NSAIDS FOR MANAGING POST-OPERATIVE ENDODONTIC PAIN IN PATIENTS WHO PRESENT WITH PRE-OPERATIVE PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

by

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Abstract

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been commonly used to treat endodontic post-operative pain. The purpose of this study was to address the Population, Intervention, Comparator, Outcome, Timing, Study design and setting (PICOTS) question: in patients with pre-operative pain who undergo initial orthograde endodontic treatment, what is the comparative efficacy of NSAIDS compared to placebo or non-narcotic analgesics in reducing post-operative pain and incidence of adverse events?

Methods: Electronic searches in Ovid, MEDLINE and Cochrane Library were conducted using strict inclusion and exclusion criteria. Hand searches in texts were also conducted. Two independent reviewers assessed eligibility for inclusion, extracted data, and assessed quality utilizing the 'Risk of bias' tool. L'Abbe plots were used for qualitative review. Where applicable, meta-analysis was conducted on pooled effect size (ES).

Results: 2,284 studies were identified through the database searches; 405 full text articles were assessed. Fifteen articles met the inclusion criteria; qualitative analysis revealed all studies had a moderate to high risk of bias. Ibuprofen was the most studied NSAID. The L'Abbe plots illustrated that NSAIDS are effective at relieving post-operative endodontic pain overall. Meta-analysis showed that ibuprofen 600mg is more effective than placebo at 6 hours post-operative (ES=10.50, p=0.037), and ibuprofen 600mg + acetaminophen 1000mg combination is more effective than placebo (ES=34.89, p=0.000) but not

significantly different than ibuprofen (ES=13.94, p=0.317). Five studies reported patients experiencing adverse events such as drowsiness, dizziness, nausea, and emesis; two studies reported that patients experienced no adverse events.

Conclusions: A combination of ibuprofen 600mg and acetaminophen 1000mg is more effective than placebo, but not significantly different than ibuprofen 600mg at 6 hours post-operative. Ibuprofen 600mg is more effective than placebo at 6 hours post-operative; however, there are insufficient data to recommend the most effective NSAID, dose amount, or dose interval for the relief of post-operative endodontic pain of longer duration in patients with pre-operative pain. Future trials need to use standardized methods for easier comparison in future reviews. These methods need to be determined purposefully to simulate clinical practice, in patients for whom severe post-operative pain is expected and management is most challenging.

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Chapter 1: Introduction and Review of the Literature

The primary reason people seek endodontic treatment is for the relief of pain caused by bacterial infection and subsequent inflammation (1). Endodontic procedures are the critical first step in treating and restoring a tooth with a root canal system irreversibly affected by bacterial infection. By debriding inflamed or necrotic pulp tissue within the tooth, and sealing the root system against communication between the oral environment and the periapical tissue, root canal therapy has been shown to effectively relieve pain. However, pain relief may not be immediate and absolute (2, 3). Although pain is diminished following treatment, there may be residual symptoms due to the effects of inflammation; approximately 30% of patients will continue to have moderate to severe post-operative pain (4). Therefore, endodontic treatment includes the management of post-operative pain and symptoms that address both the patient's primary concern and potential long term complications such as chronic pain (5, 6). A variety of drugs have been employed to manage post-operative pain, and often include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and combinations of drugs (7).

Pulpal and periapical pain can be initiated by a variety of factors, including mechanical, thermal, chemical, and immunological stimulation of afferent nociceptors, which synapse in the dorsal horn of the spinal cord and direct sensation to the thalamus (8). Endogenous inflammatory mediators that may stimulate nociceptors include bradykinin, calcitonin gene-related peptide, substance P, growth factors, cytokines, chemokines, and arachidonic acid (9). Any or all of these are generated as part of the innate immune

response to tissue injury and destruction. Arachadonic acid is converted by cyclo-oxygenase enzymes 1 and 2 (COX-1, COX-2) to prostaglandins; prostaglandins in turn cause sensitization of the afferent nociceptors and lower the pain threshold (9). The COX-1 and -2 enzymes are a target for pharmacologic intervention. By inhibiting these enzymes, a drug can limit the production of prostaglandins and mediate the sensitization of neurons due to inflammation.

Following orthograde endodontic treatment, inflammatory post-operative pain is usually at its worst in the first 24 hours post-operative, and gradually declines in the subsequent 3-7 days (4). Pain after treatment is often unrelated to elements under an operator's control such as the patient's immune response (10). The method and technique of canal instrumentation and irrigation procedures appear to have no effect on pain after treatment (11). Cleaning and shaping is generally considered the phase of treatment most likely to instigate an inflammatory reaction; this is the period when the canal system is first exposed to outside factors such as oxygen and mechanical agitation (12). In a study by Torabinejad et al. (13) it was shown that the incidence and severity of pain after obturation of root canals with gutta percha and sealer were rare and mild. The severity of post-operative pain has also been reported as unrelated to the number of treatment visits (1, 11, 14, 15). Breaking up treatment into multiple appointments has not been found beneficial to decreasing post-treatment pain incidence and severity (12). Similarly, various intracanal medications have shown no palliative effect on post-treatment pain levels (11). Pain after

treatment is largely unpreventable, therefore taking palliative measures is in the best interest of the patient.

There is a large body of research devoted to preventing, treating, and controlling pain. The bulk of these studies analyze pain related to medical conditions, and those addressing dental pain commonly use an oral surgery model of impacted third molar extraction (16). The findings from these studies may not apply to pain of endodontic origin. Patients needing endodontic treatment may present with pre-existing pain and chronic inflammation. The bacterial by-products activate cytokines and chemokines, which draw immune cells to the area and stimulate production of inflammatory mediators. This process may be longstanding. Constant peripheral inflammation can cause anatomic changes in the sensory system, specifically nociceptor terminal sprouting and upregulation of tetrodotoxin resistant sodium channels (17, 18). Nociceptor terminal sprouting describes the ingrowth of neurons into areas that are normally sparsely innervated in response to trauma. The increased number of neurons in injured tissue increases the opportunity for spatial summation. Tetrodotoxin resistant sodium channels, or voltage-gated Na+ channels, are found in increased numbers in axons in areas of inflammation and cause an increased resting potential, and are implicated as a cause for hyperalgesia and allodynia (19, 20). Both of these alterations in nerve anatomy can sensitize the neurons and increase the patient's pain experience. The pre-existing inflammatory milieu and the peripheral and central sensitization differentiate endodontic pain from surgical pain. The oral surgery model includes patients presenting with painless impacted teeth, and the pain felt following

treatment is acute surgical pain (15, 21, 28). These differences become relevant when considering the mechanism of the drugs at our disposal.

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most recommended classes of pain-relievers in dentistry today (7, 22). NSAIDs function by inhibiting the cyclo-oxygenase enzymes and preventing the generation of new prostaglandin molecules, but they have no effect against existing molecules in circulation (23). Most traditional NSAIDs are non-specific, and will block the function of both COX-1 and COX-2, while COX-2 specific NSAIDs block only the COX-2 enzyme. The COX-2 pathway is responsible for generating eicosanoid mediators for inflammation and pain, while the COX-1 pathway is involved in angiogenesis and homeostasis. Blocking the COX-2 specific enzyme would preferentially block the COX-2 pathway, protecting against gastric adverse effects (24).

There are numerous NSAIDs available, with varying analgesic efficacy according to the Oxford League Table, a chart developed by the Oxford pain group that organizes analgesics by their NNT rating (number-needed-to-treat) (25). The NNT refers to how many patients would need to take the drug to achieve 50% pain relief; the lower the NNT, the more efficacious the drug (24). Traditional NSAIDs and COX-2 selective NSAIDs top the chart, and have smaller NNT ratings than acetaminophen or moderate doses of narcotics when taken alone (15). For example, ibuprofen 400mg has an NNT of 2.4, while Tramadol 100mg has an NNT of 4.8. The Oxford League Table is based on the findings of randomized, double blind studies, and the studies are not equally powerful. The studies used do not have a standardized pain model, and pain models are not equivalent (23). Thus, while a

drug may appear to have a low NNT, the total *n* of the studies including that treatment arm may be low, which impairs a study's ability to accurately estimate analgesic effect. One of the observations made in a review of NSAIDs by Ong et al. was the need for treatment specific NNT tables (24).

Historically, acetaminophen has not been classified as a NSAID, and the mechanism for its analgesic action has been unknown (26). New evidence suggests that, similarly to NSAIDS, acetaminophen functions in part by blocking prostaglandin synthesis through the inhibition of COX-1 and COX-2, with additional activity linked to the central nervous system via endogenous neurotransmitter systems (26, 27). Acetaminophen is considered to have fewer GI and cardiovascular side effects than NSAIDs. Its NNT is higher than other NSAIDs, with acetaminophen 500mg having an NNT of 3.5 on the Oxford League Table. Recent evidence suggests that combining ibuprofen and acetaminophen has a greater analgesic effect than either drug alone (28).

Systematic reviews are a way to synthesize and combine data from numerous studies evaluating a common outcome (29). Systematic reviews can provide greater power than a single study alone, and illuminate connections and patterns that an individual study could not. Holstein et al. published a systematic review on the use of NSAIDs for treating post-operative endodontic pain in 2002 (30), and found that one of the limitations of their review was the limited number of studies that were available. They found the most effective analgesics were a combination of flurbiprofen and tramadol or a combined regimen of pre-operative and post-operative flurbiprofen. The purpose of this systematic

review is to update the review from 2002 using studies published over the past 14 years, and to focus on NSAID efficacy and non-narcotic drug efficacy to alleviate post-operative endodontic discomfort in patients who present with pre-treatment pain.

1.1 Purpose of the Study

The purpose of this study was to address the PICOTS question: in patients with pre-operative pain who undergo initial orthograde endodontic treatment, what is the comparative efficacy of NSAIDS compared to placebo or non-narcotic analgesics in reducing post-operative pain and incidence of adverse events?

Chapter 2: Materials and methods

This systematic review was undertaken using recommended guidelines (31). A review protocol was written and registered with the public registry of systematic reviews PROSPERO (CRD42015019532).

Literature Search

The literature search of the Ovid MEDLINE® and Ovid OLDMEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, EBM Reviews – Cochrane Central Register of Controlled Trials, and EBM Reviews – Cochrane Database of Systematic Reviews included papers published from inception through December 2014. The search criteria were designed to encompass all known regularly recommended NSAIDs for dental use, and included key words for NSAIDs and endodontic post-operative pain (Appendix A). The initial search was not limited by study design and no language restrictions were imposed. The reference lists of the returned reviews were cross-checked for studies missing from the electronic search, and hand searching was performed on reference lists of relevant textbooks. Additionally grey literature was searched through www.clinicaltrials.gov, however no pertinent studies were found. The search was repeated December 15th, 2015 to search for reviews published in the intervening year since the initial search and two publications were included.

Inclusion Criteria

Patients

Patients who present with endodontic pain and receive a diagnosis of pulpal pathosis necessitating initial non-surgical endodontic treatment

Intervention

Non-surgical root canal treatment initiated, and NSAIDs were dispensed for post-operative pain management to be taken per oris (PO)

Comparison

Experimental group compared to placebo, a different NSAID, a different dose of the experimental NSAID, or taken at different time points

Outcome

Outcome measured as decreased pain incidence and/or pain severity

Timing

Pain experienced post-endodontic treatment

Setting

Out-patient clinical setting

Study Design

Randomized, double- or single-blind clinical trial study design

Exclusion Criteria

- Animal study
- Absence of baseline pain
- Non-endodontic pain model
- Intracanal medicaments
- Multiple visit treatment

Study selection and quality assessment

Two independent reviewers provided evaluations at all stages. Titles and abstracts returned by the initial database search were initially screened. Relevant abstracts were retrieved as full papers and read to assess their relevance regarding the inclusion and exclusion criteria above. Selected studies underwent data extraction. Quality assessments of included studies were performed by using the Cochrane Collaboration's tool for assessing risk of bias (32); each study was evaluated for low, moderate, or high risk of bias in the categories of randomization, allocation concealment, blinding of the participants, providers, and assessors. Any disagreement between evaluators was resolved by a third party. Following data abstraction and quality assessment, the strength of evidence was evaluated based on the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPC) strength of evidence methodology (33).

Data extraction and statistical analysis

The extracted data included the type of treatment, drugs and controls used in each study, the time points the drugs were administered, the time points at which the pain was measured, and the outcome variables used to measure pain. Information on pre-operative pain and post-operative pain at measured time points was gathered from each of the treatment arms of the included articles, and derived from the figures and graphs printed in the published results using the jTechDig image digitizing program (jTechDig, open source software). The included eligible studies used a variety of pain assessment scales, including the Heft-Parker visual analogue scale, modified visual analogue scale (VAS), and categorical pain scales (34). All data were converted to a standardized 100mm VAS scale for meta-analysis. L'Abbe plots were derived from the adjusted change in pain relief scores (35). L'Abbe plots measure the effectiveness of a given treatment against the control group; a point on the graph that lies on a 45 degree line marks a treatment group that is as effective as the placebo group. A point above the line represents a treatment that is more effective than the control; a point below the line represents a treatment that is less effective than the control.

Meta-analyses were conducted on studies that listed a measure of variance data to calculate the pooled effect size of NSAID treatment groups on post-operative pain with the Dersimonian-Laird random effects model using Stata 14 (StataCorp LP, College Station, TX) Standard deviations and confidence intervals were converted into standard error measurements (36, 37, 38) . For each drug or placebo, the post-operative mean VAS score

was subtracted from the baseline VAS score to obtain the difference of the difference of the mean, or the effect size (ES).

$$\mathrm{ES} = \bar{X}_{\mathrm{Treatment(Endpoint\ mean\ -\ Baseline\ mean)}} - \bar{X}_{\mathrm{Placebo(Endpoint\ mean\ -\ Baseline\ mean)}}$$

The standard error (SE) of the effect size was measured for each treatment comparison by using the SE of treatment and placebo groups at baseline and the endpoint. Where SE_1=Treatment Baseline SE, SE_2=Treatment Endpoint SE, SE_3=Placebo Baseline SE, and SE_4=Placebo Endpoint SE:

$$\mathrm{SE}_{\mathrm{Treatment}} = \sqrt{\left(\mathrm{SE}_1{}^2 + \mathrm{SE}_2{}^2 - (2{\times}0.5 \times \mathrm{SE}_1 \times \mathrm{SE}_2)\right)}$$

$$\mathrm{SE}_{\mathrm{Placebo}} = \sqrt{\left(\mathrm{SE}_3{}^2 + \mathrm{SE}_4{}^2 - (2{\times}0.5 \times \mathrm{SE}_3 \times \mathrm{SE}_4)\right)}$$

The standard error for the study as a whole was calculated as:

$$\mathrm{SE}_{\mathrm{Study}} = \sqrt{\left(\mathrm{SE}_{\mathrm{Treatment}}{}^2 + \mathrm{SE}_{\mathrm{Placebo}}{}^2\right)}$$

In these formulas, 0.5 was the number chosen for the variable ρ (the correlation coefficient). By convention, a ρ=0.5 represents moderate correlation between the baseline and endpoint measurements. For each treatment group, the ES and SE of each study reporting data and variability was input into a data table in Stata 14 and analyzed using the *metan* command with a random effects model. If a study reported only baseline SE

measurements, the endpoint SE measurements were inputted using an average of the SEs given by the other studies for that treatment group and time point (39). Based on the available data, meta-analysis could be performed for ibuprofen compared to placebo at 6, 12, and 24 hours, ibuprofen/acetaminophen combination drugs compared to placebo at 6 hours, and ibuprofen/acetaminophen combination drugs compared to ibuprofen at all time points.

After meta-analysis, the *display r(seES)* command (Stata14) was used to retrieve the standard error of the effect size, which was used for indirect analysis. For drugs for which no head to head comparison was available, indirect analysis was completed using a common comparator, in this case the placebo group. This was calculated for naproxen compared to ibuprofen. The pooled ES and seES for ibuprofen and for naproxen were determined. These were used to calculate the grand effect size (ESg) and standard error of the grand effect size (SEg, or seESg):

$$\mathrm{ESg} = \text{ pooled } \mathrm{ES}_{\mathrm{ibuprofen}} - \text{pooled } \mathrm{ES}_{\mathrm{naproxen}}$$

$$\mathrm{SEg} = \sqrt{\left(\mathrm{SEES}_{\mathrm{ibuprofen}}{}^{2} + \mathrm{SEES}_{\mathrm{naproxen}}{}^{2}\right)}$$

Thereafter, the command *metan ESg seESg* was run (Stata14), which returned the confidence interval and p-value for the grand effect size.

Chapter 3: Results

Summary of included studies

Electronic and manual searches identified 2,284 studies (Figure 1). After de-duplication, 1,731 records remained, and 99 further records were identified through hand searching. Two independent reviewers read 1,830 abstracts, and 1,427 records were excluded in the first pass and 403 records were retrieved. The search was repeated in December 2015 to capture any additional publications produced since original search, and two studies were added. After assessment of full texts, 15 articles pertaining to post-operative endodontic pain management with NSAIDs were identified (3, 40-53). The drugs studied included ibuprofen at 200mg, 400mg, and 600mg, a combination of ibuprofen 600mg and acetaminophen 1000mg, a combination of ibuprofen 200mg, acetaminophen 325mg and caffeine anhydrous 40mg (Novafen), flurbiprofen 50mg and 100mg, a combination of ibuprofen 400mg + alprazolam 0.5mg, etodolac 400mg, ketoprofen 50mg, ketorolac 10mg, tenoxicam 20mg, salicylic acid 650mg, acetaminophen 650mg, rofecoxib 50mg, naproxen 500mg, meloxicam 15mg, and piroxicam 20mg (Table 1). Baseline demographic data were provided by most studies (3, 40-43, 45-47, 50-53). Those that did provide patient characteristics reported a mean age of 40 years, with a range of 18-80 years (3, 40-43, 46, 47, 51, 53). The population was 55% male, 45% female. Two studies reported ethnicity (3, 41), with 83% white patients, 11% black patients, and 6% Hispanic or Asian. The mean baseline pain for all studies was 59 on a 100mm VAS, with a range from 12.85 to 85.47. Six studies categorized treated teeth by tooth type and arch type, and reported an

equal distribution of incisors, premolars, and molars; there were 52% maxillary teeth and 48% mandibular teeth (3, 40, 42, 46, 51, 53). Characteristics of included studies are found in Table 2.

Qualitative review

Major differences between the studies selected included treatment drugs, dose of medication, population type, sample size, pre-operative diagnosis, time of drug administration, and time of outcome variable measurement. The overall quality of the papers was poor, with 8 of the 15 studies having a high risk of bias as measured using the quality assessment tool. Sequence generation, allocation concealment, and blinding of parties was often alluded to but not specified, and was assessed as unclear. The quality assessment and risk of bias is found in Table 3.

L'Abbe plots were generated for all treatment drugs at time points 6, 12, and 24 hours post-operatively in Figure 2. Each of the included studies is represented in at least one of these time points. A data point above the line indicates that the treatment group experienced more pain relief than the placebo group for any given study. The absolute distance of the point from the line indicates the magnitude of pain relief – the greater the distance, the more relief. The L'Abbe plots illustrate that NSAIDs are effective at relieving post-operative endodontic pain. The data were also reorganized into bar graphs as represented in Figure 3, which illustrate the VAS scores from 0-6, 12, and 24 hours.

