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Non-steroidal anti-inflammatory drugs for the common cold (Review)

Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS

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TABLE OF CONTENTS

[Intervention Review]

Non-steroidal anti-inflammatory drugs for the common cold

Soo Young Kim[1], Yoon-Jung Chang[2], Hye Min Cho[3], Ye-Won Hwang[4], Yoo Sun Moon[5]

[1]Department of Family Medicine, Kangdong Sacred Heart Hospital, Seoul, Korea, South. [2]Division of Cancer Control, National Cancer Center, Goyang-si, Korea, South. [3]Infolumi, Seongnam, Korea, South. [4]Department of Family Medicine, Korea University Ansan Hospital, Gyeonggi-Do, Korea, South. [5]Department of Family Medicine, Hallym University College of Medicine, Chunchon Sacred Heart Hospital, Chunchon, Korea, South

Contact: Soo Young Kim, Department of Family Medicine, Kangdong Sacred Heart Hospital, Gil-Dong 445, Gangdong-Gu, Seoul, 134-814, Korea, South. hallymfm@gmail.com, pclove@hallym.or.kr.

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ABSTRACT

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used for the treatment of pain and fever associated with the common cold.

Objectives

To determine the effects of NSAIDs versus placebo (and other treatments) on signs and symptoms of the common cold, and to determine any adverse effects of NSAIDs in people with the common cold.

Search methods

We searched CENTRAL (2015, Issue 4, April), (January 1966 to April week 3, 2015), EMBASE (January 1980 to April 2015), CINAHL (January 1982 to April 2015) and ProQuest Digital Dissertations (January 1938 to April 2015).

Selection criteria

Randomised controlled trials (RCTs) of NSAIDS in adults or children with the common cold.

Data collection and analysis

Four review authors extracted data. We subdivided trials into placebo-controlled RCTs and head-to-head comparisons of NSAIDs. We extracted and summarised data on global analgesic effects (such as reduction of headache and myalgia), non-analgesic effects (such as reduction of nasal symptoms, cough, sputum and sneezing) and side effects. We expressed dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI) and continuous data as mean differences (MD) or standardised mean differences (SMD). We pooled data using the fixed-effect and random-effects models.

Main results

We included nine RCTs with 1069 participants, describing 37 comparisons: six were NSAIDs versus placebo and three were NSAIDs versus NSAIDs. The overall risk of bias in the included studies was mixed. In a pooled analysis, NSAIDs did not significantly reduce the total symptom score (SMD -0.40, 95% CI -1.03 to 0.24, three studies, random-effects model), or duration of colds (MD -0.23, 95% CI -1.75 to 1.29, two studies, random-effects model). For respiratory symptoms, cough did not improve (SMD -0.05, 95% CI -0.66 to 0.56, two studies, random-effects model) but the sneezing score significantly improved (SMD -0.44, 95% CI -0.75 to -0.12, two studies, random-effects model). For outcomes related to the analgesic effects of NSAIDs (headache, ear pain, and muscle and joint pain) the treatment produced significant benefits. The risk of adverse effects was not high with NSAIDs (RR 2.94, 95% CI 0.51 to 17.03, two studies, random-effects model) but it is

difficult to conclude that such drugs are no different from placebo. The quality of the evidence may be estimated as 'moderate' because of imprecision. The major limitations of this review are that the results of the studies are quite diverse and the number of studies for one result is quite small.

Authors' conclusions

NSAIDs are somewhat effective in relieving the discomfort caused by a cold but there is no clear evidence of their effect in easing respiratory symptoms. The balance of benefit and harms needs to be considered when using NSAIDs for colds.

PLAIN LANGUAGE SUMMARY

Non-steroidal anti-inflammatory drugs for the common cold

Review question
We carried out a review on the effects of non-steroidal anti-inflammatory drugs (NSAIDs) for treating pain or respiratory symptoms such as cough associated with the common cold.

Background
The common cold is the most common and widespread illness known to humans. NSAIDs, for example, aspirin, ibuprofen and naproxen, have analgesic (pain-reducing) and antipyretic (fever-reducing) effects. NSAIDs have been widely used for over a century for the treatment of pain and fever associated with the common cold.

Study characteristics
The evidence is current to April 2015. This review found nine studies (1069 participants of both genders, including children, adults and older people from the USA, Japan, Belgium and Denmark) that compared various NSAIDs either with each other or with an inactive substance that has no treatment value (placebo).

Key results
Our findings suggest that NSAIDs may improve most analgesia-related symptoms caused by the common cold (headache, ear pain, and muscle and joint pain), but there is no clear evidence that NSAIDs are effective in improving coughs and runny noses caused by the common cold. Some of the included trials reported gastrointestinal complaints, rash and oedema (fluid retention) in the NSAIDs group.

Quality of the evidence
The quality of the evidence may be estimated as 'moderate' because of imprecision. The major limitations of this review are that the results of the studies are quite diverse and the number of studies for each outcome is quite small.

Conclusion
NSAIDs are somewhat effective in relieving the discomfort caused by a cold but there is no clear evidence of their effect in easing respiratory symptoms. The balance of benefit and harms needs to be considered when using NSAIDs for colds.

Summary of findings for the main comparison. Non-steroidal anti-inflammatory drugs for the common cold

Non-steroidal anti-inflammatory drugs for the common cold

Patient or population: patients with common cold
Settings: community or care facilities or hospital
Intervention: non-steroidal anti-inflammatory drugs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Non-steroidal anti-inflammatory drugs				
Sum of overall symptom score	—	The mean sum of overall symptom score in the intervention groups was **0.4 standard deviations lower** (1.03 lower to 0.24 higher)	—	293 (3 studies)	⊕⊕⊕⊖ **moderate** [1]	—
Duration of colds	—	The mean duration of colds in the intervention groups was **0.23 lower** (0 to 0 higher)	—	214 (2 studies)	⊕⊕⊕⊖ **moderate** [2]	—
Throat irritation score	—	The mean throat irritation score in the intervention groups was **0.01 standard deviations lower** (0.33 lower to 0.3 higher)	—	159 (2 studies)	⊕⊕⊕⊖ **moderate** [2]	—
Headache score	—	The mean headache score in the intervention groups was **0.65 standard deviations lower** (1.11 to 0.19 lower)	—	159 (2 studies)	⊕⊕⊕⊖ **moderate** [2]	—
Score of pain in muscles/joints score	—	The mean pain in muscles/joints score in the intervention groups was **0.40 standard deviations lower** (0.77 to 0.03 lower)	—	0 (2 studies)	See comment	—
Cough score	—	The mean cough score in the intervention groups was **0.05 standard deviations lower** (0.66 lower to 0.56 higher)	—	159 (2 studies)	⊕⊕⊕⊖ **moderate** [2]	—

Rhinorrhoea score	—	The mean rhinorrhoea score in the intervention groups was **0.03 standard deviations higher** (0.25 lower to 0.3 higher)	—	199 (3 studies)	⊕⊕⊕⊝ **moderate** [2]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]# NSAIDs group 141, placebo group 152.
[2]Too small sample size.

BACKGROUND

Description of the condition

The common cold is an acute respiratory tract infection (ARTI) and is the most common and widespread illness known to humans, affecting all age groups. Young children suffer an average of six to eight colds a year, while adults experience approximately two to four colds a year. Although the common cold is usually mild, with symptoms lasting one to two weeks, it is a leading cause of medical visits and days missed from school and work (Heikkinen 2003). Nasal congestion, rhinorrhoea, sneezing and coughing accompanied by general malaise are typical symptoms of the common cold. Over 200 serologically different viral types are responsible for common colds, with the rhinovirus being the most common cause (Eccles 2005).

Description of the intervention

Despite ongoing research into antiviral drugs, there are no effective therapies for the prevention or treatment of the common cold. Therefore, treatment of colds is normally aimed at relieving the symptoms of the illness. Several classes of drugs are currently available, including decongestants, anticholinergics, antihistamines and antitussives. These are effective, to a greater or lesser extent, in treating symptoms of the common cold (AlBalawi 2013; De Sutter 2012; Li 2013; Ostberg 1997; Saraswat 2011; Smith 2014).

How the intervention might work

NSAIDs have been widely used for over a century for the treatment of pain and fever associated with the common cold. Despite their widespread present day use and the long medical history of the use of NSAIDs in relieving pain associated with the common cold, there is a lack of clinical data to support the efficacy of NSAIDs treating this condition. There is some evidence that cold symptoms might be the result of inflammatory mediators such as kinins and prostaglandins, which can be blocked by NSAIDs, rather than the result of the direct cytopathic effects of viruses (Eccles 2005; Gwaltney 2002).

Why it is important to do this review

Several studies have proposed that NSAIDs could be effective in alleviating common cold symptoms, including sneezing and coughing (Sperber 1989; Sperber 1992; Winther 2001). However, no consensus has been reached on this issue. This systematic review is an update of a Cochrane review first published in 2009 (Kim 2009).

OBJECTIVES

To determine the effects of NSAIDs versus placebo (and other treatments) on signs and symptoms of the common cold, and to determine any adverse effects of NSAIDs in people with the common cold.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing NSAIDs used either alone or in combination with other medications versus placebo and other therapies for the treatment of signs and symptoms of the common cold in adults and children.

Types of participants

We included adults and children with the common cold, who had no other acute illness or severe, chronic conditions. The case definition of the common cold used was: recent onset of symptoms of runny or stuffy nose (or both), and sneezing, with or without symptoms of headache and cough. We excluded participants if they suffered from allergic rhinitis, had a concurrent lower or chronic respiratory infection or another chronic disease, atopic eczema, asthma, fever (> 38 °C), sinusitis or exudative pharyngitis.

Source populations were volunteers from the community, hospital or community outpatient departments, and primary care settings. We accessed additional evidence from studies of healthy volunteers exposed to rhinovirus in experimental conditions.

Types of interventions

NSAIDs versus placebo as a treatment for symptoms of the common cold. We considered variable doses and routes of administration of the NSAID treatments. We included trials that allowed concurrent use of other medications if they permitted equal access for patients in both the NSAIDs and placebo groups (Ta'i 2012).

Types of outcome measures

We did not consider objective assessments such as rhinometry and rhinoscopy.

Primary outcomes

1. Global evaluation of efficacy in the treatment of common cold symptoms.
2. Decrease in the number or duration of individual common cold symptoms. These symptoms were assessed by severity scale.

Secondary outcomes

1. Any reported side effects.

Search methods for identification of studies

Electronic searches

In the previous review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 1), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to March week 4, 2011), EMBASE (January 1980 to April 2011), CINAHL (January 1982 to April 2011) and ProQuest Digital Dissertations (January 1938 to April 2011).

For 2013 update we searched CENTRAL (2013, Issue 1), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 2011 to March week 4, 2013), EMBASE (January 2011 to April 2013), CINAHL (January 2011 to April 2013) and ProQuest Digital Dissertations (January 2011 to April 2013).

For this 2015 update, we searched CENTRAL (2015, Issue 4, April), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 2013 to April week 3, 2015), EMBASE (January 2013 to April 2015), CINAHL (January 2013 to April 2015) and ProQuest Digital Dissertations (January 2013 to April 2015).

See Appendix 1 and Appendix 2 for the EMBASE and CINAHL search strategies and Appendix 3 for the search strategy used for MEDLINE and CENTRAL. We combined the MEDLINE search terms with the highly sensitive search strategy designed by The Cochrane Collaboration for identifying RCTs (Lefebvre 2011). We adapted these search terms to search EMBASE.

We imposed no language or publication restrictions.

Searching other resources

We assessed non-English language papers and, if necessary and possible, translated them, with the assistance of native language speakers. We searched reference lists of review articles and of all included studies to find other potentially eligible studies. We contacted authors of the included trials to request unpublished studies.

Data collection and analysis

Selection of studies

We used the search strategy detailed above to obtain titles and abstracts of studies that might be relevant to the review. Three review authors (YSM, YJC, YWH) independently screened titles and abstracts and one review author (SYK) collated the results. All review authors participated in resolving discrepancies until a consensus was reached.

Data extraction and management

The same review authors (YSM, YJC, YWH) independently carried out data extraction using standard data extraction forms. We translated studies reported in non-English language journals before assessment. Where more than one publication of one trial existed, we included only the publication with the most complete data. We resolved disagreements by discussion.

Assessment of risk of bias in included studies

Three review authors (YSM, YJC, YWH) independently assessed the methodological quality of included studies using The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011). One review author (SYK) collated the results. All review authors participated in resolving discrepancies until a consensus was reached.

Measures of treatment effect

The effect of NSAIDs on common cold signs and symptoms was our primary measure of interest. We expressed results as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes.

We used the standardised mean difference (SMD) where continuous scales of measurement were used to assess the effects of treatment (for example, mean severity scores and time to symptom relief), because different scales were used in most of the trials.

We summarised adverse effects when reported. We calculated the RR with 95% CI for each adverse effect, where possible, either compared to no treatment or to another treatment.

Unit of analysis issues

We split trials including more than two comparisons and analysed them as individual pair-wise comparisons. By dividing the placebo cases, we ensured that we did not count cases in the placebo group more than once when conducting a meta-analysis. We had no special issues in the analysis of studies with non-standard designs.

Dealing with missing data

We attempted to contact the trial authors for additional information if data from the trial reports were unclear or missing. We have excluded data from the meta-analysis and clearly stated the reason if we judged missing data to render the result uninterpretable.

Assessment of heterogeneity

We assessed heterogeneity amongst trials by using the Chi^2 test for heterogeneity (with a 10% level of statistical significance) and the I^2 statistic.

