

Pharmacologic Treatment of Depression and Anxiety

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Disclosure

The presenter has no financial relationship to this program.

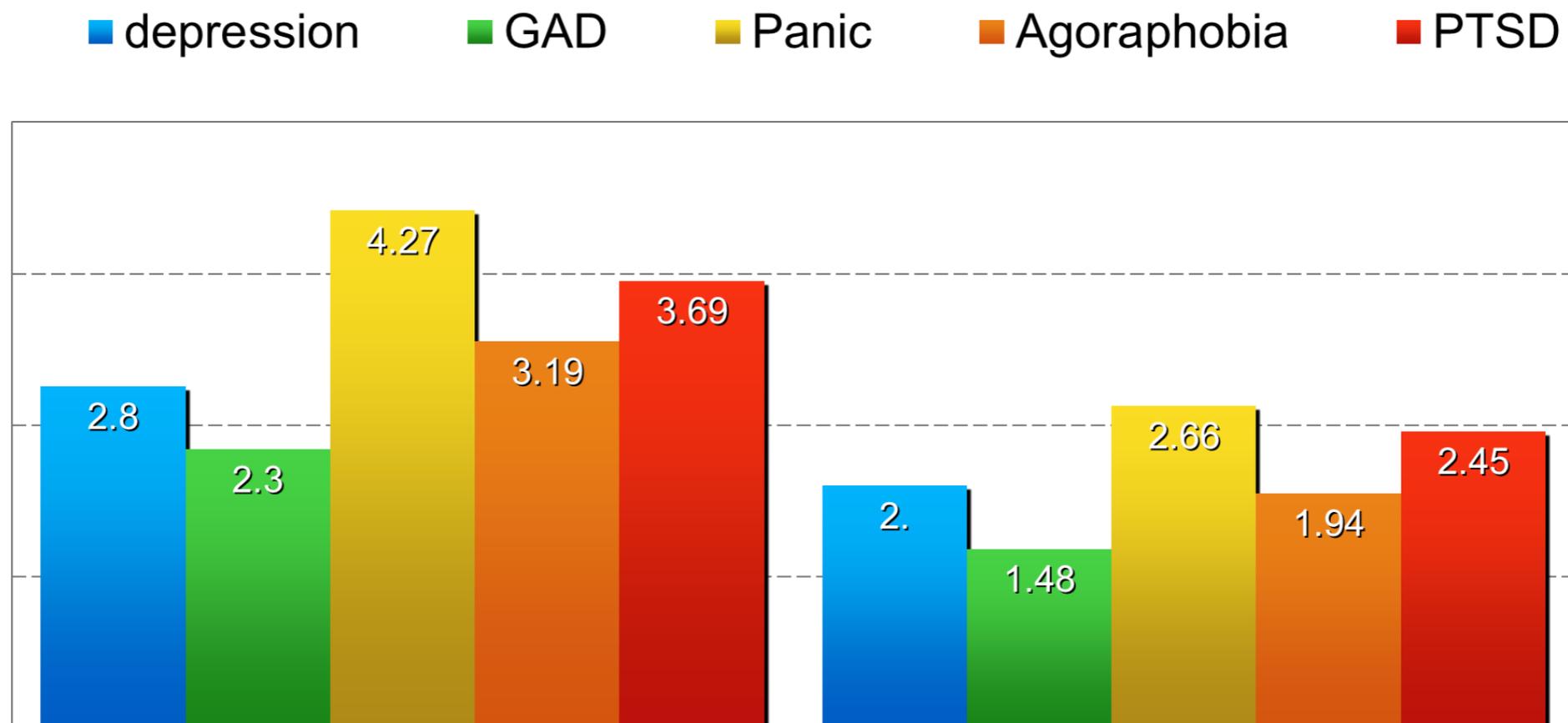
Objectives

1. Describe the treatment of Depression for pain and addiction patients
2. Describe the treatment of Anxiety for pain and addiction patients
3. Explain the mechanism of indications for, and side effects of, therapeutic agents, such as: TCAs, SSRIs, SNRIs

"[Pain] is unquestionably a sensation in part or parts of the body but it is also unpleasant and therefore also an emotional experience."

