Anti-depressants in the Treatment of Chronic Pain

Chronic pain and depression have a shared neurobiology and neuro-anatomy. Recent studies have found that anti-depressants improve pain symptoms regardless of the presence or absence of co-morbid major depression.

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There are 4 points upon which there is broad consensus in the field and that we should discuss immediately:

- Major depression and chronic pain are common conditions, and they frequently overlap.[1,2] (See Figures 1 and 2.)
- Anti-depressants can improve symptoms of major depression, regardless of the presence or absence of co-morbid pain (though pain can reduce the chances of optimal recovery).[3,4]
- Anti-depressants improve pain symptoms regardless of the presence or absence of co-morbid major depression.[5-7]
- Chronic pain and major depression have a shared neurobiology and appear to have a shared neuro-anatomy (*in the brain and spinal column*) and neuro-chemistry (*norepinephrine and serotonin*), with similar hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), and inflammatory cytokine disturbances.[8-10]

Types of Anti-depressants: A Quick Primer for the Pain Physician

Numerous classes of anti-depressants (ADs) are available for physicians to prescribe. (See Figure 3.) However, it is clear from pre-clinical and clinical data that ADs are not equally efficacious in chronic pain management.[11] Broadly speaking, they can be classified into the following categories: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants (TCAs), norepinephrine-dopamine reuptake inhibitors (NDRIs), monoamine oxidase inhibitors (MAOIs), and atypical anti-depressants (an assortment of ADs with other mechanisms of action). All of these ADs have an important role in treating depression, but in the treatment of patients with chronic pain (with or without depression), 2 classes of anti-depressants stand out—TCAs and SNRIs.[11-13]

How Do Agents Reduce Pain?

TCAs and SNRIs share the ability to modulate the neurotransmission of both serotonin and norepinephrine. This appears to affect the pain circuitry both at the cerebral and at the spinal column level.[14,15] They also appear to modulate the functioning of the dorsolateral prefrontal cortex (DLPFC), insular cortex, amygdala, and hippocampus; as well as the descending pain pathway in the spinal column.[16,17] Because these areas of the brain are also affected in patients with major depressive disorders (MDDs),

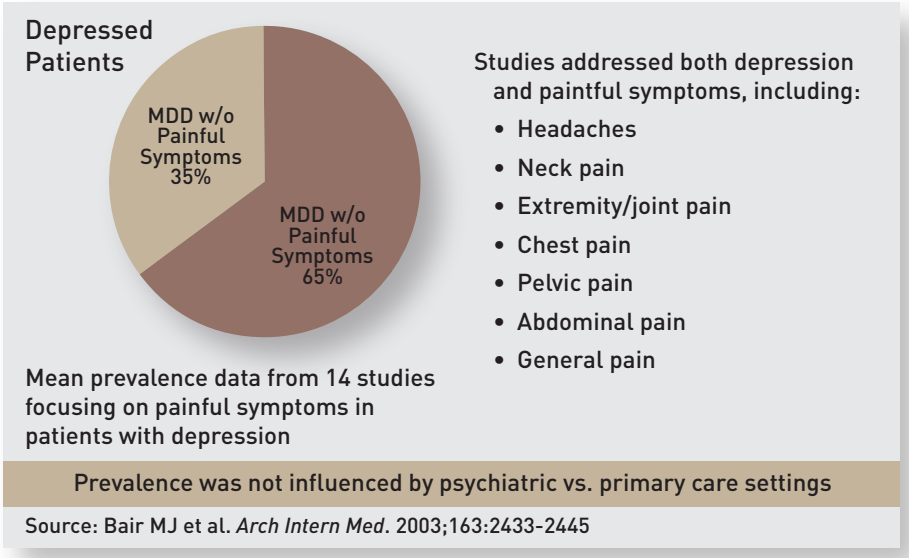
this may be the reason why these ADs have demonstrated efficacy in all 3 scenarios—in major depression alone, in major depression and chronic pain together, or in chronic pain alone.

