A COMPARISON OF FREQUENTLY PRESCRIBED ANALGESICS AT THE UNIVERSITY OF TORONTO FOR POSTOPERATIVE PAIN FOLLOWING DENTAL SURGERY: An Evidence-Based Study of the Literature

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INTRODUCTION

Throughout time, members of the health profession have sought to relive pain and suffering, yet pain remains the most common reason for which patients seek medical help. It has been estimated that approximately 16 million analgesic prescriptions are written each year in the United States for pain dental origin, and this number continues to rise[1]. In addition to that, patient surveys have shown that postoperative dental pain is often not managed well [2]. This problem can translate to costs to society, in terms of lost productivity from extended days off work, if the ideal analgesic is not prescribed. From a dentists' perspective, we are able to choose from a plethora of medications to provide patients with pain relief, but trying to judge the relative efficacy of analgesics is not easy. With these issues in mind, the following review attempts to provide an answer to the following question: *What is the most efficacious drug that I should prescribe for postoperative analgesia after dental surgery?*

The following list of drugs was chosen to be included in this review article: Tylenol # 3 (acetaminophen 300mg plus codeine 30mg), ibuprofen 400mg, ketorolac 10mg and Percocet (acetaminophen 325mg plus oxycodone 5mg). These drugs were determined to be the most frequently prescribed for postoperative pain following dental surgery at the Faculty of Dentistry, University of Toronto. These particular drugs were chosen in the method described, to narrow down the vast number of analgesic drugs found in the literature so that they would be manageable when being researched and compared; further, these prescribing practices would also be most applicable to patients in the Toronto region.

After decades of use, the efficacy and safety profile of these drugs have established themselves as the first-line choice of pain relief. The relative efficacy of these analgesics can be determined indirectly by comparing each drug with placebo under identical conditions and using a common descriptor of efficacy. To our knowledge, the relative efficacies and safety for our selection of analgesics has not been reported. Therefore, the following review was designed to compare the relative efficacy and safety of Tylenol #3, ibuprofen, ketorolac and Percocet, for the relief of pain following oral surgery.

METHODS

Due to the overwhelming number of postoperative analgesics available on the market, a prescription database of drugs prescribed by dental professionals in clinic at the Faculty of Dentistry, University of Toronto, for the period September 2004-June 2005 provided by Helen Grad, MScPhm was consulted to narrow down the search to the top five drugs prescribed following dental surgery (based on 3,000 prescriptions). This list was then compared to a list of top five drugs prescribed by the Oral Surgery Department at the Faculty of Dentistry, University

of Toronto, which was obtained by consulting with experts in the field of oral pain management and oral surgery (Daniel A. Haas, DDS, PhD, Dental Anesthesiologist, Dr.Simonton, DDS, Oral Surgeon). The two lists were found to coincide and thus narrowed the search to the following drugs: Ibuprofen, Tylenol #3, ketorolac, Tylenol #2 and Percocet.

PubMed (1966 to the present), Medline (1966 to the present) and the Cochrane Library (1966 to the present) were searched for randomized controlled trials, systematic reviews and meta-analyses. The keywords used were: *acetaminophen, paracetamol, Tylenol #2, Tylenol #3, panadol, panadeine, citadon, ibuprofen, ketorolac, Toradol, percocet, oxycodone, postoperative pain, oral surgery* and *dental surgery*. The search was limited to articles written in English and using human subjects. This resulted in 97, 34 and 5 potentially relevant articles from PubMed, Medline, and the Cochrane Library respectively. Further searches were conducted using the references of the studies obtained, based on article titles describing analgesic studies in dentistry. This generated an additional 21 articles. Furthermore, authors active in the research of analgesic efficacy following postoperative dental pain were searched. These authors were Dionne, RA, and Cooper, S, and this search yielded an additional 11 articles.