Mood/Anxiety in Pain

- N = 5877, US civilian population, survey
- OR of having chronic pain, adjusted for sociodemographics (1) and medical dx (2)



Anxiety worsens suffering in Chronic Pain

Kinesiophobia is the strongest predictor of function
(more than pain intensity, duration, biomedical findings)

Fear-avoidance beliefs about physical demands of a job are more predictive of disability and missed work than pain intensity

Reductions in pain-related anxiety improves function, pain levels, affective distress

McCracken & Gross, Journal of Occupational Rehabilitation,1998;8:179-189

Asmundson, et al. Clinical Psychology Review,1999;19:97-119

Crombez, et al. Pain, 1999;80:329-339

Turk, et al. Journal of Pain, 2004;5:483-490

Vlaeyen, et al. Journal of Occupational Rehabilitation,1995;5:235-252

Depression and Chronic Pain

40% - 50% prevalence in Chronic Pain population

Causality has not been established

In a prospective study of low back pain, baseline levels of depression increased the risk of developing chronic low back pain by a factor of 2.3

Jarvik, et al. Spine, 2005;30:1541-1548

Gatchel, Turk, et al. Psychological Bull, 2007;133(4):581-624

| | Suicidality | Plan | Attempt |
|---------------------|-------------|------|---------|
| Chronic cephalgia | | | |
| Back/Neck pain | 1.7x | 1.7x | 2.6x |
| Other non-arthritic | | | |

Medication Classes

TCA antidepressants

- Longest track record of any anti-depressants in the treatment of multiple pain conditions
- Typically, lower doses than used for anti-depressant effect, but titrating to higher doses may benefit a subset of patients
- *Analgesic effects even in the absence of depression or antidepressant effect*
- Benefits: long track record, low cost
- Risks: side effect profile [QTc prolongation, hypotension, sedation, falls in elderly, fatal in overdose]

TCA antidepressants

- A meta-analysis evaluated 55 RCTs involving TCA for treatment of somatic symptoms [a majority involved pain]: 76% of trials [41 trials] showed some benefits [O'malley et al., 1999]
- Consistent evidence in treatment of diabetic neuropathy, postherpetic neuralgia
- Also evidence for central pain, post-stroke pain, tension headaches, migraines, chronic oral-facial pain
- Less consistent data on arthritic pain and low back pain
- Overall NNT 2-4 for 50% pain reduction
- [Lynch, 2001]

TCA tips

- Focus on side effect profiles
- Amitriptyline and Doxepin very sedating
- *Nortriptyline less sedating and more tolerable in elderly*
- Start low [10-25 mg nightly] and increase dose slowly
- May go up 25 mg every week until dose reaches 75-100 mg
- Higher doses may be needed for depression
- Caution in elderly
- Avoid if cardiac risk factors present

SSRIs

- Overall, disappointing results in terms of analgesia
- Headaches: only 3 placebo controlled trials- all negative
- Diabetic neuropathy: 3 RCTs: the largest one found no difference between fluoxetine and placebo; 2 smaller ones found positive effect for paroxetine and citalopram
- Fibromyalgia: a small study showed analgesic effect with fluoxetine; another larger study did not; another negative trial for citalopram

SNRI

- Duloxetine superior to placebo in three RCTs for painful diabetic peripheral neuropathy
- 90% of analgesic effect due to direct analgesia, with 10% secondary to antidepressant effect [Perahia et al., 2006]
- NNT 5 for 50% pain reduction
- FDA approved for pain secondary to fibromyalgia
- Venlafaxine superior to placebo in treating diabetic neuropathy [Rowbotham et al., 2004]
- Duloxetine showed significant improvements in both pain AND depression [Brecht et al., 2007]

