other healthy behaviors like exercise, diet and therapy to have an optimum chance of

success off medications. When tapering off medications, it will be important to differentiate withdrawal symptoms vs. re-emergence of anxiety and depression.
    - It used to be dogma that if a patient recovered from MDD after a one year you could taper them off their antidepressant, but this was not true for everyone. Current recommendations are that if a patient has had three or more prior episodes of MDD, they should be on maintenance therapy (American Psychiatric Association, 2010; Bauer et al., 2015). Maintenance therapy can be done for five years or even indefinitely, especially in patients with great risk for recurrence (e.g. greater severity of prior episodes, family history of mood disorders, ongoing psychosocial stressors) (American Psychiatric Association, 2010; Bauer et al., 2015). Each episode of MDD increases the risk of recurrence by 16% and also increases the risk of treatment resistance (American Psychiatric Association, 2010). So be wary of taking a patient off of an antidepressant, as that would make their MDD more likely to relapse and more difficult to treat.
    - That being said, if a patient with long-term MDD really wants to get off their antidepressant, Dr. Puder recommends making sure that they are going through psychotherapy, optimizing their diet and exercising well. If all those things are going on, slowly taper them off the medication but monitor them frequently with care.
    - A meta-analysis by Karyotaki et al. (2016) looking at the long-term efficacy of psychotherapy and psychopharmacology versus monotherapy of either for MDD, found that combined therapy showed better response rates as compared to antidepressant monotherapy at six months or longer post-randomization. However, combined therapy had equivalent outcomes to psychotherapy alone in the long-term treatment of MDD, which allows more room for patient preference in the long-term treatment of the MDD.
    - Dr. Cummings would tell his patients to keep a daily log of their appetite, mood, energy because they can spot trends and patterns early while tapering off their antidepressants.

- **Activation of Mania/Hypomania**
    - Mania is described as a distinct period of anomaly and persistently elevated, expansive, or irritable mood and abnormally and persistently goal-directed behavior, or energy that last at least one week (American Psychiatric Association, 2013).
    - Most recent guidelines suggest that SSRI and SNRI treatments for bipolar disorder may have the potential to increase manic switching (Podawiltz 2012).

However, newer studies have indicated that there may also be an increased incidence of mania/bipolar disorder in patients who are treated with SSRI and SNRIs for unipolar depression.

- A retrospective study (n= 21,012) was done to assess the associations between different antidepressant therapy and the later onset of mania/bipolar disorder. The study results showed that duloxetine treatment increased incidences of later onset mania/bipolar disorder (13.8 per 1000 person) compared to other pharmacotherapies (average of 10.9 per 1000 person) (Patel et al., 2015).
- Interestingly, there have also been reports of hypomania and manic episodes following antidepressant cessation. Of the 24 cases reported, six cases responded to antimanic drugs and four cases were resolved with antidepressant reinstation (Narayan & Haddad, 2010).

- **Hyponatremia and SIADH**
  - Along with SSRIs, SNRIs are known to cause rare, but significant, hyponatremia in elderly patients with syndrome of inappropriate ADH (SIADH) as the most common mechanism (Filippatos et al., 2017).
  - The exact pathophysiology is unclear; however, one study proposed an interaction between the serotonergic pathway and SIADH by demonstrating that chronic administration of sertraline (SSRI) increased the levels of ADH and oxytocin in rats (de Magalhães-Nunes et al., 2007).
  - There is a case report of a 77-year-old woman who was prescribed duloxetine and was discontinued from ethyl loflazepate (to prevent worsening anxiety) the day before her symptoms began. The next morning, she took the oral dose and later developed headache and nausea. She then visited her physician where her systolic blood pressure was 170 but had normal vital signs otherwise. Her sodium level was 135. On the night of the second day, the headache and nausea returned. On the morning of the third day, she began to experience confusion, as well, and called emergency services. She was admitted to the hospital and presented with confusion but otherwise a normal physical exam; she had no signs of dehydration or focal deficits. Laboratory results revealed a serum sodium of 119 and urine sodium of 187. She was treated with sodium and normal saline drip which gradually improved her sodium level and level of consciousness (Yoshida et al., 2019).
  - Another case report discussed a 76-year-old woman who presented with abdominal pain, nausea, and constipation. On admission, she was taking aspirin, pantoprazole, polyethylene glycol, quinapril, and 30 mg duloxetine daily. During

