Psychiatric–Medical Comorbidity

The Psychiatric–Medical Comorbidity section will focus on the prevalence and impact of psychiatric disorders in patients with chronic medical illness as well as the prevalence and impact of medical disorders in patients with chronic psychiatric illness.

Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews

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Abstract

Objectives: Chronic pain is one of the most prevalent, costly and disabling conditions in both clinical practice and the workplace, yet often remains inadequately treated. Moreover, chronic pain commonly co-occurs with depression, anxiety and somatoform disorders, and adversely affects response of these conditions to psychiatric treatments. This article provides an evidence-based approach to the pharmacotherapy of chronic pain.

Methods: This narrative review is derived largely from meta-analyses and systematic reviews published since 2005. For a few medications, findings from multiple recent trials are synthesized if a systematic review had not yet been published. Classes of medications are first reviewed, followed by an overview of four common pain disorders: neuropathic pain, low back pain, fibromyalgia and osteoarthritis.

Results: A stepped care approach based upon existing evidence includes (1) simple analgesics (acetaminophen or nonsteroidal anti-inflammatory drugs); (2) tricyclic antidepressants (if neuropathic, back or fibromyalgia pain) or tramadol; (3) gabapentin, duloxetine or pregabalin if neuropathic pain; (4) cyclobenzaprine, pregabalin, duloxetine, or milnacipran for fibromyalgia; (5) topical analgesics (capsaicin, lidocaine, salicylates) if localized neuropathic or arthritic pain; and (6) opioids. Disease-specific recommendations for neuropathic, low back, fibromyalgia and osteoarthritis pain are reviewed.

Conclusions: A number of medications have proven effective in chronic pain disorders and their use individually or in combination should improve the management of chronic pain.
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1. Introduction

Pain is the most common symptom reported in both the general population and the general medical setting [1–3]. Pain complaints account for more than 40% of all symptom-related outpatient visits or over 100 million ambulatory encounters in the US alone each year [4]. Pain costs the US over US$100 billion each year in health care and lost productivity [5]. Pain medications are the second most prescribed class of drugs (after cardiac–renal drugs), accounting for 12% of all medication prescribed during ambulatory office visits in the United States [6]. Clinicians

are being pressured to respond to pain as the "fifth vital sign" [7]. Indeed, persistent pain is a major international health problem [8], prompting the World Health Organization to endorse a global campaign against pain [9]. Persistent pain may lead to excessive surgery or other expensive or invasive procedures and is also the leading reason for use of complementary and alternative medicine [10]. Pain is also among the most common reasons for temporary as well as permanent work disability [11].

Pain is even more prevalent in patients with psychiatric comorbidity, particularly mood disorders. The overlap between pain and depression ranges from 30% to 60% [12–14]. Pain is a strong predictor of both the onset and persistence of depression [15], and depression is likewise a powerful predictor of pain, particularly persistent pain

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[8,12]. Concurrent pain and depression have a much greater impact than either disorder alone on multiple domains of functional status as well as health care utilization [12]. Comorbid depression worsens disability and decreases active coping in patients suffering from pain [16,17]. Comorbidity decreases the likelihood of a favorable response of either condition to treatment and also diminishes patient satisfaction with treatment [18–22]. Thus, assessing the presence and severity of pain in patients with depression, particularly those not responding to initial treatment, as well as strategies for effectively and efficiently integrating evidence-based depression care into the management of patients with chronic pain, is sorely needed [23].

Although not as extensively studied, the comorbidity of pain with anxiety appears to be nearly as strong as its comorbidity with depression [1,24–27]. Indeed, a global study conducted by the WHO in 17 countries involving more than 85,000 community-dwelling adults showed that pain was associated with mood and anxiety disorders, but not with alcohol abuse or dependence [28]. The prevalence of specific mood and anxiety disorders was lowest among persons with no pain, intermediate among those with one pain site and highest among those with multisite pain problems. Relative to persons not reporting pain, the age- and sex-adjusted odds ratios were 1.8 (1.7–2.0) for mood disorders and 1.9 (1.8–2.1) for anxiety disorders for persons with single-site pain; and 3.7 (3.3–4.1) for mood disorders and 3.6 (3.3–4.0) for anxiety disorders among those with multisite pain.

The focus of this review will be twofold. First, we will discuss major classes of medications as they relate to pain management. Second, we will briefly address several specific categories of disorders chosen because they (1) account for the most common types of chronic pain; (2) are conditions for which pain management is the principal focus; and (3) have been studied in numerous clinical trials. The prototypical diseases that will be discussed will be musculoskeletal disorders [principally fibromyalgia (FM), low back pain and osteoarthritis (OA)] and neuropathic pain (NP). Musculoskeletal disorders account for more than two- thirds of pain-related outpatient visits, and NP is not only common but is also a popular target for clinical trials in pain and therefore a common reason for seeking a Food Drug Administration (FDA) indication for treatment of pain. We will not address acute pain (e.g., injury-related or post- operative pain), cancer pain, headache and visceral pain.

2. Strength of evidence

The major sources of information for this narrative review are meta-analyses and systematic reviews published since 2005. Individual randomized clinical trials (RCTs) were not included unless we found multiple recent trials on new treatments that had not yet been synthesized into a systematic review. In some reviews, the magnitude of treatment effect as a continuous outcome was reported as an *effect size (ES)*, calculated as the mean change in treatment group minus mean change in control group divided by the pooled standard deviation. By convention, an effect size <0.2 is considered trivial; >0.2–0.5 as small; >0.5–0.8 as moderate; >0.8–1.2 as important; and >1.2 as very important [29]. When comparing response rates on a categorical variable (e.g., "improved" or "≥50% reduction in pain"), the *number needed to treat (NNT)* was sometimes reported. For example, if 60% improve on an analgesic vs. 35% on placebo, this is an absolute difference of 25%. The NNT is the reciprocal of this absolute difference: 1/0.25=4. This means that for every four patients who receive this analgesic, one additional patient would achieve a therapeutic response over and above placebo. It should be noted that we are reliant on evidence from published clinical trials.