We considered other sources of heterogeneity, apart from differences in interventions, namely clinical diversity (children/adults, different classes of NSAIDs and different dosages) and study quality. Heterogeneity in treatments could be related to prior agent(s) used, and the agent, dose and duration of the therapy.

Assessment of reporting biases

There were insufficient trials for us to assess the likelihood of publication bias by examining a funnel plot for asymmetry.

Data synthesis

We pooled data using a fixed-effect model if there was no significant heterogeneity (I^2 statistic < 50%). If there was significant heterogeneity (I^2 statistic ≥ 50%), we used the random-effects model.

Subgroup analysis and investigation of heterogeneity

We intended to conduct subgroup analyses where data were available, for example, by age (adult, child), NSAID class and whether the common cold was artificial or natural.

Sensitivity analysis

We pooled data using the fixed-effect model but we also analysed the random-effects model to ensure robustness of the model chosen and susceptibility to outliers.

RESULTS

Description of studies

In the vast majority of studies, the clinical symptoms of the common cold, requirements for inclusion, type and dose of NSAIDs, outcomes of trials and duration of therapy were quite diverse, which caused difficulties in quantitative analysis.

Results of the search

In the previous searches, we identified 60 trials; of these, nine met the inclusion criteria. In this 2015 updated search, we did not identify any potential new trials. All included studies were double-blinded RCTs. Four of the six trials of community-acquired colds were multicentre trials.

Included studies

The nine included studies involved 1069 participants suffering from colds. In six studies, 891 participants had community-

acquired colds, and in three studies, 178 participants were experimentally infected with cold viruses. For experimentally infected colds, inoculated populations were analysed. Only 72.5% of experimentally infected participants had cold symptoms. Therefore, we included non-symptomatic infected participants in this analysis.

Three studies were performed in the USA, four in Japan, and one each in Belgium and Denmark. Trials took place in a total of 154 settings. Most were participants from hospitals, clinics and outpatient departments. One trial involved medical students and university staff. Three trials of experimentally infected colds did not report the trial setting. One trial involved mainly students and two trials reported participants only as volunteers.

Five trials compared NSAIDs with a placebo, three trials compared one NSAID with another, and one trial compared two NSAIDs with a placebo.

Five studies used ibuprofen, two used aspirin and two studies used loxoprofen. Ketoprofen, fenoprofen, fentiazac and naproxen were used in one study. Seven trials used visually identical capsules, one trial used a double-dummy method and one trial used coded vials. The duration of treatment varied from a single dose to two daily doses for seven days.

Three studies used a general symptom score and five studies used a symptom severity score.

The Characteristics of included studies table includes a summary of the randomisation process, cold acquisition route, inclusion criteria, population, interventions and comparisons, outcome measures, adverse events and methodological quality.

Excluded studies

We excluded 51 trials: four studies were not randomised or the randomisation allocation was unclear; one study included febrile participants; 46 studies included participants with diagnoses other than common colds (see Characteristics of excluded studies table).

Risk of bias in included studies

The overall risk of bias in the included studies was mixed, largely due to missing information regarding randomisation procedures. We assessed two studies as being of high quality (Goto 2007; Ryan 1987).

Allocation

Out of the nine included studies (Goto 2007; Graham 1990; Itoh 1980; Katsu 1993; Nagaoka 1980; Ryan 1987; Sperber 1989; Sperber 1992; Winther 2001), two studies used a computer-generated random numbers table to generate the allocation sequence (Goto 2007; Ryan 1987). The remaining studies contained insufficient information about the sequence generation process.

In four studies the allocation method was adequately concealed (Goto 2007; Itoh 1980; Nagaoka 1980; Ryan 1987). In two Japanese studies the randomisation process was carried out by two controllers who retained the key codes (Itoh 1980; Nagaoka 1980). In the remaining two studies, treatment was allocated by a third party (Goto 2007), or considered adequately concealed because the single oral dose was administered using a double-blind method (Ryan 1987).

Blinding

All studies were described as 'double-blind' and considered 'adequate'; either the active drug and placebo were identical, or an 'identical capsule double-dummy' method was used.

Incomplete outcome data

Among the included studies, eight adequately addressed incomplete outcome data (Goto 2007; Graham 1990; Itoh 1980; Nagaoka 1980; Ryan 1987; Sperber 1989; Sperber 1992; Winther 2001). Three experimental rhinovirus cold trials excluded participants who were not infected, in which case the reason for exclusion may be justifiable (Graham 1990; Sperber 1989; Sperber 1992). In six studies the number of withdrawals was zero or very small (Itoh 1980; Nagaoka 1980; Ryan 1987; Sperber 1989; Sperber 1992; Winther 2001). One study had insufficient information to permit judgement of 'low risk' or 'high risk' of bias (Katsu 1993).

Selective reporting

We considered all studies as having 'unclear' risk of bias as all trials failed to include the study protocol. They had insufficient information to permit a judgement of either 'low risk' or 'high risk' of bias.

Other potential sources of bias

Amongst the included studies, none were stopped early or had reported claims of fraudulence against them. One study did not contain data to assess the baseline balance (Winther 2001). The overall quality of studies was mixed, largely due to missing information regarding randomisation procedures (Figure 1; Figure 2).

Figure 1. 'Risk of bias' graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

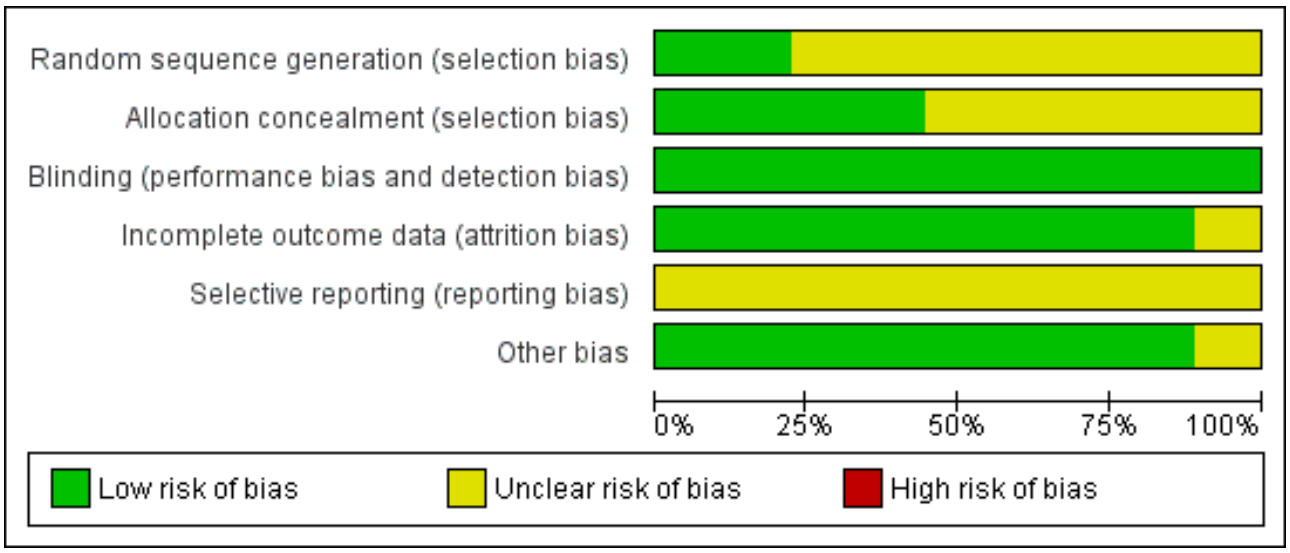
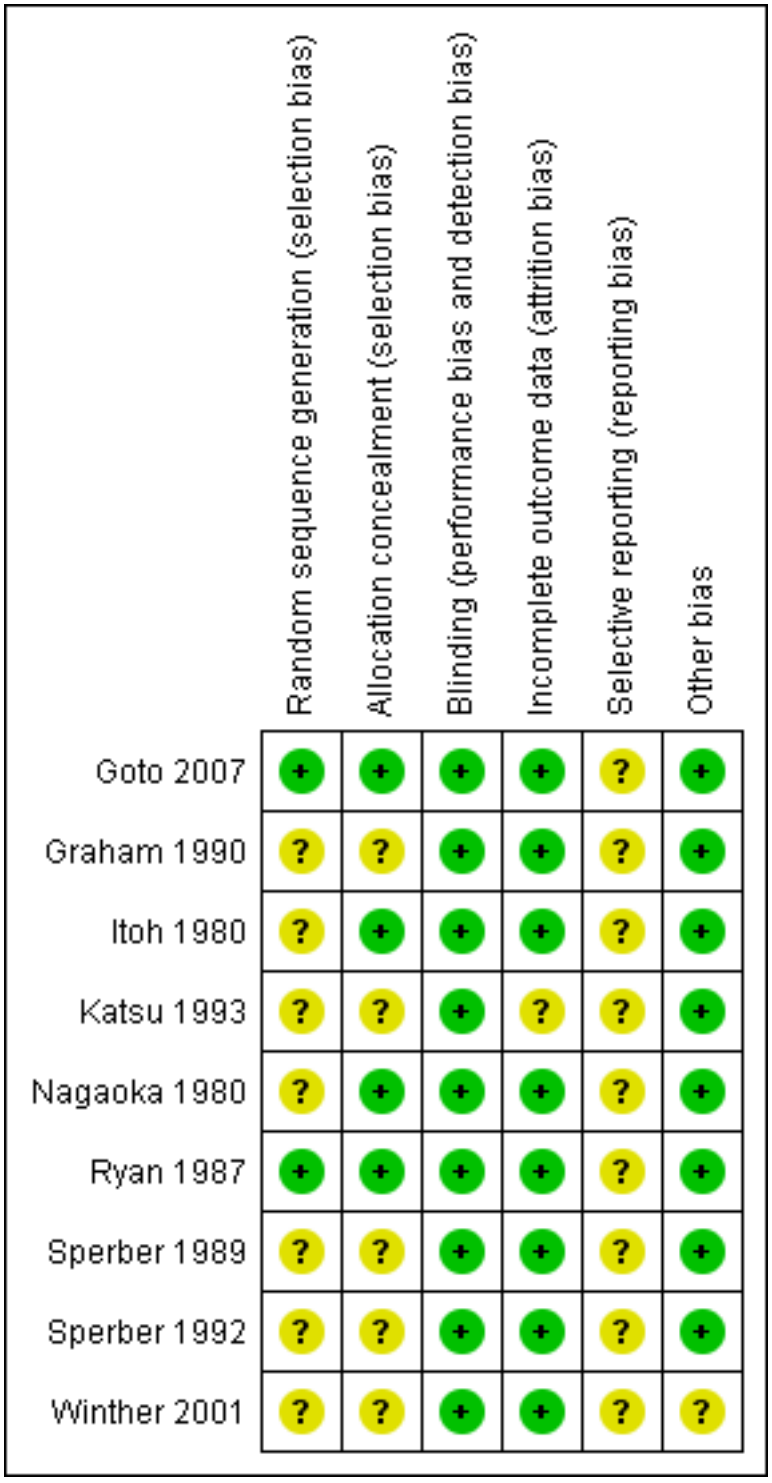


Figure 2. 'Risk of bias' summary: review authors' judgements about each methodological quality item for each included study



Effects of interventions

See: **Summary of findings for the main comparison** Non-steroidal anti-inflammatory drugs for the common cold

In total, we identified 37 outcomes. Eight studies assessed effectiveness and five studies assessed adverse effects. Twenty-one (56.7%) of the 37 outcomes were assessed only by a single trial. Among the 16 outcomes assessed by two trials or more, six outcomes had an I^2 statistic of ≥ 50% (overall symptom score, duration of colds, cough score, headache score, chills score and overall side effects).

Outcomes included in the meta-analyses

One trial reported the daily symptom scores during six post-challenge days and a six-day cumulative symptom score (Sperber 1992). Other trials reported cumulative symptom scores, therefore we included the cumulative symptom score in the meta-analysis for comparison.

One trial reported cumulative symptom scores for individual symptoms, such as rhinorrhoea and nasal obstruction, as well as cumulative symptom scores for individual areas (that is, nasal symptom score) (Sperber 1989). To prevent double counting and to compare data, we included only cumulative symptom scores of individual symptoms in the meta-analysis.

Graham 1990 used aspirin (4 g/day) and ibuprofen (1.2 g/day). The dose of ibuprofen was the usual prescribed dose for the common cold and that of aspirin was not, therefore we chose to use the ibuprofen group in the meta-analysis.

Primary outcomes

1. Global evaluation of efficacy in the treatment of common cold symptoms

i. Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo

Three trials assessed the total symptom score improvement of NSAIDs on the course of the common cold (Goto 2007; Sperber 1989; Sperber 1992). The first trial included 40 young adults and compared the effect of ibuprofen at a dose of 200 mg/four times a day for five days with that of a placebo (Sperber 1989). During six post-challenge days, the daily total symptom score was not significantly different between the two groups. The second trial included 79 young adults and compared naproxen at a dose ranging from 3.0 g to 5.0 g for five days with placebo (Sperber 1992). The total five-day symptom score judged by the modified Jackson criteria was reduced by 29% (95% confidence interval (CI) 16% to 42%) in the naproxen group compared with the placebo group. The third trial included 174 adults and compared the effects of loxoprofen at a dose of 60 mg/twice a day for seven days with placebo (Goto 2007). Duration of illness, number of days with limited daily activities and total symptom score were not significantly different between the two groups. We conducted a meta-analysis of data from the three trials. The results of the pooled analysis were not significant (standardised mean difference (SMD) -0.40, 95% CI -1.03 to 0.24, random-effects model) (Analysis 1.1) and there was heterogeneity (I^2 statistic = 83%).

