Pennsaid® Therapy for Osteoarthritis of the Knee: A Systematic Review and Metaanalysis of Randomized Controlled Trials

TANVEER E. TOWHEED

ABSTRACT. ***Objective.*** To systematically review published randomized controlled trials (RCT) evaluating a new topical diclofenac solution (Pennsaid®) in patients with osteoarthritis (OA) of the knee.

Methods. RCT were identified by searching electronic data sources as well as by contact with the manufacturer of Pennsaid. Details of study demographics, methodology, quality, and outcomes were analyzed. A metaanalysis evaluating the efficacy and safety of Pennsaid in OA of the knee was performed.

Results. Four RCT were analyzed in this systematic review (3 published reports and one published abstract). Mean trial duration was 8.5 weeks. Generally, these RCT were of excellent quality. The mean Jadad quality score was 4.5 out of 5. Many indicators of high quality in a RCT were found in these RCT, including adequate descriptions of the methods used for randomization, blinding, and allocation concealment. In comparison to a vehicle control placebo (VCP), the standardized mean differences (SMD) for the WOMAC pain, stiffness, and physical function subscales, as well as for patient global assessment, were all statistically significant in favor of Pennsaid, with SMD ranging from 0.30 to 0.39. Pennsaid was as safe as VCP, with the only exception that it was more likely to result in minor skin dryness at the site of application (relative risk 1.7). In a 12 week equivalence trial that used the WOMAC subscales to compare treatment response, Pennsaid was as effective as oral diclofenac, but was much better tolerated.

Conclusion. Pennsaid is an effective topical NSAID in patients with OA of the knee. Apart from minor localized skin reactions, Pennsaid was as safe as VCP. It is not known whether the favorable results of Pennsaid can be extrapolated to other topical NSAID preparations. Pennsaid deserves further consideration when the existing treatment guidelines for OA of the knee are updated. (J Rheumatol 2006; 33:567–73)

Key Indexing Terms:
TOPICAL DICLOFENAC OSTEOARTHRITIS
SYSTEMATIC REVIEW METAANALYSIS

Osteoarthritis (OA) is the most common form of arthritis in the population and it is often associated with significant disability and an impaired quality of life[1-3]. An estimated 12.1% of Americans age 25 and older (nearly 21 million persons in 1990) have clinical signs and symptoms of OA[4]. Among US adults age 30 years or older, symptomatic disease in the knee joint occurs in about 6%[3]. OA of the hip and knee can be especially disabling to lower extremity functioning because the hip and knee are large weight-bearing joints[5].

Although there are no curative therapies currently available for OA, individualized treatment programs are available to help relieve pain and stiffness, and to maintain and/or improve functional status[6,7]. Treatment strategies for OA include both nonpharmacological and pharmacological modalities[8,9]. Nonpharmacological therapy is considered to be the foundation for the successful management of symptomatic OA at any site[6,7].

Nonsteroidal antiinflammatory drugs (NSAID) are considered by many physicians to be the preferred agents for the pharmacological management of OA, especially in patients that have moderate or severe degrees of pain[10-13]. However, there are disadvantages to routinely using NSAID in OA, a disease that is so prevalent in the population. Systemic NSAID therapy is associated with significant potential toxicity, especially in the elderly population, who are often afflicted with multiple chronic comorbidities[14-16]. Moreover, in some studies, the cyclooxygenase-2 selective inhibitor NSAID have also been linked with an increased risk for cardiovascular disease. Rofecoxib was recently withdrawn from the world market due to safety concerns[17].

Given that OA is the most common form of arthritis and that the number of persons with OA will certainly rise substantially in the future[18], finding alternative and safer pharmacological therapies for OA is of considerable importance. Topical NSAID represent a potentially important advance in this regard, since they may be significantly safer than oral

From the Departments of Medicine and Epidemiology, Queen's University, Kingston, Ontario, Canada.

T.E. Towheed, MD, MSc, FRCPC, DABIM (Rheum), FACP, Associate Professor of Medicine (Rheumatology).

Address reprint requests to Dr. T.E. Towheed, Etherington Hall, Room 2066, Department of Medicine, Queen's University, Kingston, ON K7L 3N6, Canada. E-mail: tt5@post.queensu.ca

Accepted for publication October 19, 2005.

NSAID due to a reduced degree of systemic absorption. For example, topical application typically produces plasma concentrations 5% of the oral NSAID concentration[19-22].

Pennsaid is a novel topical NSAID preparation comprising a topical diclofenac solution containing the absorption enhancer dimethyl sulfoxide (DMSO). The DMSO moiety is believed to facilitate the site-specific drug delivery of topical diclofenac through the skin to reach the pain-generating sites in the joint[23-25]. Pennsaid was developed for the treatment of symptomatic OA of the knee (Nuvo Research Inc., Markham, ON, Canada) and is currently approved in Canada and several European countries.

