REVISTA BRASILEIRA DE ANESTESIOLOGIA

MISCELLANEOUS

Good clinical practice guide for opioids in pain management: the three Ts – titration (trial), tweaking (tailoring), transition (tapering)

Flaminia Coluzzi[a], Robert Taylor Jr.[b], Joseph V. Pergolizzi Jr.[c,d,e], Consalvo Mattia[a], Robert B. Raffa[f,*]

[a] *Department of Medical, Surgical Sciences and Biotechnologies, SAPIENZA University of Rome, Rome, Italy*
[b] *NEMA Research Inc., Naples, USA*
[c] *Johns Hopkins University, Baltimore, USA*
[d] *Department of Pharmacology, Temple University School of Medicine, Philadelphia, USA*
[e] *Georgetown University School of Medicine, Washington, USA*
[f] *Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, USA*

Abstract

Background and objectives: Achieving good clinical practice in the use of opioids as part of a comprehensive pain management regimen can face significant challenges. Despite guidelines from governmental and pain society/organization sources, there are still significant hurdles. A review of some basic tenets of opioid analgesia based on current published knowledge and experiences about this important healthcare imperative is warranted.

Content: Consistent with guidelines, the literature supports using the lowest total opioid dose that provides adequate pain control with the fewest adverse effects. Titration (or trial) during opioid initiation is a way of starting low and going slow (and assessing the appropriateness of a specific opioid and formulation). Recognizing that multiple factors contribute to an individual's personal experience of pain, the physical, psychological, social, cultural, spiritual, pharmacogenomic, and behavioral factors of the individual patient should be taken into account (tweaking, or tailoring). Finally, for those patients for whom transition (tapering) from opioid is desired, doing so too rapidly can have negative consequences and minimization of problems during this step can be achieved by proper tapering.

Conclusion: We conclude that a simultaneously aggressive, yet conservative, approach is advocated in the literature in which opioid therapy is divided into three key steps (the 3 T's): titration (or trial), tweaking (or tailoring), and transition (or tapering). Establishment of the 3 T's along with the application of other appropriate good medical practice and clinical

* Corresponding author.
  E-mail: robert.raffa@temple.edu (R.B. Raffa).

experience/judgment, including non-pharmacologic approaches, can assist healthcare providers in the effort to achieve optimal management of pain.

Orientação para boa prática clínica para opioides no tratamento da dor: os três ''Ts'' – titulação (teste), ajustes (individualização), transição (redução gradual)

Resumo
Justificativa e objetivos: A realização de uma boa prática clínica com o uso de opioides como parte de um regime abrangente de tratamento da dor pode enfrentar desafios significativos. Apesar das diretrizes provenientes de sociedades/organizações não governamentais para o manejo da dor, ainda existem obstáculos significativos. A revisão de alguns princípios bási-cos da analgesia com opioide com base na experiência e conhecimento das publicações atuais sobre esse cuidado importante da saúde é justificável.
Conteúdo: De acordo com as diretrizes, a literatura apoia o uso da dose total mais baixa de opi-oides que forneça o controle adequado da dor com menos efeitos adversos. A titulação (teste) ao iniciar a administração de um opioide é uma maneira de começar com uma concentração baixa e ir devagar (avaliando a adequação da fórmula específica de um opioide). O ajuste (individualização) é reconhecer que vários fatores contribuem para a experiência pessoal da dor de um indivíduo, tais como fatores físicos, psicológicos, sociais, culturais, espirituais, far-macogenômicos e comportamentais. Finalmente, para aqueles pacientes nos quais a transição (redução gradual) do opioide é desejada, fazer essa transição muito rapidamente podem ter consequências negativas, e é possível minimizar os problemas durante essa etapa através de uma redução gradual.
Conclusão: Concluímos que uma abordagem simultânea, agressiva, porém conservadora é defendida na literatura em que a terapia com opioides é dividida em três etapas principais (os 3 ''Ts'' – em inglês: *titration, tailoring, tapering*): titulação (teste), ajuste (individualização) e transição (redução gradual). Estabelecer os três Ts, juntamente com a aplicação de outra boa prática médica e experiência/julgamento clínico, incluindo abordagens não farmacológicas, podem ajudar os profissionais de saúde no esforço para alcançar o tratamento ideal da dor.