The single most effective drug regimen with the greatest decrease in pain at 6 hours post-operative was ibuprofen 200mg+acetaminophen 325mg (46) with a 43 VAS point pain reduction relative to placebo on a 100mm VAS scale (Table 4). This was followed by naproxen 500mg (46), ketorolac 10mg (43), ibuprofen 600mg + acetaminophen 1000mg (47), and ketoprofen 50mg (52). At 24 hours the greatest reported difference in pain was found with ketorolac 10mg (43), which decreased pain by 35 VAS points relative to placebo over 24 hours. The next four most effective drugs at 24 hours were ibuprofen 200mg + acetaminophen 325mg + caffeine 40mg (46), naproxen 500mg (46), rofecoxib 50mg (45), and ketoprofen 50mg (52).

Ibuprofen, flurbiprofen, and ibuprofen+acetaminophen combinations were represented in multiple trials; each of these categories was charted in a line graph over all time points in Figure 4. General observations include a trend towards increased pain from 6-12 hours in all groups, which may represent the peak pain levels post anesthesia.

Eight studies did not report on adverse events. Of the seven that did publish details on harms encountered during the study, two reported that there were no side effects noted by patients taking Placebo, Tenoxicam 20mg, Ibuprofen 200mg, Meloxicam 15mg, and Piroxicam 20mg (40, 48). The five that reported side effects encountered by patients classified the side effects as CNS which include sedation or drowsiness, light-headedness, headache, and euphoria (3, 43, 46, 50, 51). Side effects classified as GI include nausea, emesis, dyspepsia or upset stomach, constipation, and flatulence. Other side effects were described as xerostomia, “felt warm”, tachycardia, “itchy”, sweating, rash, wheezing, and

tightness in chest (Table 5). In studies that analyzed the side effects by treatment group, the placebo group had the same or greater incidence of side effects as at least one of the experimental drug groups (3, 44, 47, 52).

Nine studies reported supplying or recommending a rescue medication, or "escape drug." Four of these were acetaminophen of varying doses, one was acetaminophen 300mg + codeine 30mg,and one was acetaminophen 500mg + hydrocodone 5mg (40-41, 43-44, 46, 52). Seven studies reported that patients needed supplemental medication or used the rescue medication (42, 44, 46-49, 52)(Table 5).

Quantitative review

Eleven of the fifteen studies included a measure of variance, either explicitly in a data table, a p-value, or illustrated as part of a graph (41, 42, 44-48, 50-53) facilitating the inclusion of these data in a meta-analysis. Five of the eleven studies with variance had similar treatment groups with low heterogeneity, allowing their comparison (45-47, 50, 53). The remaining studies did not provide an estimate of variance.

Meta-analysis of ibuprofen versus placebo identified the study by Attar et al. (41) to have a negative effect size (in favor of placebo). This study was determined to be too dissimilar to the other studies to be included in pooled analysis, due to the small sample size, different timing of the treatment dose, and the behavior of the placebo group. The baseline characteristics of the placebo group were older patients, and more men than women, causing a potential gender bias. Because the treatments were not specifically

stated to be identical, the placebo group may have perceived their treatment to be more effective, and the patients may have been more suggestible to placebo treatment.

Meta-analysis was performed comparing studies with common treatment arms with coinciding time points, generating Forest Plots (Stata 14). At 6 hours, there was a trend for ibuprofen to elicit greater pain reduction than the placebo with an effect size of 10.5, which was statistically significant (p=0.037, I2=61.5%) (Figure 5a). No data were available to compare ibuprofen vs. placebo at 12 and 24 hours. The indirect analysis of ibuprofen and naproxen at 6 hours showed an effect size of 30.5 in favor of naproxen (p=0.052), and indirect analysis of ibuprofen and ketoprofen at 6 hours showed an effect size of 22.28 in favor of ketoprofen (p=0.156) (Figures 5b, 5c), however neither of these were significant.

Ibuprofen+acetaminophen combinations were significantly more effective than placebo at 6 hours with an effect size of 34.89 (p=0.00, I2=20.8%) (Figure 6). Comparing ibuprofen+acetaminophen to ibuprofen at all time points there was an effect size of 13.94, but it was not statistically significant (p=0.317, I2=83.4%) (Figure 7).

Excluded studies

After the full text review 390 studies were excluded for reasons listed in Appendix B. The list in Appendix B was read in full to provide extensive background information on NSAIDs and post-operative pain, but generally did not have a narrow focus on post-operative pain in endodontics managed with NSAIDs, and did not fit the inclusion criteria. In contrast, the following studies appeared to qualify for inclusion, but after scrutiny did not

pass the inclusion and exclusion criteria and deserve further explanation. A study by Menke et al. (54) was not included because although they evaluated the effect of prophylactic etodolac on post-endodontic pain, they did not report a baseline pain, and their results were reported as a change in pain rather than absolute pain score, making comparisons to other studies difficult. The lack of baseline pain reporting was an exclusion criterion to ensure that the population would have significant post-operative pain; a difference in pain without a discrete pre-operative pain value does not indicate the degree of post-operative pain patients were experiencing prior to intervention. A study by Negm (55) was excluded due to treatment rendered in multiple stages, and results summarized over all time points rather than described at each time point. Torabinejad et al. (12) was excluded, due to lack of preoperative pain. Studies by Rowe et al. (56), Parirokh et al. (57), and Madani et al. (58) were excluded due to lack of baseline pain reporting.

Strength of Evidence

The strength of evidence of the included studies was graded based on the AHRQ EPC methodology (Appendix C). The limitations of the studies were high; although the study designs were randomized controlled trials, the risk of bias was high. The studies were direct, in that the interventions and comparisons in the studies were the same as specified in the review question. The studies also show themselves to be direct by using the VAS to measure outcomes, which aligns itself with the outcome of the review question. The studies were inconsistent in that they had varying effect sizes, and in different directions. The grade for

the precision domain is imprecise, because the studies have inadequate power given the amount of difference predicted between the experimental groups and the placebo.

Chapter 4: Discussion

Findings and Conceptual Context

The goal of this study is to consolidate the available information on NSAID use for treating post-operative endodontic pain. This was the first systematic review of NSAID use for endodontic purposes that was restricted to NSAIDs and non-opioid analgesic combination drugs. Four key questions were used to direct the review and were condensed down into a single review question which rephrased the questions of interest for a specific population, intervention, comparison, outcome, timing, setting, and study type. The review question was: in patients with pre-operative pain who undergo initial orthograde endodontic treatment, what is the comparative efficacy of NSAIDs compared to placebo or non-narcotic analgesics in reducing post-operative pain and incidence of adverse events? Ibuprofen was found to be the most studied NSAID in the endodontic literature, and significantly more effective than placebo at relieving pain 6 hours post-treatment. The combination of ibuprofen+acetaminophen has also been evaluated, and was found to be significantly more effective than placebo, but not significantly more effective than ibuprofen alone at reducing pain 6 hours after treatment. However, the strength of evidence for these outcomes was insufficient, based on the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPC) strength of evidence methodology (59) (Appendix C).

This information provides growing evidence that ibuprofen and ibuprofen+acetaminophen combinations are effective at relieving pain of endodontic origin in the hours following root canal therapy. Previously, the core of the pain literature applied to endodontics came from an oral surgery or medical pain perspective, which might not be germane to pain of endodontic origin. The research done by the medical community generally applies to acute surgical pain, which may not be relevant for endodontics; a patient needing root canal treatment may have had pre-existing pain for an extended duration, and that pain may have undergone centralization and progressed from acute to chronic (60, 61). Analgesic drug regimens that are effective in cases of acute pain may not be as helpful in cases of chronic pain. The endodontic pain studies looked at a variety of NSAIDs separately, but rarely compared them to each other. In addition to differences in the quality of pain, analgesic research using an oral surgery model tend to have different baseline population characteristics than for an endodontic model; patients seeking to have their wisdom teeth extracted are likely to be young, healthy, and have no or mild pre-operative pain.

Several key questions were developed to focus the review: 1) What is the most effective combination and dosage of NSAIDs for relieving post-op pain following initial orthograde endodontic treatment? This question was designed to review whether there is one NSAID formula that is more effective at relieving post-operative endodontic pain than other NSAIDs. Analgesics go through periods of popularity with prescribing doctors (7, 22, 62), and research on efficacy can be outpaced by new drug formulations, even as these

drugs become staples in our palliative arsenal (21). Several different NSAIDs and non-opioid analgesics were analyzed by the included studies, at various doses; besides ibuprofen, the treatment groups were too few and too heterogeneous to compare by meta-analysis. Indirect analyses of ketoprofen versus ibuprofen and naproxen versus placebo were done, and although both ketoprofen and naproxen appeared to have greater efficacy than ibuprofen, the results were not statistically significant.

A subset of this first key question whether recent COX-2 inhibitor NSAID formulations are effective at post-endodontic pain reduction. COX-2 inhibitors have not seemed to gain traction in dentistry as an option for analgesia. One reason may be that ibuprofen has been so effective for many people that it is easy to continue recommending what is known to work well. It is also more convenient, as many people already have ibuprofen in some form in their home, and it is not always necessary for the provider to prescribe a high dose when the patient can take an additional tablet of over the counter ibuprofen. It is also possible that providers are risk averse to COX-2 inhibitors. Although they were created to lessen the risk of gastrointestinal side effects seen with traditional NSAIDs, by upsetting the balance between COX-1 and COX-2 activity selective inhibitors may also increase the risk of heart attack and stroke (63). Rofecoxib was withdrawn from the market in the United States in 2004 due to reports of serious heart disease after use (50). Three COX-2 inhibitors were included in this review: meloxicam, piroxicam, and rofecoxib. Meloxicam and piroxicam are indicated for treating long term, chronic conditions such as osteoarthritis and rheumatoid arthritis. Rofexocib was one of the top five most effective

treatment arms of all included studies at 6 hours, but no quantitative meta-analysis of the COX-2 inhibitors was possible due to significant clinical heterogeneity.

The second key question was, 2) What is the most effective dose schedule of NSAIDs for relieving post-operative pain following initial orthograde endodontic treatment? Different doses and different dose schedules have been recommended for analgesic use and in endodontic studies, such as ibuprofen 200mg or ibuprofen 400mg, taken once as a single prophylactic dose or "on-the-clock" every six hours. A popular post-operative instruction for analgesia is "take 1-2 tabs every 4-6 hours" which is vague and can lead to patients taking more drugs than necessary, or not enough to be palliative. The intent of this question was to examine whether one dose was more effective at relieving post-operative pain than another dose, such as whether there was a difference between ibuprofen 200mg or ibuprofen 400mg, which would give us information on whether higher doses are more effective or if there is no difference and no benefit to recommending a higher dose. Information on the timing of delivery of analgesics could provide better information on when patients should take their medication, and how the metabolism and half-life of a particular drug effect the recommended schedule. The time of initial dose and the follow-up pain measurement times varied between studies, and in order to do meta-analysis the papers were pooled at certain time points, ie. at 6 hours, and all time points within 24 hours. No conclusion can be drawn about the time of initial dose that would lead to greatest reduction in pain for the patient, or for how long they should maintain their analgesic regimen.

The third key question focuses on new implementation of classic drugs. 3) Is there an analgesic or combination of NSAIDs that is more effective than NSAIDs alone? There has been much interest recently in the increased efficacy of combining ibuprofen and acetaminophen together over the efficacy of either alone (24, 28, 62). Some studies in the medical field have found the combination to be as effective as common doses of opioid analgesics. This question evaluated whether the same holds true for post-operative endodontic pain, and whether the combination of ibuprofen and acetaminophen is more effective or equivalent to NSAIDs traditionally recommended. Ibuprofen+acetaminophen was found to be more effective than placebo at relieving post-operative pain at 6 hours, but not more effective than ibuprofen alone.

There is pharmacologic evidence that the combination of ibuprofen and acetaminophen is better than either drug alone for pain relief. Ibuprofen and acetaminophen are truly synergistic, rather than merely additive, according to a recent paper by Miranda et al. (64). These investigators measured dose response curves of a variety of intravenous NSAIDs alone and coadministered with acetaminophen in a rat acute pain model. A list of interaction indices were developed to compare the effective dose that produced 50% antinociception (ED50) of the combination versus the ED50 of the monotherapy. Of the NSAIDs tested, ibuprofen fell in the middle of the pack, while nimesulide, naproxen, and diclofenac had the greatest pain relief in conjunction with acetaminophen. Miranda et al. hypothesized that the strength of the combination is related to the COX-2 selectivity of the NSAID – the less selective, the better the synergy. While this

study was performed in rats to study acute pain, it gives pharmacological support to using ibuprofen and acetaminophen together. More research is required using the combination to treat chronic pain in humans. The findings by Miranda et al. also bring to light other NSAIDs that might benefit from coadministration with acetaminophen, and it may be worth comparing their efficacy with ibuprofen/acetaminophen – a combination with significant synergy may outperform ibuprofen.

Ibuprofen+acetaminophen combinations were not more effective than ibuprofen alone, but they were more effective than placebo alone. The two studies that compared ibuprofen+acetaminophen to ibuprofen were Menhinick et al. and Wells et al. Their findings do not agree, and this may be due to differences in inclusion criteria regarding the baseline diagnosis. The two studies that compared ibuprofen+acetaminophen to placebo were Menhinick et al. and Mehrvarzfar et al., who actually studied a combination of ibuprofen+acetaminophen+caffeine 40mg (Novafen). It was determined that Novafen could be included in meta-analysis because of findings from the Cochrane Review that doses of caffeine less than 100mg have no additional benefit to analgesics (65).

In the qualitative review, the ibuprofen 200mg+acetaminophen 325mg+caffeine 40mg (Novafen) group in Mehrvarzfar et al. was found to have the greatest reduction in VAS compared to placebo of all the treatment groups in the included studies. This is unusual, given the low doses of ibuprofen and acetaminophen; we would expect that the higher-dose combination of ibuprofen 600mg+acetaminophen 1000mg in Menhinick et al. would have greater efficacy. The Mehrvarzfar et al. study was heterogeneous from the

other studies in dosage of medication, and more importantly they restricted their patient population to patients presenting with irreversible pulpitis and normal periapices. Once a vital tooth with a normal periapex has had a pulpectomy, we expect that the primary source of pain has been addressed and pain relief is predictable, with or without analgesia. The results of this study represent an outlier among the other included trial results. Given the heterogeneous nature of this study compared to Menhinick et al. and the other studies, it is possible that including this study in the meta-analysis is not ideal; however, given that data on ibuprofen+acetaminophen combinations in endodontics is sparse, it was decided to be included in the meta-analysis and acknowledge that the studies are inconsistent, which is reflected in the strength of evidence.

The last key question was 4) If the optimal NSAID regimen does not sufficiently manage pain, what is the next best analgesic approach? This question was intended to review the studies and summarize the recommended analgesic for breakthrough pain, if the treatment drug was not sufficient for pain control. The rescue drugs recommended in the studies varied, and can be found in Tables 2 and 5. Seven of the 15 studies included a recommendation or dispensation of a rescue drug (40, 41-44, 46, 51). Attar et al. supplied "an extra dose of the treatment medication" as their rescue medication, which implies that placebo patients were given placebo rescue medication. The studies offered no explanation for their choice, and give no insight to a logical second analgesic regimen if NSAID therapy is insufficient to control post-operative endodontic pain.

The data for the number of patients who withdrew from the study due to uncontrolled pain, and the number of patients who availed themselves of the rescue medication verify that there are situations and severities of pain for which NSAID medication is not sufficient and opioid and opioid-combination medications may be indicated. The need for pain control should be weighed against the risk of side effects. Overall, NSAID treatment groups seemed to encounter the same incidence and severity of side effects as the placebo group. In contrast, in Torabinejad et al. (52) 25% of the patients who took acetaminophen 325mg + codeine 60mg had side effects and 12.5% dropped out of the study, compared to the other groups which had a mean side effect rate of 5.76% and a drop out rate of 8.72%. While this is just one data point, it illustrates that opioid combination medication may come with a higher risk of side effects that patients may find intolerable.

The inclusion criteria were designed to select for studies that analyze analgesic treatment groups in patients whose pain is expected to be moderate to severe. Patients with moderate to severe pre-operative pain are more likely to have measurable levels of post-operative pain, and these are the patients who would benefit the most from a strong, reliable course of analgesics. Post-operative pain is unpredictable, and may depend on many factors that cannot be controlled intraoperatively, such as the patient's immune response, their anxiety, their prior history with pain, and their experience with dentistry in general and fear thereof. There are few factors that can indicate a greater likelihood of increased post-operative pain. The severity of pre-operative pain is an indicator of increased

post-operative pain, and was written into the inclusion criteria. It is known that pre-existing pain can dictate post-operative pain severity (66), which makes these patients the most valid for post-operative pain management trials.

The exclusion criteria were designed to eliminate studies that did not control variables that can attenuate post-operative pain. An example of this is in the number of treatment visits. The number of treatment visits does not impact post-operative pain, but the stage of treatment does. There is more post-operative pain following cleaning and shaping of the root canal system than following the obturation of the root canal system (10, 49). Multiple visit treatment was an exclusion criterion to exclude studies that treated their patients in multiple visits where one post-operative pain measurement may have meant only measurement of post-operative obturation pain.

Strengths and Limitations of the Review

The strengths of this systematic review are that the sum of all research on endodontic post-operative pain and NSAID use were combined and evaluated as a whole. Several studies were included (39, 40, 43-46, 48-50) that were not included in the previous systematic review (29). This is also the first time NSAIDs used in alleviating post-operative endodontic pain have been subjected to a quantitative comparison and meta-analysis.

The most obvious limitation of this review is the small number of included studies, and that the sample size of all the included studies available for meta-analysis was small, ranging from n=12 to n=36. Low powered studies are more likely to have baseline

differences between treatment groups, and may represent skewed results that do not represent the true normal response. The scarcity of studies available in the endodontic literature is a severe limitation; low sample sizes may be compensated for by pooling data, but research on endodontic pain is seldom performed, and so information on many NSAIDs remains inadequate and predominantly qualitative.

Other limitations include the significant heterogeneity in the included studies; the trials differed in the timing of drug administrations, the dose, and the time after administration when the effect was measured. Many trials did not specify whether the treatment groups were identical, and so placebo effect may have been enhanced. The studies did not all use the same outcome measure, instead using a variety of VAS scales, from 4-point to HP-VAS, to modified VAS of different lengths. Of the outcome data, results were usually reported as means without a measure of variability, which makes meta-analysis of the studies difficult.

A major source of heterogeneity in endodontic pain studies is the potential difference in the stage of initial disease, and the variety of diagnostic presentations of pain. Pain can be generated by the pulp or the periapical tissue, it may be recent and acute or longstanding and chronic. A tooth that requires endodontic treatment due to irreversible pulpitis may be extremely painful, but once the inflamed tissue has been debrided the etiology of the pain has been almost totally eliminated and the pain will predictably diminish (67). This is different than a tooth that requires root canal therapy to treat a diagnosis of pulpal necrosis, in which case despite root canal treatment the periapical

region will still suffer from inflammation and the pain response may continue for several days (68). Depending on the tissue presentation and the level of endodontic disease of any given case, the patient's response to pharmacologic therapy may be variable.

Future Research

More research is indicated to elaborate on ibuprofen's impact on post-operative endodontic pain. Pharmacologists are looking at new, fast absorbing formulations of ibuprofen (48). Fast acting ibuprofen formulations achieve earlier, higher serum concentrations and can result in earlier pain relief. An analysis of the literature by Moore et al. (69) found that NNTs were lower for fast-acting formulations than standard ibuprofen formulations, and 200mg of fast-acting ibuprofen, such as an ibuprofen arginine salt, tended to perform better than 400mg of the standard formulation in terms of both speed of pain relief and efficacy of pain relief. It will be interesting to see how this affects endodontic pain management.