Three systematic reviews evaluating topical NSAID in OA (and other chronic conditions) have been published[26-28]. However, these reviews have not included any Pennsaid trials. The reviews confirm that topical NSAID are superior to placebo in relieving pain due to OA, but only in the first 2 weeks of therapy. A systematic review of all randomized controlled trials (RCT) was carried out to evaluate the efficacy and safety of Pennsaid in subjects with OA of the knee.

MATERIALS AND METHODS

Criteria for considering studies for this review. Types of studies: RCT evaluating the efficacy and/or safety of Pennsaid in OA were analyzed in this systematic review. The trial report must have explicitly stated that a randomized method of treatment allocation was used. RCT that evaluated other topical diclofenac preparations in OA were not included in this review.

Types of participants: Adults (age 18 yrs and older) with a diagnosis of either primary or secondary OA of the knee were included.

Types of interventions: Both placebo-based and comparative RCT evaluating the efficacy and safety of Pennsaid in OA of the knee were included.

Types of outcome measures: At least one outcome measure must have been used to measure response to treatment. The main outcome measures of pain, range of motion, functional assessments, and global assessments would satisfy this criterion. The hierarchy of outcomes that were extracted consisted of[29] (1) Pain measured by any method, (2) Functional assessment measured by a validated health status questionnaire [e.g., Western Ontario and McMaster University Osteoarthritis Index (WOMAC)], (3) Patient global assessment, (4) Physician global assessment, and (5) Range of motion of study joint. Toxicity of Pennsaid was also considered to represent a relevant outcome measure (measured by the number of subjects reporting localized and systemic adverse events and by the number of withdrawals due to toxicity).

Search strategy for identification of studies. A Medline search covering the time period of 1966 to February Week 2, 2005, was performed. The search strategy is described below. There were no language restrictions in any searches. The following electronic data sources were also searched using a similar search strategy (time period): Medline In-Process and Other Non-Indexed Citations (February 18, 2005), Embase (1996 to 2005 Week 8), Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club, Database of Abstracts of Effectiveness (DARE), and the Cochrane Controlled Trials Register (CCTR) (all were searched in February 2005). The manufacturer of Pennsaid (Nuvo Research Inc.) was also contacted for additional trials and to obtain additional data from trials that were already published or in press.

Medline search strategy:

1. exp osteoarthritis/
2. (degenerative adj2 arthritis). tw.
3. osteoarthr$.tw.
4. or/1-3
5. pennsaid.rn,tw.
6. topical diclofenac.rn, tw.
7. or/5-6
8. 4 and 7

Methods of the review. The above screening criteria were used to review all identified citations. All citations identified as being potentially relevant were retrieved and analyzed for suitability. Authors of abstracts and/or the Dimethaid Health Care Company were contacted requesting the full manuscript, including the raw and final data incorporating the results. At this stage, emphasis was placed on selecting RCT and excluding nonrandomized treatment studies. If the randomization status was not clear, the article was withheld, pending clarification from the principal author.

Data extraction: Each RCT was systematically reviewed and the raw data from the study were extracted using a standardized data abstraction form that was modified from the form used in our earlier systematic reviews of OA therapies[30,31]. Raw data extracted included trial characteristics, subject demographics, outcome variables, results, and features of trial quality. If outcome data were not reported in a form suitable for quantitative pooling in a meta-analysis, the primary author and/or Nuvo Research Inc. was contacted for access to this information. Data on adverse effects were also extracted from the RCT.

Data analysis: Cochrane Collaboration software (Rev Man Version 4.2) was used for the metaanalyses. For quantitative outcome data, standardized mean differences (SMD) were used to pool across RCT[32,33]. Weighted mean differences (WMD) were also calculated if the outcomes were measured with the same instrument using the same units of measurement. It is important to note that we used the end of study means and standard deviations for the meta-analyses. If either of these were not available in the trial report, the principal author and/or Nuvo Research Inc. was contacted for additional information. In the absence of this information, the end of study standard deviation was estimated by using the baseline standard deviation. For categorical outcome data with 2 categories, the relative risk ratio (RR) was calculated[33]. Heterogeneity was tested with a chi-square test. Fixed effects models were used unless heterogeneity was significant ($p < 0.10$), in which case random effects models were used. For qualitative review of the studies, the Jadad scoring system was used to score the methodological quality of the RCT[34]. For each RCT, the adequacy of allocation concealment was also recorded[35] and scored as being either adequate or inadequate.

Description of studies. Results of search strategy: Medline search identified a total of only 6 citations. Two RCT were identified from this search[36,37]. Medline In-Process search identified one additional RCT, which was included in the systematic review. This was an active comparator RCT that compared Pennsaid to oral diclofenac[38]. Embase search identified a total of 10 citations, but no additional trials. The CDSR, ACP Journal Club, DARE, and CCTR searches identified a total of 4 citations, but no additional RCT. Nuvo Research Inc. supplied the relevant outcome data from one additional RCT that was available only in abstract form at the time of this review[39].

