21 November 2018

Caroline Martin
Editor
Therapeutic Guidelines Limited
Ground Floor, 473 Victoria St
West Melbourne, VIC 3003
cmartin@tg.org.au

Dear Ms Martin,

RE: Revision of *Therapeutic Guidelines: Analgesic*

The Society of Hospital Pharmacists of Australia (SHPA) thanks Therapeutic Guidelines Limited (TGL) for giving us the opportunity to provide comments regarding *Therapeutic Guidelines: Analgesic* ahead of its revision for the next edition. This guideline is an essential reference for our members every day in a variety of clinical settings, as they carry out their responsibilities in pain management and analgesic stewardship to improve the quality of life for patients whilst minimising risk of long-term dependency on opioid analgesics.

SHPA is the national professional organisation with more than 5,000 pharmacists, pharmacist interns, students, technicians and associates working across Australia's health system. SHPA convenes both a Pain Management specialty practice network and a Surgical and Perioperative medicine specialty practice network, linking our experts in pain management and analgesia which have greatly informed this submission.

SHPA members have raised issues and considerations in the current version of *Therapeutic Guidelines: Analgesic* for the Editorial Board to review ahead of the next version.

Representation of expert clinical pharmacist on expert groups and reference groups

As a priority SHPA believes that TGL should consider having more expert clinical pharmacist representation on the expert groups and reference groups which review successive editions of TGL's publications. Whilst medical and nursing expertise is critical, the role of pharmacists as experts in medicines management is often under-represented. This expertise is frequently requested by members of multidisciplinary teams working in specialist acute settings. This would greatly assist TGL to revise and review guidelines whilst maintaining awareness of pharmacy practice-based issues, and how guidelines are used at the coalface. SHPA supports 24 networks of specialty practice to enable convenient access to experienced senior clinicians. For example, the Chair of SHPA's Pain Management Leadership Committee would be a suitable and qualified candidate to be represented on these group(s).

Terminology

SHPA prefers the use of 'persistent pain' rather than 'chronic pain'. Many organisations, colleges and researchers have increasingly used the term persistent pain as it acknowledges that pain is caused by more than musculoskeletal or tissue damage. It acknowledges that persistent pain has central nervous system involvement and its management is inclusive of techniques, methods and treatments beyond the musculoskeletal or tissue damage.

Additionally, SHPA prefers that 'pain management' is used rather than 'pain control' or 'curing pain' or its variations, as it acknowledges the holistic approach to pain perception and treatment. This will also manage

patient expectations of pain and treatment outcomes, and that the goal is not necessarily to be focused on being completely being pain-free, but to have improved functionality and quality of life.

Medicines to be included in next edition

Since the publication of the last edition, several analgesic medicines have become available on the Australian market and are increasingly being prescribed and used to treat both acute and chronic pain.

These include:

- tapentadol (immediate and sustained release)
- oxycodone/naloxone oral combinations, oxycodone (intravenous)
- buprenorphine (intravenous/subcutaneous/sublingual) which are safe and effective when the enteral route is unavailable

SHPA recommends that these new medicines are included in the next edition of *Therapeutic Guidelines: Analgesic.*

Furthermore, since the last edition, gabapentinoids such as pregabalin and gabapentin have become more widely used and increasingly embedded into clinical practice. However, our members advice indicates use is not always appropriate, as they can produce psychoactive effects and precipitate dependence when used long term. It would be appreciated if the next edition of *Therapeutic Guidelines: Analgesic* discussed gabapentinoids more throughout the guidelines, to help guide the appropriate use of these medicines.

Types of pain

SHPA recommends including a definition for nociplastic pain and including discussion for nociplastic pain throughout *Therapeutic Guidelines: Analgesic* where possible. In 2017, the International Association for the Study of Pain (IASP) formally recognised nociplastic pain as “activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain”[1]. The term nociplastic pain has also appeared in several Australian resources developed for either health practitioners or the community[2].

Pain assessment

- The reference in Note 4 should be updated to the new edition *of Pain in residential aged care facilities: management strategies*, published by The Australian Pain Society in 2018.
- Under the Aggravating and relieving factors subsection, ‘or harmful therapy’ should be added on the following statement. “Ask about any previous response to an analgesic to help determine a starting dose, and prevent the use of previously unhelpful therapy.”

