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NO TIME FOR CANCER PAIN

HIGHLIGHTS FROM
**Symposia at the
EAPC and DGP**
Aachen, Germany
April 2005

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Dr Thomas Nolte

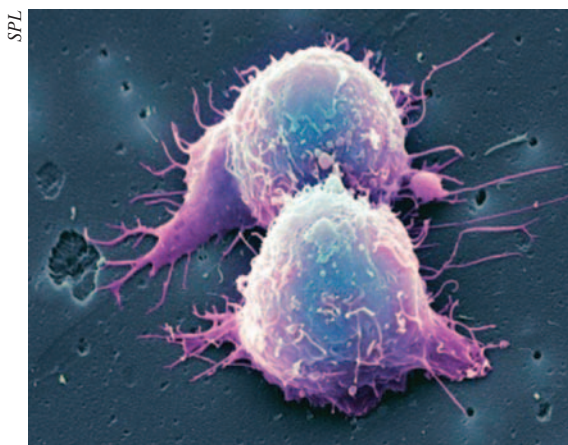
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SYMPOSIA HIGHLIGHTS FROM THE EUROPEAN ASSOCIATION OF PALLIATIVE CARE (EAPC) AND THE GERMAN PAIN SOCIETY (DGP), AACHEN, GERMANY, APRIL 2005



cancer every year and more than two-thirds of advanced cancer patients are experiencing severe pain. The number of people suffering from cancer and other chronic conditions requiring palliative care is rising, but at the same time, the drugs and formulations we have available to care for them are also increasing. As both sides of this equation change dramatically, provided clinicians are aware of the effective alternatives around them and are prepared to review and adapt their practices at the same pace, she explained, there is no reason why patients' quality of life should not be improved immeasurably.

On the opening day of the ninth annual congress of the European Association of Palliative Care (EAPC), Dr Marilène Filbet introduced and chaired a symposium with the ambitious objective of examining, debating and updating our current strategies of cancer pain management. Dr Filbet is Director of Palliative Care at the University Hospital in Lyon, France as well as President of the EAPC. She was presiding over another three of the world's leading experts in palliative care, brought together to share their experiences and the very latest knowledge in the field.

Dr Filbet introduced the symposium by briefly setting the scene of palliative care today, as recorded by the WHO: 10 million people worldwide are diagnosed with



10 million people worldwide are diagnosed with cancer every year and more than two-thirds of advanced cancer patients are in severe pain

Dr Marilène Filbet

The positive philosophy of embracing an era of change in palliative care was advanced by the first of the invited speakers, Dr Adrian Tookman, Medical Director of the Marie Curie Hospice, Hampstead and Consultant in Palliative Medicine at the Royal Free Hospital, London, UK. Dr Tookman began by pointing out that there are increasing numbers of people who are developing cancer and an increasing length of time that they survive with their illness. Where cancer was once

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Dr Marilène Filbet
Chair of 'No time for cancer pain – new options through inventive formulations'



Professor Eberhard Klaschik
The Palladone® concept: experience from Germany



Dr Adrian Tookman
Cancer pain treatment – time for a change?



Dr Thomas Nolte
Effective cancer pain treatment: paradigm shift required

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considered an acute and terminal condition, it is now thought of, for many, as a chronic illness and cancer patients frequently survive with significant symptom control problems¹. This presents a fundamental change in today's population of palliative care patients: they are likely to be taking analgesics for significantly longer than would have been expected in the mid-1980s/1990s and any side-effects, which in the past may have been of little importance in an acute, short-lived illness, must

now be reconsidered as potentially serious issues in an illness that is long term.

In this context, it is the 'low-status', poorly-recognised side-effects that may have serious implications in patients on long-term opioids. We have 20 years' experience using morphine and are aware of the common side-effects and know how to respond to them. However, in addition to common side-effects on the GI tract and CNS, there are also numerous 'other' side-effects that receive little attention: dry mouth, impaired cognitive function, hormonal/sexual impairment and impaired immune function (see Table 1).

As our ability to treat cancer improves, we must pay more attention to these long-term side-effects. In addition, there is anecdotal evidence from individual practitioners that these side-effects may be morphine specific rather than class (opioid) specific in some patients. Different opioids can have effects and side-effects that vary in an individual patient and from patient to patient. The patient population is not homogenous and this is backed up by our increasing understanding of genetics and knowledge of opioid receptors, and the precise sites of actions of different opioids. 'Morphine may no longer be the gold standard¹⁰ and we need to have superior options to replace it', suggested Dr Tookman.