Trial demographics and features: A total of 4 RCT evaluating Pennsaid in OA of the knee were included in this systematic review. Table 1 summarizes the pertinent features of these trials. Three RCT compared Pennsaid to placebo[36,37,39] and one RCT was an equivalence study comparing Pennsaid to oral diclofenac[38]. The 3 RCT available in full form were published in 2004[36-38]. The abstract was published in 2001[39]. All trials are multicenter, double-blind, randomized, parallel-group trials.

The total number of subjects randomized in the 4 RCT was 1412 (mean 353, range 216–622). The total number of subjects randomized to Pennsaid was 666 (mean 167, range 84–311). The total number of subjects randomized to comparator groups was 746 (mean 186, range 109–311). The total number of subjects who completed the RCT was 970 (mean 242, range 156–377). Therefore, 69% of subjects who were randomized completed the trials. The total number of subjects included in the analyses was 1385 (mean 346, range 212–604). Therefore, 98% of subjects who were randomized were included in the final analyses.

The mean trial duration of the 4 RCT was 8.5 weeks (range 4–12). The country of origin of the RCT was Canada (3 trials) and USA (1 trial). The

Table 1. Pennsaid trials in OA of the knee.

Study	Groups	No. Randomized	No. Completed	Design	Duration (weeks)	Overall Efficacy
Bookman, *et al,* 2004[36]	Pennsaid vs VCP* vs Placebo	248	209	Parallel	4	Pennsaid > placebo groups
Roth, *et al,* 2004[37]	Pennsaid vs VCP	326	228	Parallel	12	Pennsaid > VCP
Baer, *et al,* 2001[39]	Pennsaid vs VCP	216	156	Parallel	6	Pennsaid > VCP
Tugwell, *et al,* 2004[38]	Pennsaid vs oral diclofenac	622	377	Parallel	12	Pennsaid = oral diclofenac

* VCP: Vehicle controlled (DMSO) placebo.

comparator groups comprised a vehicle control placebo (VCP) in 3 trials[36,37,39], and oral diclofenac in 1 trial[38]. One study included both a VCP and an additional placebo arm containing a token amount of the carrier vehicle DMSO[36].

The dosage of Pennsaid evaluated in the 3 placebo-controlled RCT was 40 drops (about 1.4 ml) applied to the study knee 4 times daily without rubbing. The dosage in the equivalence study by Tugwell, *et al*[38] was 50 drops applied 3 times daily without rubbing. Subjects enrolled in all RCT had exclusively primary knee OA. The method of classification of knee OA was based on a combination of clinical features and radiographic features typical of OA. However, no trial explicitly stated that they had used American College of Rheumatology (ACR) classification criteria for OA of the knee. Radiographs were taken at baseline in all 3 fully published studies[36-38]. These 3 RCT also specified the radiographic criteria that were used by the investigators to establish the OA diagnosis. The study published in abstract form did not indicate whether subjects had radiographs[39].

All RCT used the WOMAC[40] for outcome evaluation: the WOMAC LK version was used in 3 RCT[36,37,39], and the WOMAC VA version was used in the Tugwell study[38]. In all RCT, the individual components of the WOMAC were used for evaluation, including the WOMAC pain, stiffness, and function subscales. Patient global assessment was also used in all 4 RCT. Quality of life and investigator global assessments were not used in any of the RCT.

All RCT were sponsored by the manufacturer of Pennsaid (Nuvo Research Inc.). At the time of this review, there are no independent studies evaluating Pennsaid in OA.

The mean age of subjects enrolled in the 3 published RCT was 63.2 years (range 61.8–64.2). The percentage of subjects that were male in the 3 published RCT was 37% (range 32–43%). Only the knee joint was evaluated in the 4 RCT.

Features of trial quality: In the 3 published RCT prerandomization inclusion and exclusion criteria were explicitly stated; sample size calculations were provided; usage of supplementary analgesics was controlled for; and the randomization method was described, as well as the blinding method. In all 4 RCT a main effect variable was defined, appropriate statistics were used, withdrawals were described and accounted for, and an intention-to-treat analysis was used.

The mean Jadad quality score for the 4 RCT was 4.5 (out of a possible 5) even though the unpublished study in abstract form by Baer, *et al*[39] could not be completely evaluated. Each of the 3 published RCT received a total Jadad score of 5. Allocation concealment was adequately described in each of the 3 published RCT, but could not be evaluated in the unpublished study[39].

RESULTS

Efficacy of Pennsaid versus vehicle control placebo pooled across 3 RCT[36,37,39] *(Figures 1-4).*

1. For the WOMAC pain subscale, the SMD (effect size) comparing Pennsaid to VCP was –0.33 (95% CI –0.48 to –0.18). This is statistically significant in favor of Pennsaid. This corresponds to a difference of 1.6 units (or WMD) on the WOMAC LK pain subscale, which has a range of 0–20.
2. For the WOMAC stiffness subscale, the SMD comparing Pennsaid to VCP was –0.30 (95% CI –0.45 to –0.15). This is statistically significant in favor of Pennsaid. This corresponds to a difference of 0.61 units (or WMD) on the WOMAC LK stiffness subscale, which has a range of 0–8.
3. For the WOMAC physical function subscale, the SMD comparing Pennsaid to VCP was –0.35 (95% CI –0.50 to –0.20). This is statistically significant in favor of Pennsaid and corresponds to a difference of 5.5 units (or WMD) on the WOMAC LK function subscale, which has a range of 0–68.
4. For the patient global assessment, the SMD comparing Pennsaid to VCP was –0.39 (95% CI –0.54 to –0.24). This is statistically significant in favor of Pennsaid.