3. Specific medications

3.1. Nonopioid analgesics

Aspirin and other related compounds constitute a class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have three desirable pharmacological effects — anti-inflammatory, analgesic and antipyretic. All NSAIDs and COX-2 agents appear equally effective in the treatment of pain disorders [30]. While gastrointestinal (GI) adverse effects have traditionally been considered the most common and worrisome complication, cardiovascular risk has gained increasing attention, prompting the American Heart Association to recommend acetaminophen, nonacety- lated salicylates and even short-term opioids instead of NSAIDs and particularly COX-2 agents in patients with coronary artery disease (CAD) [31] Rheumatologists, however, have disagreed that opioids should be favored over a "cardiac-neutral" NSAID like naproxen in CAD patients with chronic pain. Acetaminophen has analgesic and antipyretic effects similar to NSAIDs but lacks a specific anti-inflammatory effect. Acetaminophen is a slightly weaker analgesic than NSAIDs (<10 point difference on a 100-point visual analogue pain scale) [32–34] but is a reasonable first-line option because of its more favorable safety profile and low cost. However, acetaminophen is associated with asymptomatic elevations of aminotransferase levels at dosages of 4 g/day even in healthy adults, although the clinical significance of these findings is uncertain [35].

3.2. Tramadol

Although the mode of action of tramadol is not completely understood, it exerts an analgesic effect through binding to the mu opioid receptor as an agonist (opioid effect) and weakly inhibits the reuptake of serotonin and norepinephrine (nonopioid effect), similar to the effect of tricyclic antidepressants (TCAs). Tramadol has proven effective in OA, FM and NP (summarized under those

conditions). Because tramadol is an unscheduled drug, clinicians may not be aware of its opioid effect. However, it should be used with some caution in persons recovering from substance use disorders (SUDs). A randomized trial of 11,352 participants with chronic noncancer pain compared the abuse potential of tramadol, NSAIDs and hydrocodone [36]. Depending upon the criteria used, the potential for abuse over 12 months was 0.5–2.5% for NSAIDs, 0.7–2.7% for tramadol and 1.2–4.9% for hydrocodone. While the degree of physical dependence appears relatively mild, patients can report the psychic dependence symptom of tramadol craving when discontinuing the drug [37]. Seizures have been reported with tramadol as has serotonin syndrome. Therefore, patients with a history of seizures and those taking a tricyclic or SSRI antidepressant, a monoamine oxidase inhibitor, an antipsychotic drug, or other opioids may be at increased risk [38]. Daily doses of tramadol should not exceed 400 mg. Dose reduction is recommended in older adult patients (older than 75) and in those with renal impairment or cirrhosis.

3.3. Opioid analgesics

3.3.1. Efficacy of opioids

Furlan et al. [39] conducted a meta-analysis of opioids for chronic noncancer pain. Included were 41 trials involving 6019 patients: 80% of the patients had nociceptive pain (OA, rheumatoid arthritis or back pain); 12%, NP [postherpetic neuralgia (PHN), diabetic neuropathy or phantom limb pain]; 7%, FM; and 1%, mixed pain. Tramadol was the agent studied in 17 trials (3433 patients), propoxyphene or dextropropoxyphene in 3 trials (1074 patients), codeine in 7 trials (444 patients), oxycodone in 6 trials (517 patients) and morphine in 8 trials (551 patients). Average duration of treatment was 5 (range 1–16) weeks. On average, 33% dropped out in the opioid groups (15% because of inadequate pain relief and 21% because of side effects; some patients reported both reasons) and 38% in the placebo groups (30% because of inadequate pain relief and 10% because of side effects). The effect size for opioids compared to placebo was moderate for pain (−0.60) and small for functional outcomes (−0.31). Only eight trials compared opioids to other analgesics; for these trials, opioids did not differ significantly from nonopioids for pain (ES=−0.05) and were significantly, although slightly, worse than nonopioids for functional outcomes (ES=0.16). Propoxyphene and dextropropoxyphene are no longer recommended because of a low therapeutic/toxicity ratio. They are less than half as potent as codeine and can accumulate with repeated doses, occasionally producing respiratory depression, sedation and cognitive impairment, particularly in elderly patients or those consuming alcohol.

3.3.2. Adverse effects of opioids

A systematic review of 34 trials with 4212 patients provided information on adverse events related to opioid use in treating noncancer pain [40]. Only three side effects occurred significantly more frequently with opioids: nausea, constipation and somnolence, with excess rates over placebo of 14%, 9% and 6%, respectively. A substantial proportion of patients on opioids (22%) withdrew because of adverse events. Because most trials were short (<4 weeks) and did not titrate the dose, the implications for long-term use in clinical practice are less certain. Eisenberg et al. [41] also reported on adverse events in their systematic review of opioids for NP. Opioid therapy compared to placebo resulted in higher reporting of nausea (33% vs. 9%), constipation (33% vs. 10%), drowsiness (29% vs. 12%), dizziness (21% vs. 6%) and vomiting (15% vs. 3%). Where reported, more patients on opioids withdrew because of adverse effects (11% vs. 4%).

Endocrinological abnormalities such as hypogonadism and erectile dysfunction may be associated with opioid therapy [42,43]. In women, opioid use has been associated with amenorrhea and decreased sex hormone levels [44]. Opioid treatment may be associated with impaired neuropsychological performance regarding reaction times, psychomotor speed and working memory [45]. However, a recent systematic review concluded that stable doses of opioids did not impair driving performance [46].

3.3.3. Tolerance and addiction

A systematic review of the risk of iatrogenic addiction in patients treated with opioids for acute and subacute pain could not ascertain whether there was an increased risk [47]. Risk factors for opioid abuse in chronic pain are young age, male sex, past alcohol or cocaine abuse, previous drug conviction, mental health disorders, pain in multiple regions and pain after motor vehicle accidents [45]. It is not certain whether abuse potential varies among specific opioids.

