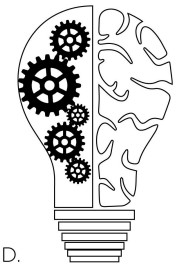
## Episode 091: Nortriptyline and the Tricyclic antidepressants

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




This PDF is a supplement to the podcast "Psychiatry & Psychotherapy" found on **iTunes**, **Google Play**, **Stitcher**, **Overcast**, **PlayerFM**, **PodBean**, **TuneIn**, **Podtail**, **Blubrry**, **Podfanatic**

There are no conflicts of interest for this episode.

In today's episode of the podcast, we'll be doing a deep-dive into nortriptyline, a lesser-talked about medication in psychopharmacology. We'll cover a little about the history of tricyclic antidepressants (TCAs) as well as the characteristics, side-effects, and indications to consider when prescribing this class of medication.

# History of TCAs

The development of TCAs, incidentally, was an outgrowth of research in the 1930s seeking to develop anti-histamines (e.g. diphenhydramine, promethazine). In the mid-1950s, Dr. Roland Kuhn, a Swiss psychiatrist, asked Geigy, a pharmaceutical company, if they had any new antipsychotic medications that he could try for his schizophrenic patients, as his hospital was no longer receiving a supply of the then expensive antipsychotic, chlorpromazine (Cahn, 2006; Steinberg & Himmerich, 2012). He received G22355, which we now know as imipramine, which had an identical chemical structure to chlorpromazine except for the difference in one side chain (Steinberg & Himmerich, 2012). In 1957, Dr. Kuhn described the effects of the first antidepressant, imipramine. Although it wasn't effective in treating psychotic symptoms, Dr. Khun was clued into the antidepressive effects of imipramine due to two things: patients with bipolar depression became more manic and patients with prominent typical depressive symptoms (i.e. neurovegetative symptoms such as decreased sleep, appetite and energy) got remarkably better (Kuhn, 1957).

# TCAs: characteristics, side effects and contraindications

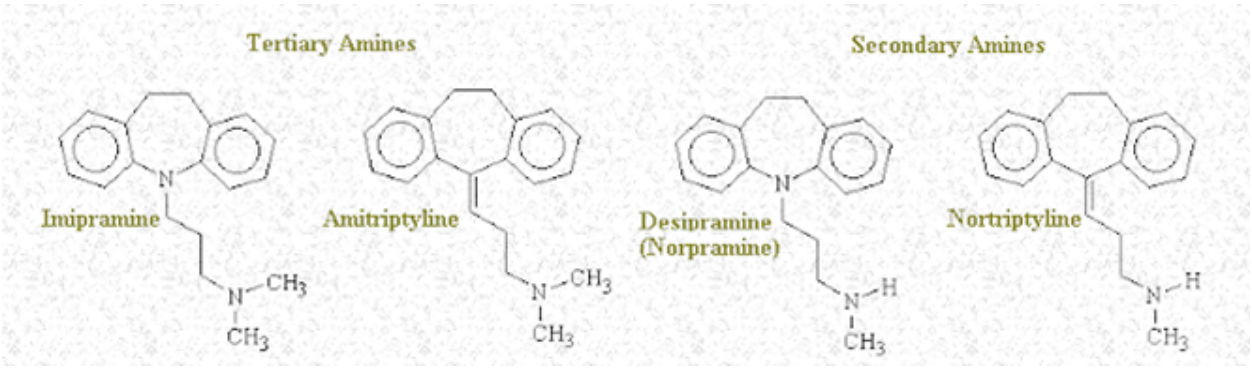
Tricyclic antidepressants are named after their chemical structures, which show three cyclic rings with varying side chains. TCAs can be classified according to the differences in their side chain amines (i.e. tertiary, secondary). Tertiary amines (e.g. imipramine, amitriptyline) have

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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

three methyl groups (CH3), as shown below, while secondary amines (e.g. nortriptyline, desipramine) have two methyl. Thus, if you demethylate amitriptyline, it becomes nortriptyline, and if you demethylate imipramine, it becomes desipramine.