initial lab analysis, she was found to have a serum sodium of 124 mmol/L. Her sodium later fell as low as 118 mmol/L while her thyroid panels and cortisol levels were unremarkable. She was given increasing doses of sodium up to 1 mg three times per day and showed no improvement. On further evaluation, they realized that duloxetine had been started two days prior to the patient's admission. Duloxetine was then discontinued and three days later the patient's serum sodium rose from 118 mmol/L to 129 mmol/L (Amoako et al., 2015).

- Increased dosage and increased age are two causes that increase the risk for hyponatremia in patients taking SNRIs (Filippatos et al., 2017). In practice, Dr. Cummings recommends checking electrolytes at baseline before pharmacotherapy and periodically measuring them once they are on the medication. Fortunately, hyponatremia does not evolve rapidly which means that most people tolerate their gradually evolving hyponatremia, unless the sodium level decreases below 120 mmol/L (Dineen et al., 2017). Symptoms of hyponatremia include lightheadedness, dizziness, confusion (if decline is rapid); in its most detrimental form, it can cause overt delirium, seizure, coma, all of which are exceedingly rare (Weissman et al., 2016).
- In some cases, serum sodium levels as low as 118 mmol/L have been reported in patients taking duloxetine; however, the adverse effect appeared reversible upon discontinuation of the causative SNRI. Elderly patients, those receiving diuretics or prone to dehydration, and those who are otherwise volume depleted (e.g., hypovolemia) appear to be at greatest risk (Kruüger & Lindstaedt, 2007).

- **Pregnancy and Breastfeeding**
  - Duloxetine is in FDA category "risk not ruled out," which means risk to fetal development is not clearly known. In animal reproductive studies, duloxetine demonstrated adverse effects on embryo/fetal development (Eli Lilly and Company, 2004).
  - Duloxetine appears to be safe in breastfeeding, except perhaps for the first few days of neonatal life, as the liver (main source of duloxetine clearance) does not function at full capacity when they are first born. Furthermore, per Dr. Cummings, only 2.3% of duloxetine gets into the breastmilk, which is a very small amount for breastfeeding (<10% is acceptable). However, due to the scarce studies existing on SNRIs and breastfeeding, no definitive conclusions can be drawn (Vitale et al., 2016).
  - One cohort study revealed that there had been a slight increase in relative risk for congenital malformations, cardiac malformations, preterm birth, a

small-for-gestational-age infant, preeclampsia, and postpartum hemorrhage in pregnant women taking duloxetine. However, the study concludes that duloxetine is unlikely to be a major teratogen, as these are small increases in risk of outcomes that are relatively uncommon (Huybrechts et al., 2020).

- The most recent meta-analysis also reported that exposure to duloxetine in the first trimester is not associated with increased relative risk for major congenital malformations (relative risk (RR) of 0.8) (Lassen et al., 2015).
- Duloxetine may very rarely cause neonatal pulmonary hypertension; however, overall risk factors for neonatal pulmonary hypertension are poorly understood (Delaney & Cornfield, 2012) . Among antidepressants, paroxetine has been specifically identified with cardiac malformation in neonates (Bérard et al., 2016).
- Dr. Cummings also adds that the major risk for all SSRIs and SNRIs is decreased fetal growth in the third trimester and increased risk for premature birth (Toh et al., 2009). In practice, he recommends that mothers continue to take their SSRIs/SNRIs and have fetal growth monitored by their obstetricians. He explains that the risk of relapse during pregnancy without antidepressant is 70% and denies myths that pregnancy is a protective factor against relapse (Cohen et al., 2006).