Determination of Relevance

After eliminating 54 duplicate articles because of overlap among the search databases, a total of 114 articles were reviewed for relevance. The following criteria were used in determining whether an article was relevant or not: 1) The article analyzed at least one of the top five drugs on the list obtained from the prescription database at the Faculty of Dentistry, University of Toronto; 2) The article used a placebo control group as the common comparison between all drugs; 3) The article analyzed single, oral doses of the prescribed drugs in the following doses: Ibuprofen 400mg, ibuprofen 600mg, ketorolac 10mg, acetaminophen 300mg with 15mg of codeine (Tylenol #2), acetaminophen 300mg with 30mg codeine (Tylenol #3), acetaminophen 600mg with 60mg of codeine (two Tylenol 3s) and acetaminophen 325mg with oxycodone 5mg (Percocet); and 4) The analgesic was evaluated 4-6 hours postoperatively.

The 114 articles remaining, after eliminating duplicates, were reviewed and 71 were eliminated by reading through the titles, 34 were eliminated after reading the abstracts and 2 were eliminated after reading the full text of the article, as they did not meet the criteria used for determining the relevance of the article. Following the elimination of the articles, 7 articles remained.

Validity Instruments

The 7 articles determined to be relevant were then reviewed according to a "checklist for a review article" and a "checklist for assessing evidence of efficacy of therapy or prevention" developed by Leake[3]. The highest possible scores on these checklists were 17 and 10 respectively. Two group members reviewed each of the 7 articles independently. If their scores differed, the investigators discussed and agreed on a final score.

RESULTS

Of the 7 studies meeting the inclusion criteria, 5 were considered to present strong evidence, as they achieved high scores on the checklists used to assess them. Studies were considered strong if they scored greater than 15 out of the maximum 17 on the efficacy of therapy checklist and 8 or greater out of 10 on the review checklist. Of the 5 studies, a meta-analysis[4], a review[2], and 3 randomized controlled trials[5, 6, 7] were reviewed. However, 2 of the randomized controlled trials were not used,[5, 7] as they were already included in the systematic review done by Moore and colleagues,[2] that was analyzed in this study.

A study by Lysell and Anzen,[8] comparing ibuprofen and acetaminophen in combination with codeine was considered weak, as it lacked a placebo group and was a single blind study performed in Sweden. It was disregarded, as it did not meet our criteria. The remaining studies[2, 3, 7] however, were considered as strong evidence because they were double blind studies, which compared each of the selected drug(s) against a placebo under identical conditions and using a descriptor of efficacy which was common to all.[2] This is important in determining the relative efficacy of these drugs indirectly, since the direct determination of efficacy is difficult, as it allows the results of each intervention to be used to quantitatively compare the relative efficacy of the analgesics.[2]

Ahmad et al.[4] and Moore et al.[2] presented the strongest evidence in their investigation for the most efficacious analgesic that dentists should prescribe for postoperative pain following dental surgery. Both studies presented level A1 evidence (see Table 1 and Table 2) according to the Canadian Task Force for Preventive Health Care (CTFPHC) research design rating (see www.ctfphc.org/). In addition, both studies stated their objectives, methods, and inclusion and exclusion criteria clearly, had comprehensive searches, and used double blind, randomized studies in their investigations. However, both failed to report the homogeneity of the primary studies. For instance, no mention of variables such as age range (simply stated that it was an adult population), gender, height and weight of the patients being studied were reported. Such variables could be confounding and therefore skew the results, as will be later addressed in the discussion.

Moore et al.[2] found acetaminophen with codeine to be an effective analgesic when compared to placebo in postoperative pain. As shown in Table 1, benefits for 300mg of acetaminophen combined with 30mg of codeine (one tablet of Tylenol #3) versus placebo were significant ($p<0.05$) with an NNT of 5.6.[2] Thus, 1 out of 6 patients with moderate to severe pain will get at least 50% pain relief, which they would not get with placebo. Benefits of taking two tablets of Tylenol #3 in one single dose, versus placebo, were also significant, with an NNT of 3.6 ($p<0.05$).[2] Therefore, 1 out of 4 patients achieve at least 50% pain relief, which they would not have with placebo. Comparing the acetaminophen codeine combination to the same dose of acetaminophen alone, gave an NNT of 7.7 (5.1-17).[2] The addition of codeine however, was accompanied by a significant increase in drowsiness and dizziness,[2] which is also outlined in Table 1.