There is certainly no shortage of alternative options, but whether they can all be considered superior to morphine is unclear. As such, there is a lack of clarity over the best prescribing pattern and in particular which opioid to use first- and second-line instead of morphine.

Dr Tookman closed his discussion with a broad picture

TABLE 1. 'LOW-STATUS' SIDE-EFFECTS OF MORPHINE

DRY MOUTH

Persistent dry mouth increases the risk of infection and the likelihood of significant dental problems in the future.

COGNITIVE FUNCTION

Morphine has been shown to produce significant antegrade and retrograde memory impairments²; reduced conceptual flexibility. However, there is enhanced psychomotor performance³. These can impact significantly on patients' quality of life.

HORMONAL/SEXUAL IMPAIRMENT

Inhibition by morphine of gonadotrophin-releasing hormone results in low testosterone, an effect which is even more pronounced in cancer patients⁴. In addition to loss of libido, the consequences of this hormonal imbalance include fatigue, loss of muscle mass and osteoporosis.

IMMUNOSUPPRESSION

Acute and chronic opioid administration inhibits neutrophil and T-cell functions, reducing antibody production and phagocytic activity⁵⁻⁹. It further modulates cytokine activity and depresses the HPA axis.

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of what an ideal opioid should look like. The avoidance of active metabolites, low dependence on renal excretion and minimum short- and long-term side-effects cover some of the key attributes described. He explained that several potential alternatives to morphine currently exist and these had preferable characteristics. These options should be seriously considered as first-line medication (Table 2).

He explained, ‘It is the right of every patient to be able to access effective pain relief and with the growing knowledge we now have about each opioid, it is our duty to be at least open to the suggestion that morphine may not be the best first choice – it may be time for a change.’

Change was at the centre of the second speaker’s discussion. Professor Eberhard Klaschik (Professor of Palliative Medicine at the University of Bonn – the first chair in the field to be established in Germany) explained that Germany has extensive experience with hydromorphone in comparison with other European countries. Morphine was not used as the opioid of choice by clinicians, unlike many other countries, and therefore there are not as many established users. This may have led

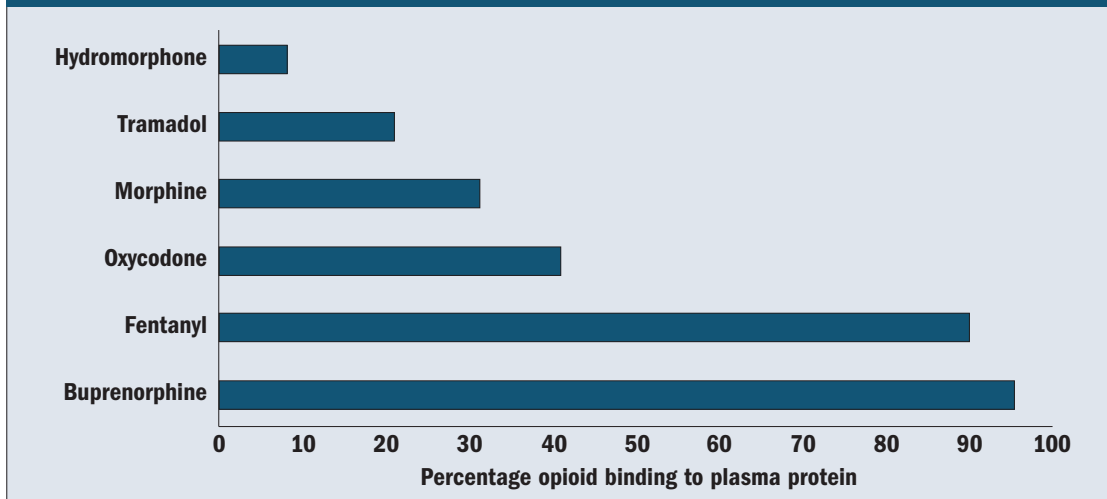
TABLE 2. THE IDEAL OPIOID

- Multiple preparations and multiple routes.
- Reliably absorbed with high bioavailability.
- Small molecule.
- Lipophilic.
- Inactive metabolites.
- Not dependent on renal excretion.
- Low incidence of short- and long-term side-effects/ adverse events.

