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Pharmacologic Management of Chronic Pain

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Chronic pain is a multifactorial condition with both physical and psychological symptoms, and it affects around 20% of the population in the developed world. In spite of outstanding advances in pain management over the past decades, chronic pain remains a significant problem. This article provides a mechanism- and evidence-based approach to improve the outcome for pharmacologic management of chronic pain. The usual approach to treat mild to moderate pain is to start with a nonopioid analgesic. If this is inadequate, and if there is an element of sleep deprivation, then it is reasonable to add an antidepressant with analgesic qualities. If there is a component of neuropathic pain or fibromyalgia, then a trial with one of the gabapentinoids is appropriate. If these steps are inadequate, then an opioid analgesic may be added. For moderate to severe pain, one would initiate an earlier trial of a long term opioid. Skeletal muscle relaxants and topicals may also be appropriate as single agents or in combination. Meanwhile, the steps of pharmacologic treatments for neuropathic pain include (1) certain antidepressants (tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors), calcium channel α_2-δ ligands (gabapentin and pregabalin) and topical lidocaine, (2) opioid analgesics and tramadol (for first-line use in selected clinical circumstances) and (3) certain other antidepressant and antiepileptic medications (topical capsaicin, mexiletine, and *N*-methyl-d-aspartate receptor antagonists). It is essential to have a thorough understanding about the different pain mechanisms of chronic pain and evidence-based multi-mechanistic treatment. It is also essential to increase the individualization of treatment. (Korean J Pain 2010; 23: 99-108)

Key Words:
chronic pain, pharmacologic management.

INTRODUCTION

Chronic pain is one of the most prevalent, costly, and disabling conditions in both clinical practice and the workplace, yet it often remains inadequately treated [1]. The available guidelines are not universally accepted by those involved in pain management, and pain treatment seems to be mainly guided by tradition and personal experience [2]. Moreover, chronic pain commonly coincides with depression and sleep disturbance, as well as mood and anxiety disorders.

Neuropathic pain has recently been defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [3]. Treatment of neu-

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ropathic pain is challenging. Compared to patients with nonneuropathic chronic pain, patients with neuropathic pain seem to have higher than average pain scores and a lower health-related quality of life (even after adjusting for pain scores); they require more medication and they report less pain relief with treatment [4,5].

Therefore, it is not so easy to plan effective pharmacologic therapy for chronic pain. In this article, we will discuss the major classes of medications as they relate to chronic pain management and we offer better treatment decisions and combination therapy by increasing physicians' knowledge of the pharmacological options that are available to manage different pain mechanisms.

SPECIFIC MEDICATIONS

1. Nonopioid analgesics

Aspirin and other related compounds constitute a class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have 3 desirable pharmacological effects: anti-inflammatory, analgesic, and antipyretic effects. All NSAIDs and COX-2 agents appear to be equally effective in the treatment of pain disorders [6]. While gastrointestinal (GI) adverse effects have traditionally been considered the most common and worrisome complication of NSAIDs, the cardiovascular risk has gained increasing attention, and this has prompted the American Heart Association to recommend acetaminophen, nonacetylated salicylates and even short-term opioids instead of NSAIDs and particularly COX-2 agents in patients with coronary artery disease [7]. Acetaminophen has analgesic and antipyretic effects similar to NSAIDs, but it lacks a specific anti-inflammatory effect. Acetaminophen is a slightly weaker analgesic than NSAIDs [8-10], but it 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 [11].

2. Tramadol

Although the mode of action of tramadol is not completely understood, tramadol is a drug with a dual activity: one-third of its activity is due to an opioid-like mechanism and two-thirds are due to a mechanism similar to amitriptyline. It truly represents a multimodal drug to consider for pain management strategies [12]. Tramadol has proven effective to treat osteoarthritis (OA), fibromyalgia (FM), and neuropathic pain (NP). 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. While the degree of physical dependence appears to be relatively mild, patients have reported symptoms of psychic dependence, such as craving tramadol when discontinuing the drug [13]. Seizures have been reported with tramadol use in the form of 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 an increased risk for seizures [14]. Daily doses of tramadol should not exceed 400 mg.

3. Opioid analgesics

Most available opioids are μ-opioid receptor agonists or drugs with direct affinity for μ-opioid receptors. The pure agonists have no apparent ceiling effect for analgesia. The exception is meperidine (Demerol®) that is limited by an active metabolite nor-meperidine, which is associated with excitatory side effects with a risk of seizures. Meperidine is not recommended for the treatment of chronic pain. Partial agonists with mixed agonist-antagonist action are generally not indicated for the treatment of chronic pain [15].