Introduction

Current estimates indicate that as many as 100 million Americans are suffering from a chronic pain condition[1] and a prevalence of 10–50% throughout European countries.[2–4] Inadequate pain treatment can have severe consequences at both the individual and societal levels. For individuals, simple daily activities can be difficult and disruptions in one's routine can further lead to mood disorders such as depression, anxiety, and stress.[5] Taken together, these problems can decrease a patient's quality of life. For society, pain patients place a burden on economic productivity and the healthcare system.[6]

In addition to non-pharmacologic options, there are several pharmacologic options for the treatment of pain, as promulgated by the WHO (World Health Organization) pain 'ladder' and modifications.[7] They include NSAIDs (nonsteroidal anti-inflammatory drugs), acetaminophen, weak and strong opioids, muscle relaxants, anticonvulsants, and antidepressants. Most of these are adequate to treat mild to moderate pain in the short term. For moderate-to-moderate severe pain, strong opioids are generally considered the first choice. Opioids have become increasingly popular in treating moderate to moderately severe; ''around the clock'' pain conditions. Their efficacy for short-term pain relief has been documented in many randomized clinical trials; their long-term benefit/risk ratio for non-cancer pain is still under debate.[8–11] The United States FDA promotes a Risk Evaluation and Mitigation Strategy (REMS).

Placing a patient on opioid therapy requires more than just telling them to take it as indicated within the prescribing leaflet. Pain sensation and perception are different for each individual, so not every patient will respond equally to the same drug. Factors such as age, sex, genetics, and organ function all play a role in analgesic outcome. Thus, administration of an opioid without thorough knowledge of both the individual and the opioid can potentially result in unsafe and inappropriate use. Unfortunately, many healthcare providers have not had the opportunity to be adequately trained to treat pain and understand the complexity

of pain and use of analgesics, especially combinations of analgesics, to treat various types of pain.

Inadequate opioid therapy can generally be traced back to errors during a few key stages of opioid treatment (titration/trial/initiation, tailoring/maintenance, tapering/rotation). Specific step-by-step protocols for each of these stages require experience and education since pain treatment is highly individualized and dynamic. Guidelines from various governmental and pain societies/organizations are available to follow, but currently there is no universal opioid guideline.[10–18] In order to facilitate the design and implementation of rational and appropriate opioid regimens, it is helpful to differentiate the basic steps of opioid therapy. In this review we seek to present current published knowledge and experiences regarding three important steps of opioid treatment: titration (or trial), tailoring, and tapering (The 3T's).

Titration (trial/initiation)

The initiation phase of opioid therapy is a critical step toward achieving the greatest benefit while obtaining the support, trust, and compliance of the patient. The ultimate goal is to be able to provide the fastest pain relief without causing an emergence of adverse effects. However, the initiation of opioids is not the same for every patient and different regimens may need to be implemented (trial of first opioid selection followed, if necessary, by alternative selection), based on the type of pain and patient.[19]

Type of pain

It is best if the healthcare provider can determine the type of pain the patient is experiencing (e.g., low-back pain, osteoarthritis, fibromylagia) and determine whether opioid therapy is appropriate. For example, certain pain conditions such as fibromyalgia do not always adequately respond to opioids[20] and thus might currently not be the first choice for this pain condition. Long-term use of opioids for certain pain conditions, e.g., low-back pain and OA (osteoarthritis) are still under debate. The effectiveness of opioids in these non-cancer conditions, as well as the potential for misuse, abuse, and side effects remain major issues.[21] However, short-term relief has been documented for many pain types including diabetic neuropathy, peripheral neuropathy, postherpetic neuralgia, phantom limb pain, spinal cord injury with pain below the level of injury, lumbar radiculopathy, OA, rheumatoid arthritis, low-back pain, and neck pain.[14] In the course of cancer, pain can start out as mostly nociceptive, but transition (due to peripheral and central sensitization) occurs to include hyperalgesia and a neuropathic component (e.g., allodynia).