Thus, Pennsaid was significantly more effective than VCP in all of the WOMAC outcomes as well as in the patient global assessment outcome.

Safety of Pennsaid compared to VCP pooled across 3 RCT[36,37,39]*. Localized adverse reactions.*

1. For the adverse reaction of minor skin dryness at the application site, the RR comparing Pennsaid to VCP pooled across 3 RCT[36,37,39] was 1.74 (95% CI 1.37 to 2.22). This is a statistically significant result, meaning that Pennsaid was more likely to result in skin dryness than was VCP. The aggregate absolute risk (%) for having this adverse reaction in the 3 RCT[36,37,39] was 37.2% for Pennsaid versus 21.4% for VCP.
2. For the adverse reaction of paresthesia at the application site, the RR comparing Pennsaid to VCP pooled across 3 RCT[36,37,39] was 0.60 (95% CI 0.33 to 1.10). Pennsaid was not more likely than VCP to result in paresthesia. The aggregate absolute risk (%) for having this adverse reaction in the 3 RCT[36,37,39] was 4.2% for Pennsaid versus 6.8% for VCP.
3. For the adverse reaction of rash, the RR comparing Pennsaid to VCP pooled across 3 RCT[36,37,39] was 1.69 (95% CI 0.96 to 2.95). Pennsaid was not more likely than VCP to result in a rash. The aggregate absolute risk (%) for having this adverse reaction in the 3 RCT[36,37,39] was 8.7% for Pennsaid versus 5.1% for VCP.

Safety of Pennsaid compared to VCP pooled across 3 RCT[36,37,39]*. Systemic adverse reactions.*

4. For the adverse reaction of any gastrointestinal (GI) event, the RR comparing Pennsaid to VCP was 1.11 (95% CI 0.74 to 1.68). The aggregate absolute risk (%) for having this adverse reaction was 12.1% for Pennsaid versus 10.8% for VCP.
5. For the outcome of any adverse event, the RR comparing Pennsaid to VCP was 1.11 (95% CI 1.0 to 1.24). The aggre-

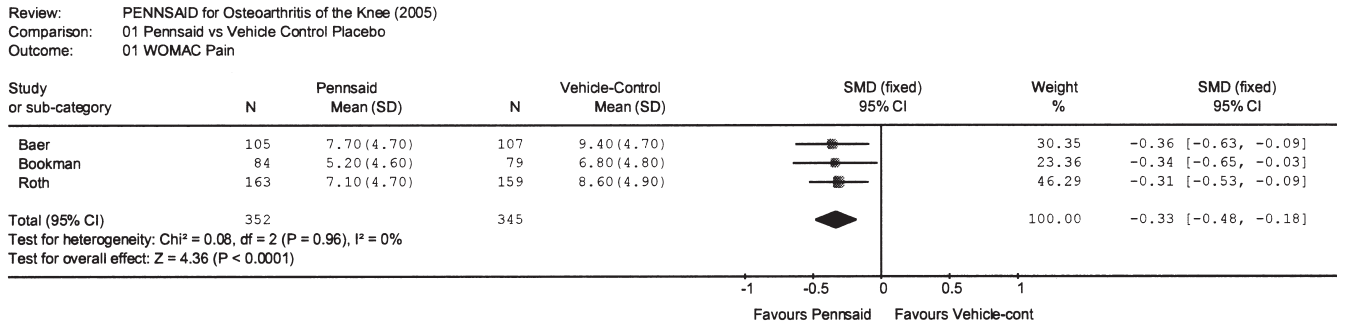

Figure 1. Metaanalysis comparing Pennsaid to vehicle control placebo (VCP) for the WOMAC pain subscale.

