ABSTRACT

Background: Pain management is an evolving area of expertise in Qatar. Gaps in knowledge, inadequate training for physicians and nurses, and the absence of policies/guidelines are the main barriers to effective pain management in Qatar. In addition, the use of certain pain medication, especially opioids, is highly regulated, limiting their availability in outpatient pain management. These factors are responsible for the undertreatment of pain in Qatar. This study aimed to standardize evidence-based local recommendations for pharmacological treatment of pain in Qatar.

Methods: An expert panel of physicians from different disciplines, with experience in diagnosis and treatment of the three pain types (i.e., acute, chronic, and neuropathic), was convened for two face-to-face meetings in Doha, Qatar, on November 29, 2019, and on February 22, 2020, with subsequent virtual meetings. A literature search was performed on Medline and Google Scholar databases from inception till December 2019, and all relevant articles were selected. Based on these articles and repeated feedback from the authors, the final pain treatment protocols were developed.

Results: Recommendations for the treatment of acute pain, based on pain severity, followed three approaches: acetaminophen/paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) for mild pain and moderate pain and referral to a pain specialist for severe pain. Acetaminophen/paracetamol or NSAIDs is recommended for chronic pain, and the use of opioids was strongly discouraged because of its long-term side effects. For neuropathic pain, tricyclic antidepressants or gabapentin or pregabalin or serotonin-norepinephrine reuptake inhibitors were
recommended first-line agents. Non-responders must be referred to neurologists or a pain specialist.

Conclusion: The expert panel provides recommendations for the management of acute, chronic, and neuropathic pain based on international guidelines adapted to local practice and treatment availability in Qatar. More importantly, the panel has recommended taking extreme caution in the use of opioids for long-term management of chronic pain and to refer the patient to a pain specialist clinician as required.

Keywords: acute pain, analgesics, chronic pain, neuropathic pain, pain management

INTRODUCTION

Pain is often classified as the “fifth vital sign”; managing pain is key to improving the quality of life (QoL) of patients. The International Association for the Study of Pain task force, based on recent advances, recommended revising the definition of pain to “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

Pain has various classifications depending on its anatomic, etiologic, chronicity (duration), intensity, and pathophysiological characteristics.

Worldwide, acute pain is one of the most common causes for patients to seek medical attention at the emergency department (ED). Lower back pain (LBP) is the leading cause of activity limitation and absence from work throughout the world. In the Global Burden of Disease 2017 study, years lived with disability (YLDs) because of LBP was 64.9 million with a point prevalence of 7.5%, accounting for 577 million people. In North Africa and the Middle East, the prevalence of LBP in 2017 was approximately 9.9% and ranked ninth among the 21 regions.

In 2013, a cross-sectional survey on the epidemiology of LBP in the primary healthcare setting was conducted in Qatar and reported an overall LBP prevalence of approximately 59.2% in a sample of 2180 subjects. The prevalence of LBP in Qatar was higher than that in developed countries, such as Canada, United Kingdom, and Sweden.

Occupation-related factors are key causal factors for LBP. The estimated prevalence of LBP among nurses in a tertiary care setting in Hamad General Hospital, Doha, Qatar, in 2015 was approximately 26.8%, with 34.3% of overall respondents requiring medical treatment for LBP.

Migraine-related pain is another important cause of disability worldwide, requiring greater research resource allocation and attention in health policy debates. Worldwide, approximately 1.04 billion individuals may have experienced a migraine in 2016, leading to 45.1 million YLDs globally. In North Africa and the Middle East, approximately 93.4 million individuals may have experienced migraines in 2016, with 0.39 million individuals reporting migraine during the same period in Qatar.

In general, challenges in pain management lie at the level of patients (i.e., culture, experience, education, and health condition), healthcare professionals, and the healthcare system. Challenges to effective pain management are multifold and stem mainly from the undertreatment and practice variations of pain, known as "oligoanalgesia." Some of the other key challenges in pain management are the inability to assess the initial pain, non-availability of pain management guidelines, and failure to acknowledge and document pain. One of the important factors adding up to the challenges in pain management is misuse and abuse of opioids to unacceptable levels.