In a 10-year follow-up study of opioid-treated patients with chronic pain, tolerance was not a problem in the majority of patients [48]. In contrast, a retrospective study of 104 chronic pain patients younger than 50 years and 102 patients older than 60 years showed that younger patients and those with nociceptive pain (as compared to NP) had much higher escalation of opioid doses over a 15-month follow-up period [49]. Some experts have classified patients or pain syndromes as opioid-responsive vs. opioid-resistant [50]. Indeed, some patients may develop opioid-induced hyperalgesia, where the balance between antinociceptive and pronociceptive systems is up-regulated after opioid exposure, leading to an enhanced vulnerability to pain [45,51].

3.3.4. General principles of opioid use

Useful suggestions for management of chronic opioid therapy have been published [45,52–55]. Evidence for the use of very high doses of opioids is scarce. Since the highest daily dose of opioids used in existing trials is 180 mg morphine or its equivalent, some clinicians may prefer to consult with a pain specialist if pain remains poorly controlled despite opioid doses approaching this level. In some cases, opioid rotation may be considered if pain relief and functional goals are not achieved with increasing doses

of one opioid. In general, because of incomplete cross-tolerance (i.e., patients may be tolerant to high doses of the first opioid yet have a lower tolerance to the new opioid), an initial dose of a new opioid should be equivalent to 50% or less of the dose of the original opioid. A more conservative approach is appropriate for methadone, considering the high inter-individual variability in its pharmacokinetics and many potential drug interactions. A recent review found that conversion ratios from oral morphine equivalents to methadone used in clinical studies ranged from 4:1 to 37.5:1 [56]. Higher ratios were used for higher doses. Equianalgesic doses of oral and transdermal opioids are summarized in Table 1. When trials of several opioids are ineffective in chronic pain, it is appropriate to consider weaning and discontinuing the drug. Weaning can usually be accomplished over 10 days, but the exact weaning schedule will depend upon dose, drug and duration of treatment.

A written agreement may be helpful for providing informed consent of the risks/benefits of opioid therapy, setting out terms of use, including obtaining opioids only from a single provider, reporting lost or stolen drugs promptly, not using more than is prescribed or requesting early refills on a regular basis and periodic urine testing to determine opioids are being taken by the patient (and not diverted for economic gain), and that illicit drugs are not being taken. Some experts recommend a "universal precautions" approach for all patients receiving opioids because clinical factors are not sufficiently predictive of who will have problems with abuse or addiction [57]. General principles for the safe and effective use of opioids in managing chronic pain are summarized in Table 2.

3.3.5. Long-acting opioids

An evidence-based review of 34 randomized trials (3608 patients enrolled) evaluated long-acting opioids in chronic noncancer pain [58]. Two or more clinical trials were published for transdermal fentanyl and long-acting oral

Table 2
An opioid management strategy when treating chronic pain

1	Maximize nonopioid analgesic strategies first (i.e., a "delayed" opioid approach)
2	Inform subjects of risks, including addiction, before initiating opioid therapy.
3	Facilitate the use of opioid agreements (contracts) for patients initiating or increasing opioids. Key points include stipulating the frequency of obtaining medications, timely refills but no early replacement for lost or stolen prescriptions, safe storage, no sharing, single-source prescribing, monitoring through urine screens, and adherence to monitoring visits.
4	Schedule follow-up visits at 2- to 3-month intervals, performing periodic urine testing to confirm adherence.
5	Monitor pain severity and pain-related functional impairment at follow-up visits since analgesic response may wane in some patients over time.
6	Avoid opioid dose escalations without first assessing pain severity and interference.
7	View opioid initiation as an empiric trial. Consider discontinuing opioids if not beneficial.
8	Consider opioid rotation if tolerance to one opioid is suspected.
9	If patient is a high-risk candidate for opioids (particularly those with a current or past SUD including alcohol or drugs), consider referral to a pain specialist.

oxycodone, morphine, codeine and dihydrocodeine. Methadone and levorphanol were each studied in only a single trial. Only 8 trials compared one long-acting opioid to another; 7 compared a long-acting opioid to a short-acting opioid; and 22 compared a long-acting opioid to a nonopioid or placebo. The most common pain disorders studied were NP (8 trials), back pain (10 trials) and OA (10 trials). Nearly all of the trials were of relatively short duration; most were 4 weeks or shorter and only three were longer than 12 weeks. All trials excluded persons with past or current substance abuse. Most trials recruited patients from specialty clinics, most commonly from rheumatology or pain practices. The author concluded that there is insufficient evidence to suggest that one long-acting opioid is superior to another. Also, the 7 trials comparing long- to short-acting opioids were unable to demonstrate superior efficacy or lesser side-effect rates for long-acting opioids.

3.3.6. Methadone

Until recently, methadone has been primarily used as a maintenance drug to prevent withdrawal in opioid-addicted adults. Although methadone is increasingly used for the treatment of chronic noncancer pain, published data is rather modest. In a literature review of 21 studies, only 1 small randomized trial (n=19 patients) was found; the remainder were either cases series (n=7) or case reports (n=13) [59]. Concerns regarding use of methadone for pain relate to its long and unpredictable half-life and associated risk of delayed overdose. Methadone has more potential drug interactions than other opioids [60]. Also, large individual variations in pharmacokinetics of methadone prevent the use of simple equianalgesic tables to calculate the required dose of methadone during rotation from other opioids. Finally, preliminary data suggests a potential mortality risk when

Table 1
Oral and transdermal opioid analgesic equivalence

Drug	Dose (mg)	Duration (h)[a]
Morphine	20–30	2–4
Codeine	200[b]	3–4
Hydrocodone	30[c]	4–6
Oxycodone	20	3–4
Hydromorphone	7.5	3–4
Meperidine	300[b]	2–4
Methadone	20[d]	4–8
Fentanyl (transdermal)	1 μg/h transdermally≈morphine 2 mg/24 h orally	48–72

[a] Duration of analgesia is dose dependent; the higher the dose, usually the longer the duration.

[b] These high doses of codeine and meperidine are not recommended clinically.

[c] Equianalgesic data not available for hydrocodone.

[d] In opioid-tolerant patients converted to methadone, start with 10–25% of equianalgesic dose. Also, the half-life of methadone can vary widely from 12 to 190 h.

methadone is used for chronic pain [61]. Opioids in general are becoming a more common cause of unintentional drug overdose fatalities, associated with nonmedical use and diversion, and methadone accounts for a disproportionate number of these accidental deaths [62,63].

