Interview

Opioids: now and the future

Mellar P Davis is Director of Research at the Harry R Horvitz Center for Palliative Medicine at the Cleveland Clinic Foundation, OH, USA. He gained his MD from Ohio State University in 1977. Initially working in oncology, he now specializes in palliative medicine and symptom control for cancer patients, with a particular interest in pain medicine. Dr Davis is Editor-in-Chief of *Progress in Palliative Care*, and acts as a peer reviewer for several high-profile journals. He is Chairman of the Palliative Section of the Multinational Association of Supportive Care in Cancer and a member of the Scientific Subcommittee of the American Academy of Hospice and Palliative Medicine.

Mellar Davis
Cleveland Clinic Foundation, Taussig Cancer Center, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Tel.: +1 216 445 4622
davism6@ccf.org

■ **What led you to specialize in pain medicine & palliative care?**

Technically, I am a palliative specialist with an interest in pain. The reasons for entering into this field was a personal sense of deficit in managing symptoms, including pain, as an oncologist. I was a practicing oncologist for around 17 years. Around 1996/1997 I took some sabbaticals in Oxford, UK, and that was my first experience in palliative and pain medicine, in a patient population who mostly had advanced cancer. That sparked my interest, because I was able to see first-hand the benefits of what good pain management and palliation can achieve as far as the quality of life of individuals. It then became an academic interest, generating positive clinical outcomes.

■ **What is the main focus of your work?**

There are several main focuses of my work. I just finished a textbook with Oxford University Press entitled *Opioids in Cancer Pain*, focusing specifically on opioid treatment, and recently I have been doing work in breakthrough pain. A recent project I have been involved with was a conference after the Multinational Association of Supportive Care in Cancer International Symposium (June 25–27, 2009, Rome, Italy) this summer, in which we were looking at managing pain in the actively dying, both in developing and developed countries.

I also have a research proposal in looking at the affective dimension in response to opioids: usually researchers measure responses to cancer pain in terms of intensity reduction and sensory intensity of pain, but have not looked at helplessness, frustration, anxiety, hopelessness and other affective components to pain. There have been prevalence studies showing that patients with high-intensity pain also have multiple other emotional symptoms associated with pain. I would like to be able to see if by reducing the intensity of pain the affective components will also diminish, because these symptoms frequently overlap with depression or demoralization. If that is true, it would be a pragmatic finding and support the treatment of pain to see if the associated symptoms would be reduced before thinking about treating depression or anxiety directly.

■ **What are the key considerations for the physician when prescribing opioid therapy?**

There are several key considerations. One is the type of opioid used. It has generally been recommended by guidelines that morphine be used first, but there is no doubt, both in Europe and the USA, that the use of morphine is diminishing in favor of fentanyl and other opioids. Part of this may be marketing, and part of it convenience, because putting a fentanyl transdermal patch on someone is easier than having them take tablets on a regular basis. We are seeing an evolution in the type of opioids used. An important factor is the strategy of titration to pain control and dosing to the temporal pattern of pain. Another significant area that is important is the use of adjuvants – when and what

"*We are seeing an evolution in the type of opioids used. An important factor is the strategy of titration to pain control and dosing to the temporal pattern of pain.*"

10.2217/THY.09.57 © 2009 Future Medicine Ltd **Therapy** (2009) **6**(5), 645–648 ISSN 1475-0708

"*There are a lot of things to look at in pain management, but these parameters ... I would consider most important: types of opioids, temporal pattern of pain, titration, reassessment intervals and adjuvants.*"

to use – and that is not quite settled yet. Finally, reassessment intervals are important to define. This is partly related to pain intensity and pain emergencies, but there is no standard approach.

The only dosing strategy that has been validated has been the WHO stepladder. Dosing strategies to temporal pattern has been based upon expert opinion and clinical experience. In terms of the use of doses for breakthrough pain, there have been some studies, but they are not level-one evidence. There are a lot of things to look at in pain management, but these parameters would be the main domains I would consider most important: types of opioids, temporal pattern of pain, titration, reassessment intervals and adjuvants.

■ **Last year you contributed to a consensus guideline on parenteral methadone use in pain & palliative care. Why did you feel that these guidelines were needed? What were the main recommendations?**

I think it was a proactive approach to a crisis that was evolving. That crisis was based on two factors, one of which was descriptions of cardiac arrests with methadone related prolongation of QTC intervals. Therefore, we wanted to develop at least some guidelines as to monitoring QTC intervals, and which individuals were most at risk. The second factor is that there is a rising number of methadone-related deaths in emergency rooms. These tend to be males aged 24–44 years who have probably obtained diverted methadone and taken it on the street. Methadone can be quite a dangerous drug because it has a long half-life, synergistic drug interactions with sedatives, which many addicted individuals use, and has a significant number of drug interactions that prolong its effect. The drug has a 'black box' warning for this reason. However, it is very effective in cancer pain, and as we did not want to lose it from the clinical armament, we thought we could at least voice some guidelines for the use of methadone, to settle, or at least shed some light on the issues and to help clinicians use methadone well.

The main recommendations are related to the population risk factors. Certainly, when using intravenous methadone, electrocardiogram (ECG) monitoring should be carried out. With oral methadone, there was not a strong consensus that an ECG was needed. When we looked at the methadone maintenance population, who use fairly significant doses, the incidence of prolongation of QTC intervals and problems occurred in a very small minority of individuals. However, in that group some people may be more at risk: those with underlying cardiac disease, electrolyte abnormalities or congenital conduction defects. We were simply looking over the data and trying to make recommendations for clinicians who were going to use methadone.