- **Very Low Risk for Seizures**
  - Among the first-generation antidepressants, the risk of seizures for TCAs at therapeutic doses are relatively high (0.4% to 1.2%) while no large studies have been done on the risk of seizures using MAOIs (Montgomery, 2005). Among second-generation and newer antidepressants (i.e. SSRIs, SNRIs), the risk of seizure is much lower (0.0% to 0.4%) as compared to TCAs and is not much higher than the incidence of first seizure in the general population (0.07% to 0.09%) (Montgomery, 2005).
  - Per the prescription insert, 0.03% of patients (3 out of 10,524) on duloxetine had seizures/convulsions while 0.01% (1 out of 7699) of patients treated with placebo had seizures/convulsions in placebo-controlled clinical trials (Eli Lilly and Company, 2004). In clinical trials involving 2418 patients, duloxetine had a seizure rate of 0.2% (Montgomery, 2005).
  - So while duloxetine is associated with a very low rate of seizures, there are two scenarios in which the risk of seizure is greatly increased in duloxetine usage, as well as almost all classes of antidepressants: medication overdose and initiation of the medication in patients with seizure history or predisposing factors to seizures (Eli Lilly and Company, 2004; Judge & Rentmeester, 2013; Montgomery,

2005). While the prescription insert already warns prescribers about starting duloxetine in a patient that has a seizure history or has predisposing factors to seizure, also take into account whether the patient has any risk factors for accidental or intentional overdosing (i.e. substance use disorder) (Bohnert et al., 2012; Eli Lilly and Company, 2004; Lyons et al., 2019).

- **No Significant Risk for Increased Blood Pressure**
  - As a noradrenergic agent, it makes sense theoretically that duloxetine would result in increased blood pressure. However, the following studies show otherwise:
    - Therapeutic doses of duloxetine showed no significant difference in blood pressure as compared to placebo; however, supratherapeutic doses of duloxetine (200 mg BID) showed an increase in mean heart rate (5.0 - 6.8 bpm) and supine blood pressure (4.7 - 6.8 mmHg systolic / 4.5 - 7.0 mmHg diastolic) as compared to placebo up to 12 hours after dosing (Eli Lilly and Company, 2004).
    - In a meta-analyses of 42 placebo-controlled studies, Wernicke, Lledo, & Raskin et al. (2007) found that for patients treated with duloxetine, there was a significant increase in mean systolic blood pressure of 0.65 mmHg and diastolic blood pressure of 0.88 mHg; however, there was not found to be a significant increase in sustained elevated blood pressure as defined by blood pressure of ≥140/≥90 mmHg or an increase in either systolic or diastolic blood pressure of 10 mmHg over 3 consecutive visits. In addition, patients with elevated blood pressure at baseline on duloxetine were not found to have increased risk for sustained elevated blood pressure as compared to placebo (Wernicke, Lledo, & Raskin et al., 2007).
    - In a 52-week, open-label clinical extension that followed a 13-week randomized, double-blind placebo period, the safety of duloxetine 60 mg BID was assessed and compared against routine care in patients with diabetic peripheral neuropathy (Wernicke, Wang, & Pritchett et al., 2007). Sustained elevation in blood pressure was defined as sitting blood pressure of ≥130/≥85 mmHg or an increase in either systolic or diastolic blood pressure of 10 mmHg over 3 consecutive visits (Wernicke, Wang, & Pritchett et al., 2007). There was not a significant difference observed in

blood pressure between the duloxetine and routine care groups (Wernicke, Wang, & Pritchett et al., 2007).

- In general, Dr. Cummings has seen blood pressure elevation occur in patients with essential hypertension. In these cases, it has been because of the increased adrenergic hormones during titration. So once again, titrate up slowly to give the patient's vascular tone time to adapt.