3.4. Antidepressants

3.4.1. Tricyclic antidepressants and SSRIs

Tricyclic antidepressants have the longest track record of any antidepressant class in the treatment of multiple pain conditions. Typically, the doses of TCAs used in clinical trials of pain have been lower (e.g., 25–100 mg amitriptyline or equivalent) than the doses typically necessary for treating depression. However, some experts have found that titrating TCAs to higher doses (with an option of monitoring serum levels) may further benefit a subset of patients. Advantages of TCAs include decades of clinical experience with TCAs in pain management and low cost. Disadvantages of TCAs are side effects (which may be less, however, when prescribing the lower doses used for analgesia), including cardiovascular (e.g., hypertension, postural hypotension, arrhythmias); falls in older adult patients; and potential lethality in overdose.

A meta-analysis of 96 RCTs evaluating antidepressants for the treatment of conditions manifested by somatic symptoms (the majority involving pain) included 55 TCA trials, of which 76% showed benefits, and 17 trials using SSRI antidepressants, of which 47% were positive [64]. Only a few trials were head-to-head comparisons of two antidepressants. Indirect comparisons using meta-regression did not show a significant difference between types of antidepressants, but TCAs were superior to SSRIs ($P<.02$) using a bivariate tally procedure. Admittedly, such statistical comparisons are not as conclusive as direct comparisons of antidepressants within the same trial. Another review concluded that SSRIs appeared to have a relatively weak effect in ameliorating chronic pain [65].

3.4.2. Serotonin–norepinephrine reuptake inhibitors

Duloxetine has proven superior to placebo in three 12-week randomized, placebo-controlled trials that enrolled patients with pain due to diabetic peripheral neuropathy [66–68]. Both patients with and without depression were enrolled in the trials, although path analysis estimated that more than 90% of the analgesic effect in duloxetine-treated patients with diabetic neuropathy was attributable to a direct analgesic effect, with less than 10% possibly explained by an antidepressant effect [69]. Duloxetine is also FDA approved for the chronic widespread pain of FM [70–72]. A 6-week trial of extended-release venlafaxine in 224 patients with diabetic neuropathy found venlafaxine superior to placebo [73]. Venlafaxine may also be useful in other painful conditions [74] but does not have an FDA pain indication.

A recent meta-analysis of five trials in depressed patients reported a very small and statistically nonsignificant ($P=.057$) analgesic effect for duloxetine [75]. Another meta-analysis of eight trials comparing duloxetine with paroxetine or placebo for the painful physical symptoms of depression likewise concluded that there was insufficient evidence for an analgesic effect of duloxetine [76]. In all of these depression trials, pain was examined as a secondary outcome, and in all but two, an important proportion of patients had no pain. A subsequent placebo-controlled trial of duloxetine in patients with depression and moderate-to-severe pain but no organic pain diagnosis found a significant benefit for both pain and depression symptoms [77].

3.5. Anticonvulsants

Anticonvulsants have been used in the management of pain since the 1960s and, along with antidepressants, constitute one of the two most important adjunctive classes of medications for pain management. The clinical impression is that they are useful for chronic NP, especially when the pain is described as lancinating or burning. Gabapentin and pregabalin have the strongest evidence for the treatment of pain. These two "gabapentinoids" act as neuromodulators by selectively binding to the $\alpha_2\delta$-subunit protein of calcium channels in various regions of the brain and the superficial dorsal horn of the spinal cord. This results in inhibition of the release of excitatory neurotransmitters that are important in the production of pain.

A systematic review of 15 trials (1468 participants) evaluating gabapentin included 1 acute pain trial and 14 trials in NP (7 in diabetic neuropathy, 2 in PHN and 1 each in cancer-related neuropathy, phantom limb pain, spinal cord injury, Guillain–Barre syndrome and miscellaneous neuropathies) [78]. In the 14 chronic NP trials, 42% of participants improved (i.e., pain relief of 50% or greater) on gabapentin vs. 19% on placebo, and the NNT for improvement in all trials with evaluable data was 4.3 (95% CI, 3.5–5.7). Withdrawal rates were 14% for gabapentin vs. 10% for placebo. The FDA has approved pregabalin for treatment of NP associated with diabetic peripheral neuropathy and PHN and for treatment of FM; evidence from these trials is discussed under these specific disorders.

A systematic review of 12 trials (404 participants) of carbamazepine included 4 placebo-controlled trials in trigeminal neuralgia, of which 2 with evaluable data yielded a NNT of 1.8 (95% CI, 1.4–2.8) [79]. For diabetic neuropathy there was insufficient data to calculate a NNT. A systematic review that included other anticonvulsants found a NNT of 2.1 (95% CI, 1.5–3.6) for phenytoin in a single trial of diabetic NP [80]. Since the latter trial has not been replicated, gabapentin and pregabalin should be considered the first-line anticonvulsants for NP conditions other than trigeminal neuralgia. Gabapentin is now available in a generic formulation, making it less costly than pregabalin. Conversely, pregabalin has a simpler dosing schedule (twice daily compared to three to four times daily), possibly simpler dose titration and an additional FDA indication (FM).

3.6. Other pharmacological agents

3.6.1. Skeletal muscle relaxants

Most skeletal muscle relaxants are FDA approved for either spasticity (baclofen, dantrolene and tizanidine) or musculoskeletal conditions (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenadrine) [81]. The mechanism of action for the latter category of agents is unclear, but may be related in part to sedative effects. Studies to date have not shown differences among skeletal muscle relaxants in their efficacy, adverse events or safety. A systematic review [81] concluded there was "insufficient data to assess comparative abuse and addiction risk of skeletal muscle relaxants, though almost all case reports of abuse and addiction have been in patients taking carisoprodol." Most trials have focused on acute rather than chronic pain. Cyclobenzaprine is the best studied muscle relaxant in musculoskeletal disorders overall; in 21 fair-quality trials it has consistently proven superior to placebo for FM as well as for pain relief, muscle spasms and functional status in other disorders. Cyclobenzaprine 5 mg TID is equally effective as 10 mg TID but has fewer side effects. In summary, muscle relaxants have a limited role in the treatment of chronic pain, except for cyclobenzaprine as one option in treating FM.