Table 1: Moore, A. et al.[2] Review Evidence Table

Population **(age range, sample size)**	Drug(s), Dose, # of Doses, Duration	Measurement of Pain	Efficacy	Side Effects	Level of Evidence	General Conclusions
• N=1407 • Adult patients with established postoperative pain of moderate to severe intensity • 22 clinical trials were analyzed • Placebo group= 664 patients • Acetamino-phen (300mg) with codeine (30mg) = 743	•Acetamino-phen (300mg) in comb. with codeine (30mg) (1 pill of Tylenol 3) vs. placebo • Acet 600mg-Cod 60mg (2 pillsTyl 3) vs. Placebo • Single dose • Oral administra-tion •4-6hrs postopera-tively	• SPID and TOTPAR were converted to NNT • NNT for one patient to achieve at least 50% pain relief over 4-6 hrs was obtained for Tylenol 3 and compared to placebo. • pain intensity scale: none, mild, moderate, severe •pain relief scale: none, slight, moderate, good or complete • **VRS** – for pain intensity • **VAS** – for pain relief	• Benefits for Acetaminophen (300mg) plus codeine (30mg) = 1 Tylenol 3 vs. placebo were significant ($p<0.05$) NNT = 5.6 • 1 out of 6 patients with mod-severe pain get at least 50% pain relief which they would not have with placebo • Benefits for Acetaminophen 600mg plus codeine 60mg = 2 Tylenol 3 pills vs. placebo were significant ($p \leq 0.05$) NNT = 3.6 ▪ 1 out of 4 patients get at least 50% pain relief which they would not have with placebo.	• Significant amount of drowsiness/ somnolence and dizziness was found when Acetamino-phen 600mg plus codeine 60mg were compared to placebo • No significant difference was found for nausea/	Review Level AI evid-ence accord-ing to CTFPHC check-list score of 85% (8.5/10)	•APAP (300mg) with codeine (30mg) – one Tylenol 3 and APAP (600mg) with codeine (60mg) – two Tylenol 3- is an effective analgesic in postoperative pain. •Adding codeine to APAP provides more pain relief, but is also accompanied by more drowsiness and dizziness.

Similarly, Ahmad et al.[4] found that non-opioids, such as acetaminophen and NSAIDs, provided better pain relief on all four pain scales including PPID, SPID, PPAR and TOTPAR, when compared to placebo (Refer to Appendix A for definitions of PPID, SPID, PPAR and TOTPAR)**.** Also, when the commonly prescribed acetaminophen 600mg with codeine 60mg was compared to placebo, it was significantly more efficacious (see Table 2). Ahmad et al.[4] further showed that while all NSAIDs as a group (ie. aspirin, diflunisal, flurbiprofen, ibuprofen, ketorolac, naproxen, ibuprofen-lysine etc.) were not statistically better at relieving pain than the acetaminophen codeine combination, NSAIDs prescribed in specific doses after dental surgery, such as ibuprofen 400mg and ketorolac10mg, were found to be significantly more effective at relieving pain than the commonly prescribed acetaminophen 600mg in combination with codeine 60mg.[4] A dose dependent effect was found with ibuprofen, as non-significant differences were found when 200mg of ibuprofen was compared to Tylenol 3; however, superior pain relief was found with 400mg of ibuprofen when the PPAR and TOTPAR scales were used, but not with PPID and SPID scales (Table 2).[4] Similarly, a dose of 10mg of ketorolac was more efficacious than Tylenol 3, with statistically significant differences for the PPAR and TOTPAR scores, but not for PPID and SPID scores (Table 2)[4]