**Chemical structures of tertiary and secondary amines**

This slight difference in chemical structure has tremendous effects on the characteristics and side-effect profiles of tertiary and secondary amines. Tertiary amines have more anticholinergic effect, more alpha receptor antagonism, and more serotonin receptor reuptake inhibition compared to secondary amines. Secondary amines (e.g. nortriptyline, desipramine) have more norepinephrine reuptake inhibition (Gillman, 2007).

The TCAs vary among themselves with regard to reuptake inhibition of serotonin (5-HT) and norepinephrine (NE). Desipramine and amitriptyline have a 1:2 5-HT to NE reuptake inhibition ratio and are thus more noradrenergic than serotonergic. Nortriptyline has 10x more NE reuptake inhibition compared to 5-HT.

# Side effects:

TCAs owe their side effects to the blockade of four types of receptors (David & Gourion, 2016; Stahl, 2013; Trindade, Menon, Topfer, & Coloma, 1998).

- Anti-muscarinic cholinergic:
    - Dry mouth and eyes due to decreased salivation and lacrimation
    - Blurred vision due to cycloplegia and mydriasis
    - Urinary retention due to inability of smooth muscles in the ureters and bladder to relax
    - Constipation due to decreased motor activity of the gut
    - Hyperthermia due to decreased sweating
    - Tachycardia

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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

- Anti-H1 histaminic:
    - Sedation and drowsiness
    - Weight gain and increased appetite
- Anti-alpha-1 adrenergic:
    - Orthostatic hypotension
    - Reflex tachycardia due to hypotension
    - Headaches and dizziness
- Blockade of voltage-sensitive sodium channels:
    - Central nervous system dysfunction (Landmark, Henning, & Johannessen, 2016)
        - Coma
        - Seizures
    - Cardiac dysfunction due to inhibited cardiac conduction (impaired depolarization at AV node and bundle of His) (Fanoe et al., 2014)
        - Arrhythmias that can lead to fatal arrest (e.g. torsades de pointes)
            - EKG shows widening of QRS and prolongation of QT interval

The likelihood of the side effects of a TCA increases as the dosage given increases and/or the plasma concentration increases. At 10 - 25 mg dosages, said side-effects are not common, but at 75 - 100 mg, they are certain. According to Dr. Cummings, above 25 - 50 mg q. day, you will definitely start to see side effects.

# Contraindications:

- Usage of monoamine oxidase inhibitors (MAOIs), linezolid, IV methylene blue due to increased risk of serotonin syndrome (e.g.) (Nortriptyline package insert, 2019)
    - Patients must discontinue MAOI 14 days before starting a TCA
    - Risks and benefits need to be weighed for usage of other serotonergic drugs (e.g. tramadol, buspirone)
- Hypersensitivity reaction to TCAs (Nortriptyline package insert, 2019)
- Family history of QT prolongation or sudden cardiac death (e.g. Brugada syndrome) (Bebarta et al., 2007)
    - Nortriptyline contraindicated in recent myocardial infarction (Nortriptyline package insert, 2019)

# Other important considerations:

- Increased risk for acute angle-closure glaucoma in patients with anatomically narrow angles due to mydriasis caused by anticholinergic effect (Lieberman & Stoudemire, 1987)

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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


- Increased risk for seizures in patients with history of seizures as certain TCAs (e.g. amoxapine) are proconvulsant (Landmark, Henning, & Johannessen, 2016)
- Increased risk of suicidal thinking and behavior (suicidality) in 18 - 24 year olds (blackbox warning) (Nortriptyline package insert, 2019)
    - This adverse effect may be true of all antidepressants because, early on in antidepressant treatment, a patient's neurovegetative symptoms improve earlier than their mood. So while a person with depression that has decreased energy may not act on their suicidal thoughts, a person with depression that is now more energized is at greater risk of suicide. So during early treatment for all antidepressants, bring back the patient sooner than later to assess for increased suicidality (i.e. rather than a 1 month follow-up, follow up in 1-2 weeks).
- TCAs have a narrow therapeutic index
    - The LD50 (amount it takes to be lethal in 50% of persons) is only about 6-8x the therapeutic plasma concentration. Therefore, caution must be taken for patients prone to overdose (so if you know a patient has a history of overdose, choose an alternative medication but absolutely don't give them a 90 day supply).
- TCAs are metabolized by CYP450 2D6
    - Caution should be taken in patients with hepatic injury. Among the TCAs, clomipramine had the highest rates of drug-induced hepatic injury (Friedrich et al., 2016).
    - Taking TCAs concomitantly with 2D6 inhibitors (strong 2D6 inhibitors include Paroxetine, Fluoxetine, Bupropion) will result in higher plasma concentrations than expected for a given dose (Nortriptyline package insert, 2019). When TCA plasma levels increase, the patient may look depressed, but it may actually be a hypoactive delirium (sedated, confused, weak) due to the anticholinergic effect on the sensorium.
    - Thus, it is worthwhile to measure plasma concentration of nortriptyline because people also inherently have different metabolic rates. According to Dr. Cummings, the average half-life of nortriptyline is 27 hours, but the range can be from 18 to 44 hours depending on how much 2D6 the person has. Since it takes about 5 half lives to reach steady state, it may take a week or two to see the effects of the medication.