SNRI tips

- **Duloxetine**
- Usual dose 60 mg/day
- No additional efficacy shown in doses more than 60 mg
- **Venlafaxine**
- Extended release formulation available
- GI side effects common- take with food
- May increase blood pressure slightly
- Start at 37.5 or 75 mg; need to go to at least 150 mg; upto 225 mg

Neuropathic pain

- Duloxetine approved by FDA
- Duloxetine superior to placebo in three RCTs for painful diabetic peripheral neuropathy
- Venlafaxine superior to placebo in treating diabetic neuropathy [Rowbotham et al., 2004]
- Several studies showing efficacy for TCAs
- Limited data for efficacy of SSRIs
- [Kroenke et al., 2009]

Fibromyalgia

- Overall, antidepressants superior to placebo with NNT of 4
- Moderate effect sizes for pain, fatigue, sleep, and overall well being
- Symptom improvement and depression scores only correlated in one study
- Nine studies for TCAs
- Five for SSRIs: effect for fluoxetine
- Duloxetine positive in several trials; FDA approved
- Not enough evidence for venlafaxine yet
- [Kroenke et al., 2009]

Low back pain

- Ten trials included in 2 systematic reviews
- Tricyclic antidepressants consistently superior to placebo for pain relief
- Uncertain results for functional outcomes
- Moderate effect size [0.41 pooled]
- NO evidence for SSRI efficacy
- No data for SNRI meds
- [Kroenke et al., 2009]

Treatment of Anxiety

Steps for Treatment of Anxiety

- Step 1: Try an SNRI or an SSRI
- Step 2: Augment with anti-anxiety medications [non-benzodiazepines first, then benzodiazepines]
 - Early in tx for faster response/”bridge”
 - Later for breakthrough anxiety
 - Consider use of gabapentin, pregabalin
- Step 3: Switch SSRI/SNRI or anti-anxiety medications
- Step 4: Continued lack of response: Consult with a specialist
- <http://hsc.unm.edu/som/psychiatry/crcbh/docs/COD%20Manual%20-%20FINAL%20-2-2010.pdf>

Table 2. Selective Serotonin Reuptake Inhibitor and Serotonin Norepinephrine Reuptake Inhibitor Antidepressant Options

| Medication | Anxiolytic Efficacy* | Advantages | Disadvantages |
|----------------|---|---|---|
| Fluoxetine | Panic, [†] PTSD* | Generic available; long half life (no withdrawal) | Most stimulating; longer half life |
| Paroxetine | Panic, [†] GAD, [†] SAD, [†] PTSD [†] | Generic available; most extensively studied across these anxiety disorders; least stimulating; no P450 3A4 effects | Most sedating; shorter half life and worse withdrawal |
| Sertraline | Panic, [†] GAD,* SAD, [†] PTSD [†] | Well-studied across these 4 anxiety disorders; least P4502D6 effects; minimal P4503A4 effects; intermediate half life (less withdrawal) | Most diarrhea |
| Citalopram | Panic* | Generic available; no P450 effects | |
| Escitalopram | Panic,* GAD, [†] SAD* | No P450 effects | |
| Venlafaxine ER | Panic, [†] GAD, [†] SAD, [†] PTSD | No P450 effects, pain effects | Short half life; withdrawal with missed dose or sudden discontinuation; increased blood pressure at >225 mg |
| Duloxetine | GAD [†] | Pain effects | Unclear efficacy for other anxiety disorders; more stimulating |

*Randomized controlled trials but no Food and Drug Administration-approved indication.