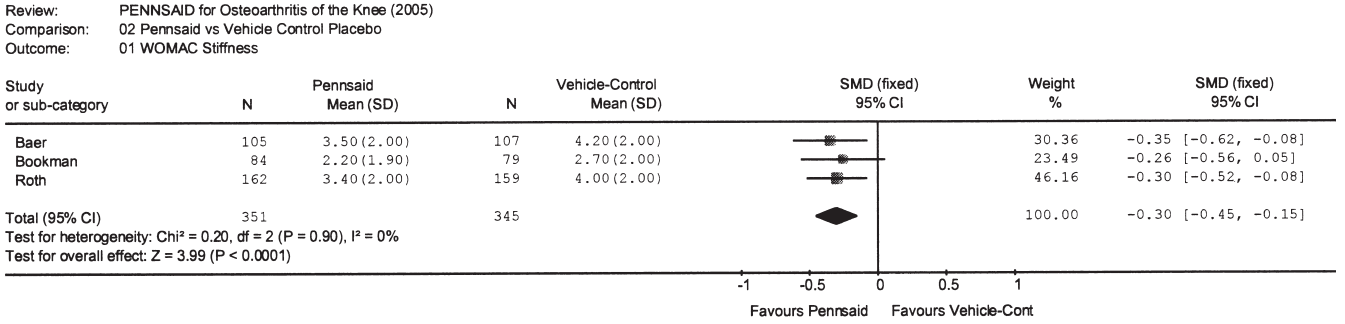

Figure 2. Metaanalysis comparing Pennsaid versus VCP for the WOMAC stiffness subscale.

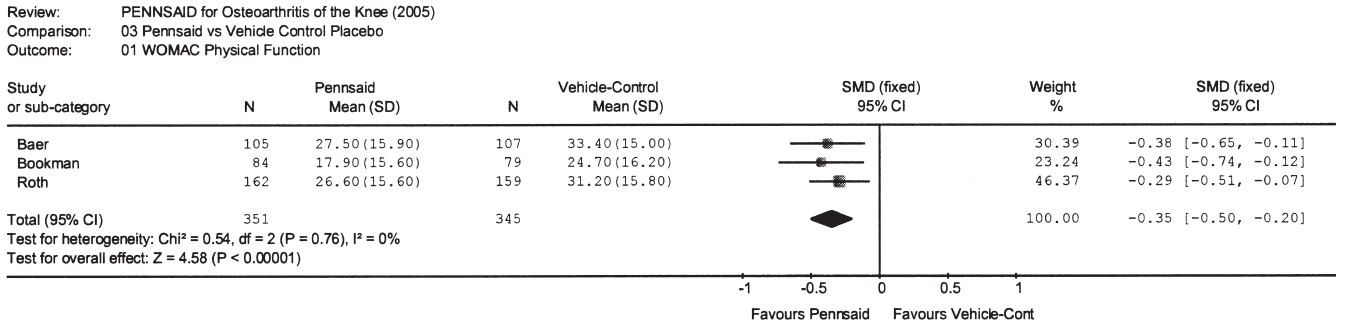

Figure 3. Metaanalysis comparing Pennsaid versus VCP for the WOMAC physical function subscale.

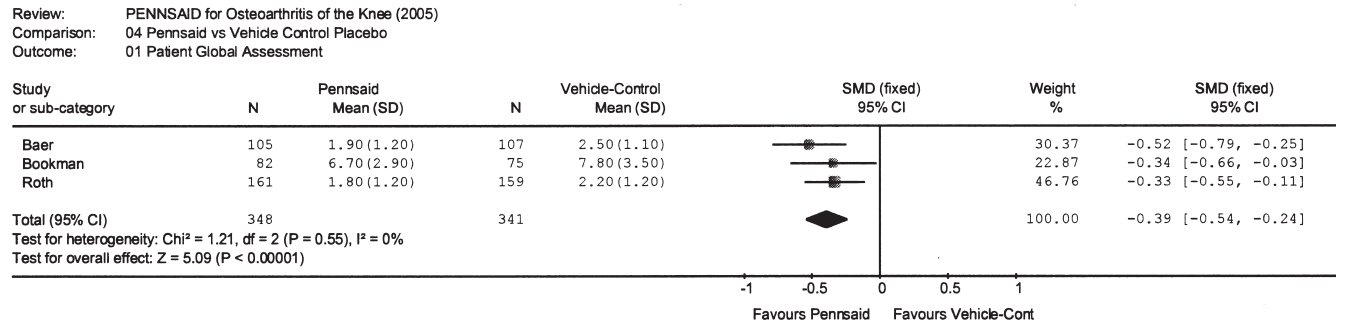

Figure 4. Metaanalysis comparing Pennsaid versus VCP for patient global assessment.

gate absolute risk (%) for having this adverse reaction in the 3 RCT[36,37,39] was 68.5% for Pennsaid versus 61.5% for VCP.
6. For the outcome of withdrawals due to toxicity, the RR comparing Pennsaid to VCP was 1.37 (95% CI 0.73 to 2.56). The aggregate absolute risk (%) for having this adverse reaction was 6.2% for Pennsaid versus 4.6% for VCP.
Thus, the only adverse reaction that was more likely to occur with Pennsaid as opposed to VCP was minor skin dryness.

Also analyzed were 2 additional outcomes pooled across 3 RCT[36,37,39]: total withdrawals due to any cause and withdrawals due to lack of efficacy. For total withdrawals due to any cause, the RR comparing Pennsaid to VCP was 0.71 (95% CI 0.55 to 0.92). For withdrawals due to lack of efficacy, the RR comparing Pennsaid to VCP was 0.55 (95% CI 0.39 to 0.80).