Two trials assessed the duration of colds (Goto 2007; Sperber 1989). The results of the pooled analysis were not significant (mean difference (MD) -0.23, 95% CI -1.75 to 1.29, random-effects model) (Analysis 1.3) and there was heterogeneity (I^2 statistic = 80%).

One trial assessed the proportion of patients with symptoms of moderate to marked severity; no significant effect was detected (Sperber 1989).

ii. Head-to-head comparisons

Three trials involving participants with natural colds assessed the effect of one NSAID compared to other NSAID and ranked the severity of global symptoms on a five- to seven-point scale; all three trials were performed in Japan (Itoh 1980; Katsu 1993; Nagaoka 1980). Nagaoka 1980, which involved 222 participants, compared fentiazac (300 mg/day) with ibuprofen (600 mg/day). Katsu 1993 involved 167 participants and compared loxoprofen (80 mg/day) with ibuprofen (600 mg/day). Itoh 1980 enrolled 184 participants with upper respiratory tract infections and compared aspirin with ketoprofen. Itoh 1980 reported that there was no statistically significant difference between the groups in a subgroup analysis for the population with common colds, but the estimates and the number of participants included in the study population were not reported. Therefore, we could not use this result in a pooled analysis of efficacy.

Marked improvement and moderate to marked improvement (on a global improvement rating) were significant in only one study (Nagaoka 1980).

2. Decrease in the number or duration of individual common cold symptoms

i. NSAIDs versus placebo: analgesic effects

Two trials measured nine outcomes evaluating the analgesic effects of NSAIDs (Sperber 1992; Winther 2001). The types of NSAIDs and the scale of outcomes differed between these studies.

As mentioned above, Sperber 1992 assessed the effect of naproxen in participants with an experimental cold and reported daily symptom scores and total (five-day) symptom scores. Winther 2001 enrolled 80 participants with natural colds. The effect of ibuprofen at a dose of 400 mg/three times a day for three days was studied and the severity of symptoms was then ranked on a four-point scale (not present, mild, moderate, severe) and a three-day cumulative symptom score was reported.

Firstly, the cumulative throat irritation score was used in two trials (Sperber 1992; Winther 2001). In Sperber 1992, total (five-day) and daily throat scores were not significantly different between the treatment groups. In Winther 2001, the total throat irritation/pain score was not significantly different between the treatment groups. As expected, the results of the pooled analysis were not significant (SMD -0.01, 95% CI -0.33 to 0.30, fixed-effect model) (Analysis 2.1) and there was no heterogeneity.

Secondly, cumulative headache scores were reported in the same two trials (Sperber 1992; Winther 2001). All trials reported that headache scores were significantly lower in the NSAIDs groups than in the placebo groups. In a pooled analysis, NSAIDs significantly reduced headache scores (SMD -0.65, 95% CI -1.11 to -0.19, random-effects model) (Analysis 2.2); there was marginal heterogeneity (I^2 statistic = 51%).

Thirdly, cumulative pain scores in the muscles and joints were also reported in these two trials (Sperber 1992; Winther 2001). In Winther 2001, the pain score in muscles and joints did not differ significantly between the treatment groups. In Sperber 1992, the myalgia score was significantly reduced in the naproxen group. In a pooled analysis, NSAIDs significantly reduced the score for pain in muscles and joints (SMD -0.40, 95% CI -0.77 to -0.03, fixed-effect model) (Analysis 2.3); there was no heterogeneity.

Fourthly, the two studies assessed a cumulative malaise score (Sperber 1992; Winther 2001). All trials reported that the malaise score was not significantly different between the two treatment groups. However, in a pooled analysis there was a trend towards

reduction of malaise (SMD -0.29, 95% CI -0.6 to 0.03, fixed-effect model) (Analysis 2.4).

Fifthly, the two studies assessed a cumulative chills score; the results were mixed. One trial reported a significant reduction (Sperber 1992) and the other reported a significant increase (Winther 2001). In a pooled analysis, the statistical significance of the difference disappeared and heterogeneity was detected (SMD -0.03, 95% CI -1.12 to 1.06, I^2 statistic = 91.5%, random-effects model) (Analysis 2.5).

The cumulative earache score was significantly reduced in the ibuprofen group compared to the placebo group (Winther 2001).

ii. NSAIDs versus placebo: non-analgesic effects

Four trials measured 15 outcomes irrelevant to the analgesic effect (Graham 1990; Sperber 1989; Sperber 1992; Winther 2001). The scales of outcomes were quite diverse. Three trials tested ibuprofen (Graham 1990; Sperber 1989; Winther 2001) and one trial tested naproxen (Sperber 1992).

Firstly, two trials reported a cumulative cough score (Sperber 1992; Winther 2001). In Sperber 1992, the cumulative cough score was not significant (0.8 and 1.6, naproxen and placebo, respectively), but the daily score was significantly reduced at four days (P value < 0.01). Winther 2001 evaluated the cumulative cough score, but there was no difference between the groups. The results of a pooled analysis for cumulative cough score were not significant.

Secondly, two trials evaluated a cumulative sneezing score (Sperber 1992; Winther 2001). In Sperber 1992, the cumulative sneezing score was not significant (1.5 and 2.2, naproxen and placebo, respectively) but daily scores were reduced in the naproxen group at one and four days. The statistically insignificant differences between scores were at two and three days. In Winther 2001, the cumulative sneezing score was significantly reduced in the ibuprofen group, and the result of a pooled analysis supported this effect (SMD -0.44, 95% CI -0.75 to -0.12, the P value of the heterogeneity test was 0.44; fixed-effect model) (Analysis 3.2). Winther also examined the total number of sneezes and the result was significant.

Three trials studied a cumulative rhinorrhoea score and a cumulative nasal obstruction score, and found no differences between the groups (Sperber 1989; Sperber 1992; Winther 2001).

The proportion of nasal obstruction scores greater than five points (Graham 1990), total mucus weight, total tissue count (Sperber 1989), total number of nose blows, cumulative nasal dryness score, cumulative score for reduced sense of smell, cumulative hoarseness score, cumulative fatigue score and cumulative malaise score were quantified in a single study (Winther 2001) and the results were not significantly different between the treatment groups.

The cumulative nose irritation score, cumulative pain on swallowing score and cumulative eye itching score were also not significantly different between the treatment groups (Winther 2001).

Secondary outcomes

1. Any reported side effects

i. NSAIDs versus placebo: adverse effects

Five trials reported adverse effects. One study reported that adverse effects were more frequent in the loxoprofen group (9.5% versus 1.1%, P value < 0.05) (Goto 2007). Otherwise we could not find any evidence of an increased frequency of adverse effects in the active treatment groups. These outcomes included overall side effects, gastrointestinal complaints and other problems such as rash and oedema.

Two trials assessed the overall side effects of NSAIDs and there was moderate heterogeneity (Goto 2007; Sperber 1989). The results of a pooled analysis for overall side effects was not significant (risk ratio (RR) 2.94, 95% CI 0.51 to 17.03, random-effects model) (Analysis 4.1). Three trials reported gastrointestinal adverse effects and found no differences between the groups (Ryan 1987; Sperber 1989; Sperber 1992). Lethargy/drowsiness, feeling hyperactive, feeling more awake, flushed face, difficulty sleeping, light-headedness and dry mouth were reported in one or two trials and the results were not significantly different between the treatment groups.

DISCUSSION

In summary, if non-steroidal anti-inflammatory drugs (NSAIDs) are administered to community-infected or experimentally infected cold patients, their analgesic effect against pain and irritation induced by the cold is relatively effective, but reports on whether they are helpful in relieving respiratory symptoms, such as coughing and sneezing, are not consistent and the evidence is insufficient.

Despite a comprehensive search, only nine studies met the inclusion criteria, six of which were placebo-controlled randomised controlled trials (RCTs) and three of which were head-to-head RCTs. When we evaluated the methodological quality of the included studies using The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011), the overall quality of studies was mixed, largely due to missing information regarding randomisation procedures. We assessed two studies as being of high quality (Goto 2007; Ryan 1987). Our outcomes were mainly subjective and blinding of participants may be critical. All nine studies were described as 'double-blind' and considered 'adequate'.

Among the results used to examine the effect of NSAIDs on the common cold, the ones looking at the analgesic effect evaluated headache, throat irritation, muscle and joint pain, ear pain, malaise and chills. Among them, headache, ear pain and muscle and joint pain showed significant results and malaise showed borderline significance. However, throat irritation was not improved, and chills showed mixed results. For some cases where symptoms did not improve, the reasons were uncertain. Whether the cold was community-acquired or experimentally infected, the trial quality and dose of NSAIDs could not explain the differences. In the case of throat irritation, if the cold was an infection with a rhinovirus, there was the possibility that the treatment was not effective because throat pain disappeared naturally over a short period of time (Heikkinen 2003). There is also the possibility that the mechanism of throat pain may be different from that of headache and muscle pain. In the case of chills, NSAIDs were obviously effective in one trial, but worsened the symptoms in the other trial. Chills are

known to happen mainly when the fever has lowered, therefore the measure of improvement may be different from the other symptoms and depend on whether there was a fever before the administration of treatment or not. However, because there was no information on the body temperature before starting the treatment in the two trials, we cannot draw a conclusion on this matter. Apart from these two symptoms, NSAIDs improved most of the analgesia-related symptoms caused by a cold. Therefore, we recommend the use of NSAIDs for these symptoms.

Three trials studied whether NSAIDs had a comprehensive effect on various symptoms caused by the common cold (Goto 2007; Sperber 1989; Sperber 1992). Two of them were conducted with participants whose cold was experimentally infected by a rhinovirus (Sperber 1989; Sperber 1992). One of those showed a statistically significant difference in the effect of NSAIDs (Sperber 1992), and when we merged the results of the two studies the results were significant. However, one recently published trial reported that the total symptom score showed no significant difference between the two groups (Goto 2007). The results of the pooled analysis were not significant and there was heterogeneity, but the reason for this was unclear.

Among the studies two trials examined whether NSAIDs reduced the duration of a cold (Goto 2007; Sperber 1989). The results of the pooled analysis were not significant and there was heterogeneity. NSAIDs did not have any effect on the severity or duration of a cold. There were only two trials and the number of participants in the studies was small, therefore it is hard to draw a definite conclusion about the effects of NSAIDs on the duration of a cold.

One of the current issues related to the administration of NSAIDs for the common cold is whether NSAIDs are helpful in relieving respiratory symptoms such as cough. Many of the studies on the common cold recommend the administration of NSAIDs to ease coughing caused by a cold (Heikkinen 2003; Irwin 2000). The recently published American College of Chest Physicians (ACCP) guidelines recommend the combined administration of first-generation antihistamine and nasal decongestant or the administration of naproxen for cough caused by a cold (Pratter 2006). Respiratory symptoms examined in this review were cough, nasal discharge and sneezing. The medication was not effective for cough in two trials and pooled results did not show a significant improvement (Sperber 1992; Winther 2001). None of the three trials showed a significant result for nasal discharge, and pooled results were not significant (Sperber 1989; Sperber 1992; Winther 2001). However, in the case of sneezing, one trial showed a significant improvement and pooled results showed a moderate effect (Winther 2001). Considering these results, which differ from existing guidelines, there is no clear evidence that NSAIDs are effective for coughs caused by a cold, or should be recommended in order to ease cough caused by a cold.

NSAIDs draw attention due to their adverse effects. For some NSAIDs, their long-term use increases the risk of cardiovascular disease (Matchaba 2004) and may cause gastrointestinal side effects (Ofman 2002). The frequency of gastrointestinal side effects increases in proportion to the dose and period of NSAID medication but the risk of gastrointestinal side effects cannot be excluded with short-term use (Hernández-Díaz 2000). In trials included in this review, the risk of side effects was not high but it is difficult to conclude that they are no different from placebo in terms of side effects.

In this review, three trials studied which specific NSAIDs were more effective in treating a cold (Itoh 1980; Katsu 1993; Nagaoka 1980). One study found that fentiazac was more effective than ibuprofen (Nagaoka 1980). However, this is probably because the dose of ibuprofen used in the trial was 600 mg/day, lower than that used in other trials.

The absence of epithelial destruction during rhinovirus infections has led to the idea that the clinical symptoms of the common cold may not be caused by a direct cytopathic effect of the viruses but instead are primarily caused by the inflammatory response of the host by media such as kinins, leukotrienes and histamines (Heikkinen 2003). Accordingly, NSAIDs are believed to ease not only fever and irritation but also respiratory symptoms such as coughing. However, this was not proven in the review. Further research is needed to examine their effects.

For analgesic effects on a cold, acetaminophen was also frequently used along with NSAIDs. However, in this review we did not examine which of the medications was superior in terms of effect and safety. Further research is needed to evaluate this.

Major limitations of this review are that the results of the research are quite diverse and the number of studies for each outcome is quite small. For this reason, it is somewhat difficult to draw clear conclusions.

In conclusion, NSAIDs are recommended for relieving irritation or pain caused by a cold but the notion that NSAIDs are effective in relieving respiratory symptoms such as cough and nasal discharge needs more solid evidence.

Summary of main results

If NSAIDs are administered to community-infected or experimentally infected cold patients, their analgesic effect against pain and irritation induced by the cold is somewhat effective but reports on whether they are helpful in relieving respiratory symptoms such as coughing and sneezing are not consistent and the evidence is insufficient.