Stepwise approach to acute pain management

- Since the last edition of *Therapeutic Guidelines: Analgesic*, immediate release formulations of tapentadol have been introduced into Australian practice settings and its clinical use has been increasing year on year. It has been viewed as a good alternative to other opioid analgesics due to lower prevalence of gastrointestinal adverse effects[3]. SHPA recommends discussion of the therapeutic use tapentadol the next edition, and where it fits in the stepwise approach to acute pain management.
- This section recommends dose reduction for people of ‘small size’, however this term can have variable interpretations and SHPA queries whether more definitive parameters could be used i.e. height, body mass index, ideal body weight.
- In the current edition, the use of codeine 30 to 60mg orally every 6-hourly is recommended as equal first-line therapy with tramadol if acute pain is not adequately relieved by a paracetamol or NSAID.

However, in recent years, codeine has been demonstrated to be less efficacious to other opioid medicines[4], as well as having variable effects on patients due to its unpredictable metabolism which can dangerous for ultra-metabolisers of codeine[5]. This has contributed to the upscheduling of codeine-containing medications from Schedule 3 Pharmacist only to Schedule 4 Prescription Only medicines in 2018. Given the comparative lack of efficacy and the risk of adverse events, we would recommend that codeine be removed as a first line treatment option for acute pain not adequately relieved by paracetamol or an NSAID. As codeine is metabolised into morphine, it follows that morphine would be an adequate replacement for codeine in this instance, and ameliorates any variations caused by CYP2D6 metabolism variation in the population.

- The oxycodone dosing range is currently presented as 2.5mg - 15mg every four hours as required with a note to use lower doses in older people and higher doses in fit healthy young adults, however, this is too open-ended and may be misinterpreted and lead to a higher dose prescribed than necessary. We also believe 15mg as the upper end of the range for a starting dose is too high. SHPA recommends presenting in increments, for example:
    - If patient is older, or has risk factors for opioid-induced ventilatory impairment or concomitant sedating medications, use 2.5mg - 5mg q4h PRN
    - If younger patient and no additional risk factors, use 5mg - 10mg q4h PRN
- In light of the numerous reported concerns regarding the use of hydromorphone, locally and internationally, its use should be restricted to clinicians who are familiar with its use, such as palliative care and pain specialists.
- The medicines suggested for NSAIDs should not recommend diclofenac as a second line therapy given its cardiovascular risks[6], and at best should be considered third line. The use of selective COX-2 inhibitors such as celecoxib should be offered as second line therapies at minimum, especially for surgical patients at risk of bleeding.
- At present, this section states “Always consider the potential benefits, harms and regulatory requirements before prescribing an opioid”, however, given the levels of opioid-related harm uncovered in the community in recent times, SHPA recommends it should be strengthened and highlighted in a breakout/alert box.
- SHPA believes the stepwise approach to pain management should also discuss and highlight the importance of stepping down, or opioid de-escalation management plans.

Introduction to acute traumatic pain

- SHPA suggests describing why the use of pethidine is recommended to be avoided for acute traumatic pain, and the advantages that other medicines have over pethidine.
- For the administration of opioids where intravenous routes are not possible, subcutaneous administration should be preferred over intramuscular administration given the pain the latter causes.

Acute pain: major trauma

In addition to the current listed therapies, SHPA recommends adding oxycodone PCA as a treatment option. Many clinicians use this as a second line agent over fentanyl in those allergic or intolerant of morphine (e.g. rash, itch, sever nausea and vomiting, renal impairment).

Introduction to perioperative pain

- SHPA recommends that the examples of organisational structures should also specifically mention analgesia stewardship services. A component of this is opioid-focused stewardship, which addresses the prevention of inappropriate opioid prescribing and supply, among other quality and safety

activities. It is an emerging model of practice that is based upon the antimicrobial stewardship model. Not-yet-published evidence from a Victorian tertiary hospital regarding opioid stewardship indicates great potential for reducing harms when supported by adequate funding and management. The recent Victorian Inquiry into Drug Law Reform has recommended that a sector-wide trial based on an opioid stewardship model be implemented to promote and audit best practice regarding the prescribing and use of medications with potential for misuse[7]. This pharmacist-led model is also supported by SHPA's *Standard of Practice for Pain Management in Pharmacy Services*.

- SHPA recommends that patients are regularly reviewed and transitioned from parenteral to enteral opioids as soon as possible, as prolonged parenteral opioid use is associated with increasing risk of opioid toxicity and dependency. Furthermore, the attachment to patient-controlled analgesia devices may impede patient mobilisation and participation in physiotherapy.
- Additionally, this section should also note the limited role gabapentionoids have in perioperative pain.
- SHPA recommends changing the phrase "education to allay fear of opioid dependence…" to "education to ensure appropriate use of opioids…"
- SHPA recommends 'nonpharmacological therapies' to the phrase "additional or alternative use of nonopioid medications to provide analgesia"

Preoperative pain

SHPA recommends rewording the following statement:

"Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided before any surgery where postoperative bleeding would be of concern."

COX-2 selective NSAIDs may be used as preoperatively as they have limited effect on platelet function.

Two clinical studies evaluating the preoperative administration (i.e. pre-emptive dosing) of parecoxib injection have demonstrated efficacy in reducing postoperative pain. Compared to placebo, administration of single doses of parecoxib injection 30 to 45 minutes prior to surgery significantly delayed development of postoperative pain. The safety profile of parecoxib injection administered preoperatively was not different from that seen with postoperative administration.[8] Meta-analysis evaluating the preoperative administration of celecoxib has demonstrated some benefit in reducing postoperative morphine consumption, pain, nausea and vomiting. [9]

Additionally, SHPA encourages discussion on the use of tramadol and morphine for preoperative pain, not just oxycodone, as these medicines are prescribed for more minor surgeries in practice.

Postoperative pain

- SHPA believes that since the publication of the first edition, that there has been emerging evidence that the use of opioids in the treatment of acute post-operative pain is indeed associated with an increased risk of dependency[10,11,12]. Thus, the sentence "There is no evidence that the use of an opioid for limited periods in the treatment of acute postoperative pain is associated with an increased risk of addiction" is no longer appropriate in light of new evidence. Furthermore, the guidelines also have the statement "Prescribers should be aware of the abuse potential", but this is only attributed to oxycodone. SHPA believes this should statement should be applied to all opioids.
- The discussion around modified-release opioid formulations should also consider discussing evidence of long-term use of these medicines and their risk with dependency, as well as the Australia and New Zealand College of Anaesthetists position statement on slow-release opioids[13]. Whilst the current edition acknowledges that sustained release opioids should not be used to treat acute pain, these

medicines are prescribed for acute pain commonly. SHPA's survey on reducing opioid-related harm found that oral modified-release opioids were used by 77% of health services to treat postoperative acute pain in opioid-naïve inpatients, and 71% prescribed these medicines on discharge to patients who were opioid-naïve on admission. This is of significant concern to SHPA, and we expect recommendations discouraging the use of modified-release opioids for acute pain to be strengthened in the next edition.

- SHPA believes the statement "Postoperative analgesics should be tailored to the patient's requirements, the severity of their pain and the level of clinical observation" should also mention that the tailoring should also consider the patient's functional ability and using common tools such as Functional Activity Scores.
- SHPA recommends that this section should also discuss the importance of reviewing response to analgesic therapy, and provide recommendations about appropriate quantities for supply on discharge from hospital, based on individualised opioid use in the post-operative period. SHPA's survey on reducing opioid-related harm found that less than a quarter (23%) of respondents always reviewed the last 48 hours of analgesic use to inform appropriate prescribing upon discharge
- In the oral opioids subsection, it should recommend that only one strong opioid is used at a time. More information and clinical considerations are required for each medicine mentioned such as:
    - Oxycodone: quicker onset than morphine, dose adjust in moderate to severe renal impairment, less itch than morphine.
    - Morphine: prolonged effect in renal impairment and histamine release.
    - Tramadol: reduce dose in renal impairment.
    - Include information on the new medicines tapentadol, and buprenorphine.
- The suggested doses of morphine in Tables 1.5 and 1.6 are also unusually high and of concern, and practically, lower doses (by 33%-50%) are used as initial doses to observe patient response before increasing dose if necessary.
- This section also mentions that codeine is a widely used medicine, however this is often no longer the case in both acute and primary settings.
- This section should also discuss the preferential use of selective NSAIDs such as celecoxib in the setting of postoperative pain, given they are associated with less blood loss and gastrointestinal ulcers compared to non-selective NSAIDs.

Introduction to acute pain and opioid tolerance

In the sentence "Physical dependence is also a normal physiological response to long-term opioid use", SHPA suggests using the term 'expected' or 'anticipated' instead of 'normal'.

Acute pain in patients with an opioid addiction

SHPA recommends that in this patient cohort, parenteral opioids should be used judiciously and only when absolutely necessary. If patients are on opioid replacement therapy (methadone or buprenorphine), it is important to contact both the community prescriber and community pharmacy early to confirm dosing as well as compliance to therapy.

Although methadone can maintain therapeutic blood levels and prevent withdrawal symptoms for 24 hours, multiple daily doses may be required to provide analgesia for 24 hours. For patients experiencing acute pain, changing methadone from a single daily dosing to split dosing for one to two weeks may improve pain control. This may require multiple daily attendances at the pharmacy or the recognition of another approved responsible person to control and supervise the second or third daily dose. Therefore, split dosing may be more appropriate in hospital inpatient setting where dose administration is supervised.

Overall, guidance around prescribing additional opioids especially for patients on opioid replacement therapy would be greatly appreciated. Often there is confusion or limited consideration on the impact of further opioid therapy in these patients. In general, while providing care for this cohort, some hospital pharmacists have initially added simple non-opioid analgesics first, then tramadol (if no contraindications), followed by referral to acute pain service for consideration of other specialised analgesic infusions such as ketamine or local anaesthetic infusions. Under the guidance of acute pain or addiction service, use of stronger opioids may be appropriate in the short-term, with the aim to return to baseline or no additional opioids at discharge. However, if this is not possible, then a clear plan should communicated with the usual/community prescriber before discharge, with consideration for referrals to pain management clinics.

The transition from acute to chronic pain

SHPA recommends including a definition for nociplastic pain and including discussion for nociplastic pain throughout *Therapeutic Guidelines: Analgesic* where possible. In 2017, the International Association for the Study of Pain (IASP) formally recognised nociplastic pain as "activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain"[1]. The term nociplastic pain has also appeared in several Australian resources developed for either health practitioners or the community[2].This is an important distinction to make as nociplastic pain is less receptive to treatment with gabapentanoids. [14,15,16]

Risk factors for postsurgical pain syndromes

Prior back surgeries are also a common risk factor for postsurgical pain syndromes and can manifest in failed back surgery syndrome.[17]

Overview of complex regional pain syndromes

This section discusses the use of medicines such as opioids, antidepressants, gabapentanoids and carbamazepine linearly as potential treatments for complex regional pain syndromes (CRPS). Whilst treatment evidence for this syndrome is lacking, the quality of evidence for these medicines and other agents vary[18]. Furthermore, opioids are described as third-fourth line treatments for complex pain regional pain syndromes. Thus, SHPA would appreciate further guidance by Therapeutic Guidelines on treatment cascades for complex regional pain syndromes. SHPA is also aware of a recent review that found only bisphosphonates were found to show any uniformly positive effects, with treatments mentioned currently in *Therapeutic Guidelines: Analgesic* to be of no effect.[19]

More detailed information on the diagnosis of CRPS would also be of great assistance to clinicians as it is often misdiagnosed.

Chronic pain: nonpharmacological management

SHPA believes this section should mention that treatments for chronic pain – both pharmacological and non-pharmacological – are not about curing the disease state, but more about management and improving and/or maintaining function. Contemporary treatment for chronic pain also focuses on 'retraining' the mind and its sensory reactions to stimuli in anticipation of pain and focusing on this can improve pain management and function in the long term.

Chronic pain: pharmacological management

As mentioned earlier, SHPA would greatly appreciate discussion around the use of newer medicines that have come onto the Australian market and subsequently gained a listing on the Pharmaceutical Benefits System (PBS), leading to increased uptake by prescribers in the treatment of chronic pain. These medicines include sustained-release tapentadol which have been shown to reduce gastrointestinal adverse effects, and

oxycodone/naloxone combinations, with the naloxone component reducing prevalence of opioid-induced constipation.

Analgesics for chronic nonmalignant pain management

Oxycodone oral modified-release tablets are no longer available as 5mg tablets by themselves but are available in a combination product with naloxone 2.5mg.

Adverse effects of invasive techniques for pain management

SHPA recommends that dependency also be added to the list of possible adverse effects for invasive techniques due to exposure to opioid analgesics. This section should also highlight the importance of adjuvant non-pharmacological interventions to maximise and extend the benefits of invasive techniques for pain management.

If you have any queries or would like to discuss our submission further please do not hesitate to contact Johanna de Wever, General Manager, Advocacy and Leadership on jdewever@shpa.org.au.

Yours sincerely,

Kristin Michaels
Chief Executive

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