Another direction for future research is a focus on drugs that are not as easy to access as ibuprofen and acetaminophen, in order to determine whether the effort to prescribe them is justified by their efficacy. Ketoprofen 50mg is a prescription regulated medication, and there was only one study that included ketoprofen as a treatment arm (52). The indirect comparison of ketoprofen 50mg to ibuprofen 600mg found that although ketoprofen showed a larger effect size than imbuprofen which would imply greater pain relief, the difference was not significant. Given more research and a larger pooled *n*, the

statistical significance may change. The other drug groups of greater efficacy were ketorolac 10mg (43, 51), and rofecoxib 50mg (45). Ketorolac is a very potent analgesic when given intramuscularly, however the drug is currently only recommended as an initial IV dose followed by a short term PO regimen, due to the higher risk of adverse effects and liver toxicity compared to other NSAID formulations (70). Rofecoxib represents the COX-2 NSAIDs, but was withdrawn from the market in the United States. Due to restrictions in prescribing these NSAIDs, further research on ketorolac and rofecoxib may be challenging despite their evident efficacy.

Going forward, research standards need to be developed as to recommended doses of common analgesics, including ibuprofen, which is reasonable at doses from 400-600mg, but not as low as 200mg or as high as 800mg which are less effective, or above the maximum effective dose, respectively. The experimental dose for acetaminophen needs to be adjusted as well now that the FDA has lower recommended doses of acetaminophen, to reflect a lower daily maximum of 3250mg (71). Regarding the synergy between ibuprofen and acetaminophen, research on dosing schedules would also be of value. There is no current consensus as to whether pain relief is more effective when analgesics are taken at 4 or 6 hour intervals, or whether ibuprofen and acetaminophen are more synergistic when taken together, or when the regimen is offset by 2-3 hours. In trials studying medications, variables such as over the counter medications that are self-prescribed by the patient should be controlled. Above all, greater detail in reporting baseline population characteristics, baseline pain measurements, and publishing data as opposed to only

reporting conclusions is needed. Systematic reviews are a tool for comprehensive analysis of data that would be impossible for a single study to collect due to size, time, or expense, but the method is powerless if the studies available do not compare similar outcomes, using similar tools.

Further recommendations for endodontic pain research guidelines include developing a protocol that includes only patients with baseline pain, studying a wider range of NSAIDs such as ketoprofen, naproxen, and flurbiprofen for which there is little comparable data, and using clinically relevant doses at periodic dose intervals that take into account the half-life and metabolism of the drug for maximum efficacy. The analgesic effect and pain relief should be measured for at least three days, rather than merely 6-8 hours post-operative because pain will continue beyond that period.

Chapter 5: Summary and Conclusions

The aim of this study was to find an optimal regimen of non-opioid analgesics as a first-line palliative treatment for unavoidable post-operative endodontic discomfort. To do so, a PICOTS question was designed to frame this question in a format answerable by systematic review. Databases were searched for keywords relating to post-operative endodontic pain and treatment by NSAID analgesics, and 2,284 records were found. After dual review of abstracts, and then dual review of full-texts, 15 eligible studies were identified.

Of the 15 studies, ibuprofen was the most common studied treatment drug, in doses ranging from 200mg to 600mg, and in combination variations including ibuprofen and acetaminophen, and ibuprofen and alprazolam. L'Abbe plots, bar graphs, and line graphs illustrated that NSAIDs are clearly more effective than placebo at relieving post-operative endodontic pain. Forest plots and meta-analysis of ibuprofen and ibuprofen+acetaminophen combinations showed that ibuprofen 600mg was more effective than placebo with a greater improvement in VAS of 10.50 at 6 hours, and ibuprofen 600mg + acetaminophen 1000mg was more effective than placebo with a greater improvement in VAS of 34.89 at 6 hours, and these results were statistically significant. Ibuprofen 600mg + acetaminophen 1000mg was not found to be significantly more effective than ibuprofen 600mg alone. Naproxen 500mg was found to have a greater improvement in VAS of 30.5 than ibuprofen 600mg at 6 hours, but this was not statistically significant; similarly,

ketoprofen 50mg was found to have a greater improvement in VAS of 22.28 than ibuprofen 600mg at 6 hours, but this was not statistically significant.

Despite these positive and affirming findings, the AHRQ strength of evidence methodology found that the strength of evidence for these findings was insufficient. This means that no treatment recommendations can be based on these findings, and more research is needed to provide more support for any clinical decisions.

As it stands, the dental literature lacks specificity in its methods, and clarity in its results. The findings of this systematic review are essentially no different from the findings from Holstein et al. in 2002; fourteen years later, and endodontics has not progressed in the area of managing post-operative pain. The studies that have been performed between then and now remain flawed, and have shown an obstinate refusal to learn from past mistakes or apply logic to their methods.

Future trials should publish explicit data tables along with figures, and measures of variance along with mean results. It is clear that NSAIDs as a group are an effective pain management strategy for post-operative endodontic pain. Of the treatment groups represented, ibuprofen is the most studied NSAID, often at a dose of 600mg. Ibuprofen 600mg is more effective at relieving pain than placebo at 6 hours following endodontic treatment. Ibuprofen 600mg + acetaminophen 1000mg is significantly more effective than placebo at 6 hours. There is a trend for ketoprofen 50mg and naproxen 500mg to be more effective than ibuprofen 600mg at 6 hours post-operative, but this is not significant. There

are insufficient data to recommend the most effective NSAID, dose amount, or dose interval for relieving post-operative endodontic pain in patients with pre-operative pain.

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Table 1. Included drugs

Drug	Trade name(s)	Recommended daily dosing for mild-moderate pain	Half-Life	Duration	Maximum Daily Dose
Acetaminophen	Tylenol, Tylenol ES	650mg every 4-6 hours	2 hours	4-6 hours	3250 (OTC recommendation)
Ibuprofen	Advil, Motrin	400mg every 6-8 hours	2 hours	6-8 hours	3200mg
Aspirin		325-650mg every 4-6 hours	3 hours	4-6 hours	4000mg
Naproxen	Aleve, Naprosyn	500mg every 12 hours	12-17 hours	<12 hours	1250mg on day one, subsequent daily dosing should not exceed 1000mg
Flurbiprofen		100mg every 12 hours	5.7 hours	-	300mg
Ketoprofen	Orudis, Actron, Oruvail	50mg every 6 hours	2-4 hours	6 hours	300mg
Ketorolac	Toradol	20mg initial dose, followed by 10mg every 4-6 hours	2-6 hours	4-6 hours	40mg
Meloxicam	Mobic	7.5mg once a day	15-20 hours	-	15mg
Piroxicam	Feldene	20mg once a day	50 hours	-	20mg
Etodolac	Lodine	300mg every 8-12 hours	6.4 hours	5-6 hours	1200mg
Tenoxicam	*Not available in the U.S.*				
Rofecoxib	*Not available in the U.S.*				

Table 2. Qualitative Analysis and Study Characteristics

Author, year	Treatment Groups (n)	Time of delivery	Time of pain evaluation	Outcome variable	Inclusion Criteria	Treatment	Escape Drug	VAS Score at Baseline	VAS Score at 6 hrs	VAS Score at 12 hrs	VAS Score at 24 hrs
Arslan, 2011	Placebo (16) Tenoxicam 20mg (16) Ibuprofen 200mg (16)	Prior to treatment (single prophylactic dose)	Baseline, immediately after treatment, 6, 12, 24, 48, 72 hours post-operative	100mm VAS	Pain originating from a tooth >= 50mm on VAS Included pulpal and periapical diagnoses not specified	Non-surgical root canal treatment	Extra dose of the treatment medication	85.5 82.6 83.2	35.1 7.92 2.83	19.8 9.62 15.3	16.4 4.09 3.49
Attar, 2008	Placebo (12) Ibuprofen 600mg tablet (14) Ibuprofen 600mg liquigel (13)	Prior to treatment (single prophylactic dose)	Baseline, during treatment, 6, 12, 18, 24 hours post-operative	100mm VAS, 170mm HP-Categorical, VAS-Categorical	Pain >= 30 on VAS Included pulpal and periapical diagnoses not specified	Non-surgical root canal treatment	Tylenol ES (500mg)	65.6 64.7 65.9	17.9 26.2 28.1	20.4 24 31.8	11.9 23.5 21.6
Baradaran, 2014	Placebo (15) Ibuprofen 400mg (15) Ibuprofen 400mg+alprazolam 0.5mg (15)	Single dose at the end of the first appointment, following cleaning and shaping	Baseline, 4, 6, 12, 24, 48, 72 hours post-operative.	10cm VAS	No systemic diseases, no allergy to NSAIDs and benzodiazepines, no sedatives or analgesics, no GI problems; initial pain in moderate-severe range in a molar tooth. Diagnosis of irreversible pulpitis.	Non-surgical root canal treatment in two visits	Two tabs of acetaminophen 325mg.	82.0 76.0 82.0	38.0 30.0 23.3	36.0 25.3 23.3	15.8 10.7 13.3

Table 2. Qualitative Analysis and Study Characteristics

Battrum, 1996	Placebo (10) Ketorolac 10mg PO (10)	Ketorolac 10mg at time 0, then q6h	Baseline, 6, 24 hours post-operative	100mm VAS, 6 point Pain Intensity Scale, 4 point Verbal Pain Relief Scale	Diagnoses of irreversible pulpitis or pulpal necrosis, or periapical diagnosis of symptomatic apical periodontitis	Non-surgical root canal treatment	Ketorolac 10mg tabs	12.9 40.2	14.7 5.14		12.9 5.14
Doroschak, 1999	Placebo (12) Flurbiprofen 50mg (12)	100mg loading dose, then 50mg q6h	Baseline, 6, 24, 36, 48, 60 hours post-operative	4 point category pain scale, 100mm VAS, Heft-Parker scale	Pain >= 30 on VAS Pulpal diagnosis of irreversible pulpitis or necrosis, periapical diagnosis of normal, asymptomatic apical periodontitis, symptomatic apical periodontitis, or acute apical abscess.	Emergency endodontic treatment (pulpectomy, cleaning and shaping)	Acetaminophen 650mg	66.2 70.6	42.8 36.6		26 20

Table 2. Qualitative Analysis and Study Characteristics

Flath, 1987	Placebo (29) Pre-operative placebo, post-operative flurbiprofen 100mg (30 Pre-operative flurbiprofen 100mg, post-operative placebo (28) Flurbiprofen (29)	Prior to treatment, post-operative dose 3 hours after treatment	Baseline, 3, 7, 24, hours after initial dose	4 point category pain scale, 100mm VAS, 5 point pain relief scale	Any pulpal and periapical diagnosis.	Pulpectomy/cleaning and shaping		48.97 37.06 33.09 41.03			30 11.91 18.53 6.18
Gopikrishna, 2003	Placebo (15) Rofecoxib 50mg (15) Ibuprofen 600mg (15)	Prior to treatment (single prophylactic dose)	Baseline, 4, 8, 12, 24, 48, 72 hours post-operativ	100mm VAS	Pain >= 30 on VAS Any pulpal and periapical diagnosis.	Cleaning and shaping	Acetaminophen 650 mg	72.6 76.3 75.1		55.4 21.7 45.9	35.3 13.1 25.0
Mehrvarzfar, 2012	Placebo (25) Naproxen 500mg (25) Ibuprofen 200mg + acetaminophen 325mg + 40mg caffeine (25)	Single dose after completing treatment	Baseline, 6, 12, 24 hours post-operative	10 point VAS	Diagnosis of irreversible pulpitis with normal periapex	Cleaning and shaping		4.7 5.8 4.8	4.8 0.8 0.6	3.7 0.5 0.7	3.2 0.7 0.4
Menhinick, 2004	Placebo (19) Ibuprofen 600mg (20) Ibuprofen 600mg + acetaminophen 1000mg (18)	Prior to treatment (single prophylactic dose)	Baseline, 1, 2, 3, 4, 6, 8 hours post-operative	100mm VAS	Severe spontaneous pain of odontogenic origin, Pain 50-100mm on VAS. Diagnosis of irreversible pulpitis or necrosis, periapical	Cleaning and shaping	Acetaminophen 300mg+ codeine 30mg	80.0 69.0 81.0	35.8 20.8 0.0		

Table 2. Qualitative Analysis and Study Characteristics

					diagnosis of normal, symptomatic or asymptomatic periapical periodontitis.						
Nekoofar, 2003	Placebo (17) Meloxicam 15mg (17) Piroxicam 20mg (17)	Single dose after completing treatment	Baseline, 8, 24 hours post-operative	9cm VAS	Pain from a posterior tooth greater than 5cm on 9cm VAS. Any pulpal and periapical diagnosis.	Non-surgical root canal treatment		6.4 7.3 6.7			1.2 1.0 1.9
Rogers, 1999	Placebo (12) Ibuprofen 600mg (12)	Single dose after completing treatment	Baseline, 6, 12, 24, 48 hours post-operative	150mm VAS, standardized to 100mm	Vital pulp with diagnosis of irreversible pulpitis or normal.	Non-surgical root canal treatment		23.6 28.4	39.4 28.8	28.3 22.1	18.3 12.5
Ryan, 2008	Placebo (14) Ibuprofen 600mg (15)	Prior to treatment, then q6h	Baseline, immediately after treatment, 6, 12, 18, 24 hours post-operative	100mm VAS	Pain >=30 on VAS. Diagnosis of irreversible pulpitis or pulpal necrosis, any periapical diagnosis.	Non-surgical root canal treatment		70.7 68.0	49.5 17.0	47.9 18.2	27.4 12.4
Sethi, 2014	Etodolac 400mg (19) Ketorolac 10mg PO (19)	Single dose thirty minutes prior to treatment, then	Baseline, 0, 6, 12, 18, 24 hours after rct.	10cm VAS	Diagnosis of symptomatic irreversible pulpitis in multirooted teeth with baseline VAS	Non-surgical root canal treatment	Ibugesic 600mg	62.6 61.6	25.3 5.3	25.8 4.2	26.8 4.2

Table 2. Qualitative Analysis and Study Characteristics

					greater than 3cm.						
Torabinejad, 1994	Placebo (53) Salicylic acid 650mg (50) Acetaminophen 650mg (57) Ibuprofen 400mg (57) Ketoprofen 50mg (53) Acetaminophen 325mg +codeine 60mg (48)	One dose after completing treatment, then q6h	Baseline, 6, 12,18, 24. 30, 36, 42, 48, 54, 60, 66, 72 hours post-operative	Modified 90mm VAS	Any pulpal and periapical diagnosis.	Non-surgical root canal treatment		7.6 8.44 *	4.9 2.79	3.5 1.77	2.4 2.05
Wells, 2011	Ibuprofen 600mg (36) Ibuprofen 600mg + acetaminophen 1000mg (35)	One dose after completing treatment, then q6h	Baseline, 1, 24, 48, 72, 96, 120 hours post-operative	170mm Heft-Parker VAS	Symptomatic tooth with pulpal necrosis and moderate-severe pain at the time of treatment. Symptomatic apical periodontitis, a radiographic periapical lesion of 2x2mm.	Non-surgical root canal treatment	Vicodin 5/500mg	130.1 118.3			62.7 54.6

*Numbers reported in table are the VAS scores reported for patients with severe pain. Data is available for Placebo and Ketoprofen groups only.

All VAS scores have been converted to 100mm scale.

Table 3. Quality assessment and risk of bias using Cochrane Quality Assessment Tool

Author, Year	**Sequence Generation Adequate?**	**Allocation adequately concealed?**	**Blinding of participants?**	**Blinding of care providers?**	**Blinding of outcome assessors?**	**Incomplete outcome data adequately addressed? Was the overall attrition sufficiently low/differential attrition sufficiently low?**	**Was the study free of selective outcome reporting?**	**Were there other sources of bias? Were there important baseline differences in prognostic factors?**	**Risk of Bias**
	Acceptable methods must be truly random; randomized table, computer generated random numbers, etc. Patients should be accepted sequentially.	*The group selection must be hidden from patients, personel, and assessors until treatment is rendered; otherwise randomization may be tampered with and bias increased.*				*How many people dropped out of the study? <20% is good, <15% is better for smaller studies. This avoids risk of bias in the population sample.*	*Did they not report data you know they observed? This is not especially relevant to these papers.*	*Were the groups similar at baseline? For any of the baseline groups, a difference of <10% is acceptable.*	
Arslan, 2011	Yes - block randomization program	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	Yes	Moderate
Attar, 2008	Unclear - methods of randomization not described	Unclear	Unclear	Unclear	Unclear	Yes/No - 13% patients lost to follow up	Yes	Yes - differences in gender and diagnosis distribution	High
Baradaran, 2014	Unclear	Unclear	Yes	Unclear	Unclear	Yes/Yes	Yes	Yes	High
Battrum, 1996	Unclear	Unclear	No	No	No	Yes/Yes	Yes	Yes	High
Doroschak, 1999	Unclear	Unclear - sealed envelopes	Yes - identical pills	Yes	Yes	Yes/Yes	Yes	Yes	Moderate
Flath, 1987	Yes - random draw	Yes - sealed envelopes,	Yes - identical tablets	Yes	Yes	Yes/Yes - 3.3% patients lost	Yes	Yes - baseline differences	Moderate

Table 3. Quality assessment and risk of bias using Cochrane Quality Assessment Tool

		serially numbered							
Gopikrishna, 2013	Unclear - methods of randomization not described	Unclear	Unclear	Unclear	Unclear	Yes/Yes	Yes	Yes - no baseline characteristics	High
Mehrvarzfar, 2012	Yes - randomized digits with excel	Unclear	Unclear	Yes	Unclear	Yes/Yes	Yes	Yes - baseline differences	Moderate
Menhinick, 2004	Yes - randomized digits with excel	Unclear	Yes - identical capsules	Yes	Yes	Yes/No - 12% patients dropped out	Yes	Yes - baseline differences	Moderate
Nekoofar, 2003	Unclear	Unclear	Yes - identical capsules	Unclear	Yes	Yes/No	Yes	Unclear - no data shown	High
Rogers, 1999	Unclear	Unclear	No	No	No	No/Unclear	Yes	Yes	High
Ryan, 2008	No	No	Yes	Unclear	Yes	Yes/Yes	Yes	Yes	High
Sethi, 2014	Unclear	Yes	Yes	Yes	Yes	Yes/Yes	Yes	Yes	Moderate
Torabinejad, 1994	No	No	Yes	Unclear	Yes	Yes/Yes	Yes	Yes - baseline differences	High
Wells, 2011	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	Yes	Moderate

Table 4. Efficacy of drugs relative to placebo

	VAS Point Reduction	Treatment Group	Author, Year
6 Hours	43	Ibuprofen 200mg + acetaminophen 325mg + caffeine 40mg	Mehrvarzfar 2012
	41	Naproxen 500mg	Mehrvarzfar 2012
	37	Ketorolac 10mg	Battrum 1997
	37	Ibuprofen 600mg + acetaminophen 1000mg	Menhinick 2004
	33	Ketoprofen 50mg	Torabinejad 1994
24 Hours	35	Ketorolac 10mg	Battrum 1997
	29	Ibuprofen 200mg + acetaminophen 325mg + caffeine 40mg	Mehrvarzfar 2012
	26	Naproxen 500mg	Mehrvarzfar 2012
	26	Rofecoxib 50mg	Gopikrishna 2003
	17	Ketoprofen 50mg	Torabinejad 1994