Overall completeness and applicability of evidence

The trials included in the analyses mainly involved young adults of both sexes. Therefore the results of these trials may not be applicable to children and older people.

Quality of the evidence

The quality of evidence was estimated as moderate because of imprecision of the evidence.

Potential biases in the review process

Among the analgesic effect outcomes of NSAIDs, headache, pain in muscles and joints, and earache were statistically significant. However, these findings were mainly based on only two trials.

Agreements and disagreements with other studies or reviews

Two studies (Heikkinen 2003; Irwin 2000) and the ACCP guidelines (Pratter 2006) recommend the administration of NSAIDs for coughs caused by a cold. However, this review concluded that there is no

clear evidence that NSAIDs are effective for coughs caused by a cold.

AUTHORS' CONCLUSIONS

Implications for practice

Non-steroidal anti-inflammatory drugs (NSAIDs) are somewhat effective in relieving the discomfort caused by a cold but there is no clear evidence of their effect in easing respiratory symptoms. The balance of benefit and harms needs to be considered when using NSAIDs for colds.

Implications for research

We are unable to support the theory that NSAIDs are effective in reducing cough, based upon the data included in this review. A large trial to study the effect of NSAIDs on colds may make this relationship clearer. For analgesic effects on the common cold, acetaminophen is also frequently used along with NSAIDs. However, in this review we did not examine which of these treatments was superior in terms of effect or safety. For this evaluation, we consider another review necessary.

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Ta'i 2012

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Kim 2007

Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS. Non-steroidal anti-inflammatory drugs for the common cold. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD006362]

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [author-defined order]

Graham 1990

Methods	Double-blind, placebo-controlled, experimental colds
Participants	59 inoculated; 42 colds. Mean age 20.1 years, 43.3% women, university students
Interventions	2 groups: aspirin 4 g/day and ibuprofen 1.2 g/day for 7 days
Outcomes	The proportion of nasal obstruction score > 5 in the aspirin group (6/15) significantly differed from that in the placebo group (0/14, P value < 0.05) Mean mucus weight, mean tissue count, mean overall symptom score and mean overall side effect score were reported but any other statistical parameters such as SD, SE, 95% CI and P value for each group or the difference between these groups were not reported
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... a randomised double-blind, placebo-controlled clinical trial"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	"... identical capsules containing aspirin (500 mg), ibuprofen (200 mg) or placebo" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"... 4 volunteers who were considered uninfected and were excluded from further analyses" Comment: probably done
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text
Other bias	Low risk	The study appears to be free of other sources of bias

Goto 2007

Methods	Double-blind, placebo-controlled, natural colds

Goto 2007 *(Continued)*

Participants	174 adults, age 18 to 65 years, 35% women, 23 outpatients facilities, URTI onset 2 days or less
Interventions	Loxoprofen 60 mg 2 times for 7 days
Outcomes	Duration of illness; the number of days with limited daily activities was not significantly different between groups
Notes	The primary outcome was duration of illness in days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was based on simple computer-generated random digits" Comment: probably done
Allocation concealment (selection bias)	Low risk	"... self-drawing a sealed opaque envelope in the physician's sight....the correspondence between the digits and the group assignment was held in the central, secured location by a third party independent of the investigators until data collection was completed. Thus, allocation was concealed and masked from both patients and physicians" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	"A double-blind, randomised, placebo-controlled trial"; "those in the control group were to take a placebo which was quite similar to active loxoprofen in shape and taste" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"... six (two in loxoprofen group and four in placebo group) withdrew from the study, because two patients (one in loxoprofen and another in placebo) did not complete the diary; three patients (one in loxoprofen and the others in placebo) did not return the diary; and one patient (placebo) decided not to continue the study after the allocation. We excluded nine more participants (two in loxoprofen and seven in placebo) from analyses" Comment: probably done (missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups)
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text
Other bias	Low risk	The study appears to be free of other sources of bias

Itoh 1980

Methods	Double-blind, head-to-head comparison, natural colds
Participants	184 adults, mean age, sex not reported for the subgroup of colds, 29 centres, outpatient departments of hospitals and clinics, URTI onset ≤ 3 days
Interventions	2 groups: ketoprofen 50 mg 3 times and aspirin 500 mg 3 times for 3 days
Outcomes	No significant difference in FGIR between 2 groups

Itoh 1980 *(Continued)*

Notes	No available data on adverse effects for the subgroup of common colds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Low risk	"... randomisation process was done by two controllers and key codes were kept by controllers (in Japanese)" Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	"... double-blind method...active drug capsule and aspirin capsule were quite similar in shape (in Japanese)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"91/93 cases in ketoprofen group and 89/91 cases in aspirin group were finally analyzed" Number of withdrawals was too small to make any important difference to the estimated intervention effect Comment: probably done
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text
Other bias	Low risk	The study appears to be free of other sources of bias

Katsu 1993

Methods	Double-blind, double-dummy, head-to-head comparison, natural colds
Participants	167 adults, mean age, sex not reported for the subgroup of colds, 32 centres, outpatient departments of hospitals and clinics, moderate to severe URTI, not requiring antibiotics
Interventions	2 groups: loxoprofen 180 mg/day and ibuprofen 600 mg for 3 days
Outcomes	No significant difference in FGIR between 2 groups
Notes	No available data on adverse effects for the subgroup of common colds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... were randomly assigned to receive" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information about the allocation concealment

Katsu 1993 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	"... double-blind, double-dummy method...active drug and placebo were quite similar in shape (in Japanese)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"112/130 of the CS-600 group and 113/132 group were evaluated in the assessment improvement ratings" Comment: there are no reasons for missing participants. Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text
Other bias	Low risk	The study appears to be free of other sources of bias

Nagaoka 1980

Methods	Double-blind, head-to-head comparison, natural colds
Participants	222 adults, sex not reported for the subgroup of colds, 51 centres, outpatient departments of hospitals and clinics, URTI onset ≤ 2 days and fever ≤ 39 °C
Interventions	2 groups: fentiazac 300 mg/day and ibuprofen 600 mg/day for 3 days
Outcomes	Moderate to marked improvement of FGIR was more frequent in the fenoprofen group than the placebo (P value < 0.05)
Notes	No available data on adverse effects for the subgroup of common colds

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Low risk	"... randomisation process was done by two controllers and key codes were kept by controllers (in Japanese)"
Blinding (performance bias and detection bias) All outcomes	Low risk	"... double-blind, double-dummy method...active drug and placebo were quite similar in shape (in Japanese)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"243 out of 244 patients were analyzed after the elimination of 1 drop-out case" Comment: number of withdrawals was too small to make any important difference to the estimated intervention effect Comment: probably done
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text

Nagaoka 1980 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Ryan 1987

Methods	Double-blind, placebo-controlled, natural colds
Participants	64 adults, age range 18 to 60 years, 75% women, single family centre, fever ≤ 37.8 °C with moderate pain due to malaise/aches
Interventions	Fenoprofen 200 mg single dose
Outcomes	No available data on efficacy
Notes	Only 2 adverse effects (1 stomach discomfort and 1 drowsiness), both in the fenoprofen group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"... assigned to one of three treatment groups via a computer-generated random table"
Allocation concealment (selection bias)	Low risk	"Each dose of medication was dispensed in identically appearing capsules" Single oral dose was given Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	"Each dose of medication was dispensed in identically appearing capsules in double-blind method" Single oral dose was given Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who entered the study completed treatment and were included in the assessment of effectiveness and side effects
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text
Other bias	Low risk	The study appears to be free of other sources of bias

Sperber 1989

Methods	Double-blind, placebo-controlled, experimental colds
Participants	40 inoculated, 31 colds, mean age 21 years, 39.1% women, setting not reported, fever ≤ 37.7 °C
Interventions	Ibuprofen 200 mg, 2 doses for the first day and 4 doses for the subsequent 4 days

Sperber 1989 *(Continued)*

Outcomes	4-point scale. Moderate to marked severity (2- to 3-point) was reduced in the ibuprofen group (18% versus 29%) but statistical significance was not reported
Notes	Adverse effects were slightly more frequent in the ibuprofen group (6/23) than in the control group (4/23)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... were randomly assigned to receive" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information about the allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	"... two identically appearing capsules" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Among 58 inoculated participants, 8 were excluded (7 not infected, 1 infected with wild type virus), 1 was withdrawn
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text
Other bias	Low risk	The study appears to be free of other sources of bias

Sperber 1992

Methods	Double-blind, placebo-controlled, experimental colds
Participants	79 inoculated (first cohort 34, second cohort 24 and third cohort 21); 56 colds. Mean age 21.4 years, 52% women. Setting not reported
Interventions	For first cohort, naproxen loading dose of 400 mg followed by 200 mg 3 times daily, and for second and third cohort, naproxen loading dose of 500 mg followed by 500 mg 3 times daily for 5 days
Outcomes	5-point symptom score. Total cumulative 5-day score for headache was lower in the naproxen group (0.5 versus 2.5, P value < 0.001)
Notes	1 in the naproxen group and 2 in the placebo group experienced gastrointestinal complaints

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participants were randomly assigned to receive..." Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information about the allocation concealment

Sperber 1992 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	"The study drug and placebo were supplied in identically appearing capsules" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Among 87 volunteers completed, 79 were considered evaluable" The reason for exclusion (infected with wild type rhinovirus, not infected, missed dose of study drug) is unlikely to be related to the outcome of the trial (symptomatic improvement of common cold symptoms) Comment: probably done
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text
Other bias	Low risk	The study appears to be free of other sources of bias

Winther 2001

Methods	Double-blind, placebo-controlled, natural colds
Participants	80 adults, mean age 30.1 years, 60% women, single centre, medical students and members of the staff at the university
Interventions	Ibuprofen 400 mg 3 times for 3 days
Outcomes	4-point symptom score by patients. Sneezing, earache, headache, and pain in muscles and joints were significantly reduced in the ibuprofen group compared with the placebo group. Number of sneezing episodes was also reduced (21.33 ± 3.3 and 12.44 ± 1.5, P value = 0.02)
Notes	No adverse effects in either group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"... randomised study of two parallel groups" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information about the allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	"Coded vials with ibuprofen and placebo tablets were provided by Benzon Pharma" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All patients who entered the study completed treatment and were included in the assessment of effectiveness and side effects" Comment: probably done
Selective reporting (reporting bias)	Unclear risk	No protocol, no convincing text

Winther 2001 *(Continued)*

Other bias	Unclear risk	No data on baseline imbalance

CI: confidence interval
FGIR: final global improvement rating
SD: standard deviation
SE: standard error
URTI: upper respiratory tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aggarwal 1997	Not common cold
Azuma 2010	Not common cold
Azuma 2011	Not common cold
Bachert 2005	Febrile URTI
Banchini 1993	Not common cold
Batista 1985	Not common cold
Bellussi 1993	Not common cold
Bellussi 1996	Not common cold
Benrimoj 2001	Not common cold
Bernstein 1974	Not common cold
Blagden 2002	Not common cold
Bonifaci 1977	Not common cold
Cappella 1993	Not common cold
Chachtel 2011	Not common cold
Ebel 1985	Not common cold
Eccles 2003	Not common cold
Fujimori 1982	Not randomised
Fujimori 1983	Not common cold
Gehanno 2003	Not common cold
Gruber 1977	Not common cold
Kandoth 1984	Not common cold
Katsu 1977	Not common cold

Study	Reason for exclusion
Katsu 1978	Not common cold
Katsu 1982	Randomisation is not clear
Katsu 1983	Not common cold
Kierszenbaum 1991	Not common cold
Lopes 1991	Not common cold
Martinez Gallardo 1994	Randomisation is not clear
Matsumoto 1984	Not common cold
Moore 2002	Not common cold
Nagaoka 1985	Not common cold
Nagaoka 1986a	Not common cold
Nagaoka 1986b	Not common cold
Nouri 1984	Not common cold
Nouri 1993	Not common cold
Pagella 2001	Not common cold
Passali 1989	Not common cold
Passali 1997	Not common cold
Reiner 1983	Not common cold
Ruperto 2011	Not common cold
Russo 2013	Not common cold
Salmon 1993	Not common cold
Salzberg 1993	Not common cold
Sanchez 1999	Not common cold
Schachtel 1993	Not common cold
Schachtel 2002	Not common cold
Stanley 1975	Randomisation is not clear
Tamura 1984	Not common cold
Ulukol 1999	Not common cold
Vauzelle 1996	Not common cold

Study	Reason for exclusion
Watson 2000	Not common cold

URTI: upper respiratory tract infection

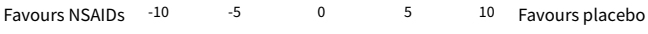
DATA AND ANALYSES

Comparison 1. NSAIDs versus placebo, global effect

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sum of overall symptom score (random-effects model)	3	293	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-1.03, 0.24]
2 Moderate to marked severity	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.18, 2.11]
3 Duration of colds (random-effects model)	2	214	Mean Difference (IV, Random, 95% CI)	-0.23 [-1.75, 1.29]
4 Duration of restriction of daily activities	1	174	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.24, 0.12]

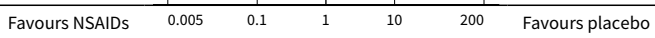
Analysis 1.1. Comparison 1 NSAIDs versus placebo, global effect, Outcome 1 Sum of overall symptom score (random-effects model).