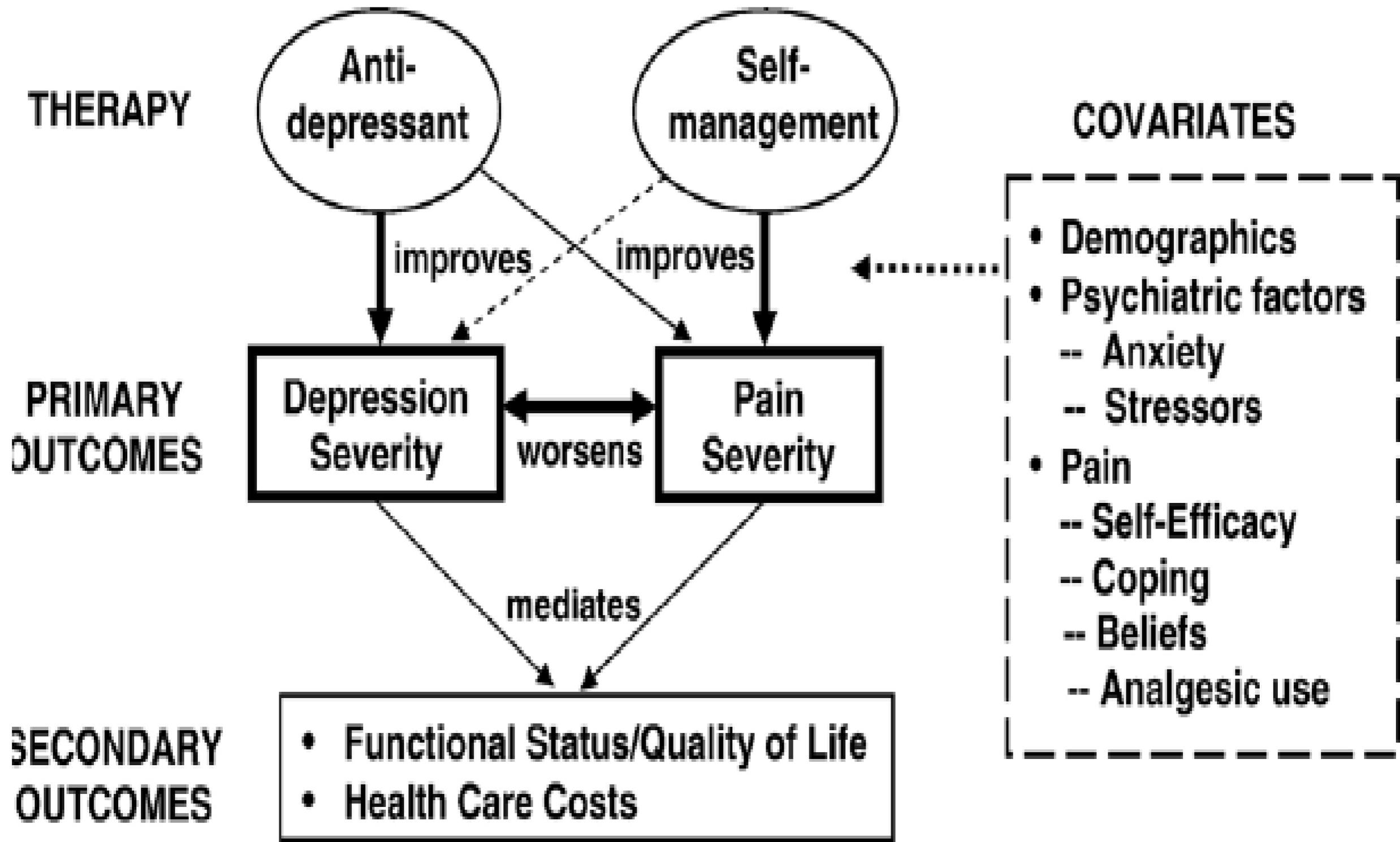
[†]Food and Drug Administration-approved indication as of January 2006.

GAD, generalized anxiety disorder; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.

Treatment of Depression

**STEPPED CARE FOR AFFECTIVE
DISORDERS AND MUSCULOSKELETAL
PAIN
[SCAMP STUDY]**

- NIMH sponsored RCT
- Population: 250 patients with clinically significant depression [PHQ > 10] and musculoskeletal pain of lower back, hips, knee AND 250 patients with no depression, but similar pain
- Follow over 12 months
- Depressed patients randomized to usual care OR stepped care intervention
- Stepped care participants receive 12 weeks of optimized anti-depressant management, followed by 6 sessions of pain self-management program



Conceptual model underlying the SCAMP trial. The thickness of each arrow indicates the postulated strength of effect.