Table 2: Ahmad, N. et al.[4] Meta-analysis Evidence Table

Population (age range, sample size)	Drug(s), Dose, # of Doses, & Duration	Measurement of Pain	Efficacy		Side Effects	Level of Evid. & ChkScore	General Conclusions
• N = 5171 healthy, adult patients undergoing third molar extractions with moderate to severe pain • Review of 294 articles • Lliterature from 1975-August 1996	• Ibuprofen (400mg) • Ketorolac (10mg) • Aceta-minophen (APAP) (600mg) with codeine (60mg) = 2 Tylenol 3's • Placebo • Single dose • Oral administration •Duration of study = 6hrs postopera-tively	•Pain Intensity (0 = no pain, 3=severe) •Pain Relief (0=none, 4=complete) •PID •SPID •Peak PID (maximum PID difference found) •PAR •TOTPAR •Peak PAR (PPAR) is the maximum PAR difference	NSAIDs(Ibu& Ket) vs. Placebo		•None report-ed	•Meta Analysis LEVEL A I evidence (CTFP HC) check-list score = 90% (9/10)	•Ibuprofen and Ketorolac (NSAIDs) are more efficacious in providing analgesia than the Acetamino-phen (600mg) codeine (60mg) combination (equivalent to taking two Tylenol 3's)
			PPID	27 (CI 95% 25-31)			
			SPID	18 (CI 95% 17-30)			
			PPAR	35 (CI 95% 32-39)			
			TOTPAR	24 (CI 95% 22-28)			
			APAP-Cod-60 vs. Placebo				
			PPID	24 (CI 95% 14-34)			
			SPID	16(CI 95% 10-24)			
			PPAR	28 (CI95%16-39)			
			TOTPAR	20 (CI 95% 11-29)			
			APAP+codeine, Ibuprofen or Ketorolac were significantly higher on all pain scales vs. placebo (P<0.05) Ibuprofen and Ketorolac had significant pain relief on the PPAR and TOTPAR scales vs. APAP+codeine (P<0.05)				

Lastly, Cooper et al.[6] investigated the efficacy and safety of various doses of oxycodone in combination with acetaminophen against placebo. While oxycodone and acetaminophen are commonly used analgesics in dentistry, this study supported the therapeutic rationale for combining a peripherally acting analgesic, acetaminophen, with a centrally acting analgesic, oxycodone. Oxycodone 5mg with acetaminophen (Percocet) proved to be an effective analgesic for treating moderate to severe postoperative pain with the least unwanted side effects (Table 3) [6]. In fact, the SPID values obtained were 0.87 for placebo and 3.00 for Percocet (Table 3). Acetaminophen with 10mg oxycodone was found to be even more effective in terms of relieving pain; yet, there was a significant increase in nausea, dizziness, lightheadedness and headaches as the oxycodone dosage increased.[6] Consequently, Cooper et al.[6] demonstrated that combining peripherally acting acetaminophen and centrally acting oxycodone are effective analgesics; nevertheless, minimal doses of oxycodone (ie.5mg) should be combined with acetaminophen in order to minimize unwanted side effects.

Table 3: Cooper, S. et al.[6] RCT Evidence Table

Population (age range, sample size)	Drug(s), Dose, # of Doses, & Duration	Measurement of Pain	Efficacy	Side Effects	Level of Evidence & Checklist Score	General Conclusions
• N = 247 • 117 patients went through entire 4-hr evaluation (17% drop out) • Adult patients undergoing surgical removal of one or more impacted 3rd molars with established moderate to severe pain intensity	•oxycodone 5mg with varying combinations of Acetamino-phen (APAP) (500 mg)	•Pain Intensity scored on a 4 category scale (0=none,1=slight, 2= moderate, 3= severe) at 1, 2, 3, 4, 5 & 6 hrs after treatment • Pain Relief scored on a 5 category scale (0=none, 1=a little, 2=some, 3=a lot, 4 = complete) at 1, 2, 3, 4, 5 & 6 hrs after treatment •PID •SPID •TOTPAR	2 conditions: 1 2 SPID 0.87 3.00 Peak PID 0.42 1.13 TOTPAR 4.76 7.49 Peak Relief 1.45 2.58 Condition: 1. Placebo 2. APAP 500mg + Oxycodone 5mg	•Nausea, drowsiness, dizziness, lightheadedness and headache when APAP and oxycodone were given •Side effects most severe as mg dose of APAP and oxycodone increased	•RCT •checklist score = 88% (15/17)	•Combining APAP and oxycodone show a positive dose-effect relationship. •Oxycodone 5mg with APAP 500mg proved effective for treating moderate to severe post-op. pain. •At higher doses, combination was more effective but increased side effects.