Table 5. Incidence of Adverse Events

Author, year	Treatment Groups (n)	Rescue Med.	# Patients Withdrawn	Adverse Events
Arslan, 2011	Placebo (16) Tenoxicam 20mg (16) Ibuprofen 200mg (16)	Extra dose of the treatment medication	No patients took the rescue medication.	No side effects were reported by patients.
Attar, 2008	Placebo (12) Ibuprofen 600mg tablet (14) Ibuprofen 600mg liquigel (13)	Tylenol ES (500mg)	6 patients lost to follow-up by not returning questionnaires. No patients took the escape medication.	Not reported
Baradaran, 2014	Placebo (15) Ibuprofen 400mg (15) Ibuprofen 400mg+alprazolam 0.5mg (15)	Two tabs of acetaminophen 325mg.	Not reported	Not reported
Battrum, 1996	Placebo (10) Ketorolac 10mg PO (10)	Ketorolac 10mg tabs	5/10 patients in the placebo group took the rescue medication.	Not reported
Doroschak, 1999	Placebo (12) Flurbiprofen 50mg (12)	Acetaminophen 650mg	Not reported	1 GI, 1 CNS, 1 Other 3 GI, 1 CNS, 0 Other GI = nausea, emesis, dyspepsia CNS = sedation, light-headedness, headache, euphoria Other = xerostomia, "felt warm", tachycardia, "itchy"
Flath, 1987	Placebo (29) Pre-operative placebo, post-operative flurbiprofen 100mg (30) Pre-operative flurbiprofen 100mg, post-operative placebo (28) Flurbiprofen (29)	Not reported	3 patients dropped out due to noncompliance with medication, 1 dropped out due to inability to complete treatment.	3 CNS, 1, GI, 3 Other 0 CNS, 1 GI, 0 Other 6 CNS, 4 GI, 2 Other 1 CNS, 2, GI, 1 Other CNS = Dizziness, drowsiness, lightheadedness GI = Upset stomach, constipation, flatulence
Gopikrishna, 2003	Placebo (15) Rofecoxib 50mg (15) Ibuprofen 600mg (15)	Acetaminophen 650 mg	26/45 patients needed additional medication	Not reported
Mehrvarzfar, 2012	Placebo (25) Naproxen 500mg (25) Ibuprofen 200mg + acetaminophen 325mg + 40mg caffeine (25)	Not reported	Not reported	Not reported

Table 5. Incidence of Adverse Events

Menhinick, 2004	Placebo (19) Ibuprofen 600mg (20) Ibuprofen 600mg + acetaminophen 1000mg (18)	Acetaminophen 300mg+codeine 30mg	8 patients did not return pain diaries. 3 placebo patients, one ibuprofen patient, and one combination patient used the rescue medication.	4 GI, 10 CNS, 0 other 1 GI, 6 CNS, 3 other 1 GI, 5 CNS, 0 other GI = nausea, emesis CNS = headache, dizziness, drowsiness Other = sweating, rash, wheezing, tightness in chest
Nekoofar, 2003	Placebo (17) Meloxicam 15mg (17) Piroxicam 20mg (17)	Not reported	5 placebo, 2 meloxicam, and 2 piroxicam patients dropped out due to inadequate pain control.	No side effects were reported by patients in any group.
Rogers, 1999	Placebo (12) Ibuprofen 600mg (12)	Not reported	6/12 needed supplemental medication 3/12 needed supplemental medication	Not reported
Ryan, 2008	Placebo (14) Ibuprofen 600mg (15)	Not reported	5/48 patients in the study dropped out; 2 took the rescue medication, 3 could not be contacted.	Not reported for placebo and ibuprofen groups.
Sethi, 2014	Etodolac 400mg (19) Ketorolac 10mg PO (19)	Ibugesic 600mg	4 patients excluded for noncompliance.	1 mild nausea, 1 severe vomiting, 2 mild headache, 1 moderate headache, 1 severe headache, 4 mild dizziness, 1 moderate heartburn. 1 mild headache, 1 mild dizziness
Torabinejad, 1994	Placebo (53) Salicylic acid 650mg (50) Acetaminophen 650mg (57) Ibuprofen 400mg (57) Ketoprofen 50mg (53) Acetaminophen 325mg +codeine 60mg (48)	Not reported	11.3% drop out 18% drop out 7% drop out 3.5% drop out 3.8% drop out 12.5% drop out	9.4% side effects 10% side effects 0% side effects 1.8% side effects 7.6% side effects 25% side effects
Wells, 2011	Ibuprofen 600mg (36) Ibuprofen 600mg + acetaminophen 1000mg (35)	Vicodin 5/500mg	19% of patients used rescue medication. 20% of patients used rescue medication.	Not reported

Table 6. Strength of Evidence

Outcome: Post-operative pain reduction						
	Domains					
Study set:	Number of studies and participants	Study limitations	Directness	Consistency	Precision	Grade for Strength of Evidence
Overall data set	15 RCTs *N* = 1,107	High	Direct	Inconsistent	Imprecise	Insufficient

Key
Study limitations: High, medium, or low.
Directness: Direct, indirect.
Consistency: Consistent, inconsistent, unknown.
Precision: Precise, imprecise.
Strength of evidence: High, medium, low, insufficient/very low.