The dynamic nature of pain and its intensity highlight the importance of "stratified care" - a targeted approach for treating pain according to the risk category (i.e., low, medium, or high risk of poor outcomes) of patients. In the Middle East, including Qatar, pain management is an evolving area of expertise, and undertreatment is related to the stigma associated with the use of pain medications, especially the use of opioids. Knowledge gap and lack of skills by physicians and nurses and absence of policies/guidelines hinder effective pain management. In 2011, approximately 69% of the physicians in Qatar reported that they had not received any formal pain management training. Furthermore, cultural differences regarding pain exist in Qatar, as it is a cosmopolitan country with different coexisting communities. Similarly, physicians practicing in Qatar come from different communities and received training from varying educational systems.

Under these circumstances, treatment guidelines can aid in evidence-based decision-making. Guidelines have been established for the pharmacological treatment of acute pain and peripheral neuropathic pain in the Middle East. However, there is an urgent need to develop standardized local guidelines,
applying similar methodology for different types of pain including acute, chronic, and neuropathic pain, in Qatar. To address this unmet need, an expert forum was constituted to provide pharmacological treatment recommendations specific to Qatar, including the best practices from existing international guidelines.

METHODS
An expert panel of physicians (Qatar Pain Expert forum, n = 15) from different disciplines (such as emergency medicine specialists, anesthesiologists, chronic pain specialist, stroke specialist, trauma and orthopedic surgeons, neurologists, and pharmacy specialists) with clinical and research experience in diagnosis and treatment of acute, chronic, and neuropathic pain was convened in Doha, Qatar, on November 29, 2019, and subsequently, on February 22, 2020, followed by virtual meetings. The experts were affiliated to Hamad Medical Corporation, the primary healthcare body in Qatar, Weill Cornell Medicine in Qatar, and Qatar University. A literature search for relevant publications was performed on the databases of Medline (PubMed) and Google Scholar from their inception till December 2019. The following key terms were used: [acute pain or perioperative pain AND management AND guideline OR protocol], [chronic pain AND management AND guideline OR protocol], and [neuropathic pain AND management AND guideline OR protocol]. "English language" and "Humans" were the applied limits. The relevant literature of 460 retrieved articles, which consisted of meta-analyses, systematic reviews, and evidence-based guidelines on the treatment, was reviewed by the authors in consultation with the expert panel to arrive at treatment protocols for acute, chronic, and neuropathic pain. Based on the experts' comments on the identified literature, a preliminary draft document was prepared and circulated among the authors for further review. The document was revised multiple times according to the authors' edits and feedback, and a final pharmacological treatment protocol for pain was achieved.

Expert review and recommendations for the management of acute, chronic, and neuropathic pain in Qatar

Expert recommendations for clinical management of pain in Qatar

Acute pain management in ED
Acute pain is a neurophysiological response to noxious injury lasting less than 3 months. Common examples of acute pain include postoperative pain, fractured bones, appendicitis, and soft tissue injury. Acute LBP is one of the common reasons for ED visits.

Evaluation of pain
The visual analog scale (VAS) and numeric pain rating scale (NRS) are commonly used for the assessment of pain intensity. A four-point verbal categorical rating scale (VRS) is also used, but the VAS and NRS are considered superior. However, consensus-based recommendations of an expert panel for the pharmacological treatment of acute pain in the Middle East concluded that both the NRS and VRS are more useful than the VAS in the general practice setting and that patient education is important to ensure accurate measurement.

Pharmacological treatment
After careful evaluation, an effective pain management plan should be drawn by each ED to establish a diagnosis with measurable outcomes that focus on improving QoL, functionality, and activities of daily living. Emphasis should be on an individualized, patient-centered approach for the diagnosis and treatment of pain. Treatment of pain in the ED has no single standard of care. Many analgesic agents have varied physiological mechanisms and therefore chosen based on pain severity. The algorithm for the initial management of undifferentiated pain in the ED is illustrated in Figure 1 adapted from expert panel consensus recommendations for the pharmacological treatment of acute pain in the Middle East.

Acetaminophen (paracetamol)
Acetaminophen is a widely used over-the-counter drug owing to its antipyretic and analgesic effect. Although its detailed mechanism of action is yet to be completely understood, it is likely to act by inhibiting cyclooxygenase (COX) enzymes through the metabolism of the peroxidase function of these isoenzymes. It also acts through serotonergic, opioid, nitric oxide, and cannabinoid pathways. It is highly selective and has an additive effect; however, it has no known synergistic effect when combined with other nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen available in both oral and intravenous (IV) formulations is approved up to the dose of ≤ 4 g/day owing to its hepatotoxicity. Acetaminophen has demonstrated a similar analgesic effect as do NSAIDs in patients who presented to the ED for acute pain. Sufficient evidence confirms the IV
use of acetaminophen in hospitalized patients for treating pain with opioid-sparing effects. Moreover, many randomized controlled trials have shown that IV administration of acetaminophen has significantly lesser side effects than morphine in patients presenting with acute renal colic to the ED. A pooled analysis of 23 studies involving over 2000 patients aged 18 years revealed that acetaminophen had lesser adverse events (AEs) than opioids.

**NSAIDs**

NSAIDs are agents that act by inhibition of COX enzymes and are proposed as the first-line drugs for mild-to-moderate pain. NSAIDs have known AEs such as gastrointestinal (GI) hemorrhage and peptic ulcers because of their effect on COX1 enzymes. Moreover, they are contraindicated in elderly patients and in patients with peptic ulcers, hypertension, renal disease or impairment, or hepatic impairment. NSAIDs should also be avoided in patients with a history of myocardial infarction, transient ischemic attack, stroke, or inflammatory bowel diseases such as Crohn’s disease or ulcerative colitis. Given these AEs, next-generation selective COX2 inhibitors were introduced with lower GI side effects. However, these agents are shown to have increased the risk of cardiovascular effects.

In general, NSAIDs have been shown to be more effective than opioids but with no additional benefits when combined with opioids/or muscle relaxants in acute pain settings. NSAIDs were found to have comparable efficacy with opioids and paracetamol in relieving acute pain at 30 minutes with lesser incidence of vomiting and requirement of rescue analgesia in treating acute renal colic pain. A double-blind, randomized controlled trial in Qatar found that intramuscular (IM) administration of diclofenac offers significantly more effective pain relief (odds ratio 1.35, 95% confidence interval [CI] 1.05 – 1.73, \( p = 0.0187 \)) than does IV administration of morphine in patients presenting with renal colic pain to the ED. However, IM use of diclofenac and IV administration of paracetamol have comparable efficacy in relieving pain. Another prospective, randomized controlled trial in Qatar found that more patients receiving IM administration of diclofenac achieved a 50% reduction in pain within 30 minutes compared with oral intake of diclofenac (99.3% vs. 86.7%, \( p < 0.001 \)). The authors, however, opted for oral over IM administration of diclofenac in patients presenting with acute musculoskeletal injuries to the ED.

NSAIDs at equipotent doses had shown similar analgesic effects. In a prospective, double-blind study, ketorolac, diclofenac, and etoricoxib have shown similar efficacy and a significant reduction in acute pain severity.
pain caused by ankle fracture over 24 hours from baseline. Moreover, two studies have reported similar pain relief with parenteral use of ketorolac and oral intake of ibuprofen in acute pain settings. Ketorolac was found to be non-inferior to naproxen for the reduction of mild-to-moderate LBP but provided a faster pain relief than did naproxen (24.2% vs 6.5%, p = 0.049). In the ED setting, IV administration of ketorolac at doses of 10, 15, and 30 mg has shown similar analgesic effects, proving that the 10 mg dose is the ceiling dose; however, 90% of patients received ketorolac above the ceiling dose in the ED settings. Additionally, IV administration of parecoxib sodium 40 mg was shown as an analgesic alternative to morphine sulfate 0.1 mg/kg in acute traumatic pain in the ED settings. A meta-analysis of seven randomized controlled trials revealed that a single IV or IM dose of parecoxib 20 mg or 40 mg in acute postoperative pain provided effective analgesia in 50%–60% of patients compared with approximately 15% with placebo. Topical NSAIDs are also used for chronic musculoskeletal pain in adults.