Efficacy of Pennsaid compared to oral diclofenac in the Tugwell, et al RCT[38].
1. For the WOMAC pain subscale, the SMD comparing Pennsaid to oral diclofenac was 0.11 (95% CI –0.07 to 0.28). There was no statistically significant difference between Pennsaid and oral diclofenac.
2. For the WOMAC stiffness subscale, the SMD comparing Pennsaid to oral diclofenac was 0.12 (95% CI –0.06 to 0.30). There was no statistically significant difference between Pennsaid and oral diclofenac.
3. For the WOMAC function subscale, the SMD comparing Pennsaid to oral diclofenac was 0.15 (95% CI –0.02 to 0.33). There was no statistically significant difference between Pennsaid and oral diclofenac.
4. For patient global assessment, the SMD comparing Pennsaid to oral diclofenac was 0.13 (95% CI –0.05 to 0.31). There was no statistically significant difference between Pennsaid and oral diclofenac.
5. Comparing the likelihood of being an OMERACT-OARSI responder in the 2 groups, the RR comparing Pennsaid to oral diclofenac was 0.95 (95% CI 0.85 to 1.06). There was no statistically significant difference between Pennsaid and oral diclofenac.
Thus, Pennsaid (50 drops 3 times daily) was equally effective to oral diclofenac (50 mg 3 times daily) in subjects with symptomatic OA of the knee.

Safety of Pennsaid compared to oral diclofenac in the Tugwell, et al RCT[38].
1. For the adverse reaction of all GI events, the RR comparing Pennsaid to oral diclofenac was 0.72 (95% CI 0.59 to 0.87). Thus, Pennsaid was significantly less likely to produce GI adverse events when compared to oral diclofenac. The absolute risk (%) for having this adverse reaction was 34.7% for Pennsaid versus 48.2% for oral diclofenac.
2. For the adverse reaction of dry skin reactions, the RR comparing Pennsaid to oral diclofenac was 20.8 (95% CI 7.7 to 55.9). The absolute risk (%) for having this adverse reaction was 26.7% for Pennsaid versus 1.3% for oral diclofenac.
3. For the adverse reaction of rash, the RR comparing Pennsaid to oral diclofenac was 7.2 (95% CI 2.9 to 18.1). The absolute risk (%) for having this adverse reaction was 11.6% for Pennsaid versus 1.6% for oral diclofenac.
4. In terms of withdrawals due to toxicity, the RR comparing Pennsaid to oral diclofenac was 0.81 (95% CI 0.61 to 1.08). The absolute risk (%) for having this adverse reaction was 20.6% for Pennsaid versus 25.4% for oral diclofenac.
5. For the adverse reaction of severe GI events, the RR comparing Pennsaid to oral diclofenac was 0.35 (95% CI 0.17 to 0.72). The absolute risk (%) for having this adverse reaction was 7.4% for Pennsaid versus 21.3% for oral diclofenac.
6. For the adverse reaction of significant changes in hemoglobin values (from normal to abnormal), the RR comparing Pennsaid to oral diclofenac was 0.21 (95% CI 0.09 to 0.51). The absolute risk (%) for having this adverse reaction was 2.2% for Pennsaid versus 10.3% for oral diclofenac.
Thus, Pennsaid (50 drops 3 times daily) was significantly better tolerated than oral diclofenac (50 mg 3 times daily) in subjects with OA of the knee.

Two additional outcomes were also analyzed in the Tugwell, *et al* RCT[38]: total withdrawals due to any cause and withdrawals due to lack of efficacy. For total withdrawals due to any cause, the RR comparing Pennsaid to oral diclofenac was 1.11 (95% CI 0.91 to 1.35). For withdrawals due to lack of efficacy, the RR comparing Pennsaid to oral diclofenac was 2.80 (95% CI 1.38 to 5.67).

DISCUSSION

The findings of this systematic review and metaanalysis support the conclusion that Pennsaid is an effective and safe therapy in patients with symptomatic OA of the knee. When compared to VCP, Pennsaid was statistically significantly superior in each of the 3 WOMAC subscales (with effect sizes approximating 0.30) as well as in the patient global assessments (effect size of 0.39). Cohen defined an effect size of 0.20 as small, one of 0.50 as moderate, and one of 0.80 as large[41]. Pennsaid was found to be extremely well tolerated with a safety profile similar to VCP. Only skin dryness at the application site was more likely to occur with Pennsaid as opposed to with a VCP.

Pennsaid was of equivalent efficacy to oral diclofenac in each of the WOMAC outcomes as well as in the patient global assessments. Importantly, however, Pennsaid was significantly better tolerated than oral diclofenac. For example, Pennsaid was much less likely to produce a GI adverse event than oral diclofenac. This finding held true for both adverse GI outcomes (all GI events and severe GI events). The Tugwell, *et al* study[38] represents the best published evidence to date that a topical NSAID is equivalent to an oral NSAID in OA[19,20,42].