Figure 1. PRISMA Flow Diagram

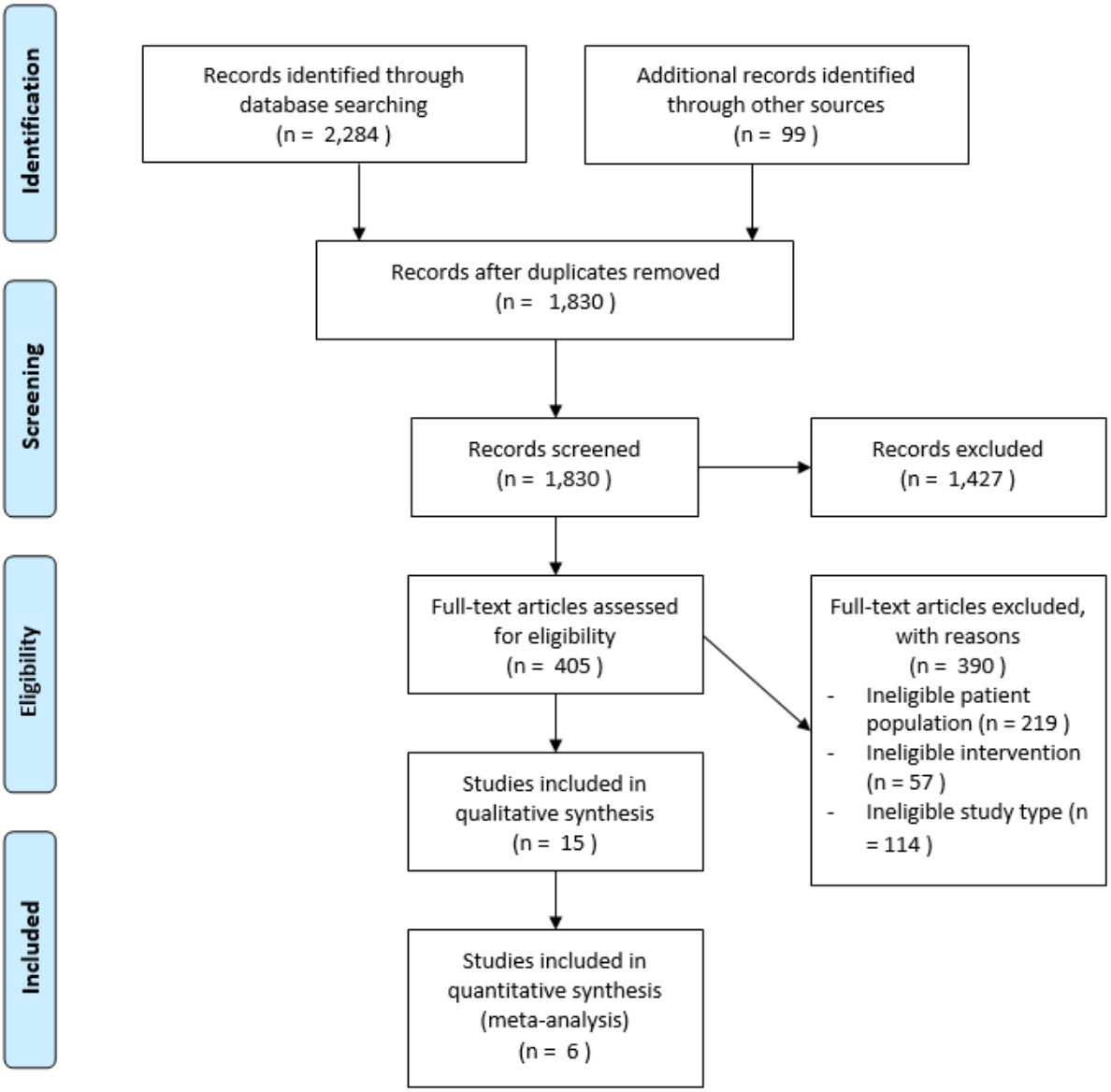


Figure 2. L'Abbe Plot of all drugs at 6 hours

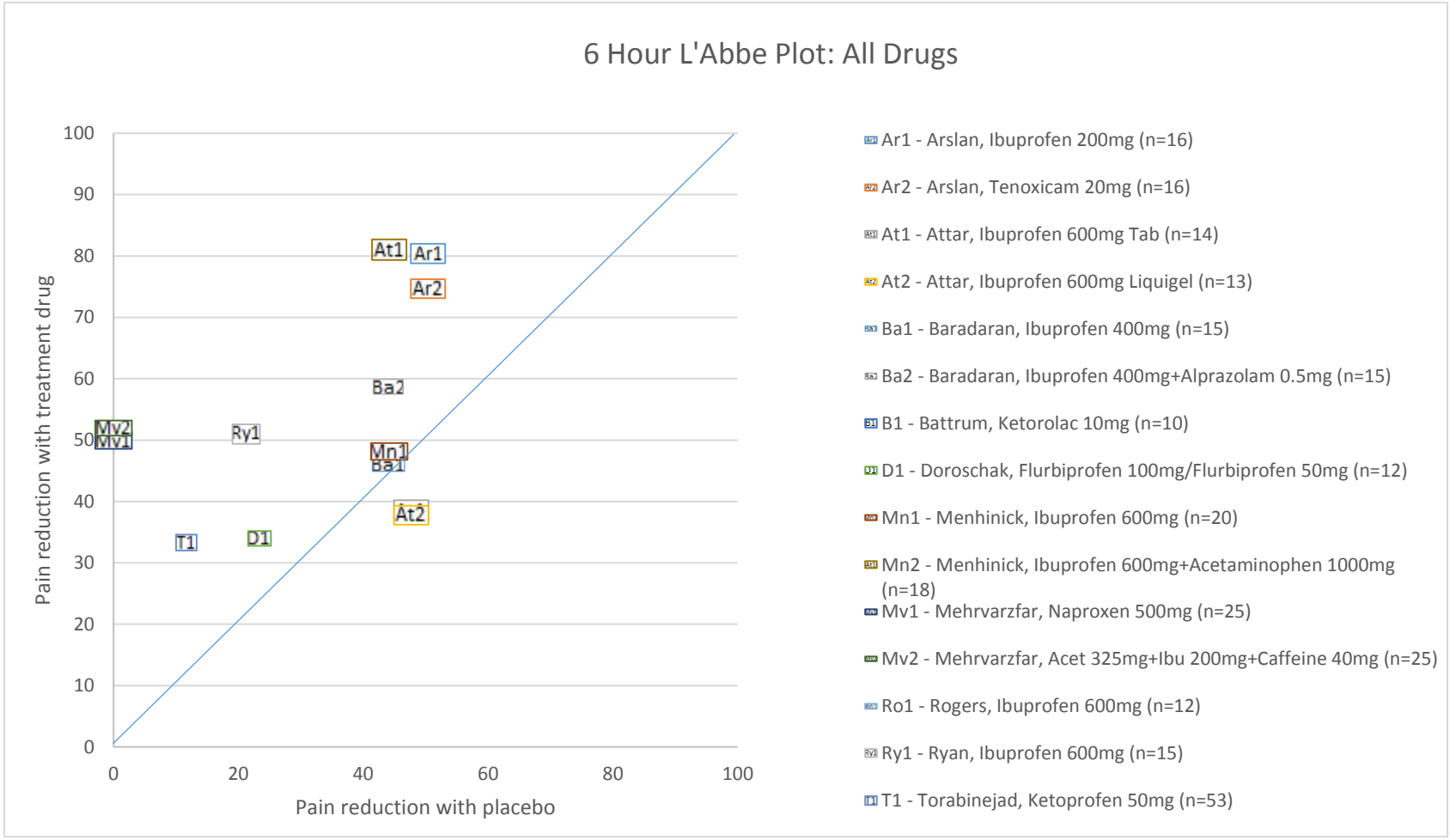


Figure 3. L'Abbe Plot of all drugs at 12 hours

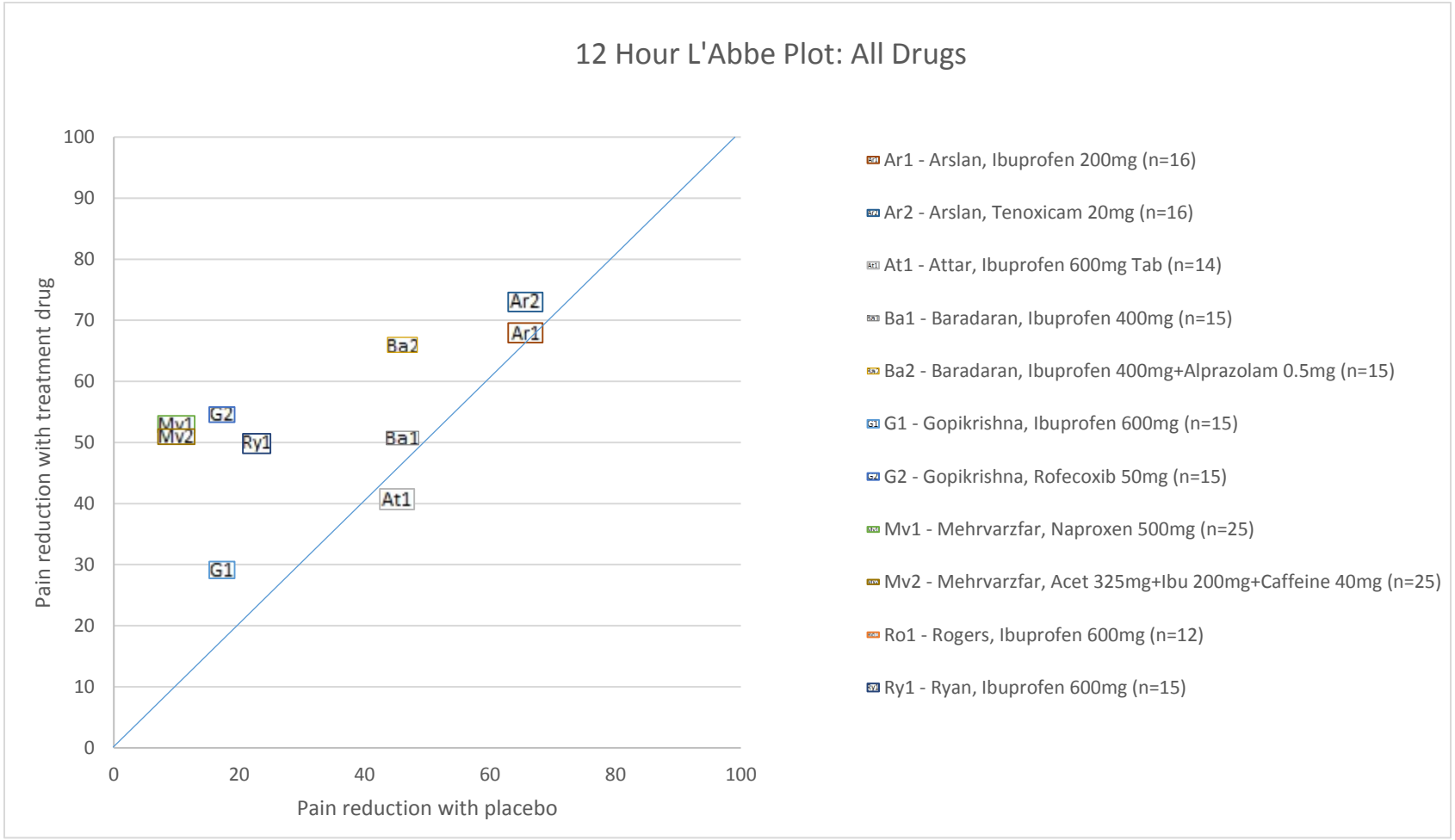


Figure 4. L'Abbe Plot of all drugs at 24hours

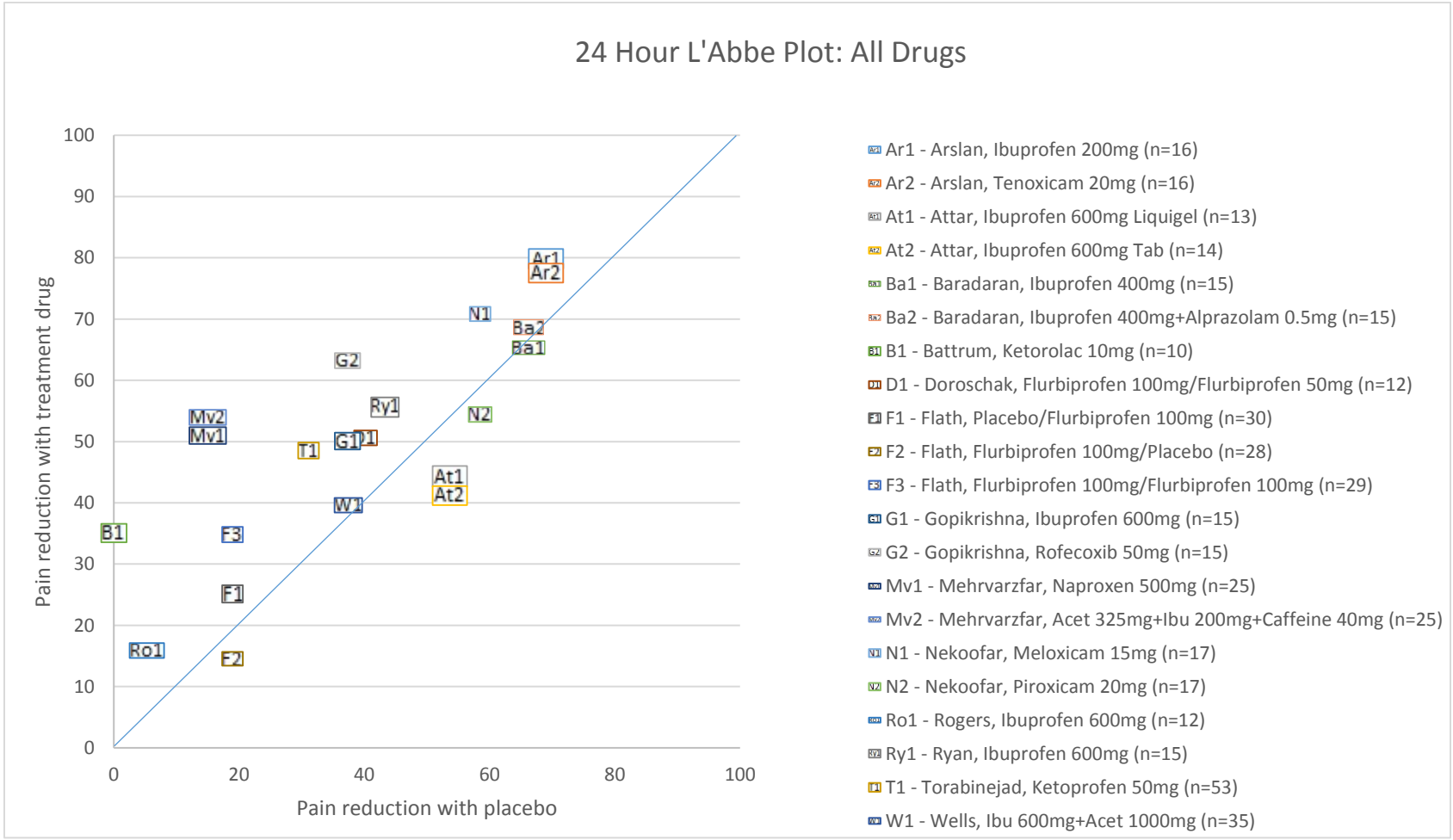


Figure 5. Bar graph of changes of VAS scores at 6 hours

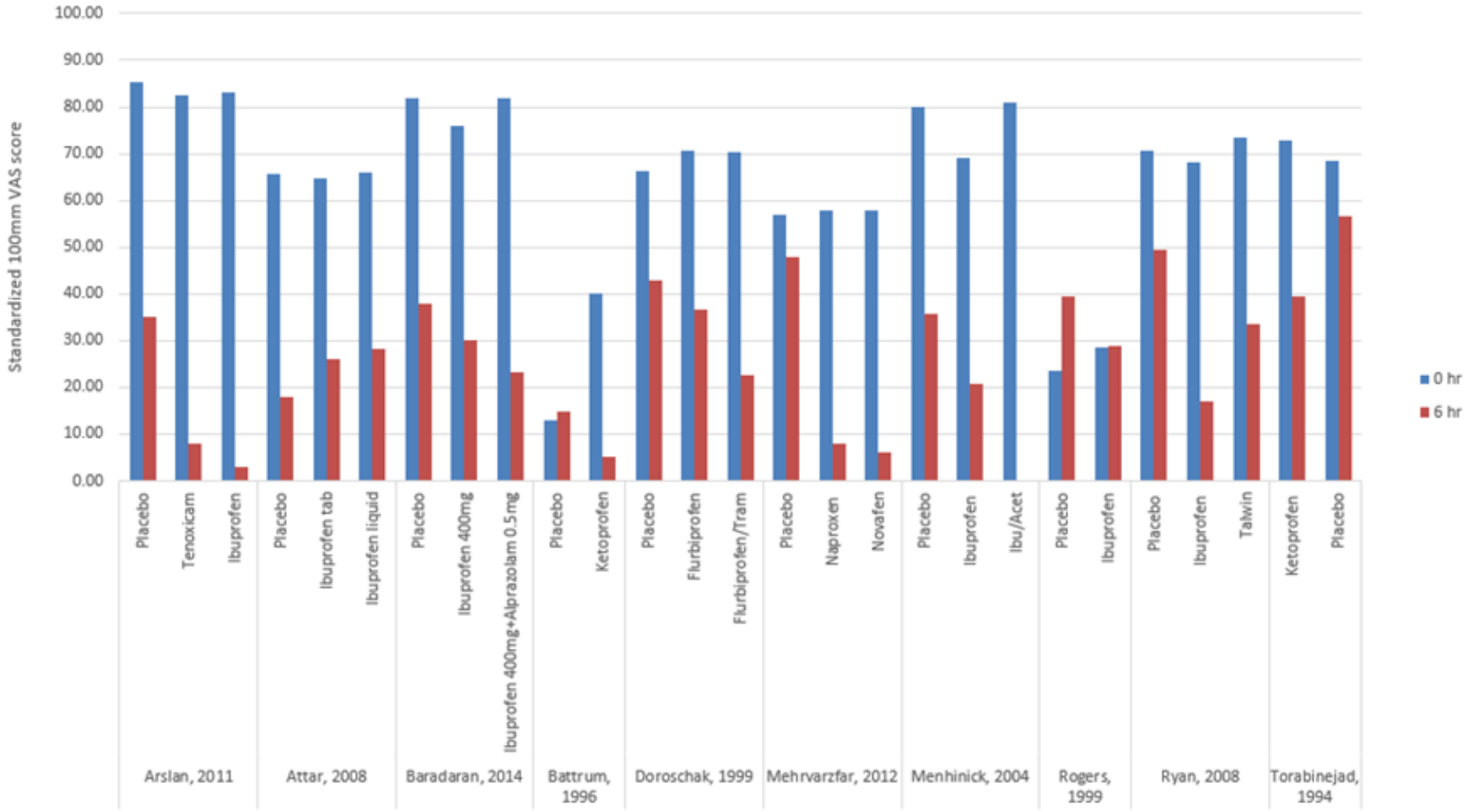


Figure 6. Bar graph of changes of VAS scores at 12 hours

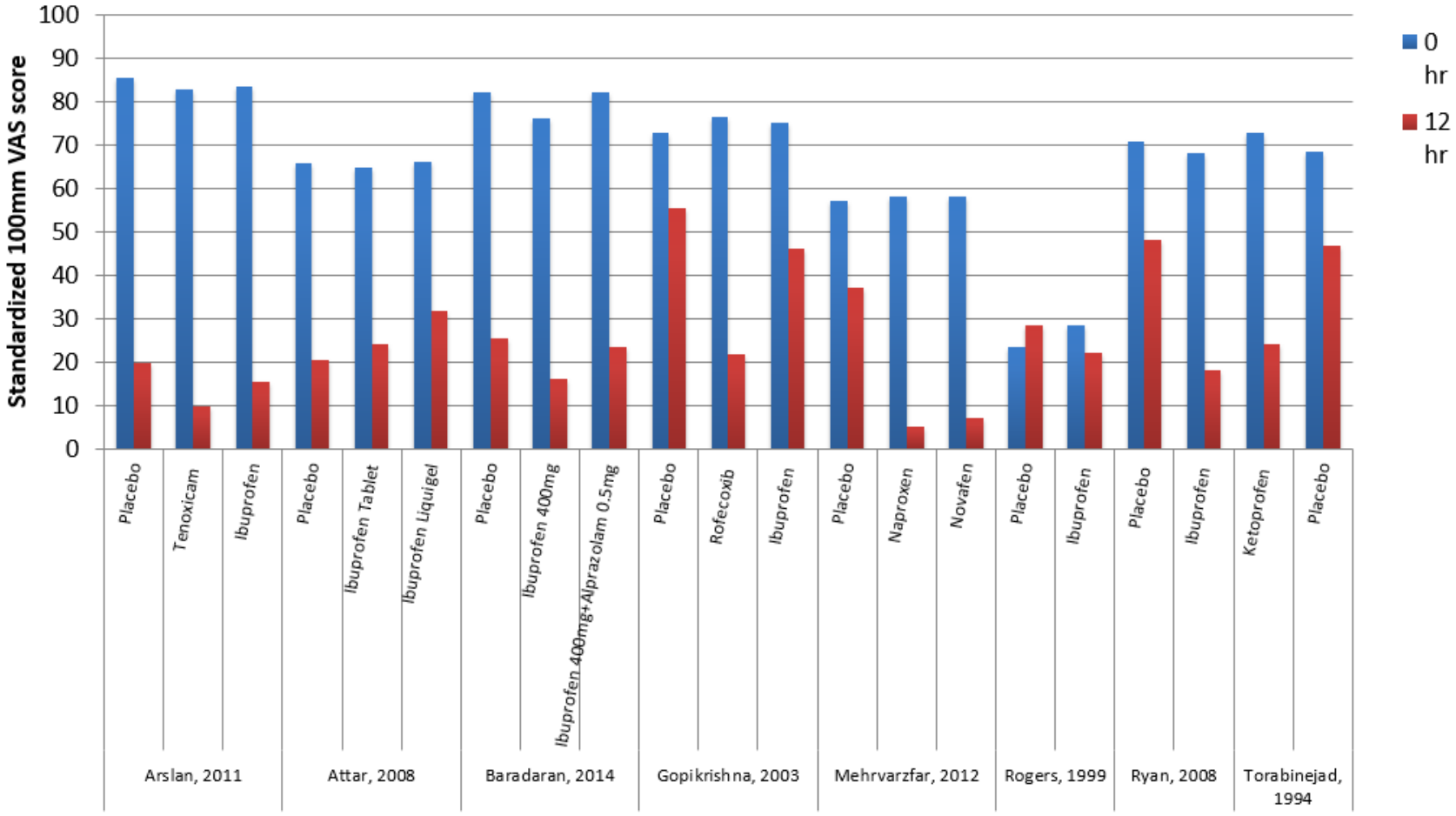


Figure 7. Bar graph of changes of VAS scores at 24 hours

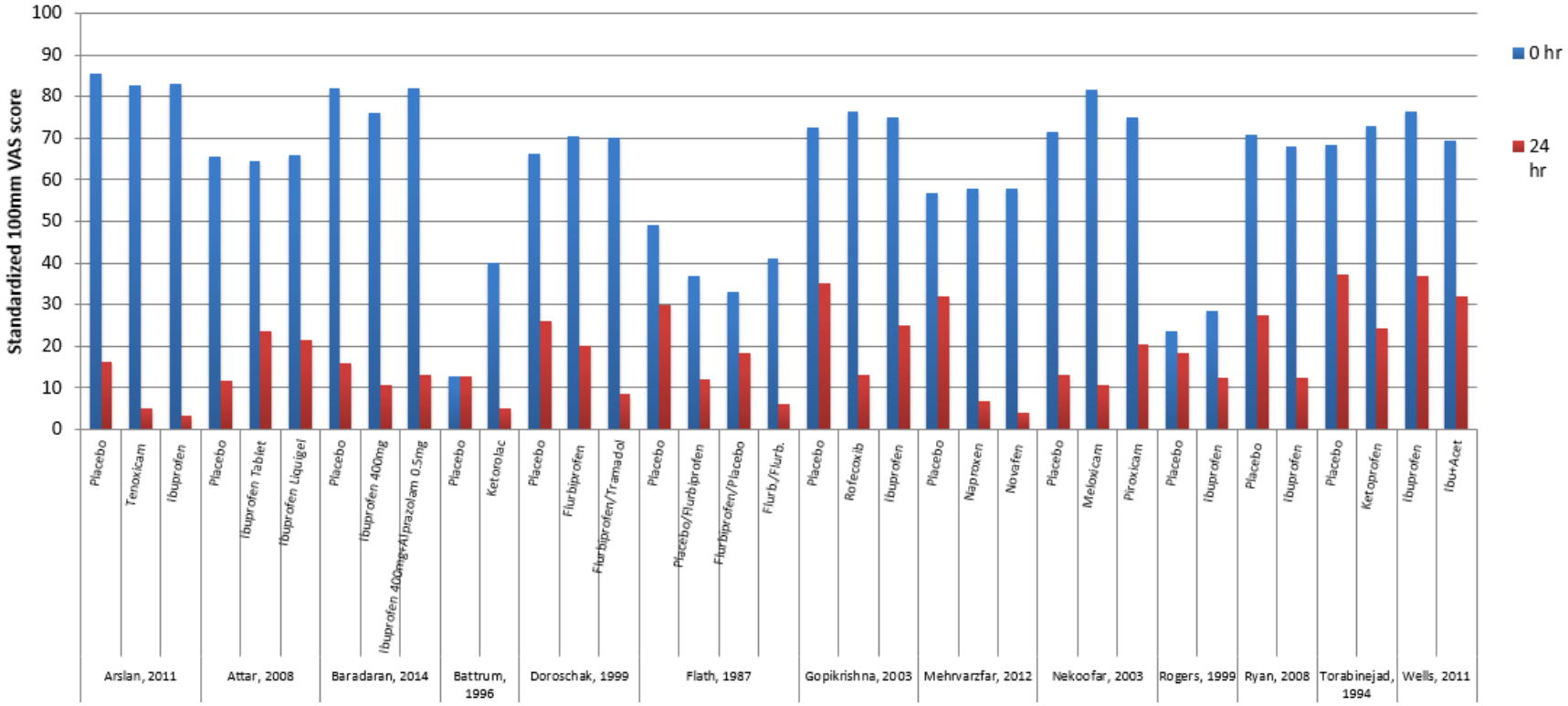
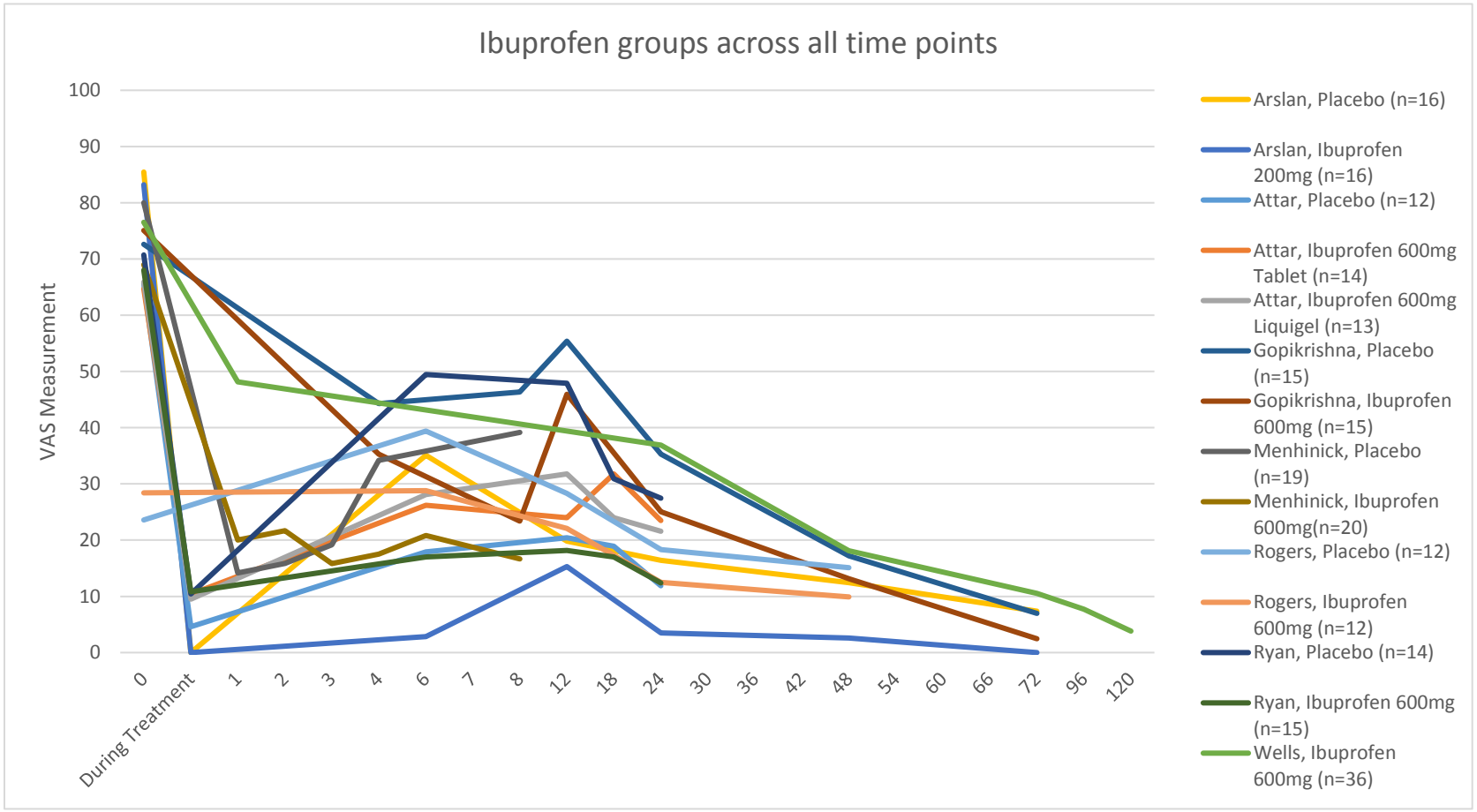