Link Between Chronic Pain and Depression

In the last decade or so, emerging and persuasive evidence reveals that inflammation plays an important role in the pathogenesis of both clinical depression and chronic pain syndromes.[18] The common denominator of inflammation between chronic pain and clinical depression may partly explain why patients with clinical depression are more prone to develop chronic pain and vice versa. This provocative view is now well supported by emerging evidence from both fields of study—depression and chronic pain—and it partly explains why patients with one condition are more prone to develop the other condition.

Stress, anxiety, and depression—all states of heightened arousal—not only provoke emotional distress, but also destabilize the HPA axis.[19] Additionally, the ANS is often dysregulated in depression and chronic pain states. Finally, the cell-mediated immune system is also affected, resulting in over-production of inflammatory cytokines and diminished production of anti-inflammatory cytokines.[20-22] Interestingly, similar changes also occur in patients with chronic pain. There is good evidence that these changes (HPA axis, ANS, and cytokine deregulation) play an important role in creating clinical depression and destabilizing an individual's innate pain regulating system.[23,24]

Figure 1. Prevalence of Pain Is High in Patients with Major Depression



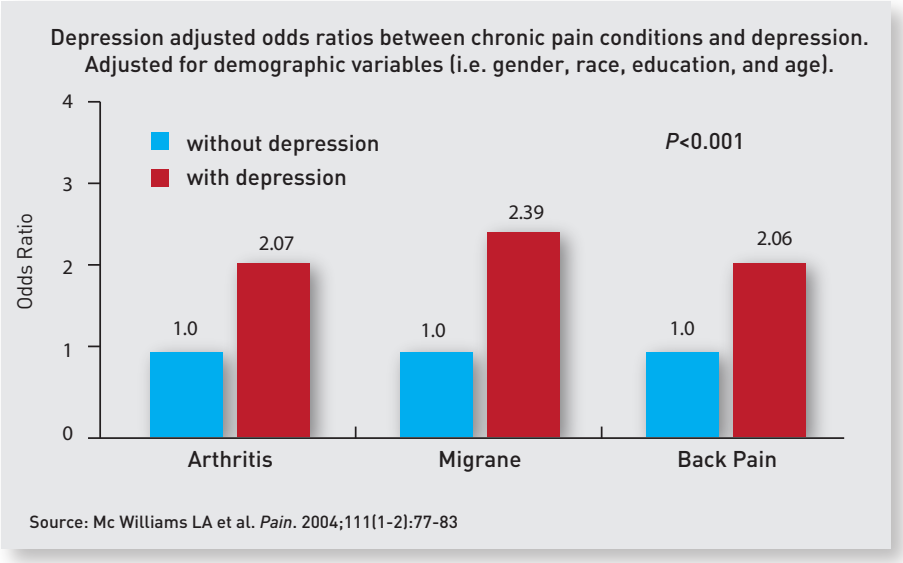
Anti-depressants as Anti-inflammatory Agents

Recent evidence indicates that ADs act as anti-inflammatory agents in both depression and chronic pain states.[25,26] Anti-depressant treatments zimprove the clinical symptoms of depression and chronic pain and appear to positively impact immune/cytokine deregulations. Research data indicate that ADs can reduce levels of inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6.[27-29] Other anti-depressant interventions that are non-pharmacological, such as cognitive behavioral therapy and physical exercise, interestingly also show the same positive and salutary effects on the immune/cytokine system.[30]

These findings raise an interesting question: Should anti-depressant use be limited to *only* those patients who have both chronic pain and depression? The answer to this question is *No*! Here's why:

- Both animal and pre-clinical data clearly show that anti-depressants (mostly the TCAs and SNRIs) have anti-nociceptive properties.[12]
- Multiple studies reveal that even in

Figure 2. Is Depression Commonly Co-morbid With Chronic Pain Conditions?



the absence of depression, these anti-depressants have efficacy in multiple chronic pain conditions irrespective of co-morbid chronic clinical depression.[31]

- In the last decade, based on multiple, large, well-conducted studies, many ADs have received US Food and Drug Administration (FDA) indication for various chronic pain conditions, even in the absence of clinical depression.[32,33]
- Obviously, the presence of significant and impairing depression in an individual with chronic pain calls for treatment with an AD. But the positive benefits of ADs—even in the absence of clinical depression—are worth keeping in mind.