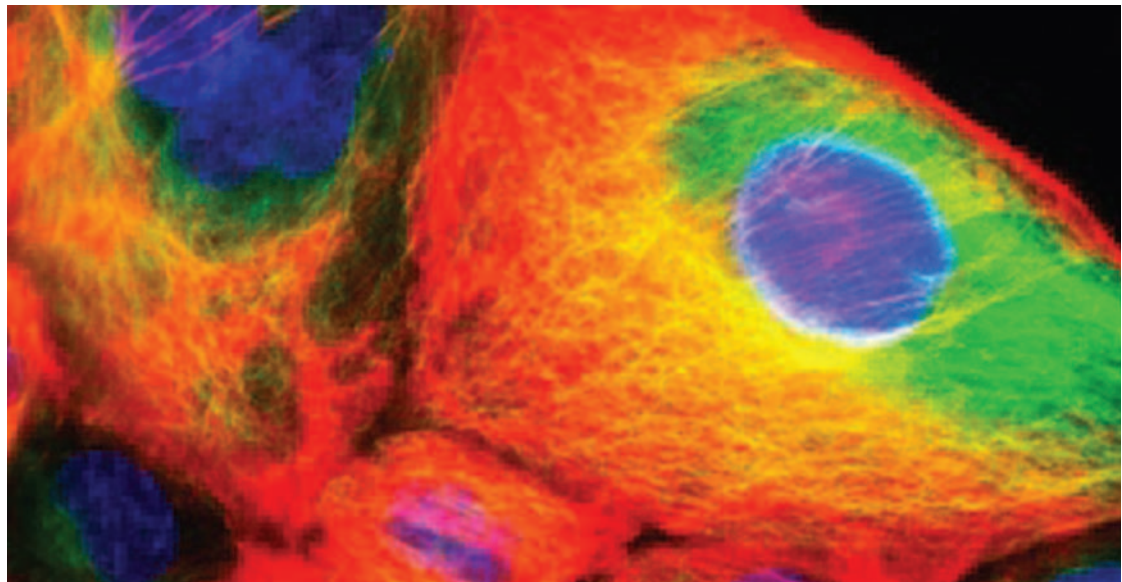
to a clinical environment more conducive to working with morphine alternatives. As a consequence, the breadth of experience with new agents like hydromorphone outweighs that of most other countries and, according to the data presented here, embracing ‘change’ has been a remarkable success.

But does hydromorphone qualify as the ‘ideal opioid’ suggested by Dr Tookman and does it justify replacing morphine as the first-line agent? Evidence of plasma binding properties of only 8 per cent in vitro are certainly very encouraging – especially when compared with around 90 per cent with fentanyl and 95 per cent with buprenorphine (see Figure 1). The obvious benefit to this is a reliable efficacy, even in the frequent event that a patient may be concurrently taking a diverse daily drug regimen. That reliability is further enhanced by the fact

FIGURE 1. COMPARISON OF THE PLASMA PROTEIN BINDING PROPERTIES OF A SELECTION OF OPIOIDS



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that the breakdown of hydromorphone does not involve cytochrome P450, pivotal in the clearance of most other drugs, meaning that additional strain on this endogenous resource can cause problems. Hydromorphone is in fact metabolised via glucuronidation, which may also help to explain the lack of therapeutically active metabolites – another valuable asset helping to improve overall tolerability, particularly relevant in patients with renal impairment. The usual equianalgesic dose ratio of hydromorphone to morphine was reported by Professor Klaschik to be 7.5:1, but this may need to be reduced even further where renal impairment is an issue.

Professor Klaschik showed a short, yet moving, video of one of the patients from his palliative care centre in Bonn. Before the patient was transferred to the centre, he described his pain as the ‘worst kind of torture’ and talked of his ‘suffering like hell’. However, after being treated at the palliative care centre, the patient was ‘practically free of pain.’ The video made clear the impact and suffering that pain can bring to a patient’s life if it is not managed appropriately.

In the discussion following his presentation, Professor Klaschik summarised by saying, ‘Hydromorphone’s reliable efficacy combined with the significant reduction in observed side-effects like drowsiness when compared to other opioids in its class, has convinced me absolutely that it should become the first-line drug of choice in the management of severe cancer pain.’

