



Te Kaporeihana Āwhina Hunga Whara

Considered Judgement Form

This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations.

Meeting date: 12 August 2004. Revised following Meeting 20th October 2005

Topic: *The effectiveness of oral tramadol in chronic non-malignant pain management*

Background and Purpose: Tramadol is commonly used in pain relief, particularly when other pain relief strategies have been tried and failed. Tramadol is a synthetic opioid-like drug so therefore has some properties of strong analgesic drugs like morphine, pethadine and codeine. Tramadol has been favoured over true opioids due to a belief that it is less addictive. Currently, if tramadol is prescribed then ACC funds it. ACC would like to be able to develop purchasing criteria to guide the purchasing of tramadol by ACC. An evidence-based review of the effectiveness of oral tramadol in chronic, non-malignant pain management has been prepared at the request of Sunita Goyal (Pharmaceutical advisor, Healthwise).

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency

Effectiveness

Twenty-eight randomised controlled trials and one systematic review were found which examined the effectiveness of oral tramadol in chronic non-malignant pain management. Of these 29 studies, 10 compared tramadol to placebo, five compared tramadol + paracetamol to placebo, four studies compared tramadol to codeine + paracetamol, four compared tramadol to a drug other than placebo or codeine + paracetamol (dihydrocodeine, diclofenac, dextropropoxyphene, and pentazocine), and six studies compared immediate release (IR) tramadol to slow release (SR) tramadol and/or the use of different titration rates. There were seven studies that were appraised as 1++, fifteen as 1+, and seven studies were assigned a 1- level of evidence.

The main findings were:

- Tramadol (+/- paracetamol) appears to be more effective than placebo
- Tramadol appears to be comparable in efficacy to codeine + paracetamol
- There appears to be insufficient evidence to show that tramadol is any more or less effective at relieving chronic pain than dihydrocodeine, diclofenac, dextropropoxyphene, or pentazocine
- Tramadol appears to be better tolerated when a slower titration rate is used
- There appears to be no difference in pain relief between immediate/normal release tramadol and sustained/once daily release, however there may be fewer side effects associated with the slow release formulation.

Reported rates of adverse events varied from study to study, as did methods of collecting this information. The adverse events commonly reported were those typical of other opioids, for example, nausea, vomiting, headache, drowsiness, dizziness, somnolence and constipation.

Addiction, tolerance and withdrawal

One study was found which examined the development of tolerance to tramadol (level 1-), one case series and four case reports (level 3 evidence) examined the addiction potential of tramadol, and a further four case reports (level 3 evidence) described withdrawal in the absence of addiction.

Even though tramadol does have a low addiction and abuse potential, it is still a possibility, especially amongst people with a history of drug or alcohol addiction. Withdrawal can occur in the absence of addiction.

A recent Cochrane review calculated the number needed to treat (NNT) as 3.5 and number needed to harm (NNH) as 7.7 in neuropathic pain patients. [1]

2. Cost

There is no information in the literature relating to the cost-effectiveness of tramadol in chronic pain management.

The current purchase price of 400mg of tramadol (the recommended maximum daily dose) is NZ\$2.96^a for either immediate or slow release (excluding GST). This is much more expensive than 240mg codeine (recommended maximum daily dose) which is NZ\$0.95^b (excluding GST). The purchase price of 4g of paracetamol (the recommended maximum daily dose) is less than 8 cents (excluding GST), therefore the cost of adding paracetamol to either tramadol or codeine is negligible.

At present ACC makes around 1000 payments for tramadol per month, at an average cost of \$96 per payment per month (including GST, mark ups and dispensing fees). This equates to an annual cost to ACC of around \$1million.

The PGAG requested further data about the prescribing pattern of tramadol in the treatment of chronic pain (this is currently being processed).

3. Clinical impact

Tramadol is a safe and effective analgesic for chronic non-malignant pain, however it has not been shown to be any more effective than codeine + paracetamol. As tramadol is more expensive than codeine, this suggests that tramadol should only be prescribed if codeine + paracetamol fails to provide adequate pain relief, cannot be tolerated, or is contraindicated in the patient.

As no difference was found between Immediate Release and Sustained Release formulations in terms of pain relief, the formulation of choice should be at the discretion of the prescriber or patient. Fewer side effects may result from the Sustained Release formulation.

Tramadol, like many other analgesics, carries with it the possibility of adverse events such as nausea, vomiting, somnolence, drowsiness, dizziness, headache, dry mouth and constipation.

Even though tramadol has a low abuse potential, several cases have been reported in the literature and prescribing clinicians need to be aware of this, particularly if their patient has a history of drug or alcohol abuse.

Cases of withdrawal in the absence of addiction have also been reported, indicating that patients should not stop treatment abruptly, rather they should be withdrawn over several days or weeks.