DISCUSSION

In this study, the relative efficacies of ibuprofen, ketorolac, acetaminophen in combination with codeine (Tylenol #3), and Percocet in relieving pain following dental surgery were compared to establish a quantitative ladder of relative analgesic efficacy. Based on information obtained from a prescription database from the clinics at the Faculty of Dentistry, University of Toronto, these were the most frequently prescribed drugs to attenuate postoperative dental pain. It should be noted that this study did not examine Tylenol #2, as there were no studies that evaluated its analgesic efficacy that met the inclusion criteria of this study. Thus, it was not considered in this review, despite the fact that it was included in the list of the top five frequently prescribed analgesics. In addition, the analgesic efficacy of ibuprofen 400mg was assessed, rather than the dose of 600mg, as was obtained from the list provided by the University of Toronto. This modification was made because the few studies that did examine ibuprofen at a dose of 600mg, also failed to meet the inclusion criteria of this study. On the contrary, many studies evaluated ibuprofen 400mg, thus allowing articles for this drug-dose combination to be found that met the selection criteria. In addition, studies have indicated that the analgesic efficacy of ibuprofen is approximately the same at both doses.[9] Furthermore, ibuprofen 400mg is not considered a prescription and is therefore not recorded in the University of Toronto

prescription database, which leaves the possibility that it is just as, if not more, frequently recommended than the 600mg dose.

Analgesic efficacy can be evaluated in many ways, as there are numerous pain measurement scales available such as SPID, PPID, TOTPAR, and PPAR (see Appendix A). All of the drugs that were examined in this study were assigned a SPID score in at least one of the articles. Thus, this scale was utilized to compare analgesic efficacy between drugs assessed in different studies. This scale has the advantage of measuring the cumulative effect of an analgesic on pain perception, although it does not provide any information about the onset and peak of the analgesic effect.[10] Nonetheless, this study focused on analgesic efficacy and not the time course of the analgesic effect, thus this scale was suitable for the purposes of this study.

To render the SPID scores more meaningful to the average reader, they were converted to Percent Analgesia (PA) scores, which reflect the average percent pain reduction over the period that the drug was evaluated. Since each study gave different PA scores for the control/placebo group, the drug PA scores for each study were standardized, by expressing them relative to the control group as a Relative Percent Analgesia (RPA) score. These RPA scores were used as a means of comparing the analgesic efficacy of each drug among all three studies. The PA and RPA calculations are shown in Appendix B.

Some of the analgesics were evaluated in more than one article out of the three that were selected, thus there were multiple RPA scores for some of the drugs. In this situation, the RPA score from the article that provided a higher level of evidence was used. For example, the RPA score from a review article was chosen over a randomized controlled trial because review articles generally produce results that are more accurate. If the studies had the same level of evidence, the RPA score from the study that ranked higher in our checklists was used. The checklists were utilized as a tool to evaluate the quality of each study's experimental design.

Based on this rationale for comparing the analgesic efficacy of each drug, it was determined that Percocet (RPA = 23%) is the most effective analgesic, followed by the NSAIDs ibuprofen and ketorolac (RPA = 18%), and then Tylenol #3 (16%). Among the NSAIDS, a sound randomized controlled study by Forbes *et al*.[5] suggested that ketorolac had a higher analgesic efficacy than ibuprofen, although the results were not statistically significant.