The metaanalysis by Moore, *et al*[26] concluded that topical NSAID were effective in relieving pain in acute and chronic pain conditions (including OA). The maximum time period for evaluating treatment efficacy was only 2 weeks. The main

outcome measure was defined as at least a 50% reduction in pain. The placebo-controlled trials had a relative benefit of 2.0 (95% CI 1.5 to 2.7) and the number needed to treat was 3.1. Topical NSAID were as safe as placebo in terms of both local and systemic adverse events. The Moore, *et al*[26] metaanalysis did not include any of the Pennsaid trials, as this review was published in 1998.

A more recent metaanalysis by Mason, *et al*[27] updated the findings of the review published earlier by Moore, *et al*[26]. Topical NSAID were again found to be significantly better than placebo in subjects with painful chronic conditions, including OA (relative benefit of 1.9; 95% CI 1.7 to 2.2). Topical NSAID were as safe as placebo. This review also looked at only 2 week outcomes. The Mason, *et al*[27] metaanalysis did not include any of the Pennsaid trials, as the search ended in April 2003.

Another metaanalysis by Lin, *et al*[28] published in 2004 found that topical NSAID were superior to placebo in relieving pain due to OA, but only in the first 2 weeks of treatment. Effect sizes for Weeks 1 and 2 were 0.41 and 0.40, respectively. They concluded that the trials analyzed were all of short duration (less than 4 weeks) and that no trial data support the longterm use of topical NSAID in OA. However, this review included only 2 RCT with efficacy data beyond 2 weeks of treatment, and further, no included trial had a treatment duration beyond 4 weeks. None of the Pennsaid trials was included in this review, since the search strategy ended in 2003. The authors' concern that there is no evidence beyond 2 weeks for use of topical NSAID in OA is no longer valid, since the mean treatment duration of the Pennsaid trials was 8.5 weeks (range 4–12 weeks).

A systematic review of topical NSAID by Bandolier[20,42] also supports the efficacy and safety of topical NSAID in OA. Indeed, they recommend that current treatment guidelines for OA be revisited to give further importance to the usage of topical NSAID in OA.

The 2000 ACR guidelines for the medical management of OA of the hip and knee have not considered in any great detail the role of topical NSAID in OA[6]. They state that topical analgesics can be considered as either adjunctive treatment or as monotherapy in patients with mild to moderate degrees of pain. They also note that there were no published trials comparing the same NSAID administered orally versus topically. Since these guidelines were published, we now have evidence from the present systematic review supporting the efficacy and safety of Pennsaid in OA of the knee. The Pennsaid trials were not considered in the ACR treatment guidelines, since the guidelines were published in 2000.

The 2003 European League Against Rheumatism (EULAR) guidelines for the medical management of OA of the knee have given greater consideration to the role of topical NSAID in OA[7]. They state that there is evidence from RCT supporting the efficacy and usage of topical NSAID in OA of the knee and that this form of therapy has a good safety record. It appears unlikely that any of the Pennsaid trials were considered in this review, since the time period of study identification extended only to February 2002.

Although our systematic review and metaanalysis adheres to the published recommendations of the QUOROM statement[43], a number of limitations of this systematic review are recognized. (1) Nonpublished trials were not systematically searched for or analyzed, and this exclusion may have resulted in a biased selection of trials that were more likely to include positive trials. (2) Conference proceedings were not manually searched. (3) All of the included studies in this review have been sponsored by the manufacturers of Pennsaid. Future independently conducted RCT evaluating Pennsaid would further strengthen the findings of this review.

A number of areas are identified for future research with Pennsaid. (1) Additional high quality RCT are needed that evaluate the efficacy of Pennsaid in patients with symptomatic OA involving other joints, including the hands. (2) The clinical predictors of response to Pennsaid need to be identified to help optimize patient selection for this form of therapy. (3) Studies are needed to determine whether Pennsaid is useful for other inflammatory intraarticular and periarticular conditions, including bursitis, tendinitis, adhesive capsulitis of the shoulder, plantar fasciitis, and gout affecting the first metatarsophalangeal joint. (4) The comparative efficacy and safety of Pennsaid in OA compared to other topical NSAID preparations are not known. (5) The cost-effectiveness of Pennsaid for OA of the knee needs to be directly compared to other commonly used pharmacological therapies.

ACKNOWLEDGMENT

The author is grateful to Lisa Thomas, PhD, Medical Writer/Scientist at Nuvo Research Inc., Markham, ON, Canada, for providing outcome data from the unpublished trial, and for providing additional outcome data from the published trials, which were used in the metaanalyses.

