TITLE: Tramadol Compared with Opioids for Pain: A Review of Addiction Potential

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CONTEXT AND POLICY ISSUES:

Recent data suggest that 16% of the Canadian population under the age of 65 years experiences chronic pain. In those aged 65 years and older, almost 25% who live in the community and 40% of those who live in institutions suffer from chronic pain. Complaints related to pain account for more than 40% of all symptom-related visits to physicians on an outpatient basis and analgesics are one of the most commonly prescribed medication classes in Canada.

Guidelines for the management of chronic pain generally recommend a step-wise approach to care, such that acetaminophen and non-steroidal anti-inflammatory drugs are first-line therapies, followed by a progression through other medication classes such as anti-epileptics and anti-depressants, reaching treatment with opioids as the final step. While opioids are effective analgesics, they have some disadvantages, the main one being the potential for dependence and abuse. This is one reason why opioids are often reserved for those patients who do not achieve adequate pain control with other agents.

Tramadol is a centrally acting synthetic opioid analgesic. While its mechanism of action is not fully understood, its analgesic effect is attributed to binding to mu-opioid receptors and weak inhibition of the neuronal reuptake of norepinephrine and serotonin. Tramadol is available in Canada in three extended release formulations (Tridural®, Ralivia®, and Zytram XL®) and one immediate release formulation in which tramadol is combined with acetaminophen (Tramacet®). Some guidelines for pain relief place tramadol as a treatment alternative before other opioids as it is purported to have a low potential for abuse and dependence; however, there have been reports of a withdrawal syndrome with its use. A review is required to determine if there is a lower risk of addiction or dependence with tramadol than with other opioids which may affect coverage decisions.
RESEARCH QUESTION:

What is the evidence for lower risk of addiction with the use of tramadol compared with opioids for pain management?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID Medline and OVID Embase, The Cochrane Library (Issue 4, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and December 2009. No filters were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS:

Two relevant randomized controlled trials (RCTs) were identified in which the addiction potential of tramadol was assessed relative to buprenorphine patches and hydrocodone containing analgesics.

Randomized controlled trials

Karlsson et al. published an RCT in 2009 in that compared the efficacy and safety of buprenorphine patches (n=69) and prolonged-release tramadol tablets (n=65) in individuals with chronic pain associated with moderate to severe osteoarthritis of the hip or knee. This was an open-label, noninferiority study. Patients over the age of 18 years with a clinical diagnosis of osteoarthritis of the hip or knee (based on criteria from the American College of Rheumatology and radiologic examination) were enrolled from 14 sites in Sweden. As well, pain control in the affected joint had to be suboptimal in the week before the baseline visit and pain control with acetaminophen 4000mg daily had to be inadequate. Patients whose osteoarthritis pain was treated for more than one week in the previous three months with high-potency opioid analgesics including morphine, fentanyl, oxycodone, methadone, hydromorphone, ketobemidone, buprenorphine or with a usual dose of tramadol, codeine, or dextropropoxyphene were excluded. As well, patients were excluded if they needed analgesics for another chronic condition, were scheduled for surgery during the screening or treatment phase of the study, or were actively abusing controlled substances or alcohol or exhibited behaviours that suggested addiction or substance abuse.

Patients were randomly assigned to treatment with low-dose 7-day buprenorphine patches that released either 5 μg, 10 μg or 20 μg per hour or to prolonged-release tramadol tablets in strengths of 75 mg, 100 mg, 150 mg, or 200 mg twice daily for 12 weeks. Patients were also permitted to take up to 2000 mg of acetaminophen daily if needed for rescue analgesia. The primary end point of the study was the difference in pain scores from baseline to the completion of treatment. A number of secondary endpoints and exploratory variables were also assessed, including abuse and diversion of the study drugs. Abuse or diversion was assessed by the investigators using three questions which they answered themselves without consultation with the participants: (1) "Was there any indication of abuse of alcohol or illicit drugs by this subject at any time during the study?" (2) "Was there any indication of abuse of the study drug by this
subject at any time during the study?" and (3) "Was there any indication of diversion of this subject's study drug to someone other than the subject at any time during the study?"

All study participants were white except for one patient in the buprenorphine group. The median age of the study population was 64.0 years (range 36 to 87 years) in the buprenorphine group and 63.0 years (range 43 to 88) years in the tramadol group. In the buprenorphine group, 59.3% of patients were female compared to 53.8% of patients in the tramadol group. For the analysis of abuse and diversion of the study drugs, 49 patients in the buprenorphine group and 41 patients in the tramadol group had data available. No indication of abuse or diversion was identified in either treatment group. No conclusions were drawn with regards to the abuse potential of either drug.

