MISCELLANEOUS

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

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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/orrganization 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

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experience/judgment, including non-pharmacologic approaches, can assist healthcare providers in the effort to achieve optimal management of pain.
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**PALAVRAS-CHAVE**
Tratamento da dor; Opioide; Titulação; Ajuste; Redução gradual

**Introduction**

Current estimates indicate that as many as 100 million Americans are suffering from a chronic pain condition and a prevalence of 10–50% throughout European countries. 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. 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.

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. They include NSAIDs (non-steroidal 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. 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

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 básicos da anágnesia 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 apola o uso da dose total mais baixa de opioides 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, farmacogenômicos e comportamentais. Finalmente, para aqueles pacientes nos quais a transição (redução gradual) do opioide é desejada, fazer essa transição muito rapidamente pode 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.

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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. 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.

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, fibromyalgia) and determine whether opioid therapy is appropriate. For example, certain pain conditions such as fibromyalgia do not always adequately respond to opioids 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. 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. 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-naive 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. 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. 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. 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.

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. 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.

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.

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-naive, 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.
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.

**Titrination: 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.

### Tweeking (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.
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.\textsuperscript{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.\textsuperscript{29} In the elderly, NSAIDs and cyclooxygenase-2 (COX-2)-selective inhibitors should only be used in rare instances.\textsuperscript{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\textsuperscript{31} plus an increased risk of cognitive impairment.\textsuperscript{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.\textsuperscript{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.\textsuperscript{34}\textsuperscript{35}

### 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.\textsuperscript{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.\textsuperscript{13} In general, opioids should be

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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 analogics, 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 analogics, 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 oxycodeone, 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., oxycodeone), 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 analogics. 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. 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. 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.

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