Weak opioids

Tramadol

Tramadol is considered a weak opioid analgesic. It has two independent mechanisms to produce analgesic effects: the opioid mechanism (binds to the μ-opioid receptor) and the nonopioid mechanism (inhibits the reuptake of serotonin and norepinephrine). Supporting pieces of evidence present the use of tramadol alone or in combination with other analgesics in acute pain care. Although tramadol has an action on the opioid receptor, several clinical trials have shown that tramadol has fewer opioid side effects, including drug dependency, than do opioids.

Codeine

Codeine is a weak opioid, as it has a 200-fold weaker affinity to μ-opioid receptor than morphine. Approximately 80% of the codeine administered is metabolized to codeine-6-glucuronide, which contributes to the analgesic effect. Codeine is available in combination with paracetamol.

Strong opioids

Opioids are effective in the management of pain but have several limitations. Opioid analgesics are associated with an increased risk of respiratory depression, sedation, and addiction. A morbidity and mortality report released by the Center of Disease Control (CDC) showed that opioid-naïve patients who received opioids were more likely to have chronic opioid use with each additional day of medication use, starting with the third day, with the sharpest rise in chronic opioid use after the fifth and 31st day of therapy. Hence, the CDC recommends, “discussion with patients about the long-term use of opioids to manage pain should occur early in the opioid prescribing process.”

The usage of opioids had increased sharply between 1990 and 2010. However, restrictions exist on access to opioids due to regulatory obstacles and concerns about misuse.

Sufficient evidence has shown effective pain relief with both oral and parenteral use of strong opioids in patients with acute severe pain. However, studies have shown an increased risk of AEs, especially opioid dependency. Hence, the use of strong opioids should be restricted, and patients referred to a pain specialist for interventional modalities of pain management.

Experts recommendations for chronic pain treatment

Pain that lasts longer than the usual course (more than 3–6 months) of an acute injury or disease is called chronic pain. Chronic pain has several pathophysiological causes. The effect of chronic pain is multifold, such as negative influence on QoL, depression, anxiety, disrupted daily routine, reduced social activity, disability, sleep disturbances, and increased healthcare cost. Often, chronic pain results from an unrelieved acute pain, e.g., LBP. Patients with chronic non-specific LBP should be referred to a specialist as the treatment might include opioids.

Evaluation of chronic pain

The PainDETECT, Douleur Neuropathique en Quatre Questions, and Leeds Assessment of Neuropathic Symptoms and Signs are some of the validated questionnaires used to prompt clinicians for the assessment of chronic pain.

Pharmacological treatment

NSAIDs

Nonopioid medications are the preferred drugs for treating chronic pain (Table 1). NSAIDs are the first-line agents for mild-to-moderate pain and form the first step of the analgesic ladder in the treatment
of chronic pain.\textsuperscript{19, 95} NSAIDs have shown modest benefits and a tolerable safety profile for the treatment of chronic back pain.\textsuperscript{96-98} However, a long-term use of NSAIDs, such as diclofenac, ibuprofen, and COX2 inhibitors, caused an increased risk of death from myocardial infarction and coronary heart disease (diclofenac, risk ratio [RR] 1.70, \( p = 0.0032 \); ibuprofen, RR 2.22, \( p = 0.0253 \); COX2 inhibitors, RR 1.76, \( p = 0.0001 \)) but not naproxen (RR 0.84, 95% CI 0.52–1.35) compared with placebo.\textsuperscript{99}

Acetaminophen (paracetamol)

Insufficient evidence supports the use of acetaminophen in chronic LBP. Acetaminophen was found to be less effective than NSAIDs in relieving chronic LBP and knee and hip pain in osteoarthritis patients,\textsuperscript{100} while the combination of ibuprofen/acetaminophen (400 mg/1000 mg) was significantly superior to regular paracetamol 1000 mg alone (\( p = 0.0002 \)) for treatment of knee pain at 1.3 weeks but had increased risk of GI bleeding.\textsuperscript{101}

Opioids

Opioids have limited efficacy in the management of chronic pain. Moreover, they are associated with drug dependency. Evidence suggests that opioids are effective in treating chronic pain for up to 3 months.\textsuperscript{102} Importantly, long-term use of opioids over a 12-month period did not improve pain-related function and was associated with significantly more AEs than the use of nonopioids (overall, \( p = 0.03 \)) in patients with chronic back pain or hip or osteoarthritis pain. The mean difference in adverse medication-related symptoms between opioids and nonopioids at 12 months was 0.9 (95% CI, 0.3 – 1.5)).\textsuperscript{103} Therefore, the use of opioids for non-cancer pain should be practiced with caution and with the recommendation/under the supervision of a specialized physician.