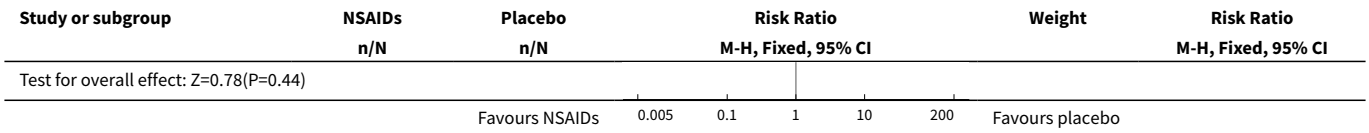
Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Goto 2007	84	76.4 (45.6)	90	75.1 (48)		37.38%	0.03[-0.27,0.32]
Sperber 1989	18	12 (9)	22	15 (10)		29.21%	-0.31[-0.93,0.32]
Sperber 1992	39	15.3 (6.7)	40	21.7 (6.7)		33.41%	-0.95[-1.42,-0.48]
Total ***	**141**		**152**			**100%**	**-0.4[-1.03,0.24]**
Heterogeneity: Tau^2=0.26; Chi^2=12.02, df=2(P=0); I^2=83.36%							
Test for overall effect: Z=1.22(P=0.22)							



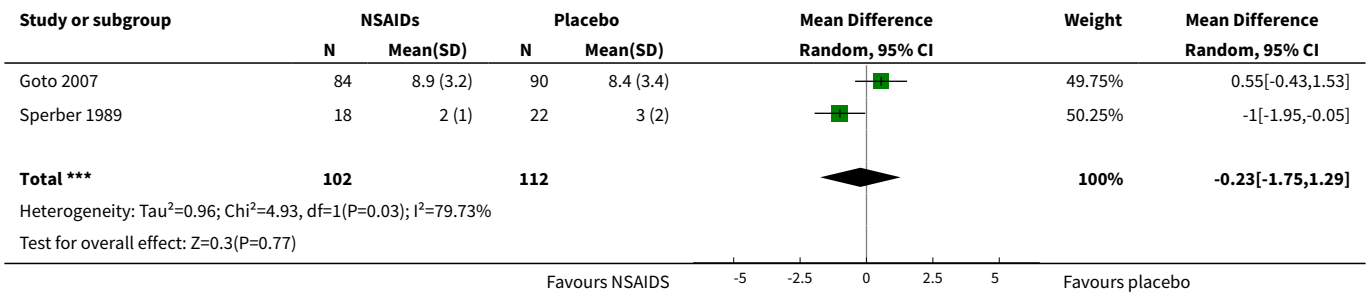
Analysis 1.2. Comparison 1 NSAIDs versus placebo, global effect, Outcome 2 Moderate to marked severity.

Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sperber 1989	3/18	6/22		100%	0.61[0.18,2.11]
Total (95% CI)	**18**	**22**		**100%**	**0.61[0.18,2.11]**
Total events: 3 (NSAIDs), 6 (Placebo)					
Heterogeneity: Not applicable					

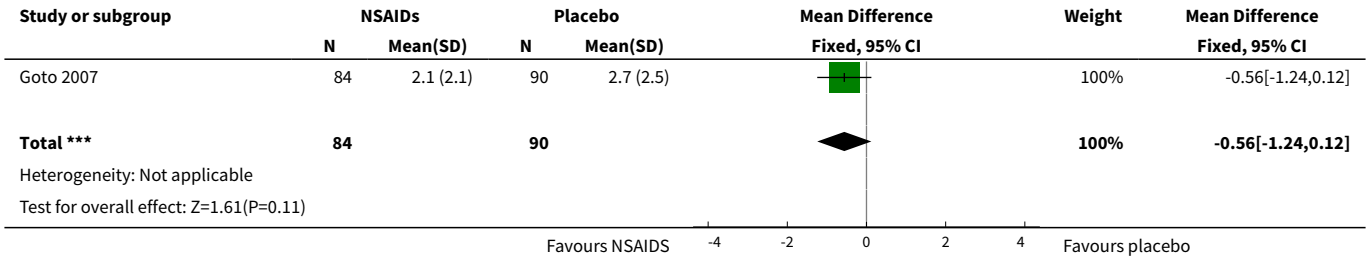




Analysis 1.3. Comparison 1 NSAIDs versus placebo, global effect, Outcome 3 Duration of colds (random-effects model).



Analysis 1.4. Comparison 1 NSAIDs versus placebo, global effect, Outcome 4 Duration of restriction of daily activities.



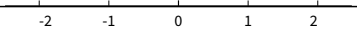
Comparison 2. NSAIDs versus placebo, analgesic effect

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Throat irritation score (fixed-effect model)	2	159	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.33, 0.30]
2 Headache score (random-effects model)	2	159	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-1.11, -0.19]
3 Score of pain in muscles/joints score (fixed-effect model)	2	114	Std. Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.77, -0.03]
4 Malaise score (fixed-effect model)	2	159	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.60, 0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Chilliness score (random-effects model)	2	159	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-1.12, 1.06]
6 Nose irritation score	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.48, 0.40]
7 Score of pain on swallowing	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.51, 0.37]
8 Eye itching score	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.58, 0.30]
9 Earache score	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.04, -0.14]

Analysis 2.1. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 1 Throat irritation score (fixed-effect model).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Sperber 1992	39	3.1 (3.2)	40	3.6 (3.2)		49.72%	-0.16[-0.6,0.29]
Winther 2001	38	3.3 (2.7)	42	3 (2.1)		50.28%	0.13[-0.31,0.57]
Total ***	**77**		**82**			**100%**	**-0.01[-0.33,0.3]**
Heterogeneity: Tau^2=0; Chi^2=0.79, df=1(P=0.37); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							



Favours NSAIDs — Favours placebo

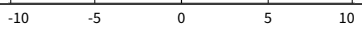
Analysis 2.2. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 2 Headache score (random-effects model).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Sperber 1992	39	0.5 (2.2)	40	2.5 (2.2)		48.94%	-0.89[-1.35,-0.42]
Winther 2001	38	1.4 (2.3)	42	2.4 (2.1)		51.06%	-0.42[-0.87,0.02]
Total ***	**77**		**82**			**100%**	**-0.65[-1.11,-0.19]**
Heterogeneity: Tau^2=0.05; Chi^2=2.02, df=1(P=0.16); I^2=50.5%							
Test for overall effect: Z=2.8(P=0.01)							

Favours NSAIDs — Favours placebo

Analysis 2.3. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 3 Score of pain in muscles/joints score (fixed-effect model).

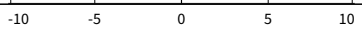
Study or subgroup	NSAIDS N	NSAIDS Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Sperber 1992	17	0.1 (0.3)	17	1.5 (2.7)		28.53%	-0.74[-1.44,-0.04]
Winther 2001	38	0.4 (1.2)	42	0.7 (1.4)		71.47%	-0.27[-0.71,0.17]
Total ***	**55**		**59**			**100%**	**-0.4[-0.77,-0.03]**
Heterogeneity: Tau^2=0; Chi^2=1.25, df=1(P=0.26); I^2=20.17%							
Test for overall effect: Z=2.11(P=0.03)							



Favours NSAIDs — Favours placebo

Analysis 2.4. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 4 Malaise score (fixed-effect model).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Sperber 1992	39	1.4 (2.7)	40	2.3 (2.7)		49.58%	-0.33[-0.77,0.12]
Winther 2001	38	2.3 (2.8)	42	2.9 (2.2)		50.42%	-0.24[-0.68,0.2]
Total ***	**77**		**82**			**100%**	**-0.29[-0.6,0.03]**
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%							
Test for overall effect: Z=1.79(P=0.07)							



Favours NSAIDs — Favours placebo

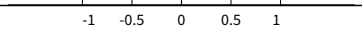
Analysis 2.5. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 5 Chilliness score (random-effects model).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Sperber 1992	39	0.2 (1.1)	40	0.9 (1.2)		49.96%	-0.58[-1.03,-0.13]
Winther 2001	38	1.5 (2.2)	42	0.6 (1.1)		50.04%	0.53[0.08,0.98]
Total ***	**77**		**82**			**100%**	**-0.03[-1.12,1.06]**
Heterogeneity: Tau^2=0.57; Chi^2=11.8, df=1(P=0); I^2=91.52%							
Test for overall effect: Z=0.05(P=0.96)							

Favours NSAIDS — Favours placebo

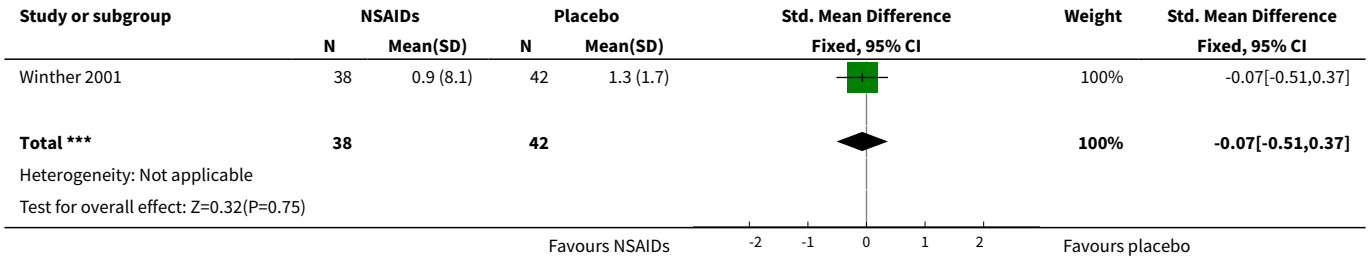
Analysis 2.6. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 6 Nose irritation score.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Winther 2001	38	5.2 (3)	42	5.4 (2.5)		100%	-0.04[-0.48,0.4]
Total ***	**38**		**42**			**100%**	**-0.04[-0.48,0.4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.19(P=0.85)							

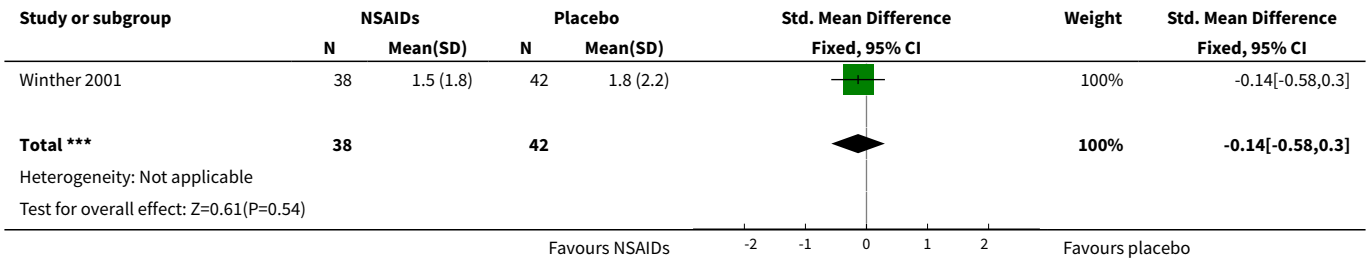


Favours NSAIDs — Favours placebo

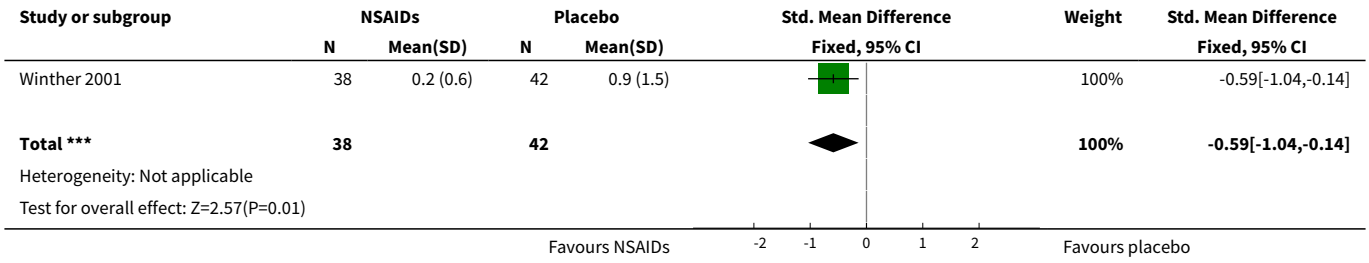
Analysis 2.7. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 7 Score of pain on swallowing.



Analysis 2.8. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 8 Eye itching score.



Analysis 2.9. Comparison 2 NSAIDs versus placebo, analgesic effect, Outcome 9 Earache score.



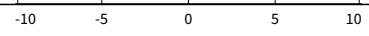
Comparison 3. NSAIDs versus placebo, non-analgesic effect

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough score (random-effects model)	2	159	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.66, 0.56]
2 Sneezing score (fixed-effect model)	2	159	Std. Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.75, -0.12]
3 Total number of sneezes	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.95, -0.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Rhinorrhoea score (fixed-effect model)	3	199	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.25, 0.30]
5 Nasal obstruction score (fixed-effect model)	3	199	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.43, 0.13]
6 Nasal obstruction score > 5	1	27	Risk Ratio (M-H, Fixed, 95% CI)	5.36 [0.28, 102.12]
7 Total number of nose blows	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.27, 0.61]
8 Total mucus weight	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.49, 0.76]
9 Total tissue number count	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.83, 0.42]
10 Score of dryness in the nose	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.40, 0.48]
11 Score of reduced sense of smell	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.36, 0.51]
12 Hoarseness score	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	0.32 [-0.12, 0.76]
13 Fatigue score	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.26, 0.62]

Analysis 3.1. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 1 Cough score (random-effects model).