Type of patient and opioid choice

The choice of an opioid should be carefully considered. For example, opioid-naïve patients run a higher risk of experiencing adverse effects and overdose. Elderly patients or patients with a number of co-morbidities may benefit from the short half life of immediate release opioids because of the reduced probability of overdose.[22] Guidelines by the

Canadian government have described the use of codeine or tramadol as first-line opioids for mild to moderate chronic pain due to their reduced potential for misuse, overdose and addiction.[14] If pain is not effectively controlled with these opioids, or if adverse effects are experienced, the use of opioids such as morphine, oxycodone, or hydromorphone are described. Other 'atypical' opioids, such as tapentadol or buprenorphine, could be considered.[23,24] Guidelines by the Department of Veteran Affairs and the British Pain Society suggest that no single opioid is superior over others, the choice should be made based on local experience and expertise and that selecting the correct opioid on the first attempt is difficult, so that several rounds of rotation may be necessary.[12,15]

Opioid formulation

It is critical that the temporal setting of pain be matched with the appropriate release-timing of the opioid: immediate release for initial titration; rapid onset breakthrough pain; and extended-release or transdermal patches for around-the-clock analgesia.[14] In general, patients should be placed on sustained/extended release formulations if they benefit from a consistent pharmacokinetic profile. However, patients will respond differently to the type and formulation of an opioid and thus it is up to the healthcare provider and patient to understand that several rounds of opioid rotation might be needed in order to find the most efficacious and safe option.[25]

Starting-dose

There is no universal agreement on the starting-doses of individual opioids. The various initiation doses recommended in several guidelines are presented in Table 1.[14,15]

Titration procedure – general rules and guidelines

With any type of opioid therapy, the end goal is to use the lowest opioid dose that provides an adequate level of pain control and a tolerable side effect profile. Some providers take the approach 'start low and start slow' and this approach seems reasonable. One of the major reasons for slowly and incrementally increasing an opioid dose is to minimize adverse effects. Patients, especially those who are opioid-naïve, require time to adjust to the opioid effects. In addition, it will be easier for providers to find the optimal dose that provides the right balance between benefits and risk. Other reasons for slow titration include: patient may experience changes that alter pain perception after opioid initiation; and the underlying pain condition may worsen (e.g., cancer progression).

Titration: how much and when to increase

There are no set guidelines on when to increase opioid dosage, because it is very difficult to establish a general guideline when pain treatment needs to be individualized. Guidelines for appropriate titration have not been tested formally in clinical trials. Some guidelines are available.[14,15]

Table 1 Initial starting dose for various opioids.

	Canadian guidelines[a]	Department of veteran affairs[a]	Agency medical directors group (opioid naïve)	American society of interventional pain physicians (opioid naïve)	American society of interventional pain physicians (opioid experienced)
Codeine	15–30 mg every 6 h	30 mg q 4–6 h		15 mg bid or tid	
CR codeine	50 mg every 12 h				
CR tramadol	100–150 mg every 24 h			Not recommended	
IR morphine	5–10 mg 4–6 h (max 40)	10–30 mg q 4–6 h	10 mg q 4 h	Not recommended	10 mg, 2–3×
CR morphine	10–20 mg (max 40)	15 mg q 8–12 or 30 mg q 24 h	15 mg q 12 h	Not recommended	15–30 mg, 2× daily
IR oxycodone	5 mg 4–6 h (max 30)	5 mg q 6 h	5 mg q 4–6 h	5–10 mg, 2–3× daily	5–10 mg, 3–4× daily
CR oxycodone	10 mg (max 30 mg/d)	10 mg q 12 h	10 mg q 12 h	Not recommended	10 mg for 12 h
IR hydromorphone	1–2 mg 4–6 h (max 8 mg/d)	2 mg q 4–6 h	2 mg q 4–6 h	2 mg bid or tid	2–4 mg, 2–3× daily
CR hydromorphone	3 mg (max 9 mg/d)			Not recommended	5–10 mg, 2× daily
Hydrocodone		5–10 mg q 4–6 h	5–10 mg q 4–6 h	5–10 mg, 2–3× daily	5–10 mg, 3–4× daily
IR oxymorphone		10–20 mg q 4–6 h	5–10 mg q 4–6 h	5 mg bid or tid	5–10 mg, 2–3× daily
IR tapentadol		50 mg q 4–6 h			
Tramadol		25 mg daily		50 mg bid or tid	50 mg, 3–4× daily
CR oxymorphone		5 mg q 12 h	10 mg q 12 h	Not recommended	10 mg q 12 h
Transdermal fentanyl		25 mcg/h q 72 h		Not recommended	12.5–25 mcg q 72 h