Although each speaker at the ‘No time for cancer pain’ symposium approached the session from a slightly different perspective and with different experiences, there was a consistent theme and message throughout. The palliative care arena in terms of its patients, the way we treat them and with what, is a remarkably different landscape to the one of 20 years ago. A great deal has been learnt in that time and huge advances have been made not only in our knowledge of diseases, but also of the drugs we use – their individual pharmacokinetics and how best they can be administered.

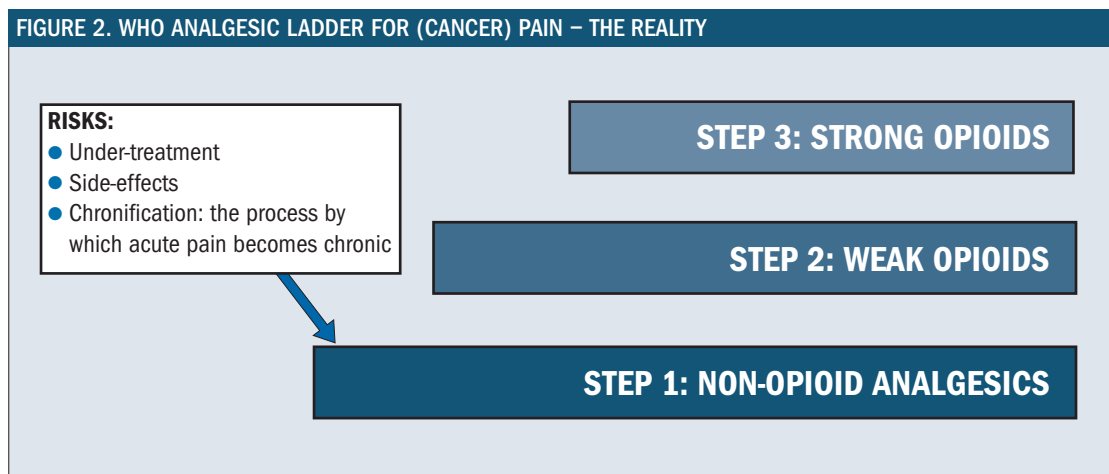


“I am convinced absolutely that hydromorphone should become the first-line drug of choice in the management of severe cancer pain”

Professor Eberhard Klaschik

Professor Klaschik went on to discuss the variety of preparations in which hydromorphone is currently available. The option of both controlled-release (CR) and immediate-release (IR) formulations allows for appropriate use in a broad spectrum of clinical scenarios, which he aptly demonstrated through discussion of two quite different case studies of hydromorphone successes.

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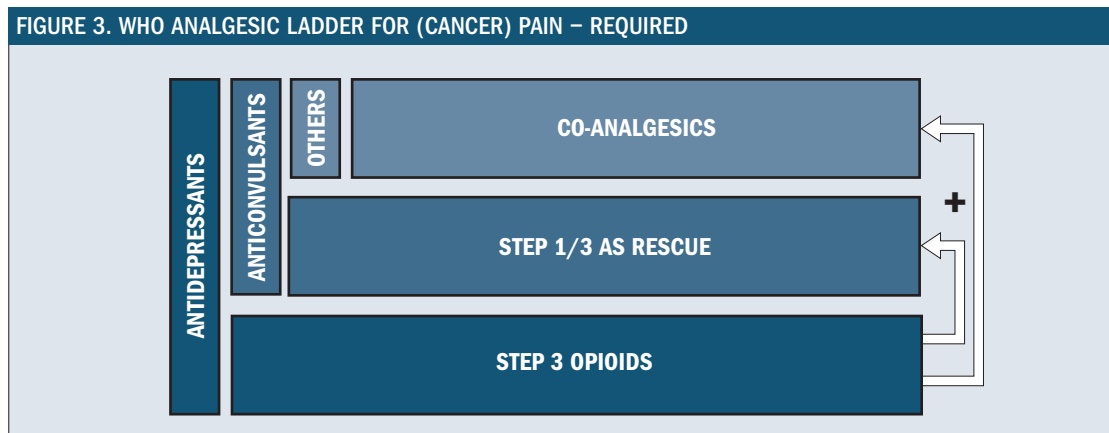


The question is surely not whether the approach to treating palliative care patients needs to change, but how quickly the improvements that have been made to the model of morphine as a gold standard can be accepted and embraced by this broad, multidisciplinary profession.