REFERENCES

1. Badley E. The effect of osteoarthritis on disability and health care use in Canada. J Rheumatol 1995;22 Suppl 43:19-22.
2. Towheed TE. The impact of musculoskeletal disorders in Canada. Ann Roy Coll Physicians Surgeons Canada 1998;31:229-32.
3. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG. Osteoarthritis: the disease and its prevalence and impact. In: Felson DT, conference chair. Osteoarthritis: new insights. Part I: The disease and its risk factors. Ann Intern Med 2000;133:635-46.
4. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778-99.
5. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW. The effects of specific medical conditions on functional limitations of elders in the Framingham study. Am J Public Health 1994;84:351-8.
6. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905-15.
7. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the Standing Committee for

International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62:1145-55.
8. Creamer P, Hochberg MC. Osteoarthritis. Lancet 1997;350:503-8.
9. Felson DT, Lawerence RC, Hochberg MC, et al. Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med 2000;133;726-37.
10. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the hip. J Rheumatol 1997;24:349-57.
11. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. Semin Arthritis Rheum 1997;26:755-70.
12. Towheed TE. Published meta-analyses of pharmacological therapies for osteoarthritis. Osteoarthritis Cartilage 2002;10:836-7.
13. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2003(2):CD004257.
14. Garner S, Fidan D, Frankish R, et al. Rofecoxib for rheumatoid arthritis. Cochrane Database Syst Rev 2005:CD003685.
15. Deviere J. Do selective cyclo-oxygenase inhibitors eliminate the adverse events associated with nonsteroidal anti-inflammatory drug therapy? Eur J Gastroenterol Hepatol 2002;14 Suppl 1:S29-33.
16. Wright JM. The double-edged sword of COX-2 selective NSAIDs. CMAJ 2002;167:1131-7.
17. Sibbald B. Rofecoxib (Vioxx) voluntarily withdrawn from market. CMAJ 2004;171:1027-8.
18. Badley EM, Wang PP. Arthritis and the aging population: projections of arthritis prevalence in Canada 1991 to 2031. J Rheumatol 1998;25:138-44.
19. Moore RA. Topical NSAID are effective in osteoarthritis of the knee. J Rheumatol 2004;31:1893-5.
20. Bandolier Evidence Based-Health Care. Topical analgesics: a review of reviews and a bit of perspective. [Internet]. Available from: http://www.ebandolier.com. Accessed December 19, 2005.
21. Evans JM, McMahon AD, McGilchrist MN, et al. Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study. BMJ 1995;311:22-6.
22. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. Drugs 2000;60:555-74.
23. Hewitt PG, Poblete N, Wester RC, Maibach HI, Shainhouse JZ. In vitro cutaneous disposition of a topical diclofenac lotion in human skin: effect of a multi-dose regimen. Pharm Res 1998;15:988-92.
24. Hui X, Hewitt PG, Poblete N, Maibach HI, Shainhouse JZ, Wester RC. In vivo bioavailability and metabolism of topical diclofenac lotion in human volunteers. Pharm Res 1998;15:1589-95.
25. Tanojo H, Wester RC, Shanhouse JZ, Maibach HI. Diclofenac metabolic profile following in vitro percutaneous absorption through viable human skin. Eur J Drug Metab Pharmacokinetics 1999;24:345-51.
26. Moore RA, Carroll D, Wiffen PJ, Tramer M, McQuay HJ. Quantitative systematic review of topically-applied NSAIDs. BMJ 1998;316:333-8.
27. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. BMC Musculoskeletal Disord 2004;5:28.
28. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomized controlled trials. BMJ 2004;329:324. Epub 2004 July 30.
29. Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis: Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.
30. Towheed TE. Systematic review of therapies for osteoarthritis of the hand. Osteoarthritis Cartilage; in press.
31. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine for osteoarthritis. Cochrane Database Syst Rev 2005:CD002946
32. Hedges L, Olkin I. Statistical methods for meta-analysis. San Diego, CA: Academic Press; 1985.
33. Petitti D. Meta-analysis, decision analysis, and cost-effectiveness analysis. In: Monographs in epidemiology and biostatistics. Vol. 24. New York: Oxford University Press; 1994.
34. Jadad AR, Moore RA, Carrol D, Jenkinson C. Assessing the quality of reports of randomized controlled trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
35. Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias: the dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.
36. Bookman AM, Williams K, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. CMAJ 2004;171:333-38.
37. Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (Pennsaid) in the treatment of primary osteoarthritis of the knee. A randomized, double-blind, vehicle-controlled clinical trial. Arch Intern Med 2004;164:2017-23.
38. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (Pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. J Rheumatol 2004;31:2002-12.
39. Baer M, Williams K, Markus GE, Shainhouse JZ. A multi-centre, double-blinded, placebo-controlled, clinical trial of diclofenac topical lotion (Pennsaid) in the treatment of the symptoms of primary osteoarthritis of the knee [abstract]. Rheumatology Oxford 2001;40 Suppl 1:107.
40. Bellamy N. WOMAC Osteoarthritis Index — A user's guide. London, Ontario: London Health Sciences Centre; 1995.
41. Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic Press; 1977.
42. Bandolier Evidence Based Health Care. Topical NSAIDs for OA: update. November 2004. [Internet.] Available from: http://www.ebandolier.com. Accessed December 19, 2005.
43. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF, for the QUOROM group. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUORUM statement. Quality of Reporting of Meta-Analyses. Lancet 1999;354:1896-900.