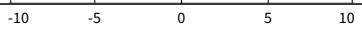
Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Sperber 1992	39	0.8 (2.2)	40	1.6 (2.2)		49.88%	-0.36[-0.8,0.08]
Winther 2001	38	4.7 (3.3)	42	3.8 (3)		50.12%	0.26[-0.18,0.7]
Total ***	**77**		**82**			**100%**	**-0.05[-0.66,0.56]**
Heterogeneity: Tau^2=0.14; Chi^2=3.78, df=1(P=0.05); I^2=73.53%							
Test for overall effect: Z=0.16(P=0.87)							



Favours NSAIDs Favours placebo

Analysis 3.2. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 2 Sneezing score (fixed-effect model).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Sperber 1992	39	1.5 (2.2)	40	2.2 (2.2)		50.43%	-0.31[-0.76,0.13]
Winther 2001	38	2.2 (1.6)	42	3.3 (2.3)		49.57%	-0.56[-1.01,-0.11]
Total ***	**77**		**82**			**100%**	**-0.44[-0.75,-0.12]**
Heterogeneity: Tau^2=0; Chi^2=0.59, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=2.71(P=0.01)							



Analysis 3.3. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 3 Total number of sneezes.

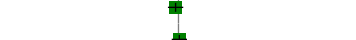
Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Winther 2001	38	12.4 (9.3)	42	21 (21.4)		100%	-0.51[-0.95,-0.06]
Total ***	**38**		**42**			**100%**	**-0.51[-0.95,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.23(P=0.03)							

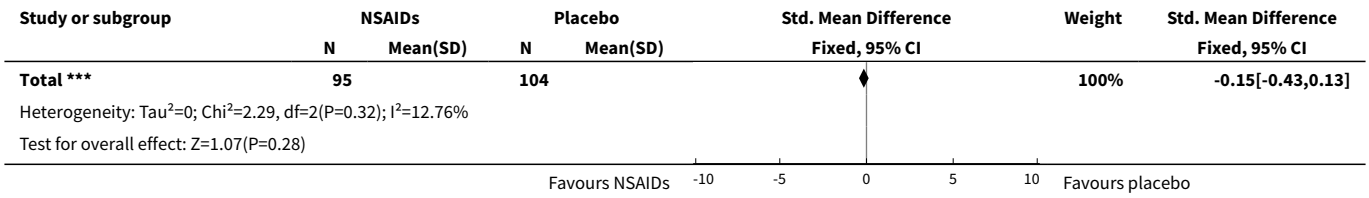
Analysis 3.4. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 4 Rhinorrhoea score (fixed-effect model).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Sperber 1989	18	2 (2)	22	2 (2)		20.04%	0[-0.62,0.62]
Sperber 1992	39	2.7 (3.1)	40	3.2 (3.1)		39.84%	-0.16[-0.6,0.28]
Winther 2001	38	4.5 (2.7)	42	3.9 (2.5)		40.12%	0.22[-0.22,0.66]
Total ***	**95**		**104**			**100%**	**0.03[-0.25,0.3]**
Heterogeneity: Tau^2=0; Chi^2=1.47, df=2(P=0.48); I^2=0%							
Test for overall effect: Z=0.18(P=0.86)							

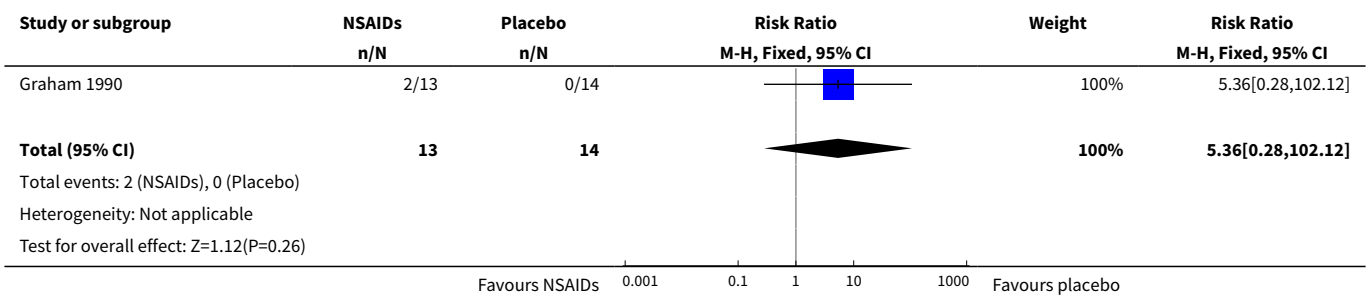
Analysis 3.5. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 5 Nasal obstruction score (fixed-effect model).

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Sperber 1989	18	4 (3)	22	6 (4)		19.36%	-0.55[-1.18,0.09]
Sperber 1992	39	5.1 (3.6)	40	5.7 (3.6)		40.05%	-0.17[-0.61,0.27]
Winther 2001	38	5.7 (2.3)	42	5.6 (2.1)		40.59%	0.05[-0.39,0.49]

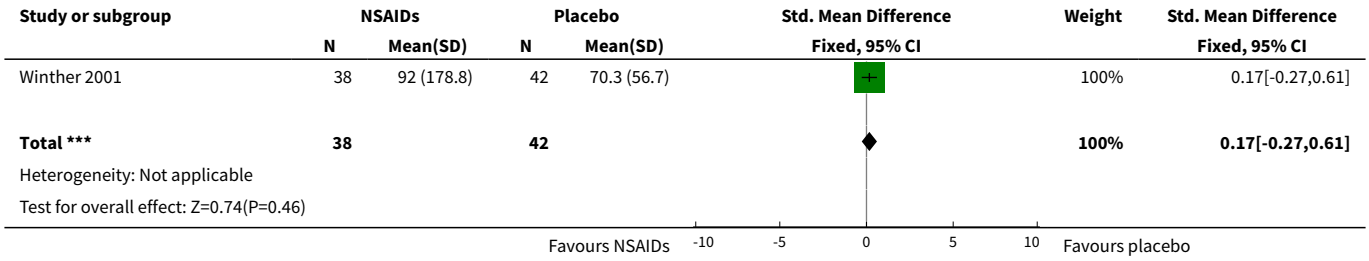




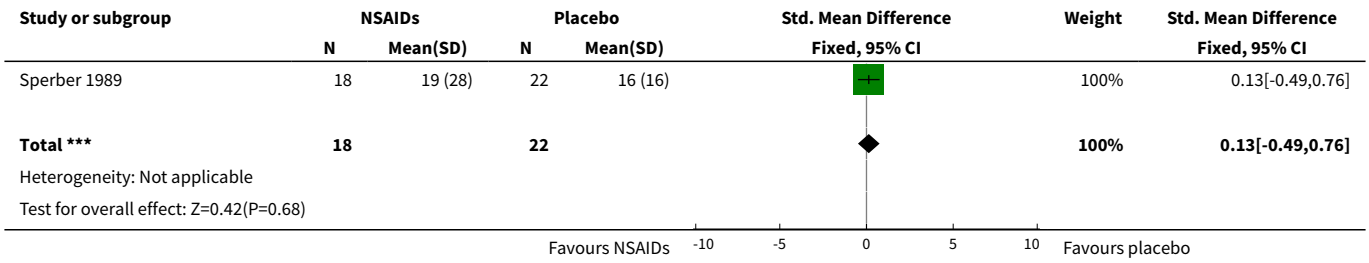
Analysis 3.6. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 6 Nasal obstruction score > 5.



Analysis 3.7. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 7 Total number of nose blows.



Analysis 3.8. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 8 Total mucus weight.



Analysis 3.9. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 9 Total tissue number count.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Sperber 1989	18	43 (50)	22	53 (48)		100%	-0.2[-0.83,0.42]
Total ***	**18**		**22**			**100%**	**-0.2[-0.83,0.42]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.63(P=0.53)							

Analysis 3.10. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 10 Score of dryness in the nose.

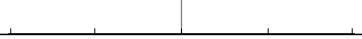
Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Winther 2001	38	1.7 (2.2)	42	1.6 (2.3)		100%	0.04[-0.4,0.48]
Total ***	**38**		**42**			**100%**	**0.04[-0.4,0.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.17(P=0.86)							

Analysis 3.11. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 11 Score of reduced sense of smell.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Winther 2001	38	5 (3.1)	42	4.7 (3.7)		100%	0.08[-0.36,0.51]
Total ***	**38**		**42**			**100%**	**0.08[-0.36,0.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.34(P=0.74)							

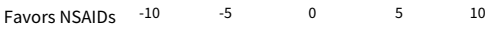
Analysis 3.12. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 12 Hoarseness score.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Winther 2001	38	3.7 (3.1)	42	2.8 (2.7)		100%	0.32[-0.12,0.76]
Total ***	**38**		**42**			**100%**	**0.32[-0.12,0.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.41(P=0.16)							



Analysis 3.13. Comparison 3 NSAIDs versus placebo, non-analgesic effect, Outcome 13 Fatigue score.

Study or subgroup	NSAIDs N	NSAIDs Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Winther 2001	38	3.5 (5.2)	42	2.8 (2.5)		100%	0.18[-0.26,0.62]
Total ***	**38**		**42**			**100%**	**0.18[-0.26,0.62]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.79(P=0.43)							

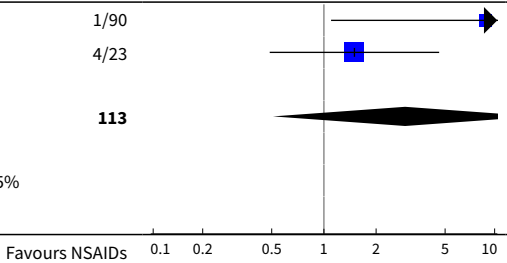


Comparison 4. NSAIDs versus placebo, adverse effects

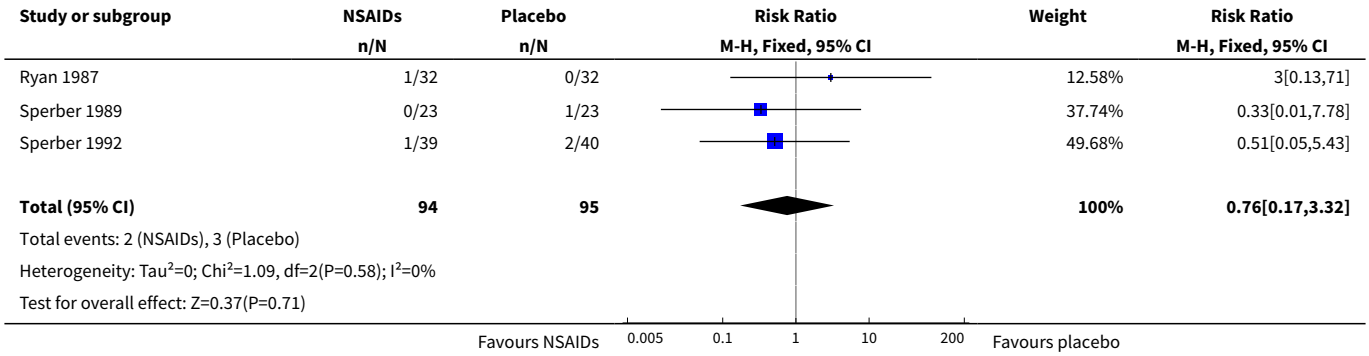
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall side effects (random-effects model)	2	220	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.51, 17.03]
2 GI complaint (fixed-effect model)	3	189	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.17, 3.32]
3 Lethargy/drowsiness (fixed-effect model)	2	110	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 6.91]
4 Feeling hyperactive	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.02]
5 Feeling more awake	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.02]
6 Flushed face	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.02]
7 Difficulty sleeping	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.78]
8 Light-headedness	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.51]
9 Dry mouth	1	46	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.02]

Analysis 4.1. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 1 Overall side effects (random-effects model).

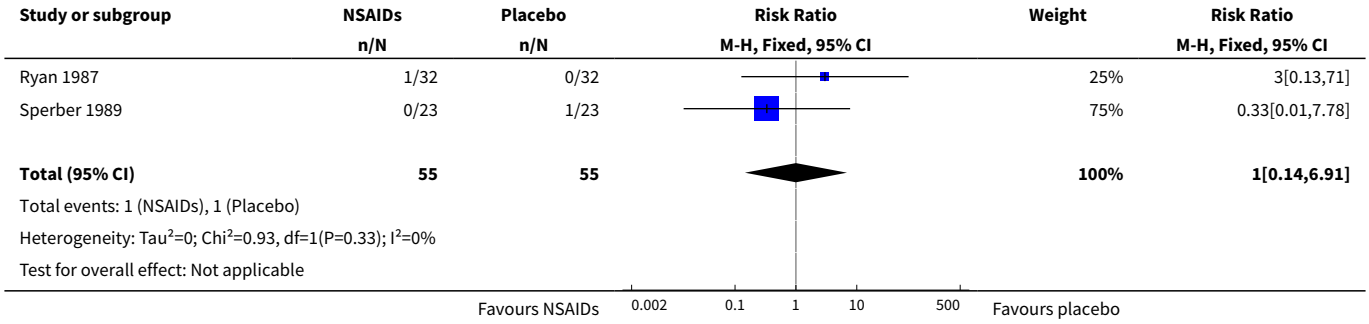
Study or subgroup	NSAIDs n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Goto 2007	8/84	1/90		38.6%	8.57[1.1,67.08]
Sperber 1989	6/23	4/23		61.4%	1.5[0.49,4.62]
Total (95% CI)	**107**	**113**		**100%**	**2.94[0.51,17.03]**
Total events: 14 (NSAIDs), 5 (Placebo)					
Heterogeneity: Tau^2=0.98; Chi^2=2.37, df=1(P=0.12); I^2=57.75%					
Test for overall effect: Z=1.2(P=0.23)					



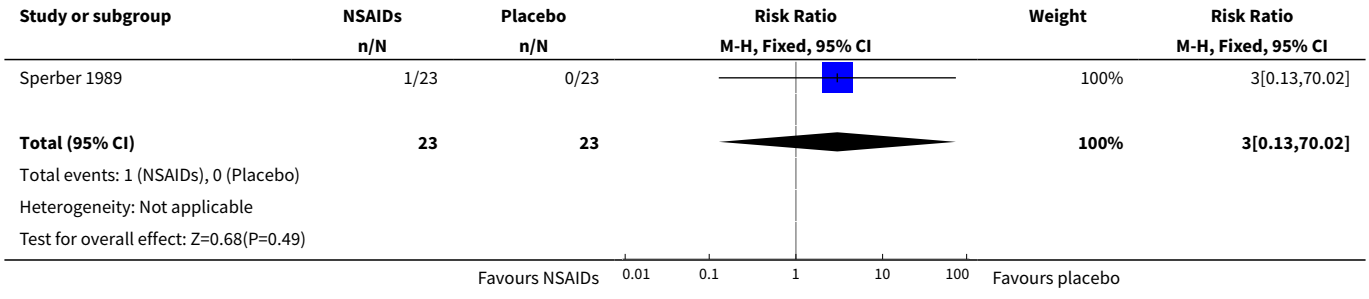
Analysis 4.2. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 2 GI complaint (fixed-effect model).