- **Akathisia**
  - Akathisia is defined as a feeling of restlessness and an urgent need to move. Subjective symptoms include inner tension, anxiety, panic, irritability, discomfort, and sleeplessness (Patel & Marwaha, 2020). On physical examination, irresistible leg movements, difficulty sitting and standing, rubbing or rocking while sitting, vocalizations such as grunting or moaning, or repetitive movements may be seen (Patel & Marwaha, 2020).
  - Although akathisia is classically seen in those taking antipsychotics, it can also present from antidepressants, antiepileptics, anticholinergics, sympathomimetics, calcium channel blockers, lithium, and antiparkinson drugs (Duma & Fung, 2019; Sachdev, 1995).
  - Akathisia seems to be worse in those with renal disease, diabetes, hyperthyroidism, iron anemia, Parkinson's Disease, and peripheral neuropathy. Diagnosis is usually through the Barnes Akathisia Rating Scale (BARS) (Salem et al., 2017).
  - Per Dr. Cummings, the pathophysiology behind akathisia in duloxetine and other SNRIs/SSRIs is through its serotonergic effects on the nigrostriatal pathway which leads to a decrease in dopamine release (Salem et al., 2017).
  - One observational study (n=1250) showed that among 58 different antidepressants, duloxetine had an increased relative odds ratio for akathisia (1.15) (Revet et al., 2020).
  - Akathisia usually presents in days to weeks of starting pharmacotherapy or increase in its doses (Salem et al., 2017). Therefore, temporal information is very helpful when working up causes for akathisia.
  - In Dr. Puder's practice, he considers medication-induced akathisia in all of his new patients that present with anxiety.
  - Another pearl is that restless leg has similar pathology to akathisia.

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

The Contraindications and Serious Considerations of Duloxetine

- Concomitant usage of monoamine oxidase inhibitors (MAOIs) due to increased risk of serotonin syndrome (Eli Lilly and Company, 2004).
    - Serotonin syndrome is a potentially life-threatening drug reaction that is a result of excessive serotonin (Boyer & Shannon, 2005). Symptoms can range from tremors and diarrhea in milder cases to the classic triad of altered mental status, autonomic hyperactivity (e.g. hyperthermia, tachycardia), and neuromuscular abnormalities (e.g. hyperreflexia, clonus, hypertonia) in severe cases (Boyer & Shannon, 2005).
    - Patients must discontinue MAOIs usage for at least 14 days before starting duloxetine (Eli Lilly and Company, 2004).
    - Patients should also discontinue duloxetine for at least five days before starting an MAOI (Eli Lilly and Company, 2004).
    - In addition to avoiding MAOIs, linezolid and methylene blue should also be avoided due to increased risk of serotonin syndrome (Cipriani et al., 2012).
- Uncontrolled, acute angle-closure glaucoma due to increased risk of mydriasis on duloxetine (Eli Lilly and Company, 2004).
    - Certain SNRIs (i.e. venlafaxine and duloxetine) and SSRIs (i.e. fluvoxamine, paroxetine and escitalopram) have been reported to cause acute angle-closure glaucoma. Possible mechanisms include the mydriatic effect of increased serotonin, weak adrenergic effects, weak anticholinergic effects and supraciliary effusions that lead to the anterior displacement of the lens-iris diaphragm (Chen et al., 2016; de Guzman et al., 2005; Eke & Bates, 1997; Shifera et al., 2014; Zelefsky et al., 2006).
- Not recommended for patients with hepatic impairment, substantial alcohol use, or chronic liver disease (Eli Lilly and Company, 2004).
    - Duloxetine is hepatically dependent for metabolization (i.e. 2D6 and 1A2) and elimination (Eli Lilly and Company, 2004; Gupta et al., 2007; Knadler et al., 2011).
    - The Child-Pugh score (aka Child-Pugh-Turcotte score) was originally designed for liver transplant patients to categorize their severity of cirrhosis and predict their mortality (Tsoris & Marlar, 2020). This scoring system divided patients into three categories based on five criteria: serum bilirubin, serum albumin, ascites, neurological disorder (i.e. encephalopathy), and clinical nutrition status. Clinical

nutrition status was later replaced by prothrombin time. Each of the five criteria were scored from 1 to 3 with 3 being the most severe.
    - Child-Pugh A is 5 to 6 points. This means that the patient's liver function is okay and that there isn't a need to adjust medications that rely on hepatic metabolism.
    - Child-Pugh B is 7 to 9 points. This means that there is moderate hepatic impairment and adjustments to medications need to be made if they rely on hepatic metabolism.
    - Child-Pugh C is 10 to 15 points. This means terminal liver failure and duloxetine is contraindicated in this circumstance, as are other antidepressants. Dr. Cummings notes that this is not really a case that most psychiatrists will deal with, as category c patients are terminally ill and would be in a more critical care setting or in hospice.
  - During the clinical trials for duloxetine, six patients with cirrhosis (Child-Pugh B) that took a single dose of duloxetine 20 mg PO had a mean plasma duloxetine exposure that was 5x higher and a mean plasma duloxetine clearance about 15% that of age- and sex-matched healthy patients (Eli Lilly and Company, 2004; Knadler et al., 2011). Elimination (i.e. half-life) of duloxetine also took about three times longer in these patients as compared to age- and sex-matched healthy patients, although C_{max} (maximal plasma concentration) was about the same for both populations (Eli Lilly and Company, 2004; Knadler et al., 2011).
- Not recommended for patients with severe renal dysfunction (i.e. end stage renal disease or severe renal impairment with estimated creatinine clearance <30 mL/min).
  - Duloxetine and its metabolites are renally excreted and in patients with severe renal disease, this can result in significantly elevated plasma levels of duloxetine and its metabolites (Eli Lilly and Company, 2004). Thus, patients with mild to moderate renal dysfunction should be closely monitored on duloxetine and patients with ESRD should avoid duloxetine all together.
  - Per Dr. Cummings, if a patient has moderate renal impairment (chronic kidney disease (CKD) stage 3 with GFR between 30-59), they need to be on a lower dose of duloxetine and the dosage should not be higher than 80 mg daily. If the patient has CKD stage 4 (GFR 15 to 29), they should not be on higher than 40 mg of duloxetine daily. If the patient has ESRD on dialysis or CKD stage 5 (GFR <15), they should not be on duloxetine.
  - By and large, patients with ESRD and moderate to advanced CKD are often excluded from large antidepressant trials due to safety concerns, which has led to a lack of data on the safety of antidepressants in this patient population

Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

(Hedayati et al., 2012). While there is limited data on the effects of duloxetine in patients with ESRD, there is some data from the clinical trials for duloxetine. Patients with ESRD receiving chronic intermittent hemodialysis that took a single dose of duloxetine 60 mg PO had approximately double the C_{max} and AUC (bioavailability) as compared to patients with normal renal function (Eli Lilly and Company, 2004).

- Most antidepressants, like duloxetine, are hepatically metabolized and their metabolites are renally excreted (Hedayati et al., 2012). Therefore, in choosing which antidepressant to use in this patient population, take into consideration the patient's medical history and the specific side-effect profile of the antidepressant. For example, ESRD and CKD is often comorbid with cardiovascular disease and so sertraline with its more favorable cardiovascular safety profile among antidepressants could be a consideration in an applicable patient (Glassman et al., 2002).

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Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

DAVID PUDER, M.D.
PSYCHIATRY & PSYCHOTHERAPY

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Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

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Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

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Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

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Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

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Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

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Episode 109: Duloxetine and the SNRIs Deep Dive Part 1

Harrison Bae B.S., Joseph Wong B.S., B.A., Michael Cummings M.D., David Puder, M.D.

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