When to Use for Pain

Physicians are faced with treating patients with multiple types of chronic pain—neuropathic pain, nociceptive pain, fibromyalgia, and mixed pain conditions. In a surprisingly large number of these conditions, we now have good clinical data revealing the effectiveness of anti-depressants (particularly TCAs and SNRIs). Some of the anti-depressants have FDA indications for certain pain conditions. Note this point from clinical trials: *ADs have broad efficacy in pain and depression.* A well-conducted study with an SNRI in a depressed population with or without co-morbid arthritis demonstrated this point.[4]

Fibromyalgia: Many anti-depressants have been used in this chronic pain condition. Currently, 2 SNRI anti-depressants have FDA approval in this condition—duloxetine and milnacipran. TCAs, particularly amitriptyline (not FDA-approved for this indication), are often used in clinical practice, and a large database reveals it's an efficacious intervention.[7,35,36]

Diabetic Peripheral Neuropathic Pain: Many anti-depressants have demonstrated effectiveness in managing the pain associated with diabetic peripheral neuropathic pain (DPNP).[6] This chronic pain condition has one FDA indicated AD for the management of pain associated with DPNP—duloxetine.[37]

Nociceptive pain: There is a long history regarding the use of ADs in the management of nociceptive pain, particularly with chronic low back pain and chronic painful osteoarthritis.[38] Recently, duloxetine, a SNRI anti-depressant received an indication for the management of chronic musculoskeletal pain, based on positive trials in chronic low back pain and chronic knee pain secondary to x-ray-proven osteoarthritis.[31]

Clinical Pearls

Several clinical "pearls" are offered in the hopes that using them will increase the odds of having a successful anti-depressant trial. We offer 6 clinical pearls below: psycho-education, be aware of drug-drug interactions, titrate slowly, pay attention to managing side effects, optimize dose, and taper carefully when stopping medication treatment.

Psycho-education: Psycho-education is imperative when managing a chronic pain condition. In managing chronic pain conditions with ADs, this issue may be particularly important, and it often requires special attention and finesse from the physician. Prescribing anti-depressants without adequate psycho-education may leave the patient with the wrong impression regarding ADs. Often, when anti-depressants are recommended, patients may fear the physician does not believe their pain is real. The patient may erroneously believe that the physician thinks "it's all in my head."

We suggest you proactively address this point and initiate a conversation. We also suggest you actively endorse your belief in the "reality" of the patient's chronic pain, educate the patient about the brain-body link in chronic pain, and finally, emphasize that anti-depressants are far more than just depression medications—substantial evidence supports their use for chronic pain conditions.

Figure 3. FDA-Approved Indications for Various Antidepressants

Class of ADs	Neuropathic	Fibromyalgia	Nociceptive
MAOI	X	X	X
TCAs	X	X	X
SSRIs	X	X	X
Atypical ADs	X	X	X

SNRIs	Neuropathic	Fibromyalgia	Nociceptive
Venlafaxine	X	X	X
Desvenlafaxine	X	X	X
Duloxetine	✔	✔	✔
Milnacipran	X	✔	X

MAOI, Monoamine oxidase inhibitor.
x, not FDA approved, check, FDA approved

Selecting an Anti-depressant

There are multiple factors to consider when selecting an appropriate anti-depressant. Some issues to consider are:

- If a previous anti-depressant (AD) was tried, what was the patient's response? Explore both the benefits and side effects from each of the previous AD trials, as they may offer valuable clues on which AD to select.
- Are there cost/insurance issues that limit access to a specific AD?
- Are there any specific drug-drug interaction worries that might make a specific AD a less optimal choice?
- Does the AD being considered have an FDA indication and/or a good data set regarding its effectiveness and tolerability?[34]
- Is there a mechanism of action advantage that a specific AD may possess that fits best with the patient's needs?
- What are the patient's beliefs about taking ADs for any of these conditions: depression only, pain only, pain and depression? A patient's adherence to medication heavily depends on a patient and the physician exploring these beliefs.