There is growing evidence that controlled-release opioid analgesics have a role to play in patients with chronic pain. A recent meta-analysis of 41 randomized controlled trials involving 6,019 patients found that opioids were more effective than placebo for both the pain and functional outcomes of patients with nociceptive and neuropathic pain [16]. The guidelines for the use of opioid analgesics for chronic noncancer pain have been established by the Canadian Pain Society [17], and the evidence supports the assertion that opioids are a reasonable and efficacious treatment for people with chronic pain [18]. The average duration of the trials was only 5 weeks (range: 1-16 weeks) and so there is a need for longer-term trials for examining the efficacy and safety parameters. The recommended front-line agents include hydromorphone, morphine, and oxycodone used orally on a time-contingent basis. Additional options include the fentanyl patch for cases where the oral route is not a reasonable option (malabsorption, vomiting) or it has failed, and methadone

if the previous conventional opioids have failed [19]. An evidence-based review evaluated the long-acting opioids and short-acting opioids for chronic noncancer pain [20]. The author concluded that there is insufficient evidence to suggest that 1 long-acting opioid is superior to the others.

A systematic review of 34 trials with 4,212 patients provided information on the adverse events related to opioid use for treating noncancer pain [21]. Only 3 side effects (nausea, constipation, and somnolence) occurred significantly more frequently with opioids at 14%, 9%, and 6%, respectively, than with placebo. A considerable proportion of patients on opioids (22%) withdrew because of adverse events. Because most of the trials were short (< 4 weeks) and the authors did not titrate the dose, the implications of opioids for long-term use in clinical practice are less certain. Eisenberg et al. [22] also reported adverse events in their systematic review of opioids for NP. Opioid therapy compared to placebo resulted in higher reports of nausea (33% vs. 9%), constipation (33% vs. 10%), drowsiness (29% vs. 12%), dizziness (21% vs. 6%), and vomiting (15% vs. 3%). More patients on opioids withdrew because of adverse effects (11% vs. 4%). Endocrinological abnormalities, such as hypogonadism and erectile dysfunction, may be associated with long term use of opioid therapy [23,24]. In women, opioid use has been associated with amenorrhea and decreased levels of sex hormones [25]. Opioid treatment may be associated with impaired neuropsychological performance regarding reaction times, psychomotor speed, and working memory [26]. However, a recent systematic review concluded that stable doses of opioids did not impair driving performance [27].

〈General principles for the safe, effective use of opioids for managing chronic pain〉

1) Maximize the nonopioid analgesic strategies first (i.e., a "delayed" opioid approach).

2) Inform subjects of the risks, including addiction, before initiating opioid therapy.

3) Facilitate the use of opioid agreements (contracts) for patients initiating opioid therapy or those with increasing doses of opioids. The key points include specifying the frequency of obtaining medications, providing timely refills but no early replacement for lost or stolen prescriptions, providing safe storage, no sharing, single-source prescribing, monitoring through urine screens, and adhering to monitored visits.

4) Schedule follow-up visits at 2- to 3-month intervals and perform periodic urine testing to confirm adherence.

5) Monitor the pain severity and pain-related functional impairment at follow-up visits since the analgesic response may wane in some patients over time.

6) Avoid opioid dose escalations without first assessing the pain severity and the pain's interference with daily life.

7) View opioid initiation as an empiric trial. Consider discontinuing opioids if they are not beneficial.

8) Consider opioid rotation according to the opioid conversion ratio (Table 1) if tolerance to 1 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.

4. Antidepressants

Patients often discontinue this type of medication because side effects occur early, while the analgesia may take several weeks to occur. They must be informed they will become tolerant to the side effect and that analgesia needs some weeks to be evident. Patients must be informed about the rationale for antidepressant therapy and that they are not being treated as though they are affected by psychological problems [28-30]. Antidepressants work at the spinal level by inhibiting the reuptake of the neural transmitters norepinephrine and serotonin, and so this potentiates the inhibitory pathway in the dorsal horn of the spinal cord and at the ectopic sites in the peripheral nerves by blocking Na channels.