New opioid formulations, recently introduced on the US and/or EU market, are not yet included in current guidelines. However, according to published RCTs, the recommended starting doses are 10/5 mg BID (q 12 h) for ER (extended-release) oxycodone/naloxone and 50 mg BID (q 12 h) for ER tapentadol. CR, controlled release; IR, immediate release.

[a] No distinction between opioid naïve vs. opioid experienced.

Particular care in dosing must be given in the elderly, especially frail elderly, low tolerant opioid patients, and those experiencing side effects. Careful monitoring should always accompany every titrated dose. Providers should also pay particular attention to the development of adverse effects.

Titration: when to stop

Optimal dose is generally considered achieved when a patient has experienced a ≥30% reduction in pain relief (e.g., 2 points on an 11-point numerical rating scale) and no serious, or tolerable, side effects or complications on the dose.[16,26,27] However, all of these are meant to provide general guidance only and the actual regimen should be customized to each patient.

Key points to consider when determining if titration needs to continue:

- Lack of efficacy.
- Side effects have become intolerable.

If efficacy is not achieved, the patient should be re-evaluated or opioid rotation or formulation change should be considered.

Tweaking (tailoring/maintenance)

Pain assessment

Pain assessment is not only determining a patient's pain intensity score. There are many factors that can contribute to an individual's chronic pain experience, including physical, psychological, social, cultural, spiritual, genetic, and behavioral factors. All of these factors should be assessed in order for optimal management to occur. Many tools are available to assess these factors and it is up to the healthcare providers and the patient to determine which ones they prefer to use at initiation and throughout treatment. In addition, it is important for the provider to understand the assessment tool in order for the physician to accurately gauge the impact of each individual factor. A list of common assessments and tools that should be considered is included in Table 2.

Type of patient

Managing pain can be particularly challenging in older patients who often have comorbidities or physiological changes that affect pharmacokinetics or side-effect profiles

Table 2 Types of assessment and tools for determining appropriateness of opioid therapy.[13–15,22,48–54]

Pain related history	Social history	Risk assessment for substance abuse
Prior pain treatment	Employment	Urine test
Pain related fear	Cultural background	Use of risk stratification tools
Pain interference with activities	Family support	Risk of suicide
Medical history	Legal history	
Allergies		
Review of diagnostic studies		
Psychiatric history	**Physical examination**	**Tools**
Depression	Mental status	Screener and Opioid Assessment for Patients with Pain (SOAPP) version 1
Anxiety disorders	Age	Revised SOAPP (SOAPP-R)
Emotional disorders	Race	Opioid Risk Tool (ORT)
Personality disorders	Gender	Diagnosis, Intractability, Risk, Efficacy (DIRE) instrument
Substance use history		CAGE-AID