Awareness of Drug-Drug Interaction Issues

Chronic pain conditions often coexist with other medical conditions (eg, cardiovascular disorders, diabetes, cancer), leading to poly-pharmacy that's often directed by more than one physician. Therefore, drug–drug interactions are a major concern for patients who have chronic pain. Needless to say, drug-drug interactions are a concern for all patients, but in chronic pain management, the worry is elevated because so many patients are on multiple medications. If too many physicians are involved, it increases the risk of drug-drug interactions as each physician may or may not be aware of all medications the patient is taking. Here are a few suggestions to help minimize the risk of drug–drug interactions:

- Always know about *all* prescribed and over-the-counter medications a patient is taking.
- Check the drug-drug interaction profile by consulting a textbook, a pharmacist, or an online resource.
- Advise the patient to inform *all* physicians of *all* medications they're taking, and not to take any new medication unless a physician is consulted and approves it.

Slow Titration

Slow titration of an anti-depressant in patients who have chronic pain is often imperative. Clinical trials often start patients on too high of a dose and increase the dose too rapidly. FDA-approved anti-depressant dose titration regimens are too aggressive for chronic pain patients, making tolerability an issue and leaving patients susceptible to side effects. This leads to high drop-out rates and is often unnecessary. Our advice is to start at a low dose and gradually increase the dose over time. We are not suggesting treating patients with sub-therapeutic doses, rather, we are suggesting that to have a successful trial with an anti-depressant, sometimes a slow titration is very helpful. Also helpful is recommending that the medication be taken after a full meal. If sedation is a side effect, taking the medication before bedtime may be appropriate.

Careful Management of Side Effects

Side effects from anti-depressants are common but are often manageable. The key to success is to predict side effects, educate patients, and then aggressively manage side effects to ensure a successful trial. Before you begin your conversation regarding anti-depressant use for chronic pain, be aware of the black-box warning regarding the potential for suicidal ideation induction. We recommend reading the label fully before you prescribe any medication.

Below are some of the common side effects of anti-depressants.

Nausea: This is a very common side effect and perhaps the most common side effect seen in clinical trials, particularly with SNRIs for patients who have chronic pain conditions. Nausea is also one of the leading causes of discontinuation in studies, but it can be avoided by following this 5-step approach:

1. Educate patient about its possibility even as you write the prescription.
2. Reassure them that the majority of patients experienced mild to moderate nausea and that in the majority of people it dissipated typically in a week's time frame.
3. Slow down the titration schedule.
4. Recommend taking the medication on a full stomach.
5. Recommend taking the medication at night.

Weight gain: This is seen more often with TCAs than with the newer SNRIs. We recommend addressing this concern even as you write your first prescription and recommend interventions that can minimize this side effect (eg, exercising more, reducing calories, a referral to a dietitian). We recommend baseline weight measurement, waist circumference measurement, and basic lab panels that include fasting glucose and lipids. We also recommend semi-annual evaluations

to continue monitoring the patient's metabolic profile. Emphasize pre-emptive initiation of dietary changes and regular physical exercise—reinforce these at every visit. Ask the patient to maintain a food and exercise log and to bring this with to every appointment.

Sexual dysfunction: This is a common side effect and a frequent reason for patient dissatisfaction and early medication discontinuation. It's also a complicated issue because so many patents start out with sexual dysfunction (anorgasmia, delayed ejaculation, decreased libido, etc) even before the medication trial. We recommend ruling out medical causes first, followed by an open and frank discussion of this possible side effect. Consider involving the patient's spouse/partner in the conversation as early as possible—obtain a psychiatry and/or urology consultation if an intervention is required to address the potential sexual dysfunction.

Table 2. Common Serotonin Withdrawl Symptoms

Nausea, dizziness, irritability, headaches, insomnia, anxiety, fatigue, abnormal dreams,'electric' shock like feelings in head and neck area, tearfulness

Suggestions to Reduce Risk of Serotonin Withdrawl Symptoms

1. Discuss risk of discontinuations symptoms with patient and family at onset of treatment
2. Recommend that patient not stop medication abruptly
3. Slow taper down, particularly if medication was taken for a prolonged period of time
4. Time period of taper should be in weeks not days
5. If discontinuation symptoms emerge despite a slow taper, substitute with a longer action serotonin reuptake inhibitor
6. Offer continuous reassurance to patient and family and stay in frequent contact with patient

Sedation/fatigue: Other common but often under-discussed side effects are sedation and/or fatigue. The source of such excessive sedation and/or fatigue due to anti-depressants can be difficult to differentiate from clinical depression. We encourage you to be aware of this potential problem and recommend pro-actively asking patients about it. This set of side effects is more common with TCAs than the newer SNRIs, but we have seen these side effects with all anti-depressants. Many techniques are recommended: lowering the dose if possible, changing the time of administration to after dinner, offering sleep hygiene advice (as many patients take day time naps that disrupt sleep at night) and recommend daily physical exercise.

Anxiety: This can happen and, interestingly, the same 5 steps we recommend for nausea management can be helpful in managing anxiety.

Refer to Table 1 for a brief synopsis of AD side effects.

Table 1. Common Side Effects of Anti-depressant Medications

Common Side-Effects	Management Tips
Nausea	Start at low dose, titrate slower, give after food, give dose at bedtime
Weight gain	Proactively educate about weight management, frequent weight measurement, refer to nutritionist if needed
Sexual dysfunction	Lower dose if possible, switch to more noradrenergic medication if appropriate, consider use of erectile dysfunction medications if appropriate, obtain urology/gynecology consult if appropriate
Sleep disturbances	If insomnia—consider AM dosing, and if it persists, consider adding trazodone (be watchful for serotonin syndrome) If somnolence—consider PM dosing, recommend against day time naps, offer sleep hygiene advise, consider switching to more noradrenergic medication
Agitation or worsening of anxiety	Consider lowering dose, offer reassurance, if difficulty is significant—consider offering a low dose, time limited course of benzodiazepines (we highly recommend only a 1-2 week course to avoid dependence development)

Optimizing Dosing

As with any other disorder, physicians use FDA indications, published literature, and a patient's individual characteristics to determine the optimum medication and dose for any patient. If tolerability and safety issues are addressed and the FDA label supports it, then increasing the dose is often recommended.

Careful Tapering When Stopping Medication

It appears most, if not all, medications affecting serotonin reuptake inhibition, can precipitate withdrawal symptoms. This can happen both with abruptly stopping a medication or even with slow tapering. Withdrawal symptoms are generally mild but on occasion can be very problematic, uncomfortable, and frightening for the patient. Table 2 lists some of the symptoms of serotonin withdrawal, and recommendations for minimizing these difficulties.

Clinical Recommendations

An influential recent publication authored by a group of respected physicians offers ways to address the needs of patients with depression and chronic pain.[39] After a full physical exam, psycho-education, exercise, and cognitive-behavioral therapy are recommended. SNRIs and TCAs are also recommended as first-line pharmacotherapy therapy (with augmentation strategies as second-line intervention if sub-optimum response is present). Exercise and CBT are appropriately highlighted and recommended in these guidelines. Figure 4 summarize the recommendations from this group.