Table 1. Oral and Transdermal Opioid Analgesic Equivalence

Drug	Dose (mg)	Duration (h)*
Morphine	20-30	2-4
Codeine	200†	3-4
Hydrocodone	30‡	4-6
Oxycodone	20	3-4
Hydromorphone	7.5	3-4
Meperidine	300†	2-4
Methadone	20§	4-8
Fentanyl (transdermal)	1 μg/h transdermally≈morphine 2 mg/24 h orally	48-72

*Duration of analgesia is dose dependent; the higher the dose, usually the longer the duration. †These high doses of codeine and meperidine are not recommended clinically. ‡Equianalgesic data not available for hydrocodone. §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.

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

TCAs are superior to SSRIs for pain management. Admittedly, the statistical comparisons that have been done 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 for ameliorating chronic pain [31].

2) Serotonin–norepinephrine reuptake inhibitors (SNRIs): Duloxetine has been proven superior to placebo in three 12–week randomized, placebo–controlled trials that enrolled patients with pain due to diabetic peripheral neuropathy [32–34]. Both the patients with and without depression were enrolled in the trials, although the path analysis estimated that more than 90% of the analgesic effect in the duloxetine–treated patients with diabetic neuropathy was attributable to a direct analgesic effect, with less than 10% possibly explained by an antidepressant effect [35]. Duloxetine is also FDA approved for treating the chronic widespread pain of FM [36–38]. A 6–week trial of extended–release venlafaxine in 224 patients with diabetic neuropathy found venlafaxine superior to placebo [39]. Venlafaxine may also be useful in other painful conditions [40], but it does not have the FDA approved indication for pain treatment.

A recent meta–analysis of 5 trials in depressed patients reported a very small and statistically insignificant analgesic effect for duloxetine [41]. Another meta–analysis of 8 trials that compared 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 [42]. In all of these depression trials, pain was examined as a secondary outcome, and in all but 2 trials, 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 from duloxetine for both pain and depression symptoms [43].

5. Anticonvulsants

Anticonvulsants have been used for the management of pain since the 1960s and along with antidepressants, they constitute 1 of the 2 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 2 "gabapentinoids" act as neuromodulators by selectively binding to the α_2-δ– subunit protein of the calcium channels in various regions of the brain and the superficial dorsal horn of the spinal cord. They also have a peripheral analgesic action [44–46]. These actions result in inhibiting the release of excitatory neurotransmitters that are important in the production of pain.

In the 14 chronic NP trials, 42% of the participants improved (i.e., pain relief of 50% or greater) on gabapentin vs. 19% on placebo. The withdrawal rates were 14% for gabapentin vs. 10% for placebo. The FDA has approved pregabalin for the treatment of NP associated with diabetic peripheral neuropathy and PHN and for the treatment of FM.

Gabapentin and pregabalin should be considered as 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 3 to 4 times daily), possibly a simpler dose titration, and an additional FDA indication (FM).

Other drugs worth trying are lamotrigine, clonazepam, and valproate. Carbamazepine and Oxcarbazepine are considered the first effective drugs for trigeminal neuralgia. Carbamazepine and Oxcarbazepine act peripherally on Na channels while the others work at spinal levels by different mechanisms with a common inhibitory effect at the

pre- and post-synaptic levels in the dorsal horn of the spinal cord [29,47].

6. 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) [48]. The mechanism of action for the latter category of agents is unclear, but it may be related in part to sedative effects. 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 improving the functional status in other disorders. Muscle relaxants have a limited role for the treatment of chronic pain, except for cyclobenzaprine as 1 option for treating FM.

7. Topical analgesics

A potential advantage of topical agents is avoiding systemic side effects that are often associated with oral medications. The 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 with other medications or as an alternative for patients who prefer not to ingest pills. Several topical analgesics (lidocaine, capsaicin, and salicylate) have been studied in multiple trials. A 5% lidocaine patch has an FDA indication for PHN. It is applied for 12 h daily. The systemic levels absorbed are very low due to lidocaine working via a local mechanism.

Capsaicin is an alkaloid derived from chili peppers; repeated application is thought to lead to depletion of substance P from the primary afferent neurons [49]. The main disadvantage of capsaicin is the initial burning sensation, which may persist for days. Capsaicin must be applied 3-4 times per day over the entire painful area for up to 6-8 weeks before optimal pain relief can be achieved. Capsaicin 0.075% is used for neuropathic pain, and Capsaicin 0.025% is used for arthritic pain. A new potent (8%) strength patch has shown promising results. It needs to be applied in the hospital after patient sedation or after the skin has been anaesthetized because it is strongly irritating, but a 1 h application can result in analgesia that lasts for several weeks. Mason et al. [50] recently reviewed the clinical trial evidence for capsaicin, including 6 trials for NP and 3 trials for musculoskeletal conditions. They found that 57% of the patients with NP achieved at least 50% pain relief with capsaicin, compared to 42% of the patients on placebo; for patients with musculoskeletal conditions, the response rates were 38% vs. 25%, respectively [50]. Around one third of the patients experienced local adverse events with capsaicin.