of drugs. The general approach includes: the use of the least-invasive route of medication, the choice of sustained-release formulations, the introduction of one agent at a time, at the lowest effective dose, according to the rule 'start low, go slow', and a strict monitoring of efficacy and safety. According to the 2009 American Geriatrics Society (AGS) guidelines on pharmacological treatment of persistent pain in older adults, acetaminophen remains the first-line recommendation among the non-opioid class.[28] NSAIDs pose a risk for causing adverse events within older adult populations. Their use should be limited, particularly in patients with reduced creatinine clearance, gastropathy, cardiovascular disease, or congestive heart failure. If needed, a topical formulation should be preferred. Among oral NSAIDs, naproxen may have a comparatively lower risk of cardiovascular events.[29] In the elderly, NSAIDs and cyclooxygenase-2 (COX-2)-selective inhibitors should only be used in rare instances.[30] Both require co-administration of an agent for gastrointestinal protection, such as a proton pump inhibitor, if the therapy is extended.

Opioids are not excluded from use for older adults. Opioid use in patients >65 years has been shown to have similar efficacy to that in younger adults. In fact, there is a current trend of under-utilization of opioids in this patient population due to the high incidence of injuries (falls and hip fractures), particularly with codeine combinations[31] plus an increased risk of cognitive impairment.[32] Opioids have been recently recognized as a risk factor for the development of osteoporosis, therefore it is reasonable to suspect that the increased incidence of fractures observed in opioid users could be related to reduced bone mass density secondary to the effects of opioids on the endocrinological system.[33] Physiological changes such as lower serum-binding, lower stroke volume, and decreased renal function might play a role in the altered pharmacokinetics and pharmacodynamic effects of opioids in this patient population. The adverse event profile varies greatly between opioids. For most opioids except buprenorphine, the half-lives of active drug and metabolites are increased in the elderly. Special consideration might be given regarding effects on respiration. In this

regard, buprenorphine might be a top-line choice for opioid treatment in the elderly.[34]

Co-morbidities

Patients with impaired liver and/or renal function are at increased risk of accumulation of parent drug or metabolites, which can lead to toxicity. However, not all opioids behave the same in renally impaired individuals and thus it is up to the prescriber to have adequate knowledge on what opioid and what dose to use in the varying levels of renal impairment. Guidelines developed by the European Palliative Research Collaborative stratified opioids, based on current literature, into groups of toxicity.[35] Fentanyl, alfentanil, methadone, and tapentadol are not known to have any clinically significant active metabolites that would cause toxicity in renally impaired patients. Tramadol and hydromorphone (some risk) are followed by morphine, diamorphine, codeine, dihydrocodeine, and oxycodone (greater risk) and by pethidine and dextropropoxyphene (high risk). Others, including buprenorphine, sufentanil, and remifentanil have limited evidence or physician experience allows for recommendation for chronic use.

In patients with severe liver disease, reduced metabolism usually results in accumulation of the parent drug. The cytochrome P450 enzymatic system is usually affected in the early stages of liver impairment. Therefore, opioids that depend on oxidation for their metabolism, such as pethidine, dextropropoxyphene, tramadol, and alfentanil, may have increased oral bioavailability due to a reduced first-pass metabolism, and/or reduced clearance (even in patients with moderate hepatic dysfunction). The oral bioavailability morphine might increase as much as 200% in liver disorders. Fentanyl appears safe and dose adjustments generally are not necessary. Conversely to other opioids, codeine may have reduced efficacy, since the liver is required for biotransformation of the drug into the active metabolite, morphine. Codeine, tramadol, methadone, and oxymorphone should be avoided if possible in moderate to severe liver impairment.[15] In general, opioids should be

prescribed at lower doses in patients with severe liver disease, with extended dosing intervals when multiple daily doses are needed.[36]

Dysphagia (difficulty swallowing) is common among elderly people and among cancer patients. Swallowing problems can cause several clinical problems that complicate administration of oral solid medications. Moreover, some drugs, including opioids, can worsen swallowing problems by inducing xerostomia (dry mouth) and by decreasing lower esophageal sphincter (LES) pressure. For patients who have difficulty swallowing and require opioid analgesics, transdermal formulations might be considered.[37]