The efficacy and benefits of CR hydromorphone were discussed further during a symposium at the 2005 conference of the German Pain Society, also held in Aachen, Germany. 'More than half of all cancer pain patients still suffer from insufficient pain treatment', said Dr. Thomas Nolte, the presenter of the symposium, and a pain specialist from the Centre for Pain and Palliative Medicine in Wiesbaden and Vice-President of the German Pain Association (Deutsche Gesellschaft für Schmerztherapie, DGS). Dr Nolte is investigating to what extent the use of opioids is accepted and implemented as

a standard in cancer pain therapy. He states: 'Numerous options exist for treatment of severe pain, but currently they are not sufficiently exploited.'

Before his discussion of CR hydromorphone, Dr Nolte questioned the current standards of pain management. The key for successful treatment of severe pain in cancer patients is the right choice of the right analgesic, at the right time. 'CR opioids should be used from the beginning onwards', believes Dr Nolte. He also strongly supports a modified WHO analgesic ladder: 'The answer to strong pain is immediate treatment with a WHO analgesic ladder step 3 opioid.' According to Dr Nolte, the WHO analgesic ladder in its current format may turn into an obstacle against efficient pain therapy in the case of severe cancer pain: 'As the WHO guidelines had been of didactic value, they now rather hinder effective pain management.'



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Patients are treated by far too much and for too long with step 1 analgesics, which are not only inadequate, but also cause strong adverse effects' (Figure 2). This is particularly applicable in concomitant and polymedication, which is a frequent occurrence in cancer patients. He claims that in these cases, the current scheme needs modification (Figure 3). As many patients need additional medication such as antidepressants, anticonvulsants, antibiotics or analgesic co-medication, this has to be accounted for in the selection of the right opioid. Morphine, regarded as 'gold standard' until recently, is being replaced increasingly by modern, semi-synthetic substances. Among these, Dr Nolte recognises hydromorphone as the most favourable for the treatment of patients with poly-medication and concomitant medication due to its pharmacological features and analgesic potency (see Table 3): Hydromorphone shows no ceiling effect and can be adapted to the patient's pain condition without limitation in dosage or a change in therapy. Its breakdown does not appear to significantly involve cytochrome P450 and so does not interfere with other medications metabolised via this pathway. At normal doses, there are no relevant metabolites produced in the course of its breakdown. Hydromorphone, therefore, is particularly well tolerated in patients with renal impairment, but lower doses may be required to achieve adequate analgesia. In addition to the CR form, hydromorphone can also be used as rescue medication in case of breakthrough pain in the IR form. Dr Nolte concluded, 'Of the options presently available, hydromorphone shows the most favourable profile of effects and adverse effects.' With respect to the advantages of hydromorphone, he also gets strong support from two recent studies presented as posters at the conference^{11,12}.



“The answer to strong pain is the immediate use of a WHO analgesic ladder step 3 opioid

Dr Thomas Nolte

In a multicentre observation study by Dr. Hans-Bernd Sittig, Director of the Pain Therapy Centre, St. Joseph Hospital, Bremerhaven, Germany, pain intensity and quality of life were assessed before and after switching from other WHO step 2 and step 3 analgesics to hydromorphone¹¹. More than half of the 487 patients

TABLE 3. ADVANTAGES OF HYDROMORPHONE

- High analgesic potency, no ceiling effect.
- Compatible with renal impairment, but a lower dose may be required to achieve adequate analgesia.
- Low constipation and emesis potential.
- Simple titration, only little fatigue.
- No interaction with cytochrome P450.
- Low plasma protein binding.
- Can be applied in multi-medication.
- Can be applied in multi-morbidity.

enrolled (54 per cent) were cancer patients. Assessments took place at the onset of treatment, and on the third and seventh days. A final examination was performed after three weeks. At this time, the intensity of pain was reduced by 65.3 per cent – it dropped from 7.2 to 2.5 using the University of Wisconsin's Numerical Rating Scale (NRS) of 0 to 10 (where 0 = no pain and 10 = severest pain) after switching to hydromorphone. As quality of life is an important indicator for overall treatment effectiveness, scores were assessed with respect to activity, mood, ability to walk, exercise tolerance, social contacts, sleep and enthusiasm for life. An improvement in score of 54 per cent was seen following the switch to SR hydromorphone treatment. In the study also the evaluation of the participating physicians was assessed: compliance, tolerance and effectiveness of therapy with hydromorphone were rated 'very good' or 'good' by 90.7 per cent, 92.2 per cent and 88.5 per cent, respectively.