A limitation of this study is that a single article that compared the analgesic efficacy of all four drugs was not found. This was a drawback because the drug scores had to be compared among different studies that varied in methodology, which is a non-ideal situation. Nevertheless, the meta-analysis by Ahmad and others[4] compared ketorolac, ibuprofen, and Tylenol #3 to each other and the article that examined Percocet scored high on the checklist, thus the ranking system used in this study remains accurate and close to an ideal situation. Further research is necessary to confirm these results and to address the limitations encountered in this study for a more comprehensive analysis of factors other than efficacy, that may influence a dentist's decision to prescribe certain analgesics to patients for postoperative pain following dental surgery.

While researchers try to determine the best possible approach to treating postoperative pain, the difficulty that pain imparts to being studied is the variability with which it presents

between people. Since pain is a multi-dimensional experience that incorporates a biological, psychological and social aspect, research in pain relief with analgesics is limited. Therefore, in prescribing analgesics or any drug for that matter, a number of factors not limited to efficacy must be taken into consideration.

It has been suggested that certain psychological factors intervene in the presence of oral or facial pain, but are not manifested when pain is present in other body regions.[11] Many patients suffer from anxiety and fear before and after oral surgeries, which may then influence the degree of post-operative pain felt by the patient. Aspects such as the type of dental procedure causing the pain that may then shape the intensity of the resulting pain, current and past treatments for pain, prior experiences of pain, and the patient's pain threshold and tolerance must also be kept in mind.[11] Similarly, factors such as patient age, cultural and educational level, the effect of pain on the physical and psychological functioning of the patient, and history of substance abuse should be assessed from the medical history and included in determining the analgesic to prescribe and in what quantity and frequency of dose.[11] Cost-effectiveness, individualized risks and benefits, and patients' treatment objectives, followed by informed consent from the patient, must then be taken into consideration before the prescription is finalized. Consequently, in recommending the prescription of any drug for post-operative pain relief following dental surgery, the risks and benefits must be considered and should not be restricted to the efficacy of the drug. A drug that may be efficacious for one individual may not have the same success in another patient whose history indicates a very low pain threshold and few experiences with dental procedures.

CONCLUSION

Pain is not only a subjective experience that is difficult to objectively assess, but is also influenced by many factors that make prescribing drugs to relieve pain even more difficult and complex. Since treatment of postoperative pain is integral to the practice of dentistry, it is important to appreciate the criteria for evaluating the patient's need for "pain killers," particularly when it involves controlled substances such as opioids. Proper treatment of any patients' pain should take into account a number of factors not limited to the efficacy of the drug that may affect the success of the analgesic in pain management before any drugs are prescribed.

For that reason, although this study purports Percocet as being the most efficacious when compared to Tylenol 3, ketorolac and ibuprofen, its side effects due to oxycodone, such as nausea, dizziness, lightheadedness and headache, must be taken into account. Furthermore, oxycodone, being the most potent constituent over codeine in Tylenol #3 of the analgesics considered, it is not surprisingly the most efficacious; but this does not necessarily equate to being the ideal drug to prescribe for all situations. Therefore, many factors must be considered and the risks and benefits weighted before a decision can be made.

APPENDIX A

Pain Measurement Definitions

Visual Analogue Scale (VAS) – method of evaluating pain using a 100-millimetre line, which is labelled 'No pain at all' on one side and 'Most severe pain imaginable' on the opposite end. Patients are asked to place a mark on the scale corresponding to their perception of their pain at the time. This allows an evaluator to compare the efficacy of various analgesics using a simple measurement of the position of the patient's recordings. This provides a repeatable and accurate tool for pain evaluation that provides for comparison and statistical analysis.

Verbal Rating Scale (VRS) – similar to VAS, however, in this scale, patient records their pain evaluation by choosing the appropriate description, which is assigned a predetermined value on the scale.

Pain Intensity Difference (PID) – difference between the pain intensity the patient records before medication (baseline pain score) and the pain intensity they experience after medication at each given time interval (i.e./ at each hour during a six hour period).