Neuropathic pain

Pain caused by a lesion or disease of the somatosensory nervous system is called neuropathic pain, which is further categorized as either peripheral or central neuropathic pain.\textsuperscript{104}

Many guidelines have defined the management of neuropathic pain, which recommend tricyclic antidepressants (TCAs) (amitriptyline), serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, and calcium channel alpha-2-delta ligands (gabapentin and pregabalin) as the first-line treatment.\textsuperscript{105-107} Figures 2–4 illustrate the algorithm for the management of various types of neuropathic pain, which was adapted from National Health Service neuropathic pain management guidelines.\textsuperscript{108}

Evaluation of pain

Profile of Mood States, Hospital Anxiety and Depression Scale, and depression, Anxiety, and Stress Scales are commonly used to identify the presence of psychosocial consequences of neuropathic pain and, thus, prompt appropriate referral to allied health.\textsuperscript{92}

Table 1. Guidelines for oral use of NSAIDs

| S. No. | Guideline | Recommendation |
|-------|-----------|----------------|
| 1     | European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) | Recommended when paracetamol or SYSADOAs and/or topical NSAIDs are not adequately effective |
| 2     | European League Against Rheumatism (EULAR) | Consider in patients unresponsive to paracetamol |
| 3     | American College of Rheumatology (ACR) | Conditionally recommended for initial therapy, strongly recommended in knee OA patients unresponsive to paracetamol |
| 4     | Osteoarthritis Research Society International (OARSI) | Appropriate for individuals without relevant comorbidities; uncertain for those with moderate comorbidity risk |
| 5     | National Institute for Health and Care Excellence (NICE) | Use when paracetamol and/or topical NSAIDs are ineffective, or in addition to paracetamol or topical NSAIDs when insufficient pain relief is achieved |

NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; SYSADOAs, symptomatic slow-acting drugs for osteoarthritis
Pharmacological treatment

**TCAs**

TCAs, such as amitriptyline, are recommended as the first-line treatment for neuropathic pain.\textsuperscript{15, 105-107} Evidences support the use of TCAs in the treatment of peripheral neuropathy, post-herpetic neuralgia, traumatic spinal cord injury (SCI)-induced neuropathic pain, chronic neuropathic pain, post-herpetic neuralgia, and painful diabetic neuropathy.\textsuperscript{53, 109-116} Amitriptyline and nortriptyline are found to have comparable efficacy in the treatment of peripheral neuropathic pain.\textsuperscript{117} Compared with selective serotonin reuptake inhibitors, such as fluoxetine, TCAs have shown better pain relief ($p = 0.036$) in...
antidepressant-naïve post-herpetic neuralgia patients. The more common AEs of these agents are nausea, dizziness, somnolence, dry mouth, diarrhea, constipation, and hyperhidrosis.

**SNRIs**

SNRIs are also recommended as first-line therapy for neuropathic pain. Duloxetine and venlafaxine had been demonstrated to reduce pain intensity significantly (p ≤ 0.05) in neuropathic pain patients. The most common AEs reported with SNRIs are nausea, dizziness, somnolence, dry mouth, diarrhea, and constipation.

**Anticonvulsants**

Anticonvulsants that are commonly used for neuropathic pain are gabapentin and pregabalin. Various clinical trials have investigated their effec-

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**Figure 3. Algorithm for trigeminal neuralgia. MRI, magnetic resonance imaging; TCA, tricyclic antidepressant.**

**Figure 4. Algorithm for post-herpetic neuralgia. TCA, tricyclic antidepressant.**
tiveness in painful diabetic neuropathy and postherpetic neuralgia. Pregabalin has shown significant pain relief (VAS score, difference from placebo 2.18; p = 0.01; adjusted difference from the placebo, 17.6; p < 0.001) in chronic central neuropathic pain following SCI. However, it has not shown promising results in patients with neuropathic pain due to chronic lumbosacral radiculopathy and in those with central poststroke pain.