Genetics

An increasing literature demonstrates that individual vulnerabilities to specific pain types and mechanisms – and variation in response to pain medication – might be partially explained or predicted by the patient's genetics.[38] There are many pharmacogenetic factors that can contribute to the efficacy and adverse effects of analgesics, especially the opioids: polymorphisms in genes encoding for proteins controlling the enzymatic metabolism of drugs (e.g., CYP2D6 and codeine), the transport of drugs out of their target organ (e.g., P-glycoprotein and fentanyl) and the target receptor (e.g., mu-opioid receptor and morphine).[39]

More than half of all current prescription drugs are metabolized by the cytochrome P450 (CYP) enzymes (specifically CYP2D6 and CYP3A4). Therefore, drugs metabolized by this pathway (phase I metabolism), which includes many opioids, such as oxycodone, codeine, dihydrocodeine, hydrocodone, and tramadol, are associated with an increased possibility for drug–drug interactions. CYP450 inhibitors can lead to excessively high serum concentrations of the parent drug. This may increase the incidence of side effects if the parent drug is active (e.g., oxycodone), or it may decrease efficacy if it is a prodrug (e.g., codeine). Conversely, CYP450 inducers can lead to lower than expected serum concentrations of the parent drug. This can lead to a reduced effect if the parent drug is active or an enhanced effect if it is a prodrug. Moreover, mutations in the CYP2D6 gene, which occur in approximately 1% to 7% of the Caucasian population, can either decrease or increase enzyme activity, leading to alterations in opioid analgesia.[40]

The future promise of pharmacogenetics is an individually tailored, rational drug regimen that maximizes efficacy and minimizes adverse events. Pharmacogenetic testing could be the alternative to one-size-fits-all prescribing of pain medication. However, pharmacogenetic testing is not widely applied in current clinical practice and drugs which do not undergo significant metabolism by CYP enzymes, such as tapentadol, morphine, and oxymorphone, hydromorphone, can be an alternative.[41]

Gender

Over the past 20 years, an increasing number of studies have suggested sex differences in response to pain and analgesics. In general, it has been suggested that the prevalence of most common forms of pain is higher among women than men, and that women report greater pain after invasive procedures than do men. Compared with men, it has been suggested that women display enhanced sensitivity to most form of experimentally induced pain.[42] It has been suggested that women have greater opioid receptor analgesia. Similarly, some evidence suggests that serotonergic agents may be more efficacious in alleviating chronic pain in women,[43] which seems reasonable given that hormonal and neurobiological factors can directly affect nociceptive responses. However, women have been traditionally under-represented in clinical trials. Currently, the evidence on sex differences in pain response is thought not to be strong enough to allow translation of the experimental work to clinical decision-making.[44]

Transition (tapering)

Current literature support for, or advice about, how to discontinue an opioid is generally lacking. As with the titration step, performing this step too rapidly can have severe consequences such as experiencing opioid withdrawal symptoms. These are generally not life threatening and may include agitation, anxiety, muscle aches, insomnia, sweating, abdominal cramping, diarrhea, nausea and vomiting.

Individualized process

The provider should recognize the various reasons for discontinuing opioid therapy and then construct a plan of action that is individualized to the patient. As a general guideline, patient removal off an opioid should occur under the following circumstances:

- Intolerable adverse effects.
- Non-adherence by the patient.
- Misuse by the patient.
- Lack of analgesic effect.
- Patient request.

Tapering: general guidelines and goals

There are not much data on this topic and guidelines vary substantially.[15,16] Some experts recommend that the longer a patient has been on opioids, the slower the tapering. Since the range is quite large, physician experience, as well as appropriate monitoring, should always be the guide.

It has been recommended that a specialist be involved in the tapering of certain patients, such as:[15]

- Those that are at high risk of aberrant behaviors (e.g., parasuicidal acts, dealing/selling medications, or those with severe impulse control disorders).
- Those with complicated withdrawal symptoms.
- Those being tapered due to concern about development of addiction.