Topical salicylate has proven superior to placebo for treating chronic pain [51]. However, the larger, more rigorous trials have tended to be negative. A recent study suggests topical ibuprofen may also be beneficial for knee OA [52].

TREATMENT PLAN

First of all, it is important that physicians understand the multifactorial nature of chronic pain and the physiological differences between nociceptive pain and neuropathic pain. They had better do a multi-mechanistic approach with taking into account stepwise selection of pharmacotherapy (Fig. 1) [15]. A multi-mechanistic approach means combining 2 substances from different drug classes, or administering an analgesic with 2 different mechanisms of action. In some circumstances, a single compound capable of addressing both nociceptive and neuropathic pain is desirable [2].

In addition, physicians have to modify treatment for pediatric, geriatric, hepatic, and renal failure patients. Generally, all drugs should be administered cautiously for these cases. The dose should be low and titrated slowly to avoid toxicity. It has been suggested that up to 40% of children lack the enzyme to metabolize codeine to morphine [53]. In these circumstances, a medication substitution should be attempted. Meperidine use is not recommended in children because of the side effects encountered due to the main metabolite, normeperidine [54]. Although NSAIDs are a good option, they should be avoided in children younger than 6 months of age and children with NSAID or aspirin allergy, hypovolemia or dehydration, renal or hepatic failure, peptic ulcer disease, or coagulopathies [54]. Children on anticoagulants, steroids, and nephrotoxic agents should not receive NSAIDs.

The considerations for geriatric patients are as

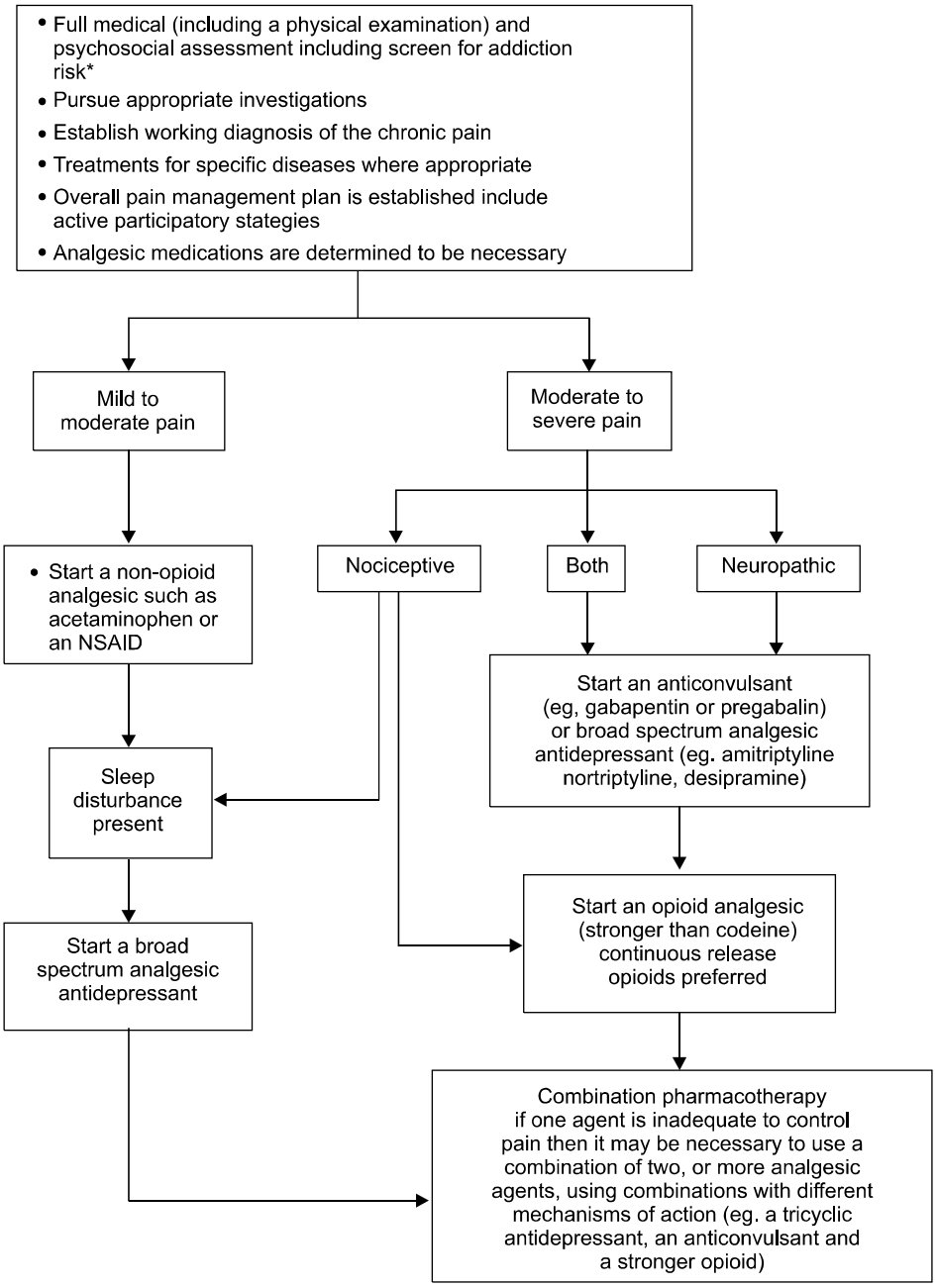

Fig. 1. Treatment algorithm for pharmacotherapy of chronic noncancer pain. In general, if one agent in a class of medications does not provide adequate analgesia or causes limiting side effects, it is worth pursuing serial trials of 1 or 2 others from the class. Topicals may be introduced at any point as a sole agent or in combination.

follows. First, consider the risk/benefit ratio of NSAIDs. Second, when using NSAIDs in persons 60 years and older, a proton pump inhibitor should be added as prophylaxis against GI bleeding in those patients with GI symptoms (dyspepsia or gastroesophageal reflux) or those patients who are on antiplatelet agents (e.g., aspirin, clopidogrel) or corticosteroids [55]. Third, amitriptyline and cyclobenzaprine should probably be avoided due to their highly anticholingergic properties. Fourth, opioids should be started at low doses and titrated slowly, and special attention should be paid to preventing constipation.

Aspirin should be avoided for patients with end-stage renal disease, and dosage adjustments should be made when ASA is used for long-term therapy in a hepatically compromised patient [56]. Acetaminophen is used with an increased dose interval in hepatic and renal failure patients [57,58]. Tramadol, hydromorphone, and morphine are used very cautiously at a reduced dose in the presence of kidney

and liver abnormalities [56,59,60]. Few studies are available to examine the safety of morphine in conjunction with liver failure; any hepatic recommendations are not available. Codeine, dihydrocodeine, and dextropropoxyphene are not recommended for use in the presence of renal failure [59,60]. Fentanyl is an ideal choice for patients with renal failure because of the lack of active metabolites, yet it is likely that fentanyl clearance is delayed because of hepatic failure, and this is because fentanyl is subject to a high hepatic extraction ratio [61].

Three evidence-based consensus guidelines for the pharmacologic treatment of neuropathic pain have recently been updated: (1) the International Association for the Study of Pain Neuropathic Pain Special Interest Group (NeuPSIG) guidelines, (2) the Canadian Pain Society (CPS) guidelines, and (3) the European Federation of Neurological Societies (EFNS) guidelines (Table 2) [62]. These guidelines all recommend TCAs, gabapentin, and pregabalin as first-line treatment options for patients with neuropathic pain (excluding trigeminal neuralgia). They also recommend reserving opioid analgesics and tramadol as second- or third-line options in most cases, despite the evidence of their efficacy for neuropathic pain. In 2 of the guidelines, topical lidocaine is recommended as a first-line treatment for patients with localized peripheral neuropathic pain (particularly in patients with postherpetic neuralgia and allodynia), whereas the other guideline considers topical lidocaine a second-line treatment. The NeuPSIG guidelines recommend duloxetine and venlafaxine as first-line treatment options, but the Canadian Pain Society and EFNS guidelines recommend these SNRIs as second-line options for patients with painful polyneuropathies.

Even if a correct treatment is started, there are some concerns to keep in mind. Insufficient dosage is another possible explanation for treatment failure. It may be difficult to maintain the balance between adequate pain relief and acceptable tolerability, as well as side effects, of the pharmacotherapy. This may be explained by the hypothesis of the Vicious Circle, which is particularly applicable to classical opioids, but also plays a role in combination therapy (Fig. 2) [2]. Informing and supplying the patient with information is mandatory not only at the beginning, but also when the effective drug combination and dosages have been found. The patient should be convinced that chronic pain needs chronic therapy. Patients frequently stop therapy due to fear of addiction and toxicity. Also, the cost of the therapy is another reason to stop the treatment. Finally, it is necessary that physicians individualize the pharmacotherapy of each patient.

SUMMARY

A number of medications have proven to be effective in chronic pain disorders and their use individually or in combination should improve the management of chronic pain. Especially for neuropathic pain, the medications rec-

Table 2. Comparison of Neuropathic Pain Treatment Guidelines, Excluding Trigeminal Neuralgia*

Medication class	NeuPSIG guidelines	CPS guidelines	EFNS guidelines
Tricyclic antidepressants	First line	First line	First line for PPN, PHN, and CP
Calcium channel α_2-δ ligands (gabapentin and pregabalin)	First line	First line	First line for PPN, PHN, and CP
SNRIs (duloxetine and venlafaxine)	First line	Second line	Second line for PPN
Topical lidocaine	First line for localized peripheral NP	Second line for localized peripheral NP	First line for PHN if small area of pain/allodynia
Opioid analgesics	Second line except in selected circumstances†	Third line	Second-third line for PPN, PHN, and CP
Tramadol	Second line except in selected circumstances†	Third line	Second-third line for PPN and PHN

NeuPSIG: Neuropathic Pain Special Interest Group, CPS: Canadian Pain Society, EFNS: European Federation of Neurological Societies, PPN: painful polyneuropathy, PHN: postherpetic neuralgia, CP: central pain, SNRIs: serotonin and norepinephrine reuptake inhibitors, NP: neuropathic pain. *Only medications considered first or second line in 1 of the guidelines are presented. †Opioid analgesics and tramadol were considered first-line options in the following circumstances: for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.

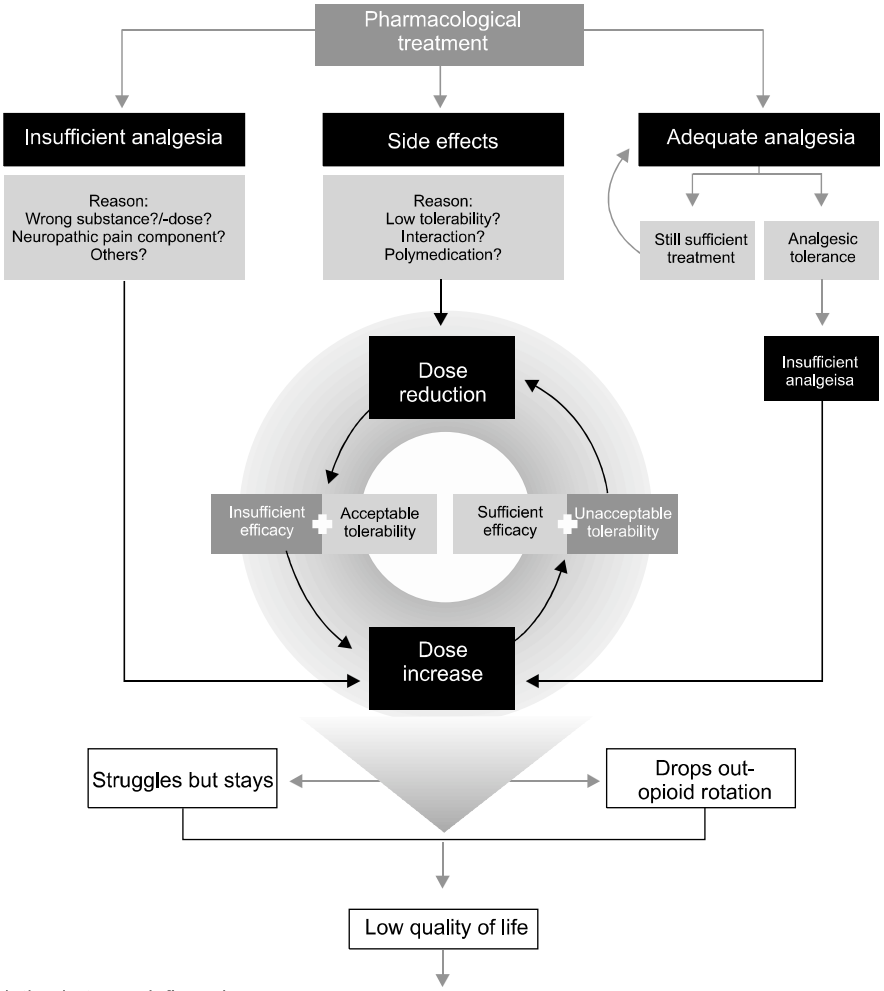

Fig. 2. The Vicious Circle showing interaction of influencing factors.