The main limitation to this study was the open-label design as the patients and investigators were not blinded to treatment status. This could be an issue because abuse or diversion was assessed based upon three subjective questions. Further, patients were not asked these questions, rather abuse or diversion was identified according to the investigator's perception or knowledge of such events, which could be limited or inaccurate. It is not clear whether the findings of this study are generalizable beyond the population with osteoarthritis or to individuals with substance abuse disorders. As well, given that substance abuse is influenced by sociocultural factors it is not clear if the results of the study would be generalizable to the Canadian context. Finally, buprenorphine patches are not currently available in Canada which could also limit the generalizability of the results of this study.

In 2006, Adams et al. published the results of a 12 month RCT which compared the prevalence of tramadol abuse with nonsteroidal anti-inflammatory drugs (NSAIDs) and hydrocodone-containing analgesics in chronic noncancer pain (CNP). The study had three arms: one in which participants were only prescribed tramadol (n=1475), one in which participants were randomized to either NSAIDs (n=4039) or tramadol (n=1517), and one in which participants were randomized to hydrocodone (n=3145) or tramadol (n=1176). The physicians decided the arm which the patients were assigned based on the participants’ clinical situation. The patients were then randomized to treatment within their arm (with the exception of the arm in which all patients received tramadol). However, after initial treatment with the drug to which the patient was randomized, physicians could prescribe any study medication that they felt was therapeutically appropriate based on the patients’ response. As such, some patients may have taken any or all of the study medications. Further, all of the study data were collected and analyzed by the drug the subject was taking at the time of the interview, which was not necessarily the drug to which they were randomized. A total of nine interviews occurred over the 12 month study. In order to be included in the study, participants had to be between the ages of 18 years and 74 years, have CNP of more than four months duration, and be initiating a new therapy that included one of the study medications. Individuals with hearing or speech impediments, serious mental disturbances, or current substance abuse problems (based upon the physicians’ judgment) were excluded. Individuals with contraindications to the study medications were also excluded. Abuse of the study medication was assessed with a questionnaire (The Abuse Index) that was designed specifically for this study, but not validated. Participants were paid $5 to $10 per completed interview.
The majority of the population was female (68.2%) and white (84%). Approximately 87% of participants were over the age of 36 years. Osteoarthritis and back disorders were the most common causes of pain. After 12 months, 2.5% of NSAID users (p<0.01 compared to hydrocodone), 2.7% of tramadol users (p<0.01 compared to hydrocodone), and 4.9% of hydrocodone users were identified as abusing the study drug. From this, the authors concluded that the prevalence of abuse or dependence was similar for tramadol and NSAIDs, which both had significantly lower rates than hydrocodone.

Limitations to this study included the potential for bias given that physicians selected the arm into which patients were enrolled. Further, despite randomization occurring within two of the three arms, there was still a potential for bias as patients were analyzed according to the drug they were on at the interview, not according to the drug that they were randomized to receive initially. Only about one-third of tramadol or hydrocodone users stayed on these medications throughout the study. The use of an unvalidated questionnaire to assess abuse is a further limitation of the study. Many details of the manner in which the study was carried out were not reported in the paper, such as the dosage of study medications, the study setting, or the country in which the study was performed. As such, it is not clear whether the study results are generalizable to the Canadian population.

Limitations

There were two studies identified\(^8,9\) that assessed the potential for abuse of tramadol relative to other narcotic analgesics. While these were both RCTs, there were limitations that could potentially affect the validity of the results. In one study,\(^8\) patients and investigators were not blinded to treatment status, while in the other,\(^9\) the randomization was questionable due to the manner in which patients were assigned to study arms and lack of intention to treat analysis. Further, both studies excluded patients suspected of having issues with substance abuse. This could be a potential source of selection bias given that this criterion was applied based upon the subjective assessment of the investigators. Generalizability of the results to individuals with substance abuse disorders is therefore limited to some degree. Further, generalizability of the results to the Canadian context is also questionable given that substance abuse is influenced by sociocultural factors.\(^10\) Finally, it is not clear whether the results could be generalized to the broader population with CNP as both studies mainly involved patients with arthritis-type pain.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Two RCTs were identified in which the abuse potential of tramadol was compared to another opioid analgesic.\(^8,9\) The results of one RCT were inconclusive given that no instances of abuse were identified.\(^8\) The other RCT suggested the abuse potential of tramadol was lower than hydrocodone-containing analgesics in patients with NCP and similar to that of NSAIDs.\(^9\) However, this study had limitations which could potentially affect the validity of the study’s findings. Further, both studies excluded patients who were at risk of abusing the study medications. While this exclusion criterion was based upon the investigators’ subjective assessment, it appeared that those patients who were at risk of becoming addicted to the study medication were screened out. Thus, based upon the available RCTs, it is not clear whether tramadol has a lower addiction risk than other opioid analgesics. As such, there is a lack of high quality evidence upon which to base formulary decisions about tramadol if such decisions were to be based upon its addiction risk profile relative to other opioid analgesics.
REFERENCES:


