Guest Editorial

South African guidelines for the treatment of cancer pain: South African Cancer Pain Guidelines Working Group

The production of these guidelines, written by South African medical practitioners, is a most welcome and important step in the treatment of cancer pain in this country. The overall prevalence of pain in cancer patients is estimated to be 53%, and 64% in patients with advanced and metastatic disease.[1] Too often, the only guidelines available to us are those written by practitioners in other countries which may be inappropriate for implementation here owing to the differing availability of drugs or disease profile.

The reproducibility of information is important in the South African situation. The direct, simple language used in these guidelines will facilitate ease of translation into different languages e.g. *isiZulu,* Xhosa and Afrikaans. The clear and precisely illustrated flow diagrams lend themselves to being reproduced in the form of charts and posters, which would be useful when disseminating this information at district hospitals and community clinics. These well thought out guidelines provide the first vital step in appropriate pain management to cancer and other terminally ill patients. The next step is education of healthcare practitioners at all levels, and the implementation of the guideline to improve the lives of patients afflicted with life-threatening diseases. With the use of multiple acronyms [precipitating factors, quality of symptom, relieving factors, severity and temporal relationship (PQRST) and (quit smoking, understand your body and get checked, eat healthily and drink less alcohol, stay sun smart every day and take time to be active (QUESTT)] and flow charts, it appears that the authors intended this when preparing this document.

The stepwise healthcare intervention for pain approach that the working group has devised involves a comprehensive review of the pharmacological treatment of pain for both children and adults. Other vital issues, such as pain assessment and the nonpharmacological treatment of pain, are covered. It is correctly stated at the outset that pain management should be multidisciplinary, and the role of psychological therapies, physiotherapy, occupational therapy, spirituality and other complementary therapies at every step is emphasised. The practical pharmacological guideline for children is especially important, since historically "opiophobia" has resulted in many suffering paediatric (and adult) patients being denied adequate analgesia.

The adopted format is the 1996 World Health Organization cancer pain relief guidelines, which, while commonplace in similar oncology treatment guides, are not without criticism. Sound treatment principles are proposed, i.e. that preferably, analgesia should be administered orally, i.e. "by the mouth", that it should be administered at regular intervals, i.e. "by the clock", and that medication should be administered in incremental steps of increasing potency, i.e. "by the ladder".[2] If we aim to achieve just these seemingly basic steps in the next few years, we will have been very successful indeed.

A few important aspects of pain management were not discussed, and these concern codeine, tramadol and methadone. The use of codeine is contentious internationally. As pointed out in the guidelines, it requires being metabloised to morphine in order to act as an analgesic, but 5-10% of patients lack the enzyme required for this conversion [cytochrome P450 (CYP) 2D6] and may receive insufficient analgesia with codeine. Conversely, 1-2% of patients (this rate is higher in some ethnic groups, e.g. 6% in Greeks[3] and 29% in Ethiopians[4]) may be ultra-rapid metabolisers of codeine, and the rapid conversion of codeine to morphine in these patients renders them at risk of sudden respiratory depression.[5] Following case reports of deaths in children from this occurrence, there are some institutions (e.g. Toronto's Hospital for Sick Children) in which codeine is not used, and only morphine given, as its effects are more predictable.[6] These guidelines follow this approach and omit the use of codeine in children with cancer pain. Caution is still warranted with regard to codeine use in adults, and it should be avoided in breastfeeding mothers[7] (unless CYP2D6 testing can be carried out, which is not routinely available in most public hospitals) and in the ethnic groups associated with ultra-fast metabolism.

The availability of codeine in South African public hospitals is another challenge. Codeine is not listed for the treatment of pain in the current adult hospital level standard treatment guidelines (STGs), and there is a possibility that it may be removed in the next edition of primary healthcare STGs. In future, drugs that are not in the Department of Health STGs will not be readily available in South African public institutions, and may include codeine. Several other drugs are also recommended in the guidelines for the treatment of cancer pain which are not in the STGs (e.g. oxycodone, hydromorphone and transdermal fentanyl). The authors of these guidelines should consider motivating for these drugs to be included in the STGs so that they can be available in South African public hospitals.

Tramadol warrants its inclusion in these guidelines as it is both available (it is in the adult hospital level STGs) and effective. Unfortunately, it is not without side-effects, and while these are briefly mentioned in the guidelines, its association with the serotonin syndrome is not included. There is a real possibility of precipitating this potentially life-threatening condition with chronic, high-dose tramadol use, particularly if given to cancer pain patients who are concomitantly receiving other drugs which increase intrasynaptic serotonin, e.g. amitriptyline

(doses up to 150 mg are recommended in these guidelines for the treatment of neuropathic pain). Those prescribing tramadol must be aware of the possibility of this syndrome, especially if patients start complaining of symptoms relating to the classical clinical triad of mental state changes, autonomic hyperactivity and neuromuscular hyperactivity.[8]

Opioid-induced hyperalgesia (increasing pain sensitivity in patients chronically exposed to opioids without any evidence of new causes of pain[9]) is an important condition relevant to the treatment of cancer pain with high-dose opioids, which is not discussed in the guidelines. Increasing morphine doses paradoxically result in escalating pain in opioid-induced hyperalgesia. There is evidence that this unpleasant scenario can be reversed by switching to methadone, but unfortunately, few practitioners in South Africa are experienced in the use of methadone for the treatment of pain, and methadone is certainly not without its problems. Careful dose titration is required, and there is the risk of accumulation. However, methadone has advantages too. It is relatively inexpensive and it may only need to be given once daily because of its long half-life. Its onset is also rapid. There is growing international experience of the use of methadone to manage cancer pain, even in an outpatient setting,[10] and it should certainly be considered in patients with opioid-induced hyperalgesia or in other difficult-to-manage cases.[11]

The spectrum of patients with cancer pain ranges from survivors living with chronic pain, to patients who have pain due to both cancer and non-cancer-related disease processes, e.g. chemotherapy and radiotherapy treatments, and procedure-related pain, as well as those requiring end-of-life care. The quality of life of patients with chronic pain can be improved by optimising both nociceptive and neuropathic analgesia. Neuropathic pain may arise from radiation-induced neuritis, chemotherapy-induced peripheral neuropathy or as a paraneoplastic phenomenon. Many cancer pain guidelines only describe the treatment of nociceptive pain, so it is of value that these guidelines clearly describe not only how to identify neuropathic pain, but also how to treat it. However, insufficient clinical trials have addressed the pharmacological treatment of neuropathic pain in cancer patients so evidence-based guidelines for this condition have not been provided. The treatment given is largely based on evidence obtained from studies on neuropathic pain arising from other conditions, and further studies are required to validate their use in neuropathic cancer pain. In addition to the drugs included in the guidelines, it is worth noting that the use of topical 5% lignocaine and 8% capsaicin has shown promise. Capsaicin depletes substance P via the transient receptor potential vanilloid receptor 1, and has demonstrated modest reductions in pain scores for up to 12 weeks in patients with painful polyneuropathy and postherpetic neuralgia.[12]

A discussion on the treatment of cancer pain with opiates is incomplete without consideration being given to the effect of opioids on survival from cancer. While the guidelines do not touch on this subject, it is worth bringing to the attention of practitioners that currently, growing evidence suggests that using opioids to treat cancer pain reduces survival.[13] How this impacts on the future use of opioids in patients with cancer pain remains to be seen. Practitioners should consider non-opioid analgesics where possible, but at present, should not completely stop using opioids for cancer pain as quality of life is as important as its duration.

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