**Opioids**

Opioid analgesics are recommended as second-, third-, and fourth-line therapy for neuropathic pain. Opioids have demonstrated their effectiveness in patients with various neuropathic pains. However, a meta-analysis had reported that morphine provided moderate benefit in adults with chronic neuropathic pain. Long-term use of opioids is associated with a high risk of AEs and misuse. Hence, various guidelines have raised concerns on long-term use of opioids. Weak opioids, such as tramadol, can be considered for neuropathic pain. A meta-analysis and a prospective study have shown good pain reduction with tramadol in neuropathy patients (number needed to treat for 50% pain relief vs. placebo: 4.73 [95% CI 3.6–6.7]). However, a systematic review reported low-quality evidence for the use of tramadol in neuropathic pain.

For further management, it is advisable to refer to a pain specialist for interventional modalities for pain management.

**DISCUSSION**

Pain is a huge global health problem and one of the most common reasons for hospital visits worldwide. Pain management is an evolving area of expertise in Qatar, and there is an undertreatment of pain in the country because of the stigma associated with pain medications. Hence, a multidisciplinary and evidence-based approach is needed for effective pain management. Although guidance on the pharmacological treatment of peripheral neuropathic pain and acute pain is available in the Middle East, no specific guidelines for pain management have been recommended in Qatar; currently, physicians are following American, European, Canadian, or Australian guidelines. Hence, the expert panel, after multiple meetings and discussion, derived the treatment protocol based on evidence, current international treatment guidelines, and best practice recommendations for management of acute, chronic, and neuropathic pain in Qatar.

The most appropriate treatment choice for a patient with acute pain is acetaminophen owing to its additive effect. The second-line choice is NSAIDs for acute pain of moderate intensity and referral to a pain specialist for the pain of severe intensity. For management of chronic pain, both nonpharmacologic and nonopioid pharmacologic therapies should be considered. Clinicians should refer the patients to a pain specialist if the patient needs opioid therapy. The pain specialist should discuss with the patients the known risks and realistic benefits of such treatment within 1–4 weeks of starting opioid therapy. For neuropathic pain, antiepileptic drugs, SNRIs, and TCAs are typically recommended as the first-line treatment. Topical lidocaine and topical capsaicin are considered second-line options, while NSAIDs are not recommended for neuropathic pain.

Neuropathic pain should be managed by a senior primary care physician in consultation with a pain specialist. Experts recommended applying a precise evidence-based clinical algorithm; as a result, patients’ pain management will improve in terms of avoiding unnecessary medications, especially opioids, decreasing time to analgesia, and achieving ideal pain control in a timely manner to patient satisfaction. A standardized treatment strategy for various types of pain could help in optimizing pain management, which is currently an unmet need in Qatar.

**CONCLUSION**

An expert panel of physicians from different disciplines in Qatar, after reviewing the literature and international guidelines and discussing among the panelists, made recommendations for the management of acute, chronic, and neuropathic pain suitable for local practice and based on treatment availability in Qatar. The panel strongly recommended to avoid the use of opioids when possible and to refer the patient to a pain specialist clinician for interventional modalities of pain management as required. The panel opines that these recommendations be re-examined regularly and updated based on future developments.

**Competing interests**

MA has participated in an advisory board for Eli Lilly and Pfizer and has received speaker fees from Novartis. UAS is an employee of Pfizer Upjohn and
holds stock in Pfizer. OZ is an employee of Pfizer Upjohn. UAS also holds stock in Pfizer. AE and AFN have no competing interests to declare.

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**Authors' contributions**
AE, AFN, and MA contributed to the concept of this paper, identified studies to be included in this review, provided intellectual inputs for interpretation of data, and reviewed all drafts critically. OZ and UAS contributed to the concept of this paper, provided intellectual inputs for interpretation of data, and reviewed all drafts critically. All authors have read and approved the final manuscript.

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