Figure 8. Line graphs of ibuprofen over time

A. Separate trials



B. *Mean ibuprofen and mean placebo*

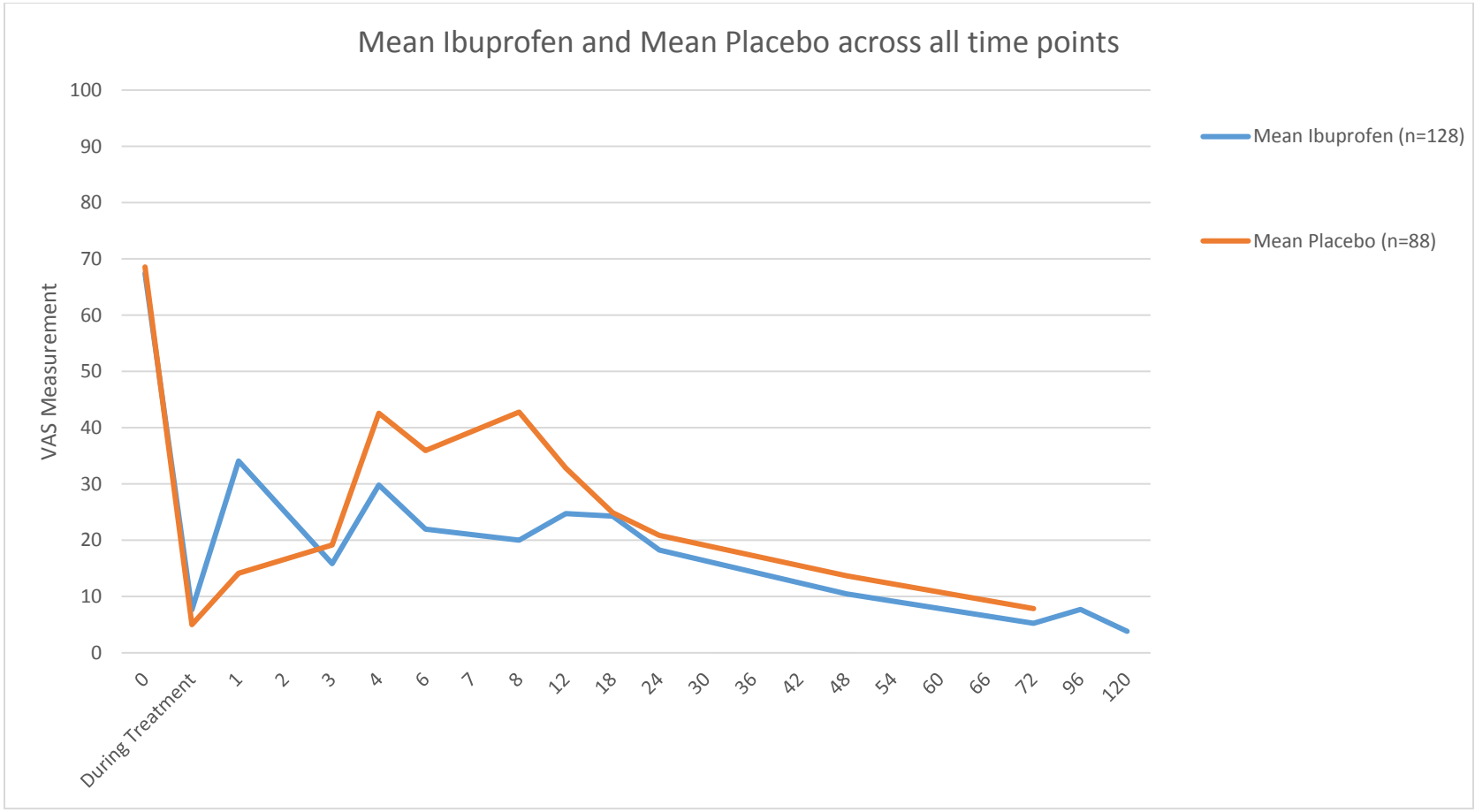
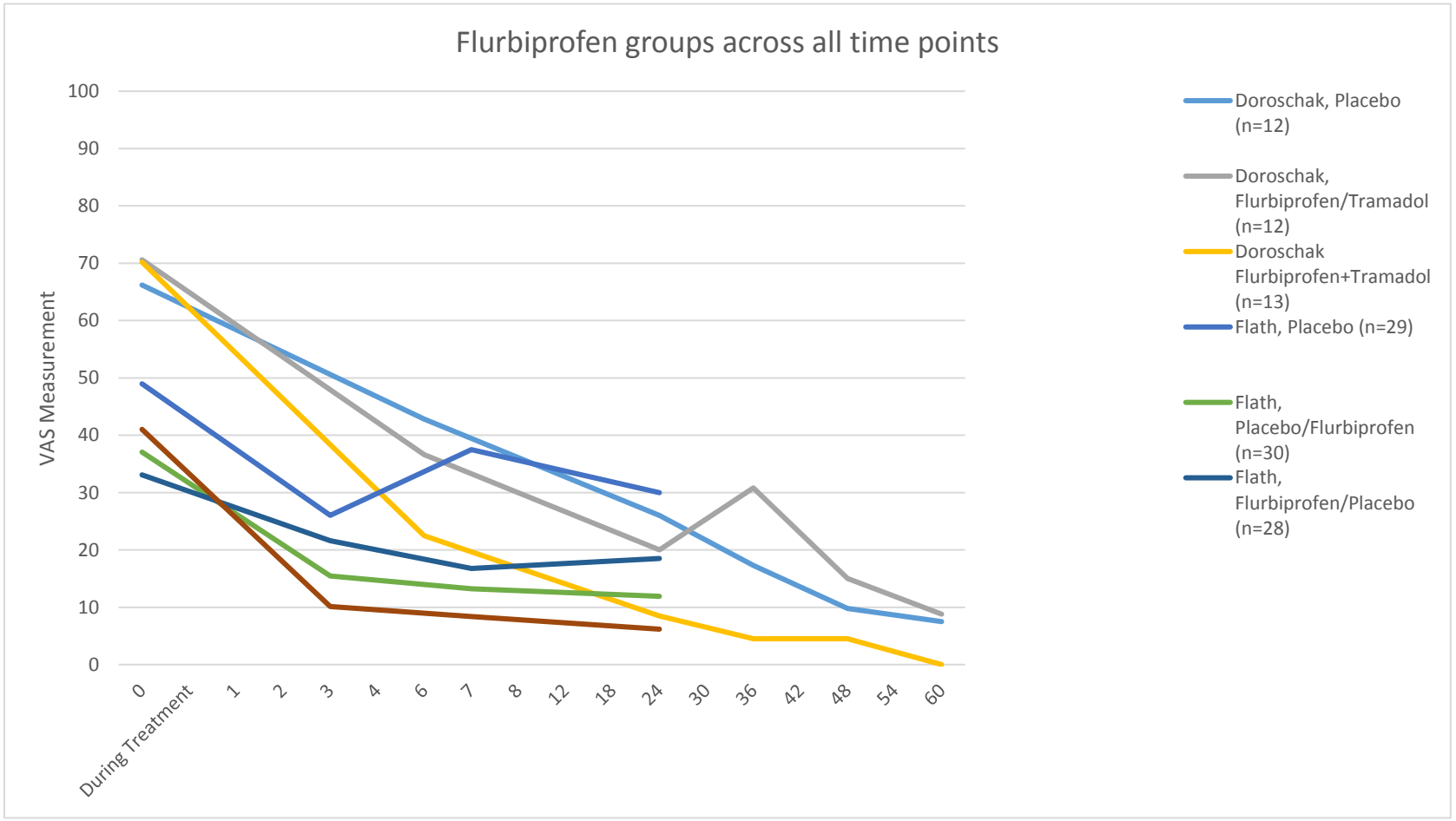


Figure 9. Line graphs of flurbiprofen over time

A. Separate trials



B. *Mean flurbiprofen and mean placebo*

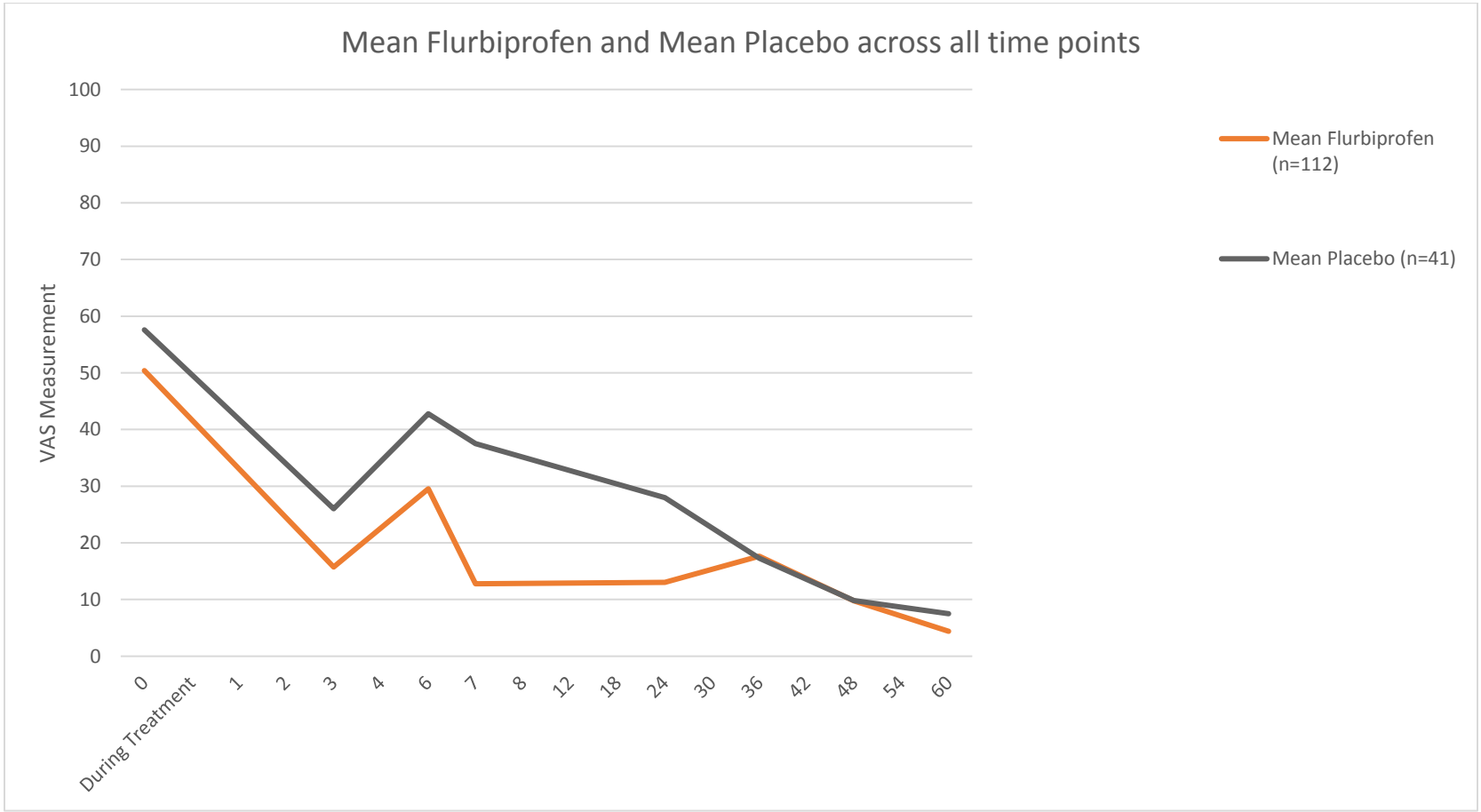
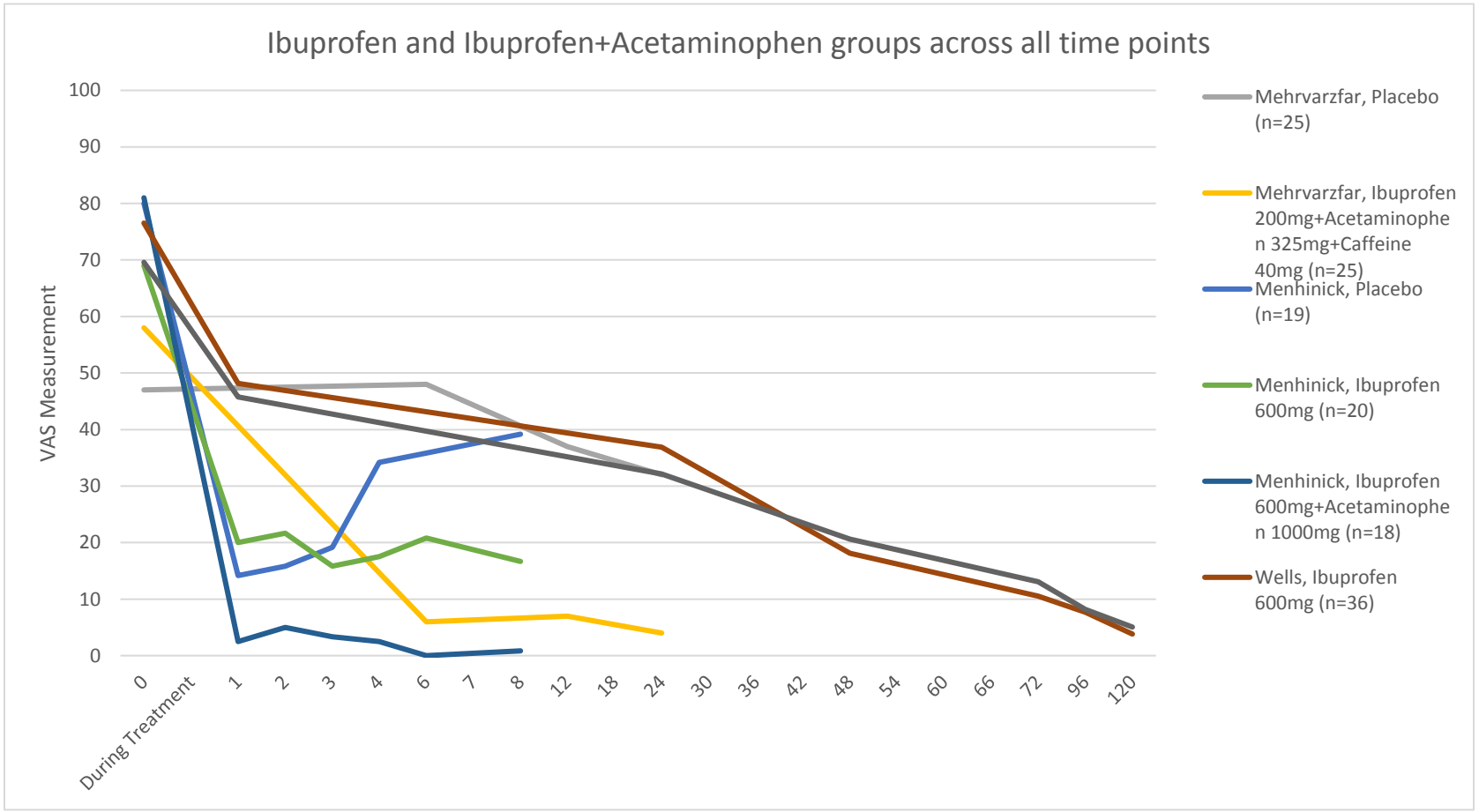


Figure 10. Line graphs of ibuprofen plus acetaminophen over time

A. Separate trials



B. *Mean ibuprofen+acetaminophen and mean placebo*

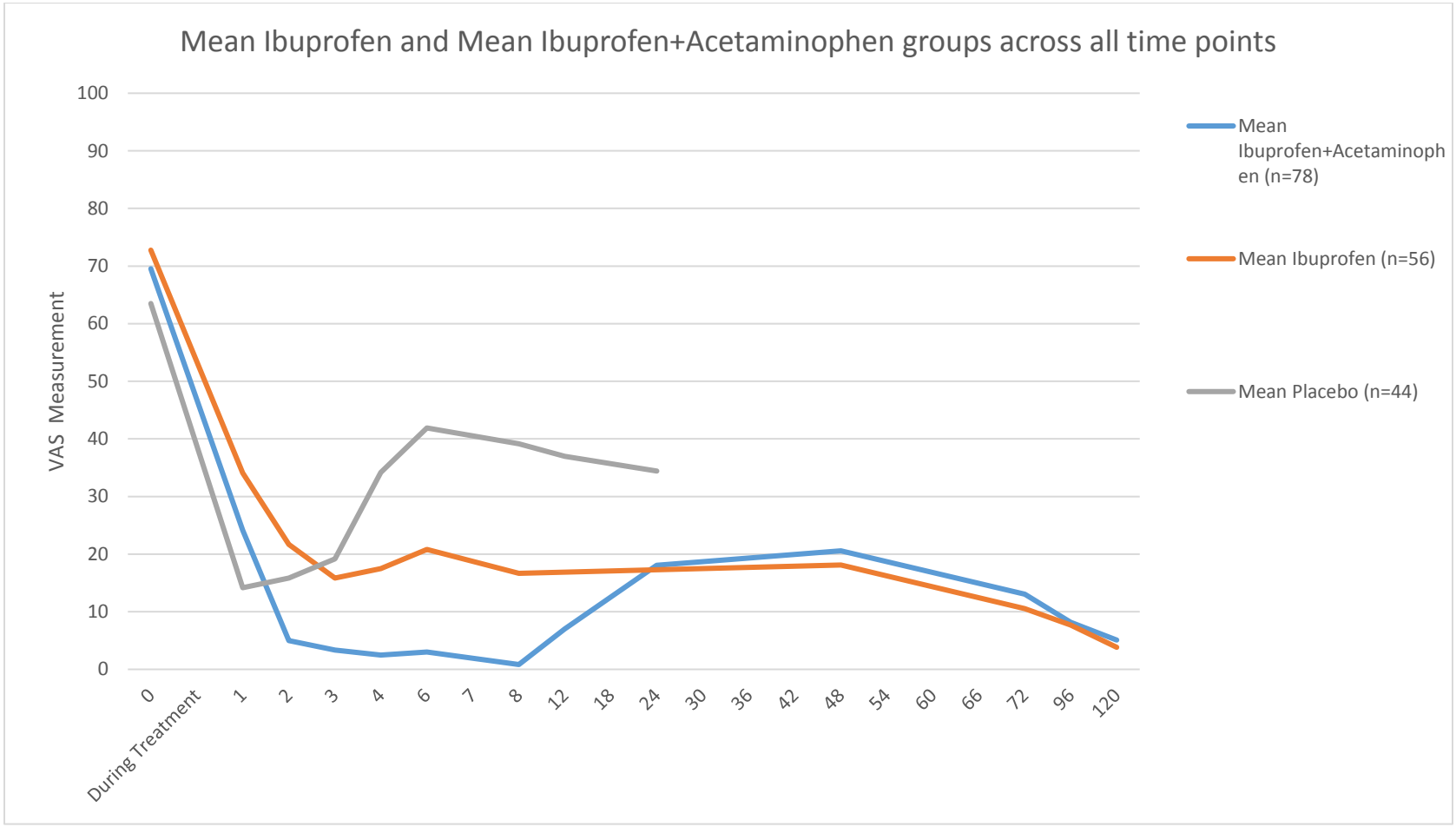
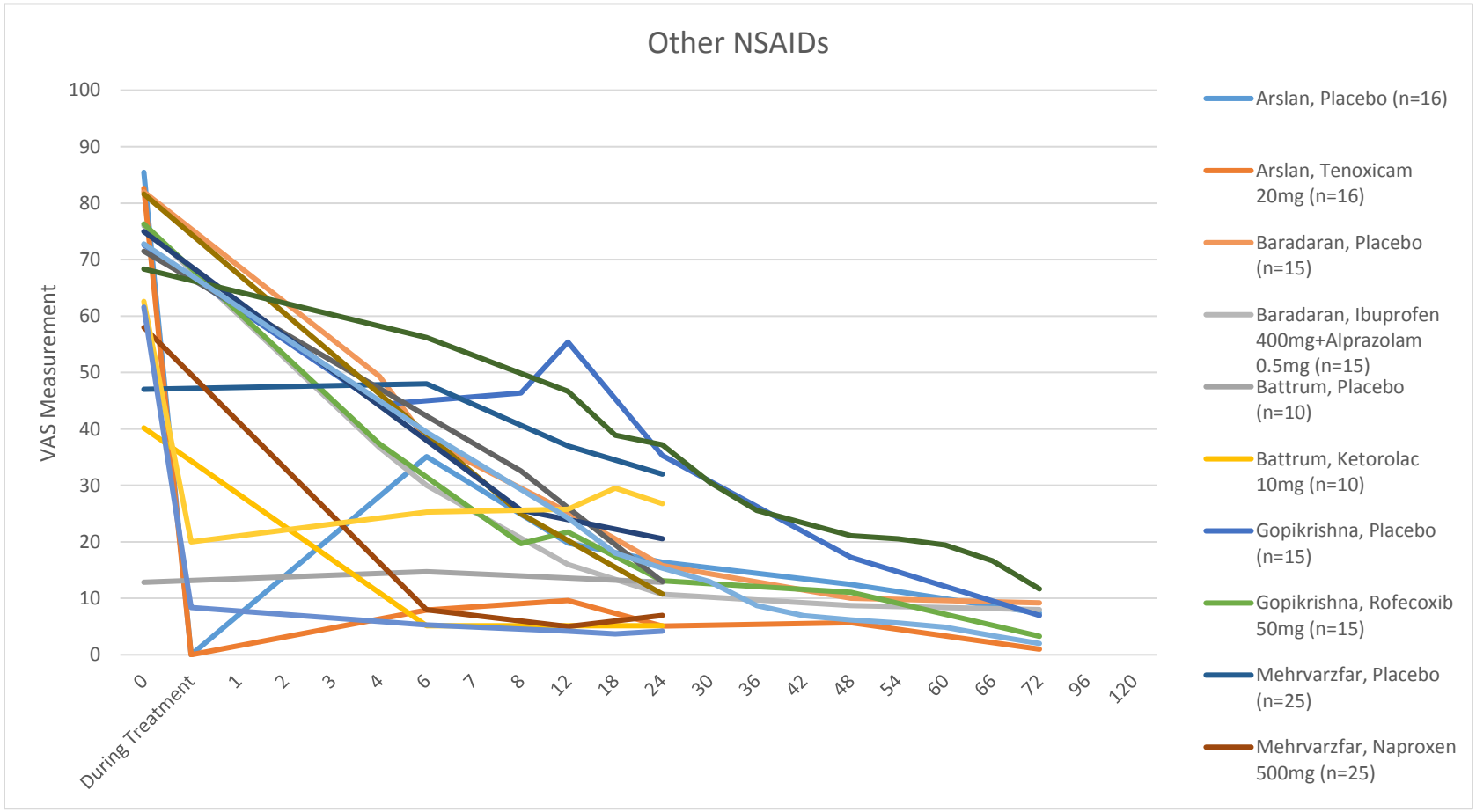