Peak Pain Intensity Difference (PPID) – highest pain intensity difference recorded during the entire course of the experiment (i.e./ PID is highest at the two hour time interval during a six hour time period).

Sum of Pain Intensity Difference (SPID) – weighted sum of each PID according to the number of patients involved.

Pain Relief Measure (PAR) – difference between the pain relief the patient records before medication (baseline pain relief score) and the pain relief they experience after medication at each given time interval (i.e./ at each hour during a six hour time period).

Peak Pain Relief (PPAR) – highest pain relief difference recorded during the entire course of the experience (i.e./ PAR is highest at the two hour time interval during a six hour time period).

Total Pain Relief (TOTPAR) – weighted sum of each PAR according to the number of patients involved.

Number Needed to Treat (NNT) – number of patients required to treat to demonstrate at least 50% medication efficacy (or analgesia) in one patient.

APPENDIX B

CALCULATION EQUATIONS

Percent Analgesia (PA) = (SPID Score / # of PID Scores) / Baseline Pain Score

Relative Percent Analgesia (RPA) = Drug Percent Analgesia – Control Percent Analgesia

REFERENCES

1) Dionne RA, Gorden SM. Nonsteroidal anti-inflammatory drugs for acute pain control. *Dent Clin North Am* 1994; 38: 645-667.
2) Moore A, Collins S, Carroll D, McQuay H, Edwards J. Single dose paracetamol (acetaminophen) with and without codeine, for postoperative pain. *The Cochrane Collaboration* 2005(4). Available from URL: http://gateway.ut.ovid.com/gw1/ovidweb.cgi. Accessed February 11, 2006.
3) Leake JL, Department of Biological and Diagnostic Sciences, Faculty of Dentistry, University of Toronto. Unpublished document. Course notes DENT 1040Y 2001. The checklist was adapted from Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology. The essentials. 3rd ed. Baltimore: Williams and Wilkins, 1996; and Sackett DL, Ricardson WS, Rosenberg W, Haynes RB. Evidence-based Medicine: how to practice and teach. EBM. 2nd ed. New York: Churchill Livingstone, 1997.
4) Ahmad N, Grad HA, Haas DA, Aronson KJ, Jokovic A, Locker D. The efficacy of non-opioid analgesics for postoperative dental pain: a meta-analysis. *Anesth Prog* 1997; 44:119–26.
5) Forbes JA, Kehm CJ, Grodin CD, Beaver WT. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen-codeine combination in postoperative oral surgery pain. *Pharmacotherapy* 1990; 10(6 Pt 2): 94S–105S.
6) Cooper SA, Prechaur H, Rauch D, Rosenheck A, Ladov M, Engel J. Evaluation of oxycodone and acetaminophen in treatment of postoperative dental pain. *Oral Surg* 1980; 50(6): 496–501.
7) Cooper SA, Schachtel BP, Goldman E, Gelb S, Cohn P. Ibuprofen and acetaminophen in the relief of acute pain: a randomized double-blind, placebo-controlled study. *J Clin Pharmacol* 1989; 29:1026–30.
8) Lysell, L. and Anzen, B. Pain control after third molar surgery - a comparative study of Ibuprofen (Ibumetin) and a paracetamol/codeine combination (Citodon). Swed Dent J 1992; 16: 151-160.
9) Seymour RA, Ward-Booth P, and PJ Kelly. 1996. Evaluation of different doses of soluble ibuprofen and ibuprofen tablets in postoperative dental pain. Br J Oral Maxillofacial Surgery 1996; 34 (110).
10) McQuay HJ, Moore RA, Eccleston C, Morely S, Williams AC. Systematic review of outpatient services for chronic pain control. Health Technology Assessment 1997; 1(6).
11) Feinmann C, Ong M, Harvey W, Harris M. Psychological factors influencing postoperative pain and analgesic consumption. Br J Oral Maxillofac Surg 1987; 25: 285-92.