Opioid formulation considerations

During the tapering process, patients may experience signs of opiate withdrawal. These may include, but not be limited to, gastrointestinal symptoms such as nausea, vomiting,

and diarrhea, musculoskeletal symptoms, insomnia, anxiety, and irritability. Occurrence of symptoms will be driven by the specific opioid, the speed of taper and patient co-morbidities. Some opioids might be easier to taper than others.[45] Appropriate tests that could be administered during the process to monitor the patient include the clinical opiate withdrawal scale (COWS) and the subjective opiate withdrawal scale.[46,47] These scales can provide the physician with the knowledge of whether the planned tapering process needs adjustment. During the tapering process, adjuvant agents should be considered for management of symptoms of withdrawal. In addition, patients should receive psychosocial support if needed during the process.

Conclusion

Pain is a highly individualized process and no one single pharmacologic or non-pharmacologic approach completely removes pain in 100% of patients 100% of the time without any side effects. This is why multiple options are needed and why the options must be optimized to the individual patient. This is particularly important when considering opioid therapy, since proper opioid, regimen, and patient selection are paramount. The three T's of titration (trial), tailoring, and tapering are useful concepts and guides for rational, safe, and appropriate opioid prescribing which should result in improved outcomes and opioid optimization.

Conflicts of interest

Dr. Pergolizzi is a consultant and speaker for Janssen Pharmaceuticals, Endo Pharmaceuticals, Purdue Pharma, and InSys. Dr. Raffa is a speaker, consultant, and/or basic science investigator for several pharmaceutical companies involved in analgesics research but receives no royalty (cash or otherwise) from the sale of any product.

References

1. Institute of medicine (US) committee on advancing pain research C, and education. Relieving pain in America: a blueprint for transforming prevention, care, education and research 2012/05/04 edition. Washington, DC: National Academies Press; 2011.
2. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10:287–333.
3. Reid KJ, Harker J, Bala MM, et al. Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. Curr Med Res Opin. 2011;27:449–62.
4. Rustoen T, Wahl AK, Hanestad BR, et al. Prevalence and characteristics of chronic pain in the general Norwegian population. Eur J Pain. 2004;8:555–65.
5. David Michaelson and Company. Voices of chronic pain: a national study conducted for American Pain Foundation; 2006.
6. Stewart WF, Ricci JA, Chee E, et al. Lost productive time and cost due to common pain conditions in the US workforce. JAMA. 2003;290:2443–54.
7. Raffa RB, Pergolizzi JV Jr. A modern analgesics pain 'pyramid'. J Clin Pharm Ther. 2014;39:4–6.
8. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. Ann Intern Med. 2007;146:116–27.
9. Deshpande A, Furlan A, Mailis-Gagnon A, et al. Opioids for chronic low-back pain. Cochrane Database Syst Rev. 2007:CD004959.
10. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Phys. 2008;11:S5–62.
11. Manchikanti L, Abdi S, Atluri S, et al. American society of interventional pain physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2 – Guidance. Pain Phys. 2012;15:S67S116.
12. The British Pain Society. Opioids for persistent pain: good practice. London: The British Pain Society; 2010.
13. American Pain Society. Guideline for the use of chronic opioid therapy in chronic noncancer pain. Evid Rev. 2009.
14. Kahan M, Mailis-Gagnon A, Wilson L, et al. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: General population. Can Fam Phys. 2011;57:1257–66.
15. The Management of Opioid Therapy for Chronic PainWorking Group. In: Affairs, D.O.V., (Ed.), Clinical practice guideline: management of opioid therapy for chronic pain, Washington, DC; 2010.
16. Agency Medical Directors Group. Interagency guideline on opioid dosing for chronic non-cancer pain: an educational aid to improve care and safety with opioid therapy; 2010.
17. Ambrosio F, Finco G, Mattia C, et al. SIAARTI recommendations for chronic noncancer pain. Miner Anestesiol. 2006;72: 859–80.
18. Coluzzi F, Pappagallo M. Opioid therapy for chronic noncancer pain: practice guidelines for initiation and maintenance of therapy. Miner Anestesiol. 2005;71:425–33.
19. Mercadante S. Opioid titration in cancer pain: a critical review. Eur J Pain. 2007;11:823–30.
20. Ngian GS, Guymer EK, Littlejohn GO. The use of opioids in fibromyalgia. Int J Rheum Dis. 2011;14:6–11.
21. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010:CD006605.
22. Chou R. 2009 Clinical Guidelines from the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain: what are the key messages for clinical practice? Pol Arch Med Wewn. 2009;119:469–77.
23. Riemsma R, Forbes C, Harker J, et al. Systematic review of tapentadol in chronic severe pain. Curr Med Res Opin. 2011;27:1907–30.
24. Wolff RF, Aune D, Truyers C, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Curr Med Res Opin. 2012;28:833–45.
25. Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. Anesth Analg. 2000;90:933–7.
26. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94:149–58.
27. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010;152:85–92.
28. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57:1331–46.
29. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes. 2009;2:155–63.