Figure 11. Line graphs of other NSAIDs over time

A. Separate trials



B. Mean other NSAIDs and mean placebo

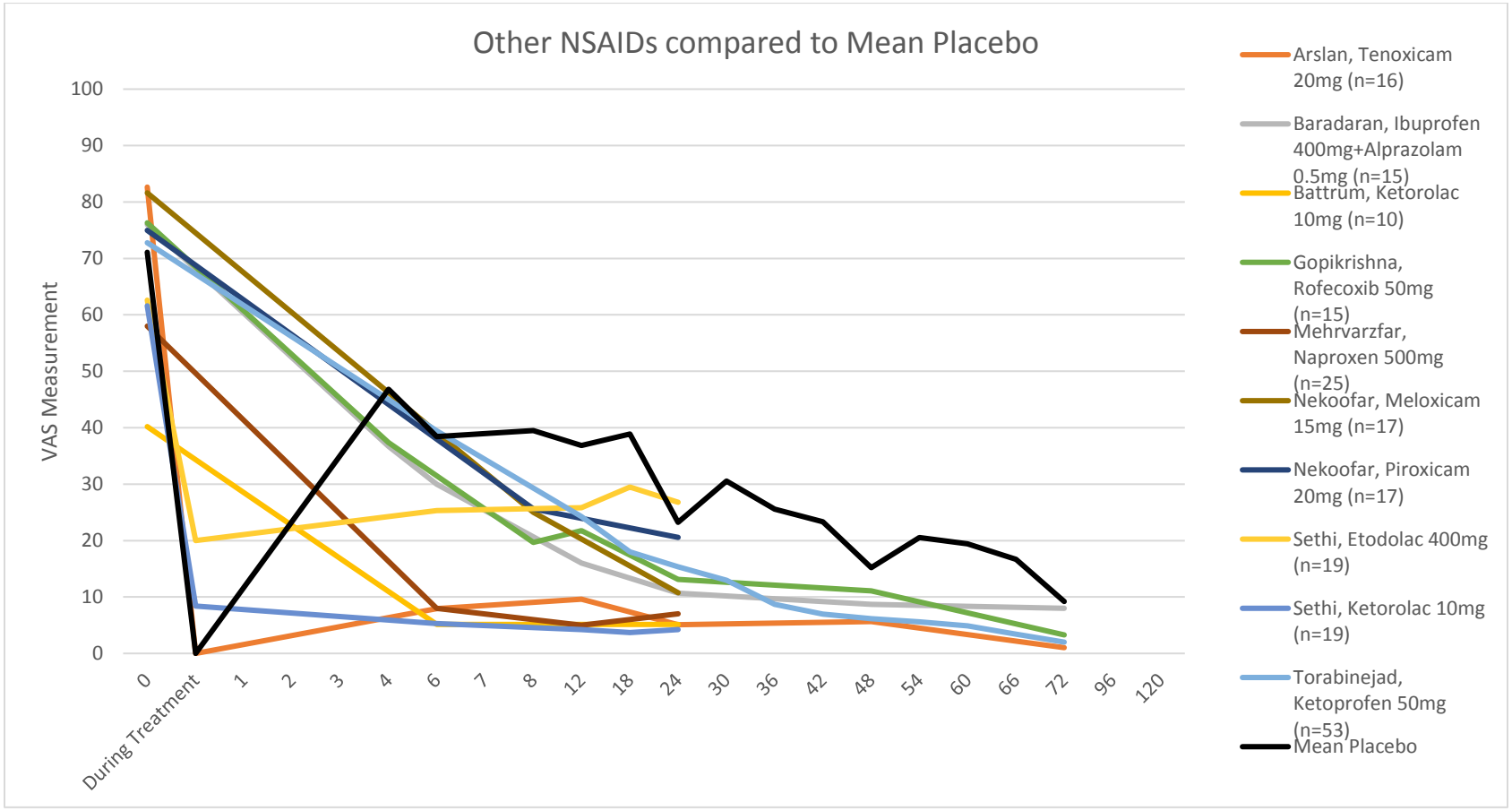
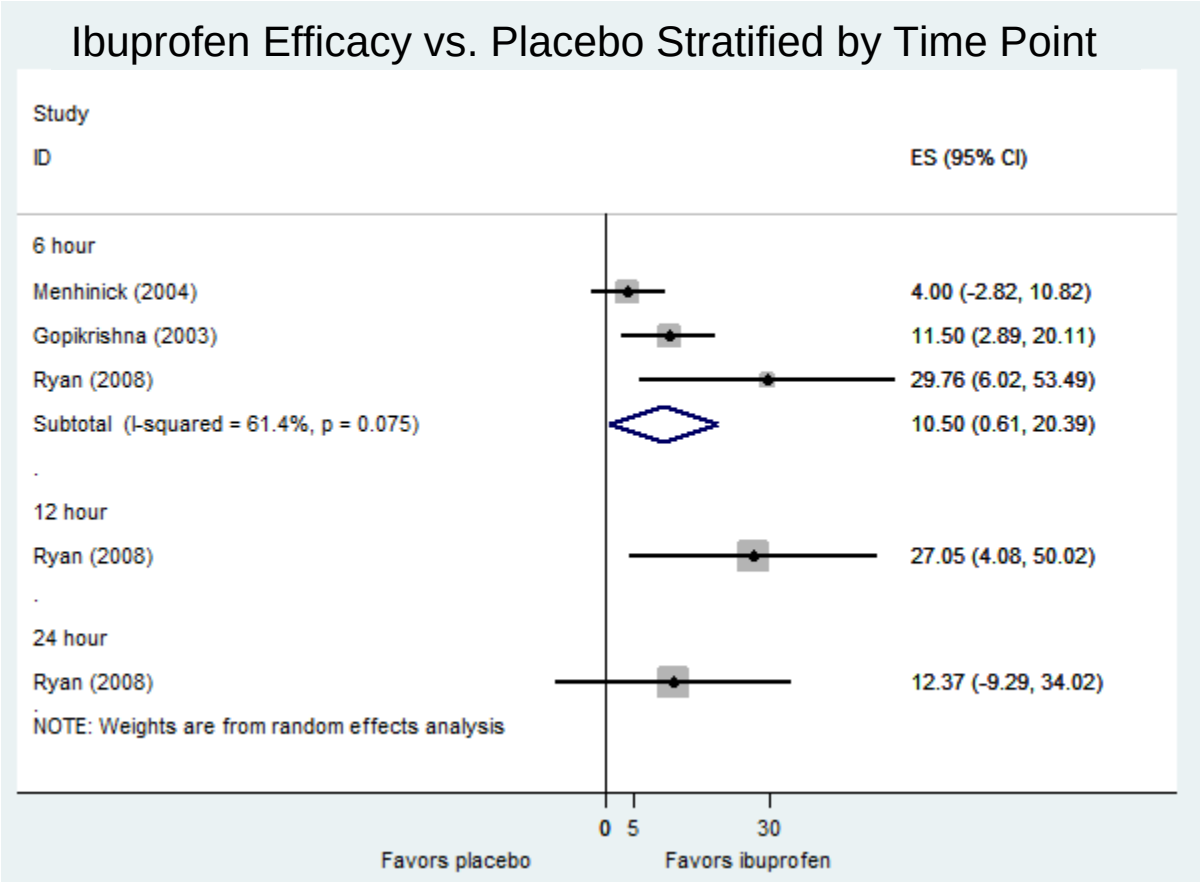


Figure 12. Forest plot of ibuprofen vs. placebo stratified by time point



Study	ES	[95% Conf.	Interval]
6 hour			
Menhinick (2004)	4.000	-2.821	10.821
Gopikrishna (2003)	11.500	2.889	20.111
Ryan (2008)	29.758	6.023	53.494
Sub-total			
D+L pooled ES	10.501	0.614	20.388

Test(s) of heterogeneity:

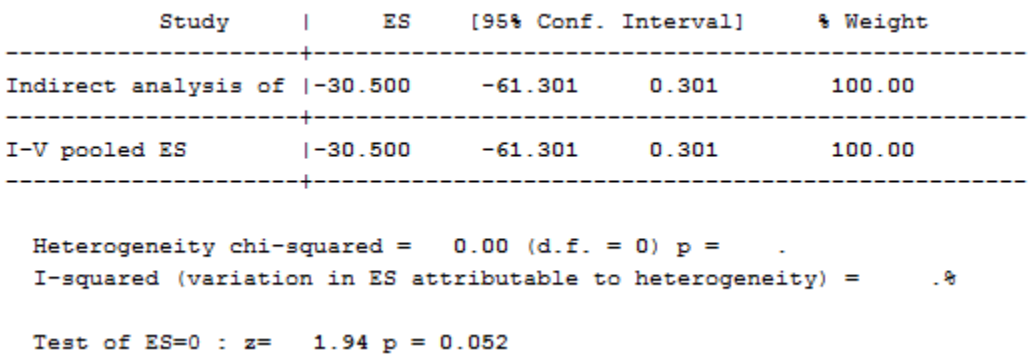
	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
6 hour	5.18	2	0.075	61.4%	43.2791

** I-squared: the variation in ES attributable to heterogeneity)

Significance test(s) of ES=0

6 hour z= 2.08 p = 0.037

Figure 13. Indirect analysis of naproxen vs. ibuprofen at 6 hours

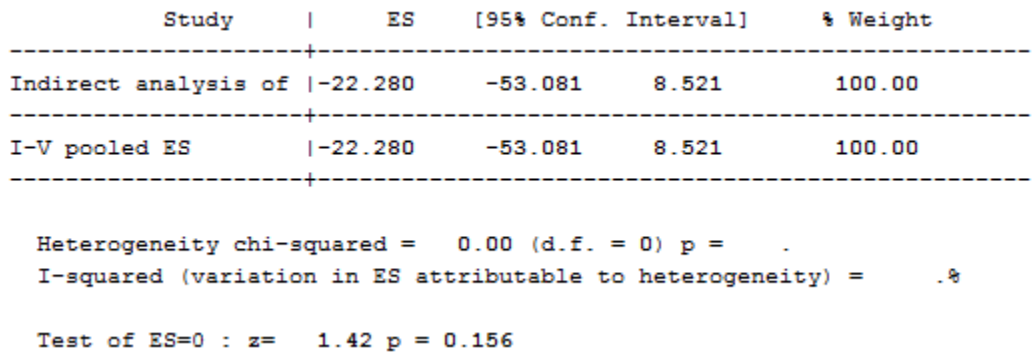


Study	ES	[95% Conf.	Interval]	% Weight
Indirect analysis of	-30.500	-61.301	0.301	100.00
I-V pooled ES	-30.500	-61.301	0.301	100.00

Heterogeneity chi-squared = 0.00 (d.f. = 0) p = .
I-squared (variation in ES attributable to heterogeneity) = .%

Test of ES=0 : z= 1.94 p = 0.052

Figure 14. Indirect analysis of ketoprofen vs. ibuprofen at 6 hours

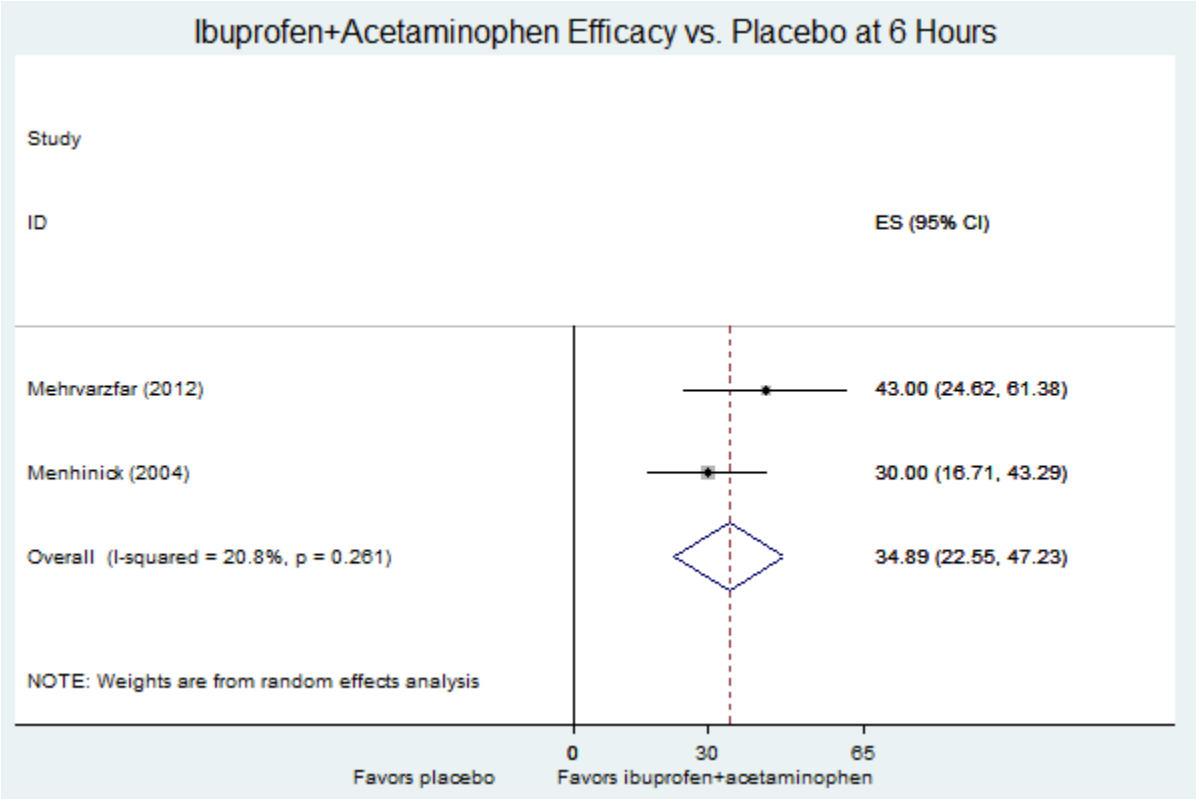


```
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Indirect analysis of |-22.280     -53.081     8.521         100.00
---------------------+---------------------------------------------------
I-V pooled ES        |-22.280     -53.081     8.521         100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =     .
  I-squared (variation in ES attributable to heterogeneity) =     .%

  Test of ES=0 : z=   1.42 p = 0.156
```

Figure 15. Forest plot of ibuprofen+acetaminophen vs. placebo at 6 hours

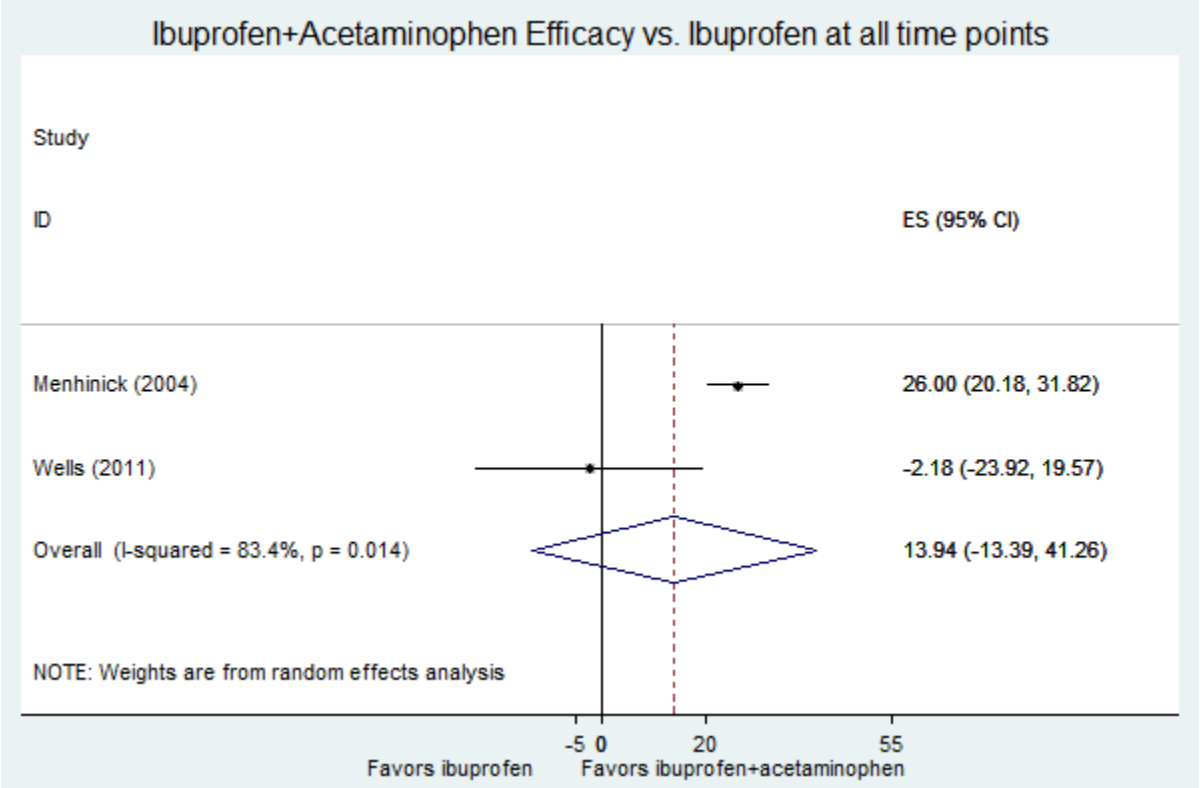


Study	ES	[95% Conf.	Interval]
Mehrvarzfar (2012)	43.000	24.624	61.376
Menhinick (2004)	30.000	16.706	43.294
D+L pooled ES	34.888	22.546	47.231

Heterogeneity chi-squared = 1.26 (d.f. = 1) p = 0.261
I-squared (variation in ES attributable to heterogeneity) = 20.8%
Estimate of between-study variance Tau-squared = 17.5436

Test of ES=0 : z= 5.54 p = 0.000

Figure 16. Forest plot of ibuprofen+acetaminophen vs. ibuprofen at all time points



Study	ES	[95% Conf.	Interval]
Menhinick (2004)	26.000	20.179	31.821
Wells (2011)	-2.176	-23.919	19.566
D+L pooled ES	13.939	-13.386	41.264

Heterogeneity chi-squared = 6.02 (d.f. = 1) p = 0.014
I-squared (variation in ES attributable to heterogeneity) = 83.4%
Estimate of between-study variance Tau-squared = 331.0157

Test of ES=0 : z= 1.00 p = 0.317

Appendix A. Search Strategy

1. ibuprofen.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
2. advil.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
3. motrin.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
4. flurbiprofen.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
5. ansaid.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
6. froben.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
7. aspirin.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
8. combunox.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
9. vicodin.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
10. ultracet.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
11. tramadol.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
12. ultram.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
13. ketoprofen.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
14. orudis.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
15. actron.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
16. oruvail.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
17. ketorolac.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
18. toradol.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
19. etoricoxib.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
20. arcoxia.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
21. etodolac.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
22. lodine.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
23. rofecoxib.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
24. vioxx.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
25. meloxicam.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
26. mobic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
27. celecoxib.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
28. celebrex.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
29. naproxen.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
30. aleve.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
31. naprosyn.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
32. NSAID.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
33. non steroidal anti inflammatory.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
34. nonsteroidal anti-inflammatory.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
35. dent$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
36. endod$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
37. teeth.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
38. tooth.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, kw, tx, ct]
39. 35 or 36 or 37 or 38
40. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
41. 39 and 40

Appendix B. Excluded studies

The following full-text publications were considered for inclusion but failed to meet the criteria for this review.