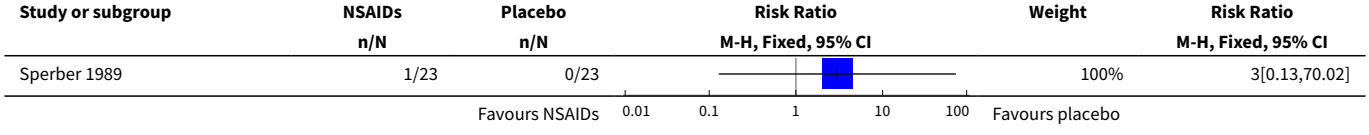
Analysis 4.3. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 3 Lethargy/drowsiness (fixed-effect model).

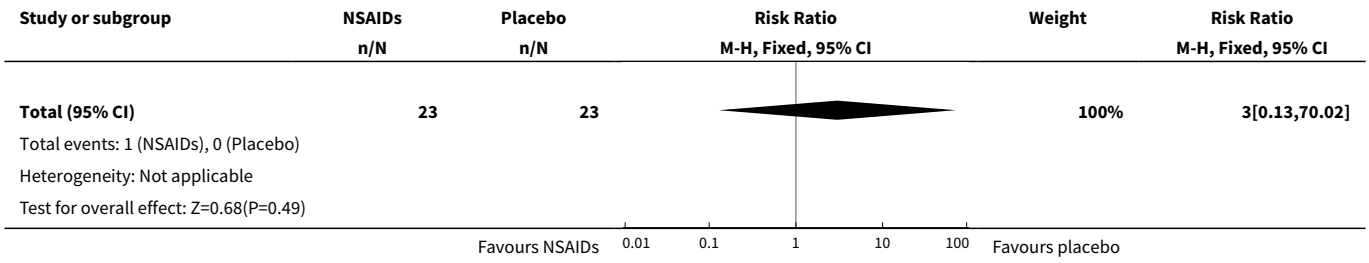


Analysis 4.4. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 4 Feeling hyperactive.

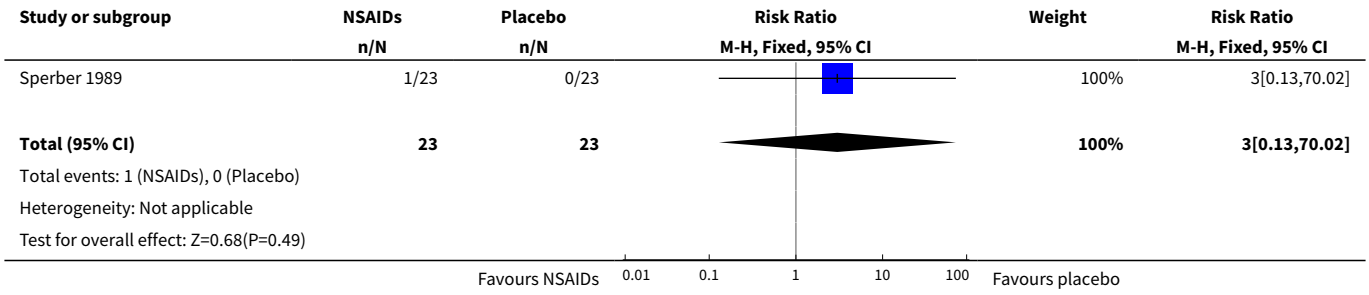


Analysis 4.5. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 5 Feeling more awake.

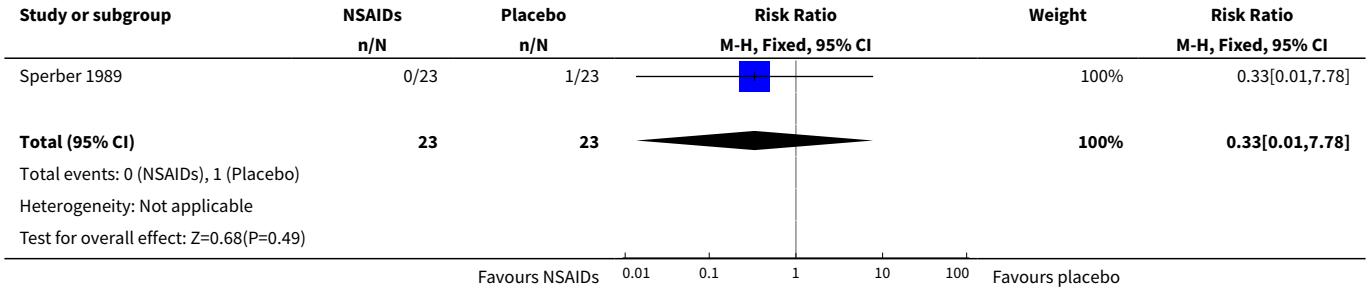




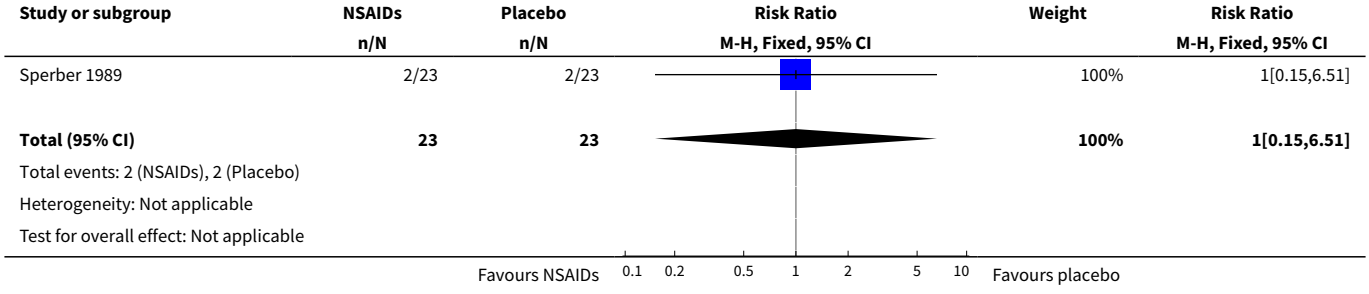
Analysis 4.6. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 6 Flushed face.



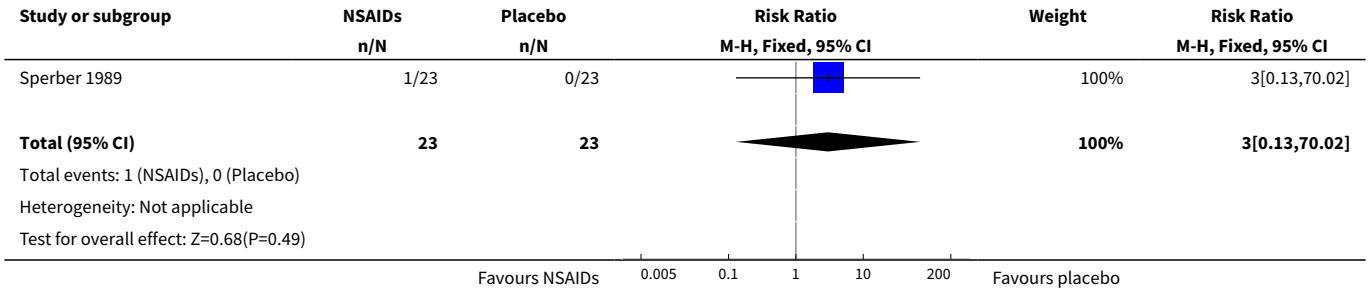
Analysis 4.7. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 7 Difficulty sleeping.



Analysis 4.8. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 8 Light-headedness.



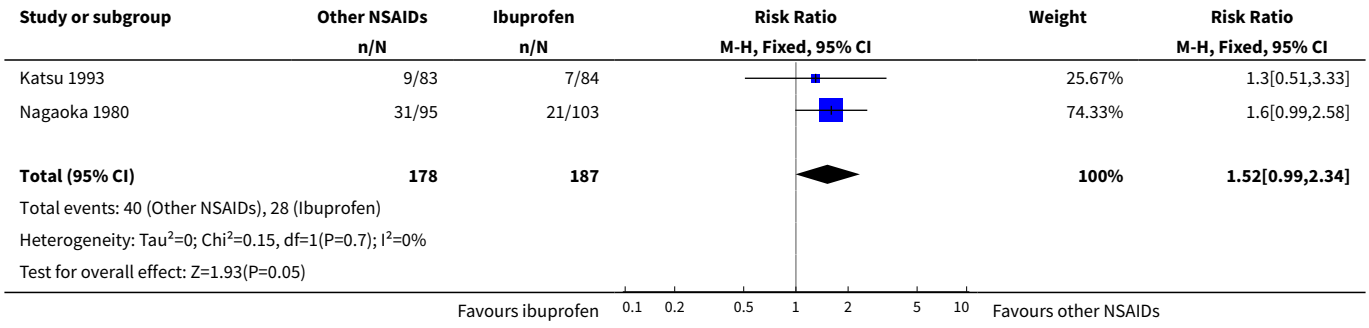
Analysis 4.9. Comparison 4 NSAIDs versus placebo, adverse effects, Outcome 9 Dry mouth.



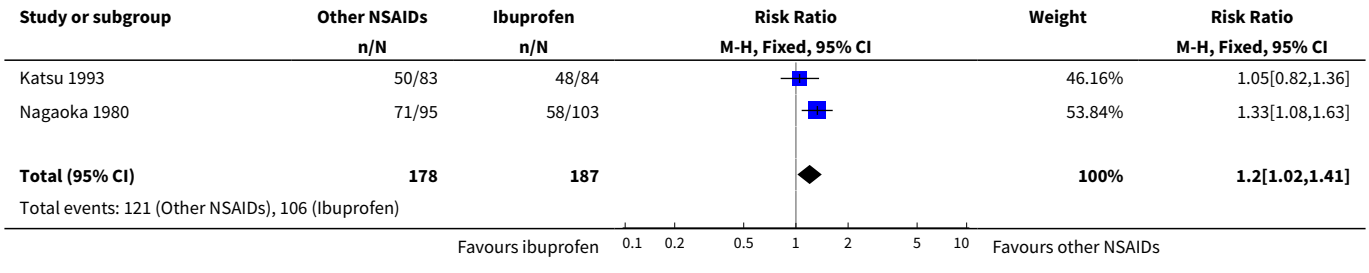
Comparison 5. Head to head comparison, global effect

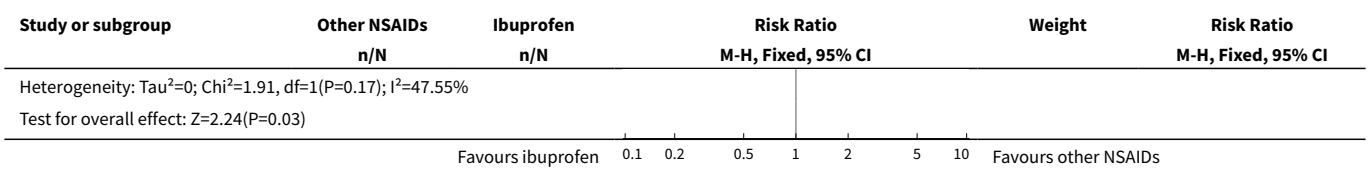
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global improvement rating, marked improvement (fixed-effect model)	2	365	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.99, 2.34]
2 Global improvement rating, moderate to marked improvement (fixed-effect model)	2	365	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.02, 1.41]

Analysis 5.1. Comparison 5 Head to head comparison, global effect, Outcome 1 Global improvement rating, marked improvement (fixed-effect model).



Analysis 5.2. Comparison 5 Head to head comparison, global effect, Outcome 2 Global improvement rating, moderate to marked improvement (fixed-effect model).