Table 1. Antidepressant Selection and Dosing Details in SCAMP Trial

| Priority | Indications and Precautions | Class | Drug | Dose, mg | |
|----------|--|---|---------------|----------|--------------------|
| | | | | Initial | Possible Increases |
| 1 | Avoid if cardiovascular disease, abnormal electrocardiogram, or hypertension not well controlled | Serotonin-norepinephrine reuptake inhibitor | Venlafaxine | 75 | 150, 225 |
| 2 | Selective serotonin reuptake inhibitor of choice | Selective serotonin reuptake inhibitor | Fluoxetine | 20 | 30, 40 |
| 2 | Selective serotonin reuptake inhibitor of choice if cardiovascular disease | Selective serotonin reuptake inhibitor | Sertraline | 50 | 100, 150 |
| 3 | If treatment failed with first selective serotonin reuptake inhibitor (fluoxetine or sertraline) | Selective serotonin reuptake inhibitor | Citalopram | 20 | 30, 40 |
| 4 | If obese or have weight gain or sexual adverse effects | Other | Bupropion | 200 | 300, 400 |
| 4 | If insomnia a problem; avoid if obese | Other | Mirtazapine | 15 | 30, 45 |
| 5 | Avoid if cardiovascular disease, abnormal electrocardiogram, or hypertension not well controlled | Tricyclic antidepressant | Nortriptyline | 25 | 50, 75 |

Abbreviation: SCAMP, Stepped Care for Affective Disorders and Musculoskeletal Pain.

Table 3

PSM program

| Program content | Session | | | | | |
|---|---------|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Overview of self-management and pain | X | | | | | |
| Factors influencing pain | X | | | | | |
| Planning — goal setting | X | X | X | X | X | X |
| Feedback and problem solving | | X | X | X | X | X |
| Dealing with negative emotions, fears | | | X | | | |
| Physical activities — stretching, strengthening, walking | X | X | X | X | X | |
| Relaxation/Deep breathing | | | | X | | |
| Pain management | | | X | | | |
| Changing your outlook with positive thinking | | | X | | | |
| Distraction | | X | X | | X | |
| Pain triggers | | | | X | | |
| Handling pain flare-ups | | | X | | X | |
| Working with health care providers and employers | | | X | | X | X |
| Evaluating nontraditional treatments | | | | | | X |
| Good body mechanics | | | | | X | |
| Tips for better sleep | | | | | | X |

Results

- At 12 months, 46 (37.4%) of the 123 intervention patients had a 50% or greater reduction in depression severity from baseline compared with 21 (16.5%) of 127 usual care patients (relative risk [RR], 2.3; 95% CI, 1.5 to 3.2)
- At 12 months, intervention group had a much lower number with major depression (50 [40.7%] vs. 87 [68.5%]; RR, 0.6; 95% CI, 0.4-0.6)
- a clinically significant ($\geq 30\%$) reduction in pain was much more likely in intervention patients (51 [41.5%] vs. 22 [17.3%]; RR, 2.4; 95% CI, 1.6-3.2)
- global improvement in pain also significantly more likely in intervention group (58 [47.2%] vs. 16 [12.6%]; RR 3.7, 95% CI, 2.3-6.1)
- combined improvement in both depression and pain also significantly more likely in intervention group (32 [26.0%] vs. 10 [7.9%]; RR = 3.3; 95% CI, 1.8 to 5.4)
- Also significantly better outcomes for pain related disability, quality of life, anxiety, and functional impairment

Take-home points

- Stepwise antidepressant treatment and pain self- management in patients with co-morbid depression and chronic pain can produce significant improvements in both depression and pain
- In this “real-life” population, SSRIs and SNRIs can play a greater role in treatment of these co-morbid conditions
- Further improvement with addition of CBT, optimized analgesic treatment?