2=ineligible population, 3=ineligible intervention, 4=ineligible outcome, 5=ineligible study design

	Excluded studies	Exclusion code
1.	Abbas SM, Kamal RS, Afshan G. Effect of ketorolac on postoperative pain relief in dental extraction cases--a comparative study with pethidine. JPMA - Journal of the Pakistan Medical Association 2004;54(6):319-322.	2
2.	Acs G, Moore PA, Needleman HL, Shusterman S. The incidence of post-extraction pain and analgesic usage in children. Anesthesia Progress 1986;33(3):147-151.	2
3.	Afzal Z, Esposito M, Weil K, Worthington HV, van Wijk A, Hooper L, et al. Ibuprofen for pain relief after surgical removal of lower wisdom teeth. Cochrane Database of Systematic Reviews 2013(9).	2
4.	Ahlstrom U, Bakshi R, Nilsson P, Wahlander L. The analgesic efficacy of diclofenac dispersible and ibuprofen in postoperative pain after dental extraction. European Journal of Clinical Pharmacology 1993;44(6):587-588.	2
5.	Ahlstrom U, Kahnberg KE, Roos BE. Pentazocine and aspirin for pain following oral surgery. Acta Pharmacologica et Toxicologica 1974;35(4):325-336.	2
6.	Ahlstrom U, Lantz B. A comparison between dextro propoxyphene hydrochloride and acetyl salicylic acid as analgesics after oral surgery. Odontologisk Revy 1968;19(1):55-63.	2
7.	Ahmad N, Grad HA, Haas DA, Aronson KJ, Jokovic A, Locker D. The efficacy of nonopioid analgesics for postoperative dental pain: a meta-analysis. Anesthesia Progress 1997;44(4):119-126.	5
8.	Akural EI, Jarvimaki V, Lansineva A, Niinimaa A, Alahuhta S. Effects of combination treatment with ketoprofen 100 mg + acetaminophen 1000 mg on postoperative dental pain: a single-dose, 10-hour, randomized, double-blind, active- and placebo-controlled clinical trial. Clinical Therapeutics 2009;31(3):560-568.	2
9.	Alpaslan C, Alpaslan G, Ugar D. Postoperative pain control by single doses of piroxicam administered sublingually and aspirin. Journal of Marmara University Dental Faculty 1997;2(4):658-664.	3
10.	Al-Sukhun J, Al-Sukhun S, Penttila H, Ashammakhi N, Al-Sukhun R. Preemptive analgesic effect of low doses of celecoxib is superior to low doses of traditional nonsteroidal anti-inflammatory drugs. Journal of Craniofacial Surgery 2012;23(2):526-529.	2
11.	Altman RD. A rationale for combining acetaminophen and NSAIDs for mild-to-moderate pain. Clinical & Experimental Rheumatology 2004;22(1):110-117.	2

12.	Amabile CM, Spencer AP. Parecoxib for parenteral analgesia in postsurgical patients. Annals of Pharmacotherapy 2004;38(5):882-886.	3
13.	Aoki T, Yamaguchi H, Naito H, Shiiki K, Izawa K, Ota Y, et al. Premedication with cyclooxygenase-2 inhibitor meloxicam reduced postoperative pain in patients after oral surgery. International Journal of Oral & Maxillofacial Surgery 2006;35(7):613-617.	2
14.	Arafa AS, El-Kerdawy H, Hafez N, El-Agati A. A comparative study of the efficacy and tolerability of parecoxib, tramadol, and parecoxib plus tramadol for postoperative pain management after oral surgery. Egyptian Journal of Anaesthesia 2004;20(3):283-290.	3
15.	Ashley PF, Parekh S, Moles DR, Anand P, Behbehani A. Preoperative analgesics for additional pain relief in children and adolescents having dental treatment. Cochrane Database of Systematic Reviews 2012;9:CD008392.	2
16.	Atbaei A, Mortazavi N. Prophylactic intraligamentary injection of piroxicam (feldene) for the management of post-endodontic pain in molar teeth with irreversible pulpitis. Australian Endodontic Journal: the Journal of the Australian Society of Endodontology 2012;38(1):31-35.	3
17.	Averbuch M, Katzper M. A search for sex differences in response to analgesia. Archives of Internal Medicine 2000;160(22):3424-3428.	2
18.	Averbuch M, Katzper M. Baseline pain and response to analgesic medications in the postsurgery dental pain model. Journal of Clinical Pharmacology 2000;40(2):133-137.	2
19.	Bagan JV, Lopez Arranz JS, Valencia E, Santamaria J, Eguidazu I, Horas M, et al. Clinical comparison of dexketoprofen trometamol and dipyrone in postoperative dental pain. Journal of Clinical Pharmacology 1998;38(12 Suppl):55S-64S.	2
20.	Bailey E, Worthington H, Coulthard P. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth, a Cochrane systematic review. British Dental Journal 2014;216(8):451-455.	2
21.	Balaban FS, Skidmore AE, Griffin JA. Acute exacerbations following initial treatment of necrotic pulps. J Endod 1984;10(2):78-81.	3
22.	Balani M, Gawade P, Maheshgauri S, Ghole S, Shinde V, Sathe V. Results of two multicentric, comparative, randomized, parallel group clinical trials to evaluate the efficacy and safety of dexketoprofen trometamol in the treatment of dental pain and dysmenorrhoea in Indian patients. Journal of Clinical and Diagnostic Research 2008;2(5):1086-1091.	2
23.	Bannwarth B, Berenbaum F. Clinical pharmacology of lumiracoxib, a second-generation cyclooxygenase 2 selective inhibitor. Expert Opinion on Investigational Drugs 2005;14(4):521-533.	2
24.	Barden J, Derry S, McQuay HJ, Moore AR. Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2011(11).	2

25.	Barroso AB, Lima V, Guzzo GC, Moraes RA, Vasconcellos MC, Bezerra MM, et al. Efficacy and safety of combined piroxicam, dexamethasone, orphenadrine, and cyanocobalamin treatment in mandibular molar surgery. Brazilian Journal of Medical & Biological Research 2006;39(9):1241-1247.	2
26.	Bauduin H, Famaey JP. A double blind, randomized study of short versus long acting ibuprofen using a dental pain model. J Pharm Care Pain Symptom Control 1994;2(1):5-16.	2
27.	Bauduin H, Famaey JP. Comparison of the analgesic effects of beta-cyclodextrin-piroxicam, sodium naproxen, and potassium diclofenac utilizing the dental pain model. Journal of Pharmaceutical Care in Pain and Symptom Control 1995;3(2):19-29.	2
28.	Baygin O, Tuzuner T, Isik B, Kusgoz A, Tanriver M. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. International Journal of Paediatric Dentistry 2011;21(4):306-313.	2
29.	Beaver WT. Review of the analgesic efficacy of ibuprofen. International Journal of Clinical Practice 2003;Supplement.(135):13-17.	2
30.	Beaver WT, Forbes JA, Shackleford RW. A method for the 12-hour evaluation of analgesic efficacy in outpatients with postoperative oral surgery pain. Three studies of diflunisal. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 1983;3(2 Pt 2):23S-37S.	2
31.	Becker DE. Considerations for selecting effective analgesic regimens in dental practice. General Dentistry 1992;40(2):111-116.	5
32.	Becker DE, Phero JC. Drug therapy in dental practice: nonopioid and opioid analgesics. Anesthesia Progress 2005;52(4):140-149.	5
33.	Bellamy N. Etodolac in the management of pain: a clinical review of a multipurpose analgesic. Inflammopharmacology 1997;5(2):139-152.	5
34.	Benvenuti C, Beretta A, Longoni A, Pickvance NJ. A multi-centre general practice study evaluating the efficacy and tolerance of ibuprofen in common painful conditions. Pharmatherapeutica 1984;4(1):9-12.	2
35.	Betancourt JW, Kupp LI, Jasper SJ, Farooqi OA. Efficacy of ibuprofen-hydrocodone for the treatment of postoperative pain after periodontal surgery. Journal of Periodontology 2004;75(6):872-876.	2
36.	Biddle C. Meta-analysis of the effectiveness of nonsteroidal anti-inflammatory drugs in a standardized pain model. AANA journal 2002;70(2):111-114.	5
37.	Bjornsson GA, Haanaes HR, Skoglund LA. Ketoprofen 75 mg qid versus acetaminophen 1000 mg qid for 3 days on swelling, pain, and other postoperative events after third-molar surgery. Journal of Clinical Pharmacology 2003;43(3):305-314.	2
38.	Bjornsson MA, Simonsson US. Modelling of pain intensity and informative dropout in a dental pain model after naproxcinod, naproxen and placebo administration. British Journal of Clinical Pharmacology 2011;71(6):899-906.	2

39.	Bjornsson MA, Simonsson USH. Modelling of pain intensity and informative dropout in a dental pain model after naproxcinod, naproxen and placebo administration. British journal of clinical pharmacology 2011;71(6):899-906.	2
40.	Black JA, Liu S, Tanaka M, Cummins TR, Waxman SG. Changes in the expression of tetrodotoxin-sensitive sodium channels within dorsal root ganglia neurons in inflammatory pain. Pain 2004;108(3):237-247.	2
41.	Black P, Max MB, Desjardins P, Norwood T, Ardia A, Pallotta T. A randomized, double-blind, placebo-controlled comparison of the analgesic efficacy, onset of action, and tolerability of ibuprofen arginate and ibuprofen in postoperative dental pain. Clinical Therapeutics 2002;24(7):1072-1089.	2
42.	Bloomquist DS. Pain control in endodontics. Dental Clinics of North America 1979;23(4):543-553.	5
43.	Boerlin V, Maeglin B, Hagler W, Kuhn M, Nuesch E. Analgesic activity of propyphenazone in patients with pain following oral surgery. European Journal of Clinical Pharmacology 1986;31(2):127-131.	2
44.	Bonnefont J, Daulhac L, Etienne M, Chapuy E, Mallet C, Ouchchane L, et al. Acetaminophen recruits spinal p42/p44 MAPKs and GH/IGF-1 receptors to produce analgesia via the serotonergic system. Molecular pharmacology 2007;71(2):407-415.	5
45.	Borel JF, Deschaumes C, Devoize L, Huard C, Orliaguet T, Dubray C, et al. [Treating pain after dental surgery: a randomised, controlled, double-blind trial to assess a new formulation of paracetamol, opium powder and caffeine versus tramadol or placebo]. Presse Medicale 2010;39(5):e103-111.	2
46.	Bracco P, Debernardi C, Coscia D, Pasqualini D, Pasqualicchio F, Calabrese N. Efficacy of rofecoxib and nimesulide in controlling postextraction pain in oral surgery: a randomised comparative study. Current Medical Research & Opinion 2004;20(1):107-112.	2
47.	Breivik EK, Barkvoll P, Skovlund E. Combining diclofenac with acetaminophen or acetaminophen-codeine after oral surgery: a randomized, double-blind single-dose study. Clinical pharmacology and therapeutics 1999;66(6):625-635.	2
48.	Bridgman JB, Gillgrass TG, Zacharias M. The absence of any pre-emptive analgesic effect for non-steroidal anti-inflammatory drugs. British Journal of Oral & Maxillofacial Surgery 1996;34(5):428-431.	2
49.	Broome IJ, Robb HM, Raj N, Girgis Y, Wardall GJ. The use of tramadol following day--case oral surgery. Anaesthesia 1999;54(3):289-292.	2
50.	Brown JD, Daniels SE, Bandy DP, Ko AT, Gammaitoni A, Mehta A, et al. Evaluation of multiday analgesia with etoricoxib in a double-blind, randomized controlled trial using the postoperative third-molar extraction dental pain model. Clinical Journal of Pain 2013;29(6):492-498.	2
51.	Bubani G. The analgesic activity and tolerability of Aceclofenac in the treatment of odontalgia. A double-blind placebo-controlled evaluation. Clinical-Trials-Journal 1988;25(4):244-253.	2

52.	Bulley S, Derry S, Moore AR, McQuay HJ. Single dose oral rofecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2010(12).	5
53.	Bunczak-Reeh MA, Hargreaves KM. Effect of inflammation on the delivery of drugs to dental pulp. Journal of Endodontics 1998;24(12):822-825.	5
54.	Butler SH, Colpitts YH, Gagliardi GJ, Chen AC, Chapman CR. Opiate analgesia and its antagonism in dental event-related potentials: evidence for placebo antagonism. Psychopharmacology 1983;79(4):325-328.	5
55.	Buvanendran A, Barkin R. Lumiracoxib. Drugs of Today 2007;43(3):137-147.	5
56.	Caviedes-Bucheli J, Munoz HR, Azuero-Holguin MM, Ulate E. Neuropeptides in dental pulp: the silent protagonists. J Endod 2008;34(7):773-788.	5
57.	Chalini S, Raman U. Comparative efficacy of aceclofenac and etoricoxib in post extraction pain control: randomized control trial. Indian Journal of Dental Research 2005;16(2):47-50.	2
58.	Chang DJ, Bird SR, Bohidar NR, King T. Analgesic efficacy of rofecoxib compared with codeine/acetaminophen using a model of acute dental pain. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics 2005;100(4):e74-80.	3
59.	Chang DJ, Desjardins PJ, Chen E, Polis AB, McAvoy M, Mockoviak SH, et al. Comparison of the analgesic efficacy of rofecoxib and enteric-coated diclofenac sodium in the treatment of postoperative dental pain: a randomized, placebo-controlled clinical trial. Clinical Therapeutics 2002;24(4):490-503.	2
60.	Chang DJ, Desjardins PJ, King TR, Erb T, Geba GP. The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial. Anesthesia and analgesia;99(3):807-815.	2
61.	Chang DJ, Desjardins PJ, King TR, Erb T, Geba GP. The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial.[Erratum appears in Anesth Analg. 2005 Sep;101(3):644]. Anesthesia & Analgesia 2004;99(3):807-815, table of contents.	5
62.	Chang DJ, Fricke JR, Bird SR, Bohidar NR, Dobbins TW, Geba GP. Rofecoxib versus codeine/acetaminophen in postoperative dental pain: a double-blind, randomized, placebo- and active comparator-controlled clinical trial. Clinical Therapeutics 2001;23(9):1446-1455.	2
63.	Chavez ML, DeKorte CJ. Valdecoxib: a review. Clinical Therapeutics 2003;25(3):817-851.	5
64.	Cheer SM, Goa KL. Parecoxib (parecoxib sodium). Drugs 2001;61(8):1133-1141; discussion 1142-1133.	5
65.	Chen LC, Elliott RA, Ashcroft DM. Systematic review of the analgesic efficacy and tolerability of COX-2 inhibitors in post-operative pain control. Journal of Clinical Pharmacy & Therapeutics 2004;29(3):215-229.	5
66.	Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. Drugs 1996;51(5):713-737.	5

67.	Cheung R, Krishnaswami S, Kowalski K. Analgesic efficacy of celecoxib in postoperative oral surgery pain: a single-dose, two-center, randomized, double-blind, active- and placebo-controlled study. Clinical Therapeutics 2007;29 Suppl:2498-2510.	2
68.	Chopra D, Rehan HS, Mehra P, Kakkar AK. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of paracetamol, serratiopeptidase, ibuprofen and betamethasone using the dental impaction pain model. International Journal of Oral & Maxillofacial Surgery 2009;38(4):350-355.	2
69.	Christensen KS, Cawkwell GD. Valdecoxib versus rofecoxib in acute postsurgical pain: results of a randomized controlled trial. Journal of Pain & Symptom Management 2004;27(5):460-470.	2
70.	Cicconetti A, Bartoli A, Ripari F, Ripari A. COX-2 selective inhibitors: a literature review of analgesic efficacy and safety in oral-maxillofacial surgery. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics 2004;97(2):139-146.	2
71.	Clark MS, Lindenmuth JE, Silverstone LM, Fryer GE, Jr. A double-blind single-dose evaluation of the relative analgesic efficacy and safety of carprofen in the treatment of postoperative pain after oral surgery. Oral Surgery, Oral Medicine, Oral Pathology 1989;68(3):273-278.	2
72.	Clarke R, Derry S, Moore AR. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2014(5).	2
73.	Clem WH. Posttreatment endodontic pain. J Am Dent Assoc 1970;81(5):1166-1170.	5
74.	Collins M, Young I, Sweeney P, Fenn GC, Stratford ME, Wilson A, et al. The effect of tramadol on dento-alveolar surgical pain. British Journal of Oral & Maxillofacial Surgery 1997;35(1):54-58.	2
75.	Cooper SA. Models for clinical assessment of oral analgesics. American Journal of Medicine 1983;75(5A):24-29.	5
76.	Cooper SA. The relative efficacy of ibuprofen in dental pain. The Compendium of continuing education in dentistry 1986;7(8):578, 580-571, 584-578 passim.	5
77.	Cooper SA. Review of ketoprofen. Journal of Clinical Dentistry 1988;1(1):1-5.	5
78.	Cooper SA. Treating acute pain: do's and don'ts, pros and cons. J Endod 1990;16(2):85-91.	5
79.	Cooper SA, Berrie R, Cohn P. Comparison of ketoprofen, ibuprofen, and placebo in a dental surgery pain model. Advances in therapy 1988;5(3):43-53.	2
80.	Cooper SA, Engel J, Ladov M, Precheur H, Rosenheck A, Rauch D. Analgesic efficacy of an ibuprofen-codeine combination. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 1982;2(3):162-167.	3
81.	Cooper SA, Fielding AF, Lucyk D, Hersh EV, Quinn PD, Betts N, et al. Lornoxicam: Analgesic efficacy and safety of a new oxicam derivative. Advances in Therapy 1996;13(1):67-77.	2

82.	Cooper SA, Hutton C, Reynolds DC, Gallegos LT, Allen C, Marriott JG, et al. Dose-response analgesic activity of meclofenamate sodium in dental pain. Adv 1991;THER. 8(4):157-165.	2
83.	Cooper SA, Itkin A, Zweig B. Comparison of oxaprozin, aspirin, and placebo in a dental impaction pain model. Advances in therapy 1992;9(3):184-194.	2
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The Oregon Health & Science University School of Dentistry

Master of Science in Endodontology Data Sheet

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Major____Endodontology_____ Date of Graduation _6/30/2016__

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Exact Title of Thesis:

___NSAIDs for Managing Post-Operative Endodontic Pain in Patients Who Present With Pre-Operative Pain: A Systematic Review and Meta-Analysis_____

_____

Special Field of the Thesis:

___Endodontology_____

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Previous Degrees

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Chair, Thesis Committee

Brief Summary of Thesis:

This research confirms that there is evidence that ibuprofen and ibuprofen plus acetaminophen combinations provide greater pain relief than placebo after orthograde endodontic treatment. It also emphasizes the needs for increased rigor in endodontic pain research.