ommended as first-line treatments include TCAs, SNRIs, calcium channel α_2-δ ligands, and lidocaine patch. Opioid analgesics and tramadol are recommended as second-line treatments that can be considered for first-line use in selected clinical circumstances. A thorough understanding of pain mechanisms and good communication between physicians and patients are required to improve patient outcomes. Avoiding ineffective treatments and maximizing the treatments that have been proven beneficial in clinical trials (i.e., evidence-based treatments) are likely to produce better outcomes than have 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 promise for improving both the physical and psychological outcomes. Furthermore, the multi-modality treatment of chronic pain incorporates not only this approach to pharmacological treatment, but also non-pharmacological strategies such as interventional pain management, physiotherapy, psychotherapy, and pain rehabilitation.

REFERENCES

1. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hosp Psychiatry 2009; 31: 206-19.
2. Varrassi G, Müller-Schwefe G, Pergolizzi J, Orónska A, Morlion B, Mavrocordatos P, et al. Pharmacological treatment of chronic pain - the need for CHANGE. Curr Med Res Opin 2010; 26: 1231-45.
3. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky

JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical research purposes. Neurology 2008; 70: 1630–5.
4. Torrance N, Smith BH, Watson MC, Bennett MI. Medication and treatment use in primary care patients with chronic pain of predominantly neuropathic origin. Fam Pract 2007; 24: 481–5.
5. Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. Clin J Pain 2007; 23: 143–9.
6. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: an updated Cochrane review. Spine 2008; 33: 1766–74.
7. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007; 115: 1634–42.
8. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: a meta-analysis. Arthritis Rheum 2004; 51: 746–54.
9. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006; 1: CD004257.
10. Wegman A, van der Windt D, van Tulder M, Stalman W, de Vries T. Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. J Rheumatol 2004; 31: 344–54.
11. Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA 2006; 296: 87–93.
12. Bonezzi C, Allegri M, Demartini L, Buonocore M. The pharmacological treatment of neuropathic pain. Eur J Pain Suppl 2009; 3: 85–8.
13. McDiarmid T, Mackler L, Schneider DM. Clinical inquiries. What is the addiction risk associated with tramadol? J Fam Pract 2005; 54: 72–3.
14. Sansone RA, Sansone LA. Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. Psychiatry (Edgmont) 2009; 6: 17–21.
15. Lynch ME. The pharmacotherapy of chronic pain. Rheum Dis Clin North Am 2008; 34: 369–85.
16. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006; 174: 1589–94.
17. Jovey RD, Ennis J, Gardner-Nix J, Goldman B, Hays H, Lynch M, et al. Use of opioid analgesics for the treatment of chronic noncancer pain--a consensus statement and guidelines from the Canadian Pain Society, 2002. Pain Res Manag 2003; 8(Suppl A): 3A–28A.
18. Lynch ME, Watson CP. The pharmacotherapy of chronic pain: a review. Pain Res Manag 2006; 11: 11–38.
19. Lynch ME. A review of the use of methadone for the treatment of chronic noncancer pain. Pain Res Manag 2005; 10: 133–44.
20. Fine PG, Mahajan G, McPherson ML. Long-acting opioids and short-acting opioids: appropriate use in chronic pain management. Pain Med 2009; 10(Suppl 2): S79–88.
21. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther 2005; 7: R1046–51.
22. Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain. Cochrane Database Syst Rev 2006; 3: CD006146.
23. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003; 349: 1943–53.
24. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain 2002; 3: 377–84.
25. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J Pain 2008; 9: 28–36.
26. Højsted J, Sjøgren P. An update on the role of opioids in the management of chronic pain of nonmalignant origin. Curr Opin Anaesthesiol 2007; 20: 451–5.
27. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Are opioid-dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review. J Pain Symptom Manage 2003; 25: 559–77.
28. McQuay HJ, Tramér M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain 1996; 68: 217–27.
29. Collins SL, Moore RA, McQuay HJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manage 2000; 20: 449–58.
30. Mendell JR, Sahenk Z. Clinical practice. Painful sensory neuropathy. N Engl J Med 2003; 348: 1243–55.
31. Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. J Gen Intern Med 1997; 12: 384–9.
32. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005; 116: 109–18.
33. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med 2005; 6: 346–56.
34. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, et al. A randomized controlled trial of duloxetine

in diabetic peripheral neuropathic pain. Neurology 2006; 67: 1411–20.
35. Perahia DG, Pritchett YL, Desaiah D, Raskin J. Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? Int Clin Psychopharmacol 2006; 21: 311–7.
36. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004; 50: 2974–84.
37. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005; 119: 5–15.
38. Arnold LM, Pritchett YL, D'Souza DN, Kajdasz DK, Iyengar S, Wernicke JF. Duloxetine for the treatment of fibromyalgia in women: pooled results from two randomized, placebo-controlled clinical trials. J Womens Health (Larchmt) 2007; 16: 1145–56.
39. Rowbotham M, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004; 110: 697–706.
40. Grothe DR, Scheckner B, Albano D. Treatment of pain syndromes with venlafaxine. Pharmacotherapy 2004; 24: 621–9.
41. Spielmans GI. Duloxetine does not relieve painful physical symptoms in depression: a meta-analysis. Psychother Psychosom 2008; 77: 12–6.
42. Krebs EE, Gaynes BN, Gartlehner G, Hansen RA, Thieda P, Morgan LC, et al. Treating the physical symptoms of depression with second-generation antidepressants: a systematic review and metaanalysis. Psychosomatics 2008; 49: 191–8.
43. Brecht S, Courtecuisse C, Debieuvre C, Croenlein J, Desaiah D, Raskin J, et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. J Clin Psychiatry 2007; 68: 1707–16.
44. Carlton SM, Zhou S. Attenuation of formalin-induced nociceptive behaviors following local peripheral injection of gabapentin. Pain 1998; 76: 201–7.
45. Field MJ, Holloman EF, McCleary S, Hughes J, Singh L. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. J Pharmacol Exp Ther 1997; 282: 1242–6.
46. Chen SR, Xu Z, Pan HL. Stereospecific effect of pregabalin on ectopic afferent discharges and neuropathic pain induced by sciatic nerve ligation in rats. Anesthesiology 2001; 95: 1473–9.
47. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ 1995; 311: 1047–52.
48. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Cochrane Back Review Group. Muscle relaxants for non-specific low back pain: a systematic review within the framework of the cochrane collaboration. Spine 2003; 28: 1978–92.
49. Chong MS, Hester J. Diabetic painful neuropathy: current and future treatment options. Drugs 2007; 67: 569–85.
50. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ 2004; 328: 991.
51. Mason L, Moore RA, Edwards JE, McQuay HJ, Derry S, Wiffen PJ. Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain. BMJ 2004; 328: 995.
52. Underwood M, Ashby D, Cross P, Hennessy E, Letley L, Martin J, et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. BMJ 2008; 336: 138–42.
53. Nandi R, Beacham D, Middleton J, Koltzenburg M, Howard RF, Fitzgerald M. The functional expression of mu opioid receptors on sensory neurons is developmentally regulated; morphine analgesia is less selective in the neonate. Pain 2004; 111: 38–50.
54. Lönnqvist PA, Morton NS. Postoperative analgesia in infants and children. Br J Anaesth 2005; 95: 59–68.
55. Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2008; 118: 1894–909.
56. Barkin RL, Barkin SJ, Barkin DS. Pharmacotherapeutic management of pain with a focus directed at the geriatric patient. Rheum Dis Clin North Am 2007; 33: 1–31.
57. Barkin RL, Sable KS. Caution recommended for prescribing and administering COX-1/COX-2 and COX-2 specific NSAIDs. P T 2000; 25: 196–202.
58. Innes GD, Zed PJ. Basic pharmacology and advances in emergency medicine. Emerg Med Clin North Am 2005; 23: 433–65.
59. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care 2005; 33: 311–22.
60. Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet 1996; 31: 410–22.
61. Stern SS, Ponticello MN. Current concepts in pain management: pharmacologic options for the pediatric, geriatric, hepatic and renal failure patient. Clin Podiatr Med Surg 2008; 25: 381–407.
62. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 2009; 122(Suppl 10): S22–32.