APPENDICES

Appendix 1. EMBASE search strategy

/* COMMON COLD */

#1 'common cold'/exp OR (common cold*):ti,ab

#2 coryza:ti,ab

#3 ('upper respiratory infection'):ti,ab OR ('upper respiratory infections'):ti,ab

#4 ('upper respiratory tract infection'):ti,ab OR ('upper respiratory tract infections'):ti,ab

#5 urti:ti,ab

#6 ((respiratory tract infection:ti,ab) OR (respiratory tract infections:ti,ab)) AND upper:ti,ab

#7 'rhinitis'/exp OR rhinit*:ti,ab

#8 'pharyngitis'/exp OR pharyngit*:ti,ab

#9 'sore throat':ti,ab OR 'sore throats':ti,ab

#10 'rhinopharyngitis'/exp OR nasopharyngit*:ti,ab

#11 'laryngitis'/exp OR laryngit*:ti,ab

#12 'coughing'/exp OR cough*:ti,ab

#13 'nose obstruction'/exp OR 'nasal obstruction':ti,ab

#14 'sneezing'/exp OR sneez*:ti,ab

#15 'rhinovirus'/exp OR rhinovirus:ti,ab

#16 OR/#1-#15

/* NSAIDS */

#17 'nonsteroid antiinflammatory agent'/exp OR nsaid*:ti,ab OR (((non-steroid OR nonsteroid OR 'non steroid' OR 'non steroids') AND (anti-inflammatory OR antiinflammatory OR 'anti inflammatory')):ti,ab)

#18 'azapropazone'/exp OR apazone:ti,ab

#19 'acetylsalicylic acid'/exp OR aspirin:ti,ab

#20 'celecoxib'/exp OR celecoxib:ti,ab

#21 'diclofenac'/exp OR diclofenac:ti,ab

#22 'diflunisal'/exp OR diflunisal:ti,ab

#23 'etodolac'/exp OR etodolac:ti,ab

#24 'fenoprofen'/exp OR fenoprofen:ti,ab

#25 'flurbiprofen'/exp OR flurbiprofen:ti,ab

#26 'ibuprofen'/exp OR ibuprofen:ti,ab

#27 'indometacin'/exp OR indomethacin:ti,ab

#28 'ketoprofen'/exp OR ketoprofen:ti,ab

#29 'ketorolac'/exp OR ketorolac:ti,ab

#30 'meclofenamic acid'/exp OR meclofenamate:ti,ab

#31 'meloxicam'/exp OR meloxicam:ti,ab

#32 'salicylic acid methyl ester'/exp OR methylsalicylate:ti,ab OR 'methyl salicylate':ti,ab

#33 'nabumetone'/exp OR nabumetone:ti,ab

#34 'naproxen'/exp OR naproxen:ti,ab

#35 'nimesulide'/exp OR nimesulide:ti,ab

#36 'oxaprozin'/exp OR oxaprozin:ti,ab

#37 'phenylbutazone'/exp OR phenylbutazone:ti,ab

#38 'piroxicam'/exp OR piroxicam:ti,ab

#39 'salicylic acid'/exp OR salicylate:ti,ab

#40 'sulindac'/exp OR sulindac:ti,ab

#41 'tenoxicam'/exp OR tenoxicam:ti,ab

#42 'tolmetin'/exp OR tolmetin:ti,ab

#43 OR/#17-#42

/* RCT */

#44 'clinical trial'/exp OR 'clinical trial':ti,ab

#45 'randomized controlled trial'/exp OR 'randomized controlled trial':ti,ab

#46 'randomisation'/exp OR random*:ti,ab

#47 'single blind procedure'/exp OR (singl*:ti,ab AND (mask*:ti,ab OR blind*:ti,ab))

#48 'double blind procedure'/exp OR (doubl*:ti,ab AND (mask*:ti,ab OR blind*:ti,ab))

#49 'triple blind procedure'/exp OR (trip*:ti,ab AND (mask*:ti,ab OR blind*:ti,ab))

#50 'placebo'/exp OR placebo:ti,ab

#51 OR #44-#50

/* Combine & Limit */

#52 #16 AND #43 AND #51

#53 #16 AND #43 AND [randomized controlled trial]/lim

#54 (#52 OR #53) AND [human]/lim

#55 #54 AND [2009-2011]/py

Appendix 2. CINAHL search strategy

/* COMMON COLD */

S1 (MH "Common Cold") OR (TX "common cold*")

S2 TX coryza

S3 (MH "Respiratory Tract Infections") or TX "upper respiratory infection*"

S4 TX "upper respiratory tract infection*"

S5 TX URTI

S6 (TX "respiratory tract infection*") AND (TX upper)

S7 (MH "Rhinitis") OR (TX rhinit*)

S8 (MH "Pharyngitis") OR (TX pharyngit*)

S9 TX "sore throat*"

S10 (MH "Nasopharynx") OR (TX nasopharyngit*)

S11 (MH "Laryngitis") OR (TX laryngit*)

S12 (MH "Cough") OR (TX cough*)

S13 (MH "Nasal Obstruction") OR (TX nasal obstruction*)

S14 (MH "Sneezing") OR (TX sneez*)

S15 TX rhinovirus

S16 OR/S1-S15

/* NSAIDS */

S17 (MH "Antiinflammatory Agents, Non-Steroidal") OR (TX nsaid*) OR (TX (non-steroid* OR nonsteroid* OR "non steroid*") AND TX (anti-inflammator* OR antiinflammator* OR "anti inflammator*"))

S18 TX azapropazone

S19 MH "Aspirin" OR aspirin

S20 MH "Cox-2 Inhibitors" OR TX celecoxib

S21 MH "Diclofenac" OR TX diclofenac

S22 TX diflunisal

S23 MH "Etodolac" OR TX etodolac

S24 TX fenoprofen

S25 MH "Flurbiprofen" OR TX flurbiprofen

S26 MH "Ibuprofen" OR TX ibuprofen

S27 MH "Indomethacin" OR TX indomethacin

S28 TX ketoprofen

S29 MH "Ketorolac" OR TX ketorolac

S30 TX meclofenamate

S31 TX meloxicam

S32 TX (methylsalicylate OR "methyl salicylate")

S33 TX nabumetone

S34 MH "Naproxen" OR TX naproxen

S35 TX nimesulide

S36 TX oxaprozin

S37 MH "Phenylbutazone" OR TX phenylbutazone

S38 MH "Piroxicam" OR TX piroxicam

S39 MH "Salicylic Acids" OR TX salicylate

S40 MH "Sulindac" OR TX sulindac

S41 TX tenoxicam

S42 MH "Tolmetin" OR TX tolmetin

S43 OR/S11-S42

/* RCT */

S44 MH "Clinical trial" OR TX "clinical trial"

S45 MH "Randomized Controlled Trials" OR TX "randomized controlled trial"

S46 MH "Random Sample" OR TX random*

S47 MH "Single-Blind Studies" OR TX (singl* AND (mask* OR blind*))

S48 MH "Double-Blind Studies" OR TX (doubl* AND (mask* OR blind*))

S49 MH "Triple-Blind Studies" OR TX (trilp AND (mask* OR blind*))

S50 MH "Placebos" OR TX placebo

S51 OR S44-S50

/* Combine & Limit */

S52 S16 AND S43 AND S51

S53 S16 AND S43 AND [crinical trial]/lim

S54 S52 OR S53

S55 S54 AND [2009-2011]/py

Appendix 3. MEDLINE and CENTRAL search strategy

MEDLINE (Ovid)

1 Common Cold/
2 common cold*.tw.
3 coryza.tw.
4 upper respiratory infection*.tw.
5 upper respiratory tract infections*.tw.
6 urti.tw.
7 respiratory tract infections.sh. and upper.tw.
8 Rhinitis/
9 rhinit*.tw.
10 exp Pharyngitis/
11 pharyngit*.tw.
12 sore throat*.tw.
13 exp Nasopharyngitis/
14 nasopharyngit*.tw.
15 exp Laryngitis/

16 laryngit*.tw.
17 Cough/
18 cough*.tw.
19 Nasal Obstruction/
20 nasal obstruction*.tw.
21 Sneezing/
22 sneez*.tw.
23 Rhinovirus/
24 rhinovirus*.tw.
25 or/1-24
26 exp Anti-Inflammatory Agents, Non-Steroidal/
27 nsaid*.tw.
28 ((non-steroid* or nonsteroid* or non steroid*) and (anti-inflammator* or antiinflammator* or anti inflammator*)).tw.
29 Apazone.sh. or apazone.tw.
30 Aspirin.sh. or aspirin.tw.
31 celecoxib.nm. or celecoxib.tw.
32 diclofenac.sh. or diclofenac.tw.
33 diflunisal.sh. or diflunisal.tw.
34 etodolac.sh. or etodolac.tw.
35 fenoprofen.sh. or fenoprofen.tw.
36 flurbiprofen.sh. or flurbiprofen.tw.
37 ibuprofen.sh. or ibuprofen.tw.
38 indomethacin.sh. or indomethacin.tw.
39 ketoprofen.sh. or ketoprofen.tw.
40 ketorolac.sh. or ketorolac.tw.
41 Meclofenamic Acid/
42 meclofenamate.tw. or meloxicam.nm. or meloxicam.tw.
43 methyl salicylate.nm. or methylsalicylate.tw. or methyl salicylate.tw.
44 nabumetone.nm. or nabumetone.tw.
45 naproxen.sh. or naproxen.tw.
46 nimesulide.nm. or nimesulide.tw.
47 oxaprozin.nm. or oxaprozin.tw.
48 phenylbutazone.sh. or phenylbutazone.tw.
49 piroxicam.sh. or piroxicam.tw.
50 salicylate.mp.
51 sulindac.sh. or sulindac.tw.
52 tenoxicam.nm. or tenoxicam.tw.
53 tolmetin.sh. or tolmetin.tw.
54 or/26-53
55 25 and 54

F E E D B A C K

Non-steroidal anti-inflammatory drugs for the common cold, 8 December 2009

Summary

In their Cochrane Review on non-steroidal anti-inflammatory drugs for the common cold, Kim et al. (1) "recommend NSAIDs for relieving discomfort or pain caused by the common cold" without any reservations. However, the common cold is a rather harmless condition, whereas NSAIDs can have serious and even lethal adverse effects (2-4). The review also has methodological shortcomings.

One problem is the excessive number of outcomes; the review authors report on no less than 26 primary outcomes. Four of these, sneezing, headache, pain in muscles/joints and earache, were statistically significant, but the first 3 outcomes were based on only 2 trials, including 159 participants, and the last outcome on only 1 trial.

One of these 2 trials was an experimental study (5) of 87 healthy volunteers that were inoculated with rhinovirus. The trial had unclear sequence generation, unclear concealment of allocation and was not analysed using intention to treat, as 8 people were excluded from the analysis. The volunteers were treated with very high doses of naproxen, up to 1500 mg daily, which is higher than what has been approved for treatment of acute pain conditions (6), and as the risk of harms increases linearly with the dose (7), this is particularly problematic. This trial is also included in the analysis for global effects where it had the largest effect of the 3 included trials and contributed to substantial heterogeneity, which suggests bias or problems with generalisability. Further, as it can be problematic to generalise findings from experimental settings to patients (8), it is questionable to pool this trial with trials from clinical settings.

The second trial (9) included 80 patients with natural colds that received 1200 mg ibuprofen daily. This trial also had unclear sequence generation and unclear allocation concealment. Additionally, for analysis 2.9 and 2.10 of Chilliness score, the authors have erroneously extracted the results from the placebo arm of this trial as though they belonged to another trial (5) and vice versa. This raises the question whether there were other data extraction errors. Data extraction errors are frequent in meta-analyses using SMD (10).

Adverse effects are not mentioned in the Discussion and only briefly in Results. According to the authors, 5 trials assessed adverse effects but they only reported data from 4 trials. The omitted trial (9) reported adverse effects (e.g. pain in abdomen, ear buzzing) as continuous outcomes, and not as binary (5). While it is reasonable not to pool trials with binary and continuous outcomes, we are puzzled as to why the authors omitted reporting any adverse effects data from this trial in their Cochrane Review. We wonder whether adverse effects from other trials were similarly ignored.

The 4 trials where the review authors reported adverse effects assessed 9 outcomes and for all outcomes, the confidence intervals were wide (e.g. for overall adverse effects, RR 2.94 [0.51, 17.03]). Based on this uncertainty, adverse effects of NSAIDs cannot be dismissed and it is therefore surprising that the authors did not refer to additional evidence, as recommended in *The Cochrane Handbook* (11). NSAIDs are known to cause serious harms (2-4).

Additionally, in Methods the authors state “We assessed heterogeneity amongst trials by using the Chi^2 test for heterogeneity with a 10% level of statistical significance and I^2 test.” In their protocol the I^2 is not mentioned at all. While there was substantial heterogeneity for overall side effects (I^2 = 58%) the Chi^2 test for heterogeneity was not statistically significant (P = 0.12). So, based on their own criteria the authors should have analysed the data using a fixed-effect model, which would have shown a significant increase in overall side effects, relative risk 2.88 [1.11, 7.45] (P = 0.03).

Additionally, there are some discrepancies between what was reported in the protocol and what was done in the review. Kim et al. originally stated in their protocol (1) that they would search databases for unpublished trials, contact authors for missing data and examine publication bias, but apparently did not do any of this. The identified trials were all very small. It is therefore likely that the identified sample of published trials is biased (12), as small trials with non-statistical findings are often not published.

In their abstract, the authors recommend NSAIDs for “reliving discomfort or pain”. This statement is highly misleading, as it indicates that NSAIDs have other clinical effects than their analgesic effect. The authors do not use the word “discomfort” anywhere else in the review, but we assume it refers to either global outcomes or non-analgesic outcomes. However, the authors found no effect on global outcomes and the effect on “