■ **Methadone is being increasingly used for cancer pain. Is it likely that this trend will continue?**

I think its use will continue. You need experienced clinicians prescribing the drug: it is not the drug for a naive prescriber. It has a unique pharmacological profile which involves blocking *N*-methyl-D-aspartic acid (NMDA) receptors. How much this plays a role in analgesia is not known. It certainly binds to different subtypes of opioid receptors than morphine, and that may be why there is no cross-tolerance between the two opioids. It is a very inexpensive opioid, particularly in an economic crisis, it is a good option. It is both short- and long-acting, so you do not need a sustained release preparation. There are various safe dosing strategies that have been used based upon a stop–start strategy. There is a graded morphine to methadone equianalgesia ratio based on the morphine dose.

■ **Recently, there has been a great deal of discussion regarding the use of opioids in chronic noncancer pain: what is your view on this?**

Most of the studies that use opioids in noncancer pain are 7–8-week studies: we do not yet have long-term studies that look at 1–2 years of opioid therapy. There are a significant number of people in these studies who drop out either because of side effects, or because they get tired of taking the medications. One of the things that I think has recently arisen is the idea that opioids can produce pain: hyperalgesia. Researchers are certainly looking at various ways of using opioids in the noncancer setting, and there are guidelines published on the

use of opioids on chronic noncancer pain. The basic premise to using it is to balance risk and benefit, function and dysfunction. Opioids are drugs in the armamentarium for noncancer pain, and can be very effective. I have a patient who had a war injury causing neuropathic pain: he has been on methadone for approximately 3 years and is now able to walk without pain and has not required dose escalation. It can be an effective modality in treating noncancer pain, but I think most physicians would tend to use nonopioids initially before using opioids, unlike the cancer pain population, where opioids tend to be used more frequently as a first-line medication because of the degree and severity of pain.

■ **Dependence is often a major concern of both patients and clinicians. What precautions do you take in your clinical practice with regard to opioid dependence?**

It is important to recognize that there are two types of dependence: physical and psychological dependence. The majority of patients will have physical dependence. It is frequently mistaken by the public as psychological dependence, but it is not. It is important to educate patients about his and tell them not to abruptly stop their opioids.

There will be a group of patients who are psychologically dependent, and this is more due to a personality than a drug. There tends to be a genetic predisposition – if the family history is positive, that is probably the greatest risk factor. There are different gradations of misuse of opioids; for instance, patients may just not follow what a physician has prescribed, but they are not addicted. Part of this may be a personality issue: they are suspicious, and might self-escalate the dose when they have pain.

True addiction is defined by someone who continues drug use despite harm, which can be psychological, social, physical or financial harm, and they cannot stop. Generally, addiction involves polysubstances rather than a single substance. Usually if you are dealing with someone with addiction you use a pain contract with expected behaviors, and strategies for managing this, in which people can keep their dignity but receive good pain control. A good pain contract makes the patient responsible for their own behavior, and a good physician will hold the patient to that contract.

The worst offenders are those who may not be addicted themselves, but divert the drugs to the street for financial reasons, thereby putting others at risk.

Probably the largest mistake that physicians make is mistaking pseudo-addiction for addiction. There are certain individuals who, when their pain is out of control, have personality changes. They will demand a drug, any of us would do, to get some relief, and they may become angry and hostile if they do not receive the drug. A naive physician may think that this person is addicted. In addition, some patients require a large dose to maintain pain control, and physicians may think that simply by dose the patient is addicted. If you bring patients with pseudo-addiction into the hospital and titrate their opioids to give them pain control, their personality changes back to normal.

■ **How do you expect opioid use to change over the next 10 years?**

There is low-lying fruit that has yet to be harvested. One of them is simply taking the acetaminophen or paracetamol out of hydrocodone. Hydrocodone is a good drug, but it is limited because there is no pure hydrocodone on the market, and it is hard for me to believe that no company has decided to take that on as a product.

The second is using old drugs: bringing out old friends that we have not used for a while as a renaissance. One of these is buprenorphine. Buprenorphine is decades old, and large numbers of cancer patients have been treated with it in the past. In the USA it is only licensed for addiction, but it has a unique analgesia profile: it is not hyperalgesic, it is safe in renal failure, and its analgesic potency is almost equal to fentanyl. I have been using this drug in my practice and have had some really nice results. I think this is a drug that pain management physicians should consider adopting. The other drug that was used a couple of decades ago is levorphanol, which may be a 'safe methadone'. It is a potent, long-acting opioid and, like methadone, blocks the NMDA receptor. The advent of sustained-release products probably led to its gradual decline, but it has a unique profile and someone could market that.

"Opioids are drugs in the armamentarium for noncancer pain, and can be very effective."

The other thing I think we are going to see more of is a change in the route of administration. The transdermal and sublingual routes are being explored, and new formulations are likely to be released, for example, sublingual methadone. The other route that may become more common is the intranasal route, which is a direct route to the subarachnoid space. The kinetics of administration are almost equivalent to giving an intravenous bolus. Most of us have used nasal sprays or drops so it is easy to administer. There are ways of making it safe with lock-out intervals and personal identifiers on the devices. There may be problems with this gaining regulatory approval, however, as intranasal administration is associated with illegal drugs.

Combination therapy, using an opioid combined with another drug, is another area of development. We have this already with buprenorphine, predominantly to prevent illicit changing of route by combining the drug with an opioid antagonist to prevent illicit conversion to parenteral injection. Combining an opioid with a low-dose opioid antagonist may paradoxically improve pain control. By preventing activation of GS proteins in the receptor it may block hypersensitivity. Ketamine has also been used to improve pain control in combination with opioids.

Another area that is more distant, but very exciting, are the nonopioid analgesics, such as cannabinoid-2 receptor agonists. We have been so dependent on opioids for pain management, but now we may start seeing classes of drugs that would improve or even forestall the use of opioids in certain patients or populations.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.