Additional data from a study by Dr Heinrich Lannert from the Medical Centre of Ruprecht Karls University, Heidelberg, Germany, also demonstrated an improvement in efficacy and tolerability for CR hydromorphone versus transdermal fentanyl in patients with stage III multiple myeloma¹². Pain intensity reduced from an average of eight as measured by a visual analogue scale (VAS) down to an average of less than one for CR hydromorphone (against an average of over two for transdermal fentanyl). Four out of 19 fentanyl patients had to be switched to hydromorphone.

Despite results clearly pointing to existing options for improving cancer pain therapy, deficits still exist to a great extent. As Dr Nolte stated, 'More than 95 per cent of the patients could be relieved from suffering pain by

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means of effective and multimodal pharmacotherapy.' He identified the major reasons for this under-treatment as a significant lack of knowledge of physicians on current options as well as prejudices against opioid treatment: 'Most commonly, opioids are regarded as being insufficient in analgesic effect and bearing the risk of inducing tolerance and addiction.' When comparing the advantages and disadvantages of opioids, the reality is quite different. As many studies show, opioids are highly effective in analgesia, lack organ toxicity and avoid chronification of pain. However, 'opiophobia' remains widespread, not only among patients, but also among physicians. As a current survey of the OPENMinds group (Opioids for Pain European Network of Minds) shows, this is true for most European countries. The use of new substances such as hydromorphone could help to fight this myth. 'As morphine is replaced with semi-synthetic opioids for reasons of better compatibility and reduced side-effects, they will help to improve patients and physicians acceptance for this highly effective treatment', Dr Nolte concluded.

Summary

The reports from these symposia clearly highlight that the management of cancer pain is experiencing a significant period of change, and physicians are beginning to question more traditional protocols and treatments. Pain associated with cancer tends to be prolonged, persistent and progressive; therefore, pain control should be effective all of the time.

Dr Adrian Tookman questioned whether morphine should remain as the 'gold standard' for treating cancer pain, particularly as there are many newer products with fewer side-effects, which are also available in CR formulations. Indeed, Professor Klaschik strongly believes that CR hydromorphone should become the first-line drug of choice in the management of severe cancer pain because of its reliable efficacy and the significant reduction in observed side-effects.

As Dr Filbet stated in her introduction, a patient's quality of life can be significantly improved provided clinicians are aware of the effective alternatives around them, and are prepared to review and adapt their practices.

References

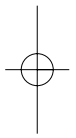
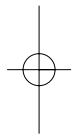
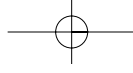
1. Coleman MP et al. Cancer survival trends in England and Wales, 1972-1995: deprivation and NHS Region. Studies in Medical and Population Subjects No.61. London: The Stationary Office, 1999
2. Kamboj S et al. The effects of breakthrough morphine on cognitive function (Poster EAPC Aachen)
3. Jamison J et al. Neuropsychological effects of long-term opioid use in chronic pain patients. *J Pain Symptom Manage* 2003; 26: 913-921.
4. Rajagopal MR et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer* 2004; 100: 815-818.
5. Budd K. Immunosuppressive effects induced by opioid analgesics *IMRAPT* 2002; 14: 3-7.
6. Risdahl JM et al. Opiates and infection. *J Neuroimmunol* 1998; 83: 4-18.
7. Hall DM et al. Opioid mediated effects on the immune system: sympathetic nervous system involvement. *J Neuroimmunol* 1998; 83: 29-35.
8. Menzebach A et al. Effects of endogenous and synthetic opioid peptides on neutrophil function in vitro. *Br J Anaesth* 2003; 91: 546-550.
9. Vallejo R et al. Opioid therapy and immunosuppression: a review. *Am J Ther* 2004; 11: 354-365.
10. Kurowska A et al. Morphine: yesterday's drug or yardstick for the future? *Br J Hosp Med* 1996; 56: 256-259.
11. Sittig HB. Results of a multicentre study in 487 patients: pain reduction and improvement in quality of life with sustained-release hydromorphone. Poster at the 9th Congress of the EAPC, 6-10 April 2005, Aachen, Germany
12. Lannert H. Pain Therapy in Patients with Multiple Myeloma. Poster at the 9th Congress of the EAPC, 6-10 April 2005, Aachen, Germany.

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