30. Gloth FM. Pharmacological management of persistent pain in older persons: focus on opioids and nonopioids. J Pain. 2011;12:S14–20.
31. Buckeridge D, Huang A, Hanley J, et al. Risk of injury associated with opioid use in older adults. J Am Geriatr Soc. 2010;58:1664–70.
32. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med. 2010;25:310–5.
33. Mattia C, Di Bussolo E, Coluzzi F. Non-analgesic effects of opioids: the interaction of opioids with bone and joints. Curr Pharm Des. 2012;18:6005–9.
34. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract. 2008;8:287–313.
35. King S, Forbes K, Hanks GW, et al. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. Palliat Med. 2011;25:525–52.
36. Hanna M. The effects of liver impairment on opioids used to relieve pain in cancer patients. Palliat Med. 2011;25:604–5.
37. Muijsers RB, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs. 2001;61:2289–307.
38. Skorpen F, Laugsand EA, Klepstad P, et al. Variable response to opioid treatment: any genetic predictors within sight? Palliat Med. 2008;22:310–27.
39. Droney J, Riley J. Recent advances in the use of opioids for cancer pain. J Pain Res. 2009;2:135–55.
40. Overholser BR, Foster DR. Opioid pharmacokinetic drug-drug interactions. Am J Manage Care. 2011;17 Suppl. 11:S276–87.
41. Afilalo M, Stegmann JU, Upmalis D. Tapentadol immediate release: a new treatment option for acute pain management. J Pain Res. 2010;3:1–9.
42. Fillingim RB, King CD, Ribeiro-Dasilva MC, et al. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain. 2009;10:447–85.
43. Greenspan JD, Craft RM, LeResche L, et al. Studying sex and gender differences in pain and analgesia: a consensus report. Pain. 2007;132 Suppl. 1:S26–45.
44. Hurley RW, Adams MC. Sex, gender, and pain: an overview of a complex field. Anesth Analg. 2008;107:309–17.
45. Hale M, Upmalis D, Okamoto A, et al. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. Curr Med Res Opin. 2009;25:1095–104.
46. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoact Drugs. 2003;35:253–9.
47. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13:293–308.
48. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10:113–30.
49. Butler SF, Budman SH, Fernandez K, et al. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain. 2004;112:65–75.
50. Butler SF, Fernandez K, Benoit C, et al. Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). J Pain. 2008;9:360–72.
51. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain Med. 2005;6:432–42.
52. Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: predicting outcomes of opioid prescribing for chronic pain. J Pain. 2006;7:671–81.
53. Couwenbergh C, Van Der Gaag RJ, Koeter M, et al. Screening for substance abuse among adolescents validity of the CAGE-AID in youth mental health care. Subst Use Misuse. 2009;44:823–34.
54. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J. 1995;94:135–40.