In the absence of depression in chronic pain, the guidelines are less clear but most of them recommend considering ADs at some point in the treatment paradigm. Pre-clinical and clinical research for ADs use in treating chronic pain is expanding—keep a close eye on the evolving literature in this field. ■

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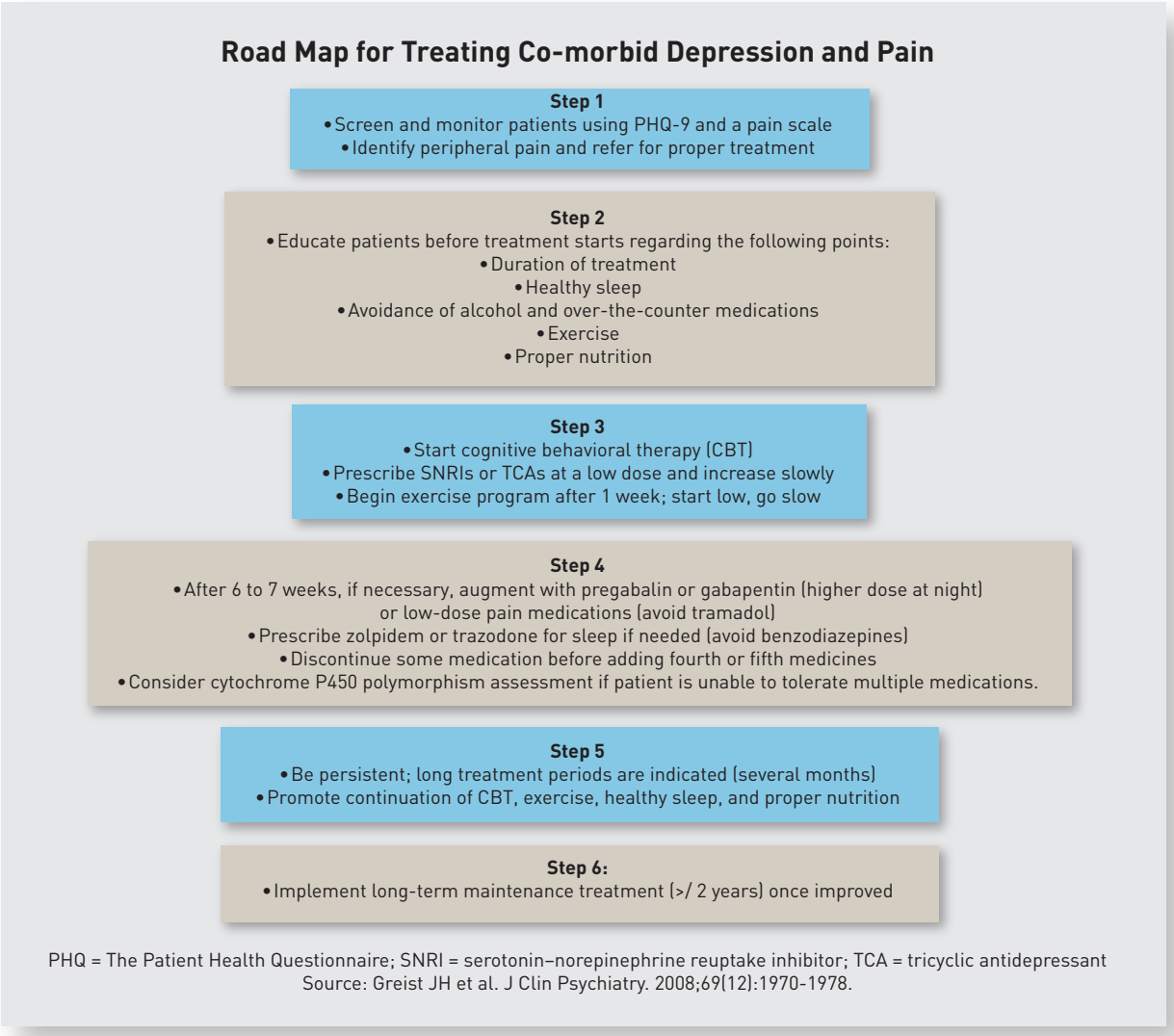

PHQ = The Patient Health Questionnaire; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant
Source: Greist JH et al. J Clin Psychiatry. 2008;69(12):1970-1978.

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