



the PRUDENT prescriber

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Antidepressants for Chronic Pain?

In its most recent guidance on the management of chronic pain, the UK National Institute for Health and Care Excellence (NICE) evaluated the benefits and harms of medications used for chronic pain. Antidepressants were the only drugs where this balance proved favorable and NICE recommended clinicians “consider” their use because of the current gaps in the science of pain management.

In February 2023, Ferreira in the [BMJ](#) (2023, February 1) conducted an overview of 26 systematic reviews in which any antidepressant drug was compared with placebo for any pain condition in adults. There were 156 unique trials (44% were industry sponsored) involving more than 25,000 participants. The reviewers reported on the efficacy of eight antidepressant classes covering 22 pain conditions. There was a total of 42 distinct comparisons.

Results

- No review provided high certainty evidence on the efficacy of antidepressants for pain for any condition.
- 11 comparisons for nine conditions were found where antidepressants were efficacious:
 - Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs e.g., duloxetine, desvenlafaxine, and milnacipran) were efficacious for back pain, postoperative pain, fibromyalgia, and neuropathic pain. (moderate certainty evidence)
 - Selective Serotonin Reuptake Inhibitors (SSRIs - (e.g., fluoxetine, sertraline, citalopram and more) were efficacious for depression with comorbid chronic pain, but NOT for back pain, fibromyalgia or functional dyspepsia.
- Tricyclic Antidepressants (TCAs - (e.g., amitriptyline, nortriptyline) were efficacious for irritable bowel syndrome, neuropathic pain, and chronic tension headache (low certainty evidence). TCAs were NOT efficacious for functional dyspepsia (moderate certainty evidence).
- For the other 31 comparisons, antidepressants were either not efficacious or evidence on efficacy was inconclusive.



My Take:

- In reviewing the data tables of this paper, it appears that duloxetine 60 mg to 120 mg per day (\$14/mo) is associated with the best evidence. (moderate certainty of evidence) in treating back pain, postoperative pain, fibromyalgia, and neuropathic pain. Desvenlafaxine - generic for Pristiq, not Khedezla (150-225 mg/d at \$15/mo) and Savella (milnacipran 200mg/day) at \$439 /month were equally effective for treating these conditions.
- Be careful in terms of interpreting these data, because 44% of the trials forming this evidence had ties to industry. This is particularly relevant for the evidence on the efficacy of SNRIs where 68% of the trials were identified as having industry ties.
- In an accompanying editorial Stannard and Wilkinson BMJ 2023 Feb1 suggest as my Irish grandmother would say, “Ca canny wi the butter.” Be prudent using antidepressants for pain. The editorialists suggest exercise and physical activity are useful adjuncts for people with pain. Further, they remind us that compassionate and consistent relationships with clinicians remain the foundations of successful care.

Post-Covid Conditions

We have been aware of post-infections syndromes since the Spanish influenza pandemic of 1918. The July 2023 Mayo Clinic Proceedings summarizes our knowledge to date about the Post-Covid Condition (PCC).

- PCC is common; it is estimated to occur in 20% to 40% of patients who experience Covid-19.
- PCC commonly involves fatigue, post-exertional malaise, dyspnea, memory loss, diffuse pain, and orthostasis. The challenge with diagnosis of PCC is uncertain terminology and diagnostic criteria. According to the CDC, post-acute sequelae of COVID-19 infection encompasses all patients with persistent symptoms beyond 28 days.
- The medical, psychosocial, and economic impacts of PCC have been immense. (are there any projections on the cost? I haven't seen anything in a bit)
- Risk factors for development of PCC are female gender and severity of acute Covid-19 infections.
- Proposed pathophysiologic mechanisms are myriad and include CNS inflammation, viral reservoirs, persistent spike protein, and auto- immunity.
- Evaluation should be comprehensive with a broad differential diagnosis of diseases that can masquerade as PCC. Routine laboratory tests, such as metabolic panels, CBCs, D-dimers, thyroid function studies, sed rates and C reactive proteins usually fail to reveal organ damage due to COVID-19, despite the persistence of function limiting symptoms.
- Treatments of PCC are little researched and are largely expert opinion. Therapies are symptom targeted: optimizing fluid intake, compression garments, progressive activity, medications, bio-feedback, cognitive rehabilitation, and attending to concomitant mood disorders.



- Prudence in evaluating these patients requires significant history-taking time as well as comprehensive laboratory studies; the latter likely resulting in few true positive and more false positive results.
- The authors propose use of naltrexone (generic Revia) and aripiprazole (generic Abilify) for treating post viral fatigue. They later mostly withdraw their support of both of these medicines claiming the

studies were limited by small size and poor design. The authors: “These medications should be prescribed with great caution to patients with PCC until more evidence emerges.”

Short and Sweet

Does enteric coating on aspirin reduce effectiveness or increase safety in patients with cardiovascular disease?

A post hoc analysis of over 10,000 patients with known cardiovascular disease, all taking aspirin, showed no significant difference in myocardial infarction, stroke, death or with lower G.I. bleeding risk comparing coated and uncoated aspirin, regardless of the dose. (JAMA Cardiol. October 4, 2023)

Optimizing Iron Absorption

In a small study of 34 healthy non-anemic, iron deficient females, each of whom served as their own control, researchers utilized 100 mg of radio- labeled ferrous fumarate. (Lancet Haematol. 2017;4). Compared with the control condition - *overnight fasting followed by a morning iron dose taken with water three hours before coffee or breakfast* - a morning dose taken with either 80 mg or 500 mg of ascorbic acid (vitamin C) significantly improved the iron absorbed by about 30%. All the other strategies reduced iron absorption: afternoon dosing reduced by 37%; co-administration with coffee in the morning reduced by 54%; administration in the morning with coffee and food reduced by 66%.

False Positive Rapid Antigen Tests for COVID-19

There is increasing evidence that rapid antigen tests for COVID-19 are not very sensitive and finding a negative result on a test does not give you much more information than you had before you did the test. On the other hand, what’s the prevalence of false positives? In a Canadian study, reported as a research letter in JAMA on January 7, 2022, utilizing over 900,000 rapid antigen tests, the number of false positive results was 462 (0.05% of those screened). How relevant are these results now that they are 22-month-old and a few variants ago?

Appendicitis Treated with Antibiotics: A Long-Term Follow-up

The Swedes have recently reported the longest follow-up of patients with acute appendicitis treated non-operatively. (JAMA Surg. 2023, August 9) This 25-year study presented the outcomes for 137 patients who were treated non-operatively in two early randomized trials conducted in the 1990s. The nonoperative approach failed 15% during the initial hospital admission and in another 25% who underwent appendectomy mostly in the first year after the initial clinical presentation. There were no cases of bowel obstruction or appendiceal tumors reported among those non-operated patients. My Take: Small “n” but great time of follow-up. Certainly, non-operative management of acute appendicitis is a reasonable game plan for residents of submarines and space stations. Should we be considering it more often in other clinical situations?

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