3.6.2. Topical analgesics

A potential advantage of topical agents is avoidance of the systemic side effects often associated with oral medications. Disadvantages are that only localized areas of pain can be effectively treated and that irritating skin reactions occur in a minority of patients. Topical analgesics probably have a circumscribed role in treating localized areas of mild to moderate neuropathic or osteoarthritic pain, either as an adjunct to other medications or as an alternative to patients preferring not to ingest pills. Several topical analgesics — lidocaine, capsaicin and salicylate — have been studied in multiple trials. Lidocaine 5% patch has an FDA indication for PHN and is discussed in more detail under NP.

Capsaicin is an alkaloid derived from chili peppers; repeated application is thought to lead to depletion of substance P from primary afferent neurons [82]. The main disadvantage of capsaicin is the initial burning sensation, which may persist for days. Capsaicin must be applied three to four times per day over the entire painful area for up to 6–8 weeks before optimal pain relief can be achieved. Mason et al. [83] recently reviewed the clinical trial evidence for capsaicin, including 6 trials in NP and 3 trials in musculoskeletal conditions. They found that 57% of patients with NP achieved at least 50% pain relief with capsaicin, compared with 42% of patients on placebo; for patients with musculoskeletal conditions, the response rates were 38% vs. 25% [83]. Around one third of patients experienced local adverse events with capsaicin.

Topical salicylate has proven superior to placebo in both acute pain (3 trials, 182 patients; NNT=2.1; 95% CI, 1.7–2.8) and chronic pain (6 trials, 429 patients; NNT=5.3; 95% CI, 3.6–10.2) [84] However, larger more rigorous trials tended to be negative. A recent RCT suggests topical ibuprofen may also be beneficial for knee OA [85].

4. Selected pain disorders

4.1. Neuropathic pain

Neuropathic pain is characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching or shooting. Up to 3% of the general population reports NP at some time [86]. NP is most commonly associated with painful diabetic neuropathy, PHN or lumbar nerve root compression. Other causes of NP include cancer-related pain, spinal cord injury, post-stroke pain, HIV-associated neuropathy, phantom limb pain and trigeminal neuralgia.

Four drugs are FDA approved for treatment of diabetic neuropathy or PHN: gabapentin, pregabalin, duloxetine and lidocaine patch [86]. Carbamazepine is also approved for trigeminal neuralgia based upon three trials including a total of 150 patients published in the 1960s. Other drugs used for NP, particularly TCAs and other anticonvulsants, are not FDA approved for this indication.

Chou et al. [86] also summarized the results of six systematic reviews that evaluated the benefits of gabapentin, pregabalin, serotonin–norepinephrine reuptake inhibitor (SNRIs) or topical lidocaine for NP. All of the newer medications for NP were superior to placebo in at least one systematic review. The systematic reviews included a total of 17 unique placebo-controlled trials of gabapentin, 5 trials of pregabalin, 3 trials of venlafaxine, 6 trials of topical lidocaine and 2 trials of duloxetine. None of the systematic reviews found any published reports of a head-to-head trial of one of these drugs vs. another. Several of the reviews also concluded that TCAs were effective (best evidence for amitriptyline), and there was limited data for the effectiveness of SSRIs. It should also be noted that many of the TCA studies performed several decades ago had smaller samples than trials of currently approved drugs. For example, the sum total of patients with diabetic neuropathy studied in all TCA trials is less than 120 [82]. Also, a number of the TCA studies used a cross-over rather than a parallel group design.

In a systematic review of 23 trials evaluating the use of opioids for NP, 14 trials were classified as short-term (<24 h) and nine as intermediate-term (median=28 days; range=8 to 70 days) [41]. The short-term trials had contradictory results but are less relevant to chronic pain treatment. All nine intermediate-term trials demonstrated opioid efficacy: 13 points lower (95% CI, −16 to −9) than placebo on a 0-to-100 pain scale. Tramadol has also proved beneficial in 4 placebo-controlled trials [87].

The European Federation of Neurological Sciences guidelines on pharmacological treatment of NP concluded that there was good evidence for the efficacy of TCAs,

gabapentin, pregabalin and opioids, as well as topical lidocaine for PHN, and SNRIs for diabetic neuropathy [88]. They also concluded that diabetic and nondiabetic painful polyneuropathies are similar in symptomatology and response to treatment. The only exceptions are that HIV- and chemotherapy-induced neuropathy may be more refractory to treatment. The principal opioids studied have been oxycodone and tramadol, both of which have proven superior to placebo. Trials of topical capsaicin have yielded mixed results.

A consensus panel from the International Association for the Study of Pain (IASP) likewise concluded that first-line treatments for NP include certain antidepressants (i.e., TCAs and SNRIs), calcium channel α2-δ ligands (i.e., gabapentin and pregabalin) and topical lidocaine [89]. Opioid analgesics and tramadol were recommended as second-line treatments. The IASP also noted: "Although few clinical trials have been conducted, no medications have demonstrated efficacy in patients with lumbosacral radiculopathy, which is probably the most common type of NP." Indeed, an RCT evaluating nortriptyline, morphine and their combination in patients with chronic lumbar root pain found no greater efficacy with the combination than with either medication alone or placebo [90]. The IASP also noted that little is known regarding the treatment response of those with mild to moderate NP since most trials have enrolled patients with more severe NP, and long-term effectiveness is unknown since most RCTs have been less than 3 months. The IASP also favored secondary amine TCAs (nortriptyline and desipramine) over tertiary amine TCAs (amitriptyline and imipramine) because of comparable analgesia [91–93] and fewer side effects.

4.2. Fibromyalgia

Fibromyalgia is one of the most common musculoskeletal disorders seen in both rheumatology practice and primary care. The American College of Rheumatology (ACR) core diagnostic criteria for FM are (1) generalized pain that is both widespread (i.e., both right and left sides of the body, upper and lower halves, and axial as well as proximal arms and legs) and chronic (≥3 months); and (2) multiple tender points on physical examination (located at front and back of neck, upper chest and back areas, iliosacral and posterior gluteal areas, elbows and knees). The primary problem in FM appears to be not that there is too much input coming from the pressure nociceptors peripherally, but rather that there is inadequate filtering of that activity, perhaps because of decreased activity of descending antinociceptive pathways [94]. This mechanism has been denoted as central sensitization.