Information about the addictive potential of codeine was outside the scope of this review.

4. Equity, Maori Health, Other Ethnic Group Health Issues, Acceptability

Pharmac does not currently fund Tramadol.

There is anecdotal evidence that tramadol does not have a "street" value.

5. Possible Purchasing Options

Option 1: Don't purchase

^a New Ethicals Catalogue May 2004

^b The Pharmaceutical Schedule April 2004, subject to change

Option 2: Purchase if codeine + paracetamol fails to provide adequate pain relief after a specified time period, cannot be tolerated, or is contraindicated in the patient.

Option 3: Purchase if prescribed

Any other options?

6. Evidence Statement

There is high quality evidence that oral tramadol is effective in the management of chronic, non-malignant pain. There is high quality evidence that tramadol is no more effective than codeine and paracetamol. There is insufficient evidence that tramadol is any better or worse at relieving chronic pain than dihydrocodeine, diclofenac, dextropropoxyphene or pentazocine. The side effect profiles of codeine and tramadol are similar in their use in chronic pain management.

There is evidence to suggest that tramadol has a low addiction potential, however it remains a possibility, especially in those with a history of alcohol or drug abuse.

There was no evidence found to support or refute the long-term use of tramadol.

7. Purchasing Recommendations

Updated October 2005 (following review of use of Tramadol for the treatment of acute pain)

Purchase as a second line treatment according to the following prescribing criteria:

- An adequate trial to have sufficient analgesia of codeine & paracetamol (e.g at least 3 days) has been tried (at maximum daily adult dose 240mg/1g respectively).
- If sufficient analgesia is not obtained consideration should be given to patient compliance and the possibility of using an increase dose of codeine (to the recommended daily adult dose)
- Prescribing tramadol depends on the status of the individual; it should be prescribed if it is equally effective to an alternative medication, but safer for the patient. (Second best line of treatment). Tramadol should only be prescribed when there are specific reasons to do :

Tramadol should be used as a second line agent when:

- An opioid dependent patient needs stronger pain relief than paracetamol
- NSAIDS are contraindicated
- Patient has respiratory depression
- An alternative adequate dose of paracetamol/codeine has been tried

Tramadol should not be used when:

- In conjunction with SSRIs or other serotonergic drugs
- Any drug contraindicated with tramadol that may cause harmful drug interactions.
- Paediatric use
- If pulse and blood pressure are not in the normal range

Depending on the severity of pain and situation, tramadol is usually replaced with paracetamol or codeine once pain severity has decreased.

Caution should also be taken if the patient is over 65 years of age.

- Once tramadol has been prescribed its continued use should be monitored every three

months.

1. Duehmke, R., J. Hollingshead, and D. Cornblath, *Tramadol for neuropathic pain*. Cochrane Database of Systematic Reviews, 2004. 2

PGAG Main Discussion Points August 2004

The main concern for ACC is the cost of prescribing Tramadol beyond the “acute” treatment phase.

Tramadol is often prescribed in the acute setting, but the effectiveness of Tramadol in the acute setting was not part of this current review.

The PGAG felt they were unable to make a purchasing recommendation for Tramadol in chronic pain management as stopping treatment begun in the acute setting may have detrimental effects in terms of perpetuating disability and escalating indirect costs such as home help. The main question raised by the PGAG was “should we start prescribing” in the acute setting and this was not addressed in this current review.

There appears to be a clear need to educate prescribers. The PGAG recommended that the review be published in a peer reviewed journal (after completion of a review of the effectiveness of Tramadol’s use in the acute setting) and be featured in ACC news, ACC internet and intranet.

The PGAG suggested that EBH consider carrying out a review of the effectiveness of Tramadol in the acute setting.

PGAG Main Discussion Points October 2005

The PGAG agreed that the purchasing recommendations for the use of Tramadol for chronic pain should reflect the recommendations made for the use of Tramadol for acute pain.

Glossary

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency

Comment here on:

- the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible,
- any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand Population,
- the degree of consistency demonstrated by the available evidence.

Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

2. Cost

Comment on:

- any economic costs associated with this service, product or procedure

3. Clinical impact

Comment on:

- the clinical impact eg size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit

4. Equity, Maori/Pacific Health, Acceptability

Comment on the extent to which:

- the service, product or procedure reduces disparities in health status (equity of access, resources, health outcome),
- is consistent with the treaty of Waitangi and encourages Maori/ Pacific participation in providing and using service, product and procedures, and
- is consistent with values and expectations of New Zealanders.

5. Purchasing Options

List the possible purchasing options.

6. Evidence Statement

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

7. Recommendations

What recommendation(s) does the advisory group draw from this evidence?