# Indications for nortriptyline (and TCAs)

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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

Nowadays, TCAs are not first-line treatments, but there are several conditions and situations in which TCAs are effective and could be considered.


# Depression

TCAs are FDA-approved for the treatment of depression and have been shown to be effective in treating depression. However, the dose of TCAs required to show antidepressant efficacy (50-150 mg q. day) is associated with significant side effects. In a meta-analysis of the efficacy of TCAs and selective serotonin reuptake inhibitors (SSRIs) vs. placebo in treating depression in the primary care setting, TCAs and SSRIs were both found to be more efficacious compared to placebo. However, TCAs were much less tolerated than SSRIs due to their side effects (Arroll et al., 2005). Thus, since SSRIs came out, the use of TCAs for major depressive disorder (MDD), anxiety, and panic has decreased dramatically.

Although SSRIs have replaced TCAs as a first-line treatment for depression, TCAs are still used in treating treatment-resistant depression (TRD). In a study of the use of nortriptyline in TRD (n = 92 that had not responded to 1-5 trials of antidepressants), 40% showed improvement after 6 weeks of nortriptyline as defined by a >50% decrease of baseline Hamilton Rating Scale for Depression (HAM-D) score, and 12% had remission of their symptoms (Nierenberg et al. 2003). Although nortriptyline was shown to be effective for a significant proportion of the patients with TRD, a third of the patients were unable to complete the trial due to side effects. A study of TRD treatment approaches suggests that if a patient is not responsive to the initial SSRI, then they should be switched to venlafaxine or another SNRI (e.g. duloxetine, milnacipran, or levomilnacipran), then they should be switched to a TCA or, if that is not tolerated, combine mirtazapine with a SSRI or venlafaxine, or other SNRI. The TCA should be reserved as a third-line treatment.

# Neuropathic pain

TCAs have been shown to be effective in the off-label treatment of neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia, postmastectomy pain) due to their ability to inhibit reuptake of serotonin and norepinephrine. In a study comparing the efficacy of nortriptyline vs amitriptyline in treating masticatory myofascial pain (MFP), both TCAs were shown to be effective, but nortriptyline was shown to be more efficacious than amitriptyline in terms of post-treatment pain scores, and was associated with fewer side effects and greater tolerability (Haviv, Zini, Sharav, Almoznino, & Benoliel, 2019).

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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


Serotonin–norepinephrine reuptake inhibitors (SNRIs) and TCAs have the same mechanism of action, and are also useful treating neuropathic pain. However, in treating neuropathic pain, TCAs have been shown to be more efficacious compared to SNRIs, which are more effective than SSRIs (Sindrup, Otto, Finnerup & Jensen, 2005). Thus, while the inhibition of noradrenergic reuptake appears to be most important in treating neuropathic pain, there is likely a multimodal mechanism of action of TCAs that includes blockade of other receptors (e.g. NMDA, calcium channels) that explains their increased efficacy compared to SNRIs (Sindrup, Otto, Finnerup & Jensen, 2005).

According to Dr. Cummings, another reason why you see better efficacy of TCAs compared to SNRIs is that TCAs have increased antihistaminic effect, which slightly sedates the patient. So aside from directly inhibiting ascending pain pathways with norepinephrine, you're also dulling the cortical ability to appreciate pain, which creates an increased subjective feeling of pain relief as compared to SNRIs. So, it may be appropriate for neuropathic pain patients on SNRIs with inadequate response or sleep problems due to nocturnal pain to start nortriptyline at a low dose (10-25 mg) at bedtime.

## Fibromyalgia

A wide variety of medication classes have been used to treat fibromyalgia including antidepressants (SSRIs, SNRIs, TCAs, MAOIs), anti-epileptics, opioids, muscle relaxants, and NSAIDs. According to Mease (2005), amitriptyline, doxepin, and cyclobenzaprine were the most commonly-used medications for fibromyalgia in the US. TCAs as compared to placebo were shown to greatly improve pain, sleep quality, fatigue, tenderness, and stiffness (Mease, 2005). These conclusions were further bolstered by Häuser, Bernardy, Üçeyler & Sommer (2009), who, while looking at 18 randomized control trials involving 1,427 participants, found that the effect size for pain reduction among the antidepressants tested was largest for TCAs (e.g. amitriptyline), followed by MAOI, and then by SNRIs and SSRIs. There were also large effect sizes of TCAs (e.g. amitriptyline) for reducing fatigue and sleep disturbances (Häuser, Bernardy, Üçeyler & Sommer (2009).

## ADHD

In a review of TCA usage in treating ADHD, Raleigh & Garner (2015) looked at three double-blind, randomized, controlled trials (n = 125) that found desipramine and nortriptyline were superior as compared to placebo in reducing ADHD symptoms, according to the Clinical Global Impression (CGI) scale (odds ratio = 18.50; 95% confidence interval [CI], 6.29 to 54.39. Number needed to treat to benefit one additional person was two). Although TCAs have been

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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

found more efficacious than placebo in reducing ADHD symptoms, they are not the recommended treatment for ADHD in children and adolescents as they are not FDA-approved for that purpose. Stimulants, which are FDA-approved for ADHD, are first-line.


## Smoking cessation

TCAs are a second-line option for smoking cessation, behind nicotine replacement therapy, bupropion, and varenicline (Nides, 2008). Antidepressants such as TCAs, SNRIs and SSRIs may help in smoking cessation as they may take the place of nicotine's antidepressant effects in smokers dependent on nicotine for that purpose, and may have a neuromodulatory effect on the neural pathways that support nicotine addiction (Hughes, Stead, Hartmann-Boyce, Cahill & Lancaster, 2014). In a systematic review of the usage of antidepressants in smoking cessation by Hughes, Stead, Hartmann-Boyce, Cahill & Lancaster (2014), there is moderate-quality evidence that nortriptyline used as sole pharmacotherapy significantly increased long-term smoking cessation (six trials, N = 975, RR 2.03, 95% CI 1.48 to 2.78), and that based on a limited amount of data from direct comparisons, bupropion and nortriptyline appear to be equally effective and of similar efficacy to nicotine replacement therapy (NRT) (bupropion versus nortriptyline 3 trials, N = 417, RR 1.30, 95% CI 0.93 to 1.82; bupropion versus NRT 8 trials, N = 4096, RR 0.96, 95% CI 0.85 to 1.09; no direct comparisons between nortriptyline and NRT).

## Parkinson's disease

Although depression is not a key symptom of Parkinson's disease (PD), it has a well-established association with PD (Csoti, Herbst, Urban, Woitalla & Wüllner, 2019). In a randomized, placebo-controlled trial comparing paroxetine and nortriptyline to a placebo in 52 patients with PD and depression, nortriptyline was found superior to paroxetine and placebo in several aspects: reduction in depressive symptoms according to the HAM-D scale, response rates, sleep, anxiety and social functioning (Menza et al., 2009). Nortripyline's efficacy in treating depression associated with PD can be attributed to its unique receptor activity. It's mostly-noradrenergic activity helps boost cognition and alertness, and its slightly anticholinergic activity helps with the motor symptoms of PD (Csoti, Herbst, Urban, Woitalla & Wüllner, 2019). The efficacy of nortriptyline in treating PD-associated depression was further supposed by a meta-analysis by Liu et al. (2013), which showed that TCAs (e.g. nortriptyline) had the greatest antidepressant efficacy, followed by pramipexole and SNRIs, then SSRIs.

## Migraines

TCAs have been known to be effective in preventing headaches since 1964 (Lance & Curran, 1964). In a meta-analysis by Jackson et al. (2010), TCAs were found to be equally effective in treating tension headaches, migraines and mixed headaches with patients reporting 1 standard

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

deviation of improvement in headache burden. However, the beneficial effects of TCAs for headaches was found to increase over time (more efficacious at 6 months compared to 1 month), which suggests that they need to be taken for several months to reach their full efficacy. In another meta-analysis of 13 studies looking at the efficacy of various pharmacological treatments for vestibular migraines, including anti-epileptics, calcium channel blockers, TCAs, beta-blockers and SNRIs, beta-blockers were associated with the largest reduction in dizziness and frequency of monthly vertigo attacks while 68.25% of patients on TCAs (95% CI: 54.02 to 80.35) and 76.67% of patients on calcium channel blockers (95% CI: 67.36 to 84.40) reported >50% improvement in symptoms (Byun, Levy, Nguyen, Brennan & Rizk, 2020).

# Clinical pearls and key takeaways

- Know the 3 most potent 2D6 blockers, which affect TCA metabolism: Paroxetine, Fluoxetine, Bupropion
- TCAs have a narrow therapeutic window and 6-8x the therapeutic dose can get into a toxic range that kills 50% of people (LD50). Thus, don't give a 90-day supply of TCAs to patients that have a history of overdose
- For treating pain, smaller doses of TCAs (10-25 mg) are effective and are less likely to bring about negative side effects
- If you have any suspicion that a patient is a poor 2D6 metabolizer, don't hesitate to get a plasma concentration, which is much more accurate than using prescribed dosages to assume effective drug concentration
- If you are using a TCA, use a secondary amine (e.g. nortriptyline, desipramine) as compared to a tertiary amine (e.g. imipramine, amitriptyline) as tertiary amines are much less tolerable and have active metabolites, making it easier to make a person toxic if their hepatic metabolism is impaired (by D26 inhibitors or by poor liver function)

# References

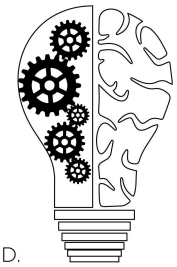
Cahn, C. (2006). Roland Kuhn, 1912–2005. *Neuropsychopharmacology*, *31*(5), 1096-1096.

Steinberg, H., & Himmerich, H. (2012). Roland Kuhn-100th Birthday of an Innovator of Clinical Psychopharmacology. *Psychopharmacology bulletin*, *45*(1), 48–50.

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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



DAVID PUDER, M.D.
PSYCHIATRY & PSYCHOTHERAPY

KUHN R. (1957). Uber die Behandlung depressiver Zustände mit einem Iminodibenzylderivat (G 22355) [Treatment of depressive states with an iminodibenzyl derivative (G 22355)]. *Schweizerische medizinische Wochenschrift*, *87*(35-36), 1135–1140.

Gillman, P. K. (2007). Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *British journal of pharmacology*, *151*(6), 737-748.

David, D. J., & Gourion, D. (2016). Antidepressant and tolerance: determinants and management of major side effects. *L'Encephale*, *42*(6), 553.

Stahl, S. M. (2013). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (4th ed.). Cambridge University Press.

Trindade, E., Menon, D., Topfer, L. A., & Coloma, C. (1998). Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. *Cmaj*, *159*(10), 1245-1252.

Landmark, C. J., Henning, O., & Johannessen, S. I. (2016). Proconvulsant effects of antidepressants—What is the current evidence?. *Epilepsy & Behavior*, *61*, 287-291.

Fanoe, S., Kristensen, D., Fink-Jensen, A., Jensen, H. K., Toft, E., Nielsen, J., ... & Bundgaard, H. (2014). Risk of arrhythmia induced by psychotropic medications: a proposal for clinical management. *European heart journal*, *35*(20), 1306-1315.

Nortriptyline (Pamelor) [package insert]. Hazelwood, MO: Mallinckrodt Inc; 2019

Bebarta, V. S., Phillips, S., Eberhardt, A., Calihan, K. J., Waksman, J. C., & Heard, K. (2007). Incidence of Brugada electrocardiographic pattern and outcomes of these patients after intentional tricyclic antidepressant ingestion. *The American journal of cardiology*, *100*(4), 656-660.

Lieberman, E., & Stoudemire, A. (1987). Use of tricyclic antidepressants in patients with glaucoma: Assessment and appropriate precautions. *Psychosomatics*, *28*(3), 145-148.

Friedrich, M. E., Akimova, E., Huf, W., Konstantinidis, A., Papageorgiou, K., Winkler, D., ... & Kasper, S. (2016). Drug-induced liver injury during antidepressant treatment: results of AMSP, a drug surveillance program. *International Journal of Neuropsychopharmacology*, *19*(4).

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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


Arroll, B., Macgillivray, S., Ogston, S., Reid, I., Sullivan, F., Williams, B., & Crombie, I. (2005). Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *The Annals of Family Medicine*, *3*(5), 449-456.

Tundo, A., de Filippis, R., & Proietti, L. (2015). Pharmacologic approaches to treatment resistant depression: evidences and personal experience. *World journal of psychiatry*, *5*(3), 330.

Nierenberg, A. A., Papakostas, G. I., Petersen, T., Kelly, K. E., Iacoviello, B. M., Worthington, J. J., ... & Fava, M. (2003). Nortriptyline for treatment-resistant depression. *The Journal of clinical psychiatry*.

Sindrup, S. H., Otto, M., Finnerup, N. B., & Jensen, T. S. (2005). Antidepressants in the treatment of neuropathic pain. *Basic & clinical pharmacology & toxicology*, *96*(6), 399-409.

Haviv, Y., Zini, A., Sharav, Y., Almoznino, G., & Benoliel, R. (2019). Nortriptyline Compared to Amitriptyline for the Treatment of Persistent Masticatory Myofascial Pain. *Journal of Oral & Facial Pain & Headache*, *33*(1).

Mease, P. (2005). Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *The Journal of rheumatology Supplement*, *75*, 6-21

Heymann, R. E., Helfenstein, M., & Feldman, D. (2001). A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. *Clinical and experimental rheumatology*, *19*(6), 697-702.

Häuser, W., Bernardy, K., Üçeyler, N., & Sommer, C. (2009). Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *Jama*, *301*(2), 198-209.

Raleigh, M. F., & Garner, K. K. (2015). Tricyclic Antidepressants for the Treatment of ADHD in Children and Adolescents. *American family physician*, *92*(5), 352-353.

Nides, M. (2008). Update on pharmacologic options for smoking cessation treatment. *The American journal of medicine*, *121*(4), S20-S31.

Hughes, J. R., Stead, L. F., Hartmann-Boyce, J., Cahill, K., & Lancaster, T. (2014). Antidepressants for smoking cessation. *Cochrane database of systematic reviews*, (1).

Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.

## Episode 091: Nortriptyline and the Tricyclic antidepressants

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


Csoti, I., Herbst, H., Urban, P., Woitalla, D., & Wüllner, U. (2019). Polypharmacy in Parkinson's disease: Risks and benefits with little evidence. *Journal of Neural Transmission*, *126*(7), 871-878.

Menza, M., Dobkin, R. D., Marin, H., Mark, M. H., Gara, M., Buyske, S., ... & Dicke, A. (2009). A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology*, *72*(10), 886-892.

Liu, J., Dong, J., Wang, L., Su, Y., Yan, P., & Sun, S. (2013). Comparative efficacy and acceptability of antidepressants in Parkinson's disease: a network meta-analysis. *PloS one*, *8*(10), e76651.

Lance, J. W., & Curran, D. A. (1964). Treatment of chronic tension headache. The Lancet, 283(7345), 1236-1239.

Jackson, J. L., Shimeall, W., Sessums, L., DeZee, K. J., Becher, D., Diemer, M., ... & O'Malley, P. G. (2010). Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMj*, *341*, c5222.

Byun, Y. J., Levy, D. A., Nguyen, S. A., Brennan, E., & Rizk, H. G. (2020). Treatment of Vestibular Migraine: A Systematic Review and Meta‐analysis. *The Laryngoscope*.


Copyright: David Puder, M.D., 2020, Please share this without changing any of the content.