Five types of medications are effective in FM: (1) TCAs; (2) cyclobenzaprine; (3) tramadol; (4) SNRIs (duloxetine, milnacipran); and (5) $\alpha_2\delta$-ligand anticonvulsants (pregabalin, gabapentin). Although classified as a muscle relaxant, cyclobenzaprine has a chemical structure closely related to

TCAs, which may partly account for its effectiveness in FM. While trials have shown the efficacy of tramadol in FM, the few studies of stronger opioids have not shown benefit. There is no RCT evidence that NSAIDs are effective monotherapy for FM [95].

A meta-analysis of antidepressants published in 2000 found 13 trials with evaluable data involving three classes of antidepressants: TCAs (9 trials), SSRIs (3 trials) and s-adenosylmethionine (2 trials) [96]. Overall, antidepressants were superior to placebo with a NNT of 4. The effect sizes for pain, fatigue, sleep and overall well-being were all moderate (ES, 0.39–0.52). In the five studies where there was adequate assessment for treatment response independent of depression, only one study found a correlation between symptom improvement and depression scores. Antidepressant class did not make a difference, although only 3 trials tested SSRIs. Since this meta-analysis, two more trials of SSRIs in FM have been published: a flexible dose trial showing that fluoxetine (mean=45 mg) was superior to placebo in 60 women [97], and an inconclusive placebo-controlled trial of citalopram in 40 patients [98]. There is better evidence for TCAs in FM than for SSRIs; however, evidence for the superiority of TCAs compared with SSRIs in FM is not as convincing as the evidence for their superiority in NP.

A meta-analysis of 4 trials found that cyclobenzaprine (10–40 mg) was also superior to placebo [99]. Again, this is not surprising given that its structure and pharmacological properties are quite similar to TCAs. Finally, 2 trials involving 100 patients [100] and 313 patients [101] showed that tramadol was superior to placebo in treating FM, though the largest trial combined tramadol with acetaminophen.

Most research on pharmacotherapy for FM over the past 5 years has involved the SNRI antidepressants and the $\alpha_2\delta$-ligand anticonvulsants. Pregabalin, duloxetine and milnacipran have each proven effective in several positive Phase III RCTs [70–72,102–106], and are the first FDA-approved drugs for the treatment of FM. Gabapentin, another $\alpha_2\delta$-ligand, was studied in a single trial, which was positive [107]. Another SNRI, venlafaxine, was tested in a low-dose trial (75 mg) and did not differ from placebo [108]. Certainly, the strongest evidence exists for pregabalin, duloxetine and milnacipran. Tramadol could also be a second-line choice, though the fact it is a weak opioid should be taken into consideration. Generic gabapentin and venlafaxine would be less expensive than the recently approved drugs, although neither is FDA approved and there is only a single trial supporting gabapentin.

In the Phase III trials, pregabalin was dosed at 300–450 mg/day (divided into BID dosing), duloxetine at 60–120 mg once a day and milnacipran at 50–100 mg twice a day. In all trials, separation of the higher dose from the lower dose of the drug was small to minimal, while side effect rates were somewhat increased at higher doses. The most bothersome side effect of duloxetine and milnacipran (as well as venlafaxine) is nausea, which may be lessened by

starting at a lower dose (e.g., 30 mg duloxetine or 37.5 mg venlafaxine) for the first 1–2 weeks and taking the drug with food. The most bothersome side effects with pregabalin and gabapentin are somnolence (which often improves with treatment and may be reduced by a low starting dose and starting initially with the only or highest dose at bedtime), dizziness and weight gain.

4.3. Low back pain

Low back pain is the fifth most common reason for all physician office visits in the US and the second most common symptomatic reason. Total incremental direct health care costs attributable to low back pain in the US were estimated at US$26.3 billion in 1998. In addition, indirect costs related to days lost from work are substantial, with approximately 2% of the US work force compensated for back injuries each year. A series of systematic reviews by Chou et al. [109–111] provide a comprehensive update on the evaluation and management of low back pain.

The most commonly prescribed medications for low back pain are NSAIDs, skeletal muscle relaxants and opioid analgesics [110]. Benzodiazepines, systemic corticosteroids, antidepressant medications and antiepileptic drugs are also prescribed. Frequently used over-the-counter medications include acetaminophen, aspirin and NSAIDs. No treatments for back pain have good-quality evidence for substantial benefit. Pharmacotherapy with lower level evidence includes acetaminophen, NSAIDs, tramadol and TCAs. For all medications, the evidence of beneficial effects on functional outcomes is limited. Skeletal muscle relaxants, which may be beneficial in acute back pain, do not have established efficacy for chronic pain. Though systematic reviews of opioids for various chronic pain conditions have shown moderate benefits, the evidence for opioids specifically for low back pain is sparse and inconclusive [112]. A recent prospective study found that early prescription of opioids for acute occupational low back injury was associated with an increased risk of work disability at 1 year, even after adjustment for severity of pain, function and initial injury [113]. No convincing evidence exists that systemic corticosteroids are effective for low back pain with or without sciatica. One systematic review identified only 7 trials evaluating medications for sciatica [114]. Two small trials suggest gabapentin may be useful in the subset of patients with radiculopathy.

Ten trials were included in two systematic reviews of antidepressants [115,116]. In all of the trials, the duration of therapy ranged from 4 to 8 weeks. Antidepressants were consistently superior to placebo for pain relief, whereas the benefits for functional outcomes were uncertain. The pooled effect size for pain relief was moderate (0.41). Indirect comparisons suggested modest benefits for TCAs but not for paroxetine or trazodone. A recent review did not identify any relevant trials in back pain for SNRI antidepressants such as duloxetine or venlafaxine [110].

4.4. Osteoarthritis

Osteoarthritis is one of the most common musculoskeletal pain disorders (along with low back pain and FM) in both primary care and specialty settings. Its prevalence typically increases with age (particularly >50), with the majority of individuals over age 65 having at least one joint affected by OA. Common joints involve the distal and proximal interphalangeal (but not metacarpal) joints of the fingers, the base of the thumb, the knees, the hips, and the cervical and lumbar regions of the spine. The shoulder and elbow are rarely involved. The most common finding on physical examination is an increase in joint size secondary to osteophyte formation. Plain radiographs are typically the only diagnostic test required to confirm the diagnosis of OA, which will be manifested by loss of joint space or osteophyte formation.

Unlike rheumatoid and other inflammatory types of arthritis, the structural changes in OA are not amenable to specific disease-modifying treatments. Thus, the focus of treatment in OA is reduction of pain and preservation of function. Acetaminophen and NSAIDs, which are inexpensive and available without a prescription, are the mainstays of pharmacotherapy.

Avouc et al. [117] conducted a meta-analysis of 18 trials evaluating opioid therapy in OA. Six studies evaluated stronger opioids (oxycodone in four studies, fentanyl and morphine in one study each) and seven, weaker opioids (tramadol in four studies, tramadol/acetaminophen in two studies and codeine in one study). The median trial duration was 12 weeks. The pooled ES was moderate for pain intensity at −0.79 (95% CI, −0.98 to −0.59) and small for physical function at −0.31 (95% CI, −0.39 to −0.24). Sensitivity analysis showed no changes in the conclusion by type of opioids, type of scale used to assess pain, or methodological quality of the study. The average treatment discontinuation rate for toxicity was 25% in the opioid group (31% for strong opioids and 19% for weak opioids) vs. 7% in the placebo group.

Unlike the many trials of antidepressants for NP, FM and chronic low back pain, antidepressants have not been well studied as a treatment for the pain of OA. However, recent studies have shown that when depression co-occurs with arthritis, it can explain as much of the variance in pain intensity as objective severity of the arthritis [118]. Also, RCTs have shown that treatment of depression in arthritis patients may reduce pain as well as depression [119,120]. Thus, while antidepressants cannot currently be recommended in OA patients without depression, screening for and co-management of depression may benefit pain outcomes.

5. Summary discussion

5.1. Stepwise selection of pharmacotherapy

This review has synthesized conclusions from evidence-based reviews of pharmacotherapy for chronic pain. In

addition to summarizing the various classes of medications, we have discussed four of the most common disorders in which pain is a predominant treatment target: NP, FM, low back pain and OA. Table 3 provides a stepped approach to the selection of pharmacotherapy based upon the evidence from clinical trials. Table 4 highlights the classes of medications that should be considered in the event simple analgesics (acetaminophen and NSAIDs) fail to provide adequate pain relief. The drugs in Table 4 might be considered "intermediate" options since simple analgesics are inexpensive, available without a prescription and often sufficient for mild to moderate pain. Thus, medications in Table 4 are most commonly used after (or in conjunction with) simple analgesics with the aim of

controlling pain without the need for chronic opioid use. Also, as with the treatment of other chronic medical and psychiatric disorders, drugs from different classes may need to be used in combination to improve pain control. Caution should be exercised in combining drugs with serotonin effects (e.g., SNRI antidepressants and tramadol), particularly when higher doses are used, to minimize the rare occurrence of serotonin syndrome [121,122].

5.2. Modifying treatment in older patients

There are a few modifications that should be considered in applying the algorithm in Table 3 to older adults. First,

Table 3
Evidence-based medication algorithm for chronic pain

Step	Type of pain	Medication	Comments
1	Most	● Acetaminophen 650–1000 mg q 6 h (maximum of 2000 mg/day if cirrhosis or ≥3 alcoholic drinks/day) ● NSAIDS (try at least 2 different ones before considering class failure) □ Naproxen 500 mg q 12 h, or 500 mg in a.m. and then 250 bid (maximum of 1000 mg/day) □ Salsalate 1000 mg q 8 h or 1500 mg q 12 h (maximum 3000 mg/day) □ Etodolac 300 mg q 8 h or 500 q 12 h (maximum 1000 mg/day) □ Ibuprofen 600 mg q 6 h (maximum 2400 mg/day) □ Diclofenac 50 mg q 8 h (max 150) □ Naproxen 500 mg q 12 h, or 500 mg in a.m. and then 250 bid (maximum of 1000 mg/day)	All NSAIDs appear equally effective as analgesics. While GI adverse effects have traditionally been considered the most common and worrisome complication, cardiovascular risk has gained increasing attention. Naproxen has the safest cardiovascular profile
2	Neuropathic Fibromyalgia Low back	● Tricyclic antidepressant □ Amitriptyline, start at 10–25, titrate to 100 mg □ Nortriptyline, start at 10–25, titrate to 100 mg	Do not exceed 50 mg if on SSRI or SNRI Relatively contraindicated in elderly or cardiovascular disease
2	Neuropathic Fibromyalgia Osteoarthritis	● Tramadol: start 25 mg BID or TID; titrate to maximum of 100 mg QID	Can be combined with acetaminophen Lower maximum daily doses in patients >75 years (300 mg), renal insufficiency (200 mg) or cirrhosis (100 mg)
3	Neuropathic	● Gabapentin, begin 100 mg TID; titrate up to 900–1200 mg TID ● Duloxetine 60 mg daily ● Pregabalin 300-450 mg daily in divided doses	
3	Fibromyalgia	● Cyclobenzaprine, 5–10 mg BID to TID ● Pregabalin 300-450 mg daily in divided doses ● Duloxetine 60 mg daily ● Milnacipran 50-100 mg BID	
4	Neuropathic Osteoarthritis	● Topical creams □ Capsaicin cream 0.025% 4 times per day over painful area □ Lidocaine 5% patch (maximum, 3 patches) □ Salsalate cream 4 times per day over painful area	Local skin irritation can limit use Less practical if pain not localized Benefits are modest
5	Opioids	● Codeine 30 mg (often combined with acetaminophen) ● Hydrocodone (combined with acetaminophen) ● Oxycodone ● Morphine sustained-release, begin 15 mg BID and increase as needed ● Oxycodone, sustained-release, begin 5–10 mg QD to BID ● Methadone ● Fentanyl patch, begin 25 μg/h patch every 72 h	Codeine and hydrocodone are lower scheduled (Class III) and easier to refill Oxycodone sustained-release and fentanyl patch are fairly expensive Short-acting opioids should be used first to determine dosing and side effects Constipation prophylaxis (e.g., stool softener, senna) is important in patients at risk

Table 4
Evidence-based pharmacotherapy for common pain conditions as intermediate treatment options between simple analgesics (acetaminophen and NSAIDs) and opioids[a]

Disorder	Epidemiology	Tricyclic antidepressants	SNRI antidepressants	$\alpha_2\delta$ Anticonvulsants	Tramadol	Other	Comments
Neuropathic pain	3% general population at some point, and 10% of diabetics	+	+	+	+	Topicals	Opioids can be used when other drugs fail
Fibromyalgia	3.4% of women and 0.5% of men in general population	+	+	+	+	Cyclobenzaprine	Strongest data for TCAs, duloxetine, pregabalin, milnacipran, tramadol Opioids lack good evidence
Osteoarthritis	Most common arthritis, increasing sharply with age. Present in >one-third of persons >65 years				+		Simple analgesics are mainstay of pharmacotherapy Joint replacement is effective for severe knee/hip disease Low-dose opioids may be useful in some patients
Low back pain	5th most common reason for outpatient visits and a leading cause of disability	+	±		+		Opioids can be used selectively but with caution, since younger age of patients might require years of use

[a] Among *TCAs*, low-dose amitriptyline is best studied, with some evidence for nortriptyline and other TCAs. Among *SNRI antidepressants*, duloxetine and milnacipran (both FDA approved) have been best studied, with smaller trials providing some evidence for venlafaxine. Preliminary evidence exists for SNRIs in back pain, but more research is needed. Among $\alpha_2\delta$ *anticonvulsants*, gabapentin and pregabalin have strong evidence for NP, and pregabalin has strong evidence (and gabapentin modest evidence) for FM. Though not a controlled substance, *tramadol* has some weak opioid-like effects, some risk of abuse and rare occurrences of seizures and serotonin syndrome in high doses.

acetaminophen would typically be tried prior to NSAIDs because of the slightly higher risk/benefit ratio of NSAIDs in older adults. Second, when using NSAIDs in persons 60 years and older, a proton pump inhibitor should be added as prophylaxis against GI bleeding in those with GI symptoms (dyspepsia or gastroesophageal reflux) or who are on antiplatelet agents (e.g., aspirin, clopidogrel) or corticosteroids [123]. Although some experts believe non-acetylated salicylates may lessen GI side effects and serve as an alternative to NSAIDs, the amount of evidence supporting this is only modest [124] .Third, amitriptyline and cyclobenzaprine should probably be avoided due to their highly anticholinergic properties. Fourth, a TCA (e.g., nortriptyline) would only be used early in the algorithm for low back pain and be deferred to later in the algorithm for NP and FM which have more non-TCA evidence-based treatments. Fifth, opioids should be started at low doses and titrated slowly, and special attention should be paid to preventing constipation. More detailed recommendations on management of chronic pain in the elderly are reviewed elsewhere [125,126].

5.3. Limitations of available evidence

There are several important gaps in our knowledge regarding treatment which, in fact, are probably not unique to chronic pain. First, there are a paucity of head-to-head trials, meaning that while we can draw conclusions about the effectiveness of a particular monotherapy compared to placebo or minimal treatment controls, we have much less

information about the comparative effectiveness of different treatments. Second, few trials evaluate different strategies for choosing initial treatment, so that deciding between "first-line" vs. subsequent treatments is more a matter of expert consensus, clinician experience and patient preferences. Third, evidence is sparse on the effectiveness of dual-medication or other combination therapy relative to mono-therapy or sequential treatment, even though patients are frequently prescribed more than one medication or treatment [127,128]. One small cross-over trial found that gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent [129]. Fourth, most treatment trials are short-term, so that the evidence of sustained benefits beyond 4–12 weeks is often lacking; this is a critical gap given the fact that our focus is on the management of chronic pain. Fifth, patients with a SUD and, oftentimes, other psychiatric comorbidity are frequently excluded from clinical trials of opioids and other analgesics as well. Paradoxically, pain is not only more prevalent in these patients but may be more challenging to treat and also complicate the management of the SUD or other psychiatric disorders.

Sixth, lack of evidence of efficacy is not the same as evidence of lack of efficacy. For a number of drugs, there are simply too few well-conducted trials to draw convincing conclusions. To convincingly establish lack of efficacy may require several negative trials (just as more than one positive trial is typically required to establish efficacy). There are funding, publication and investigator disincentives to conducting multiple trials for a treatment which does not

appear promising. Seventh, while a drug from a particular class may receive an FDA indication for treatment of a specific disorder, other agents from the same class may be effective but have never been tested in large trials nor have a sponsor that seeks an FDA indication. Clinicians then need to weigh drug costs (particularly if there is a generic drug from the same class), the quantity and quality of published evidence for the alternative agent including the data that comes from nonregistration trials, and the medicolegal implications of off-label use. Eighth, the impact of pharmaceutical sponsorship is being increasingly scrutinized. For example, a greater proportion of industry-funded clinical trials report positive results for treatments across a variety of conditions than do trials not funded by industry [130,131]. In contrast, it is often difficult to obtain funding to study generic drugs that could be effective if examined in sufficiently large trials. Also, since treatment guideline panels have often included experts with financial ties to industry, the guideline development process must incorporate appropriate safeguards to minimize conflict of interest.

5.4 Conclusion

Despite these gaps, substantial evidence has accumulated over the past several decades about what works and does not work for chronic pain. Avoiding ineffective treatments and maximizing treatments proven beneficial in clinical trials are likely to produce better outcomes than has often been experienced by clinicians and patients in the management of chronic pain. Additionally, identifying and co-managing pain that is comorbid with psychiatric disorders have the promise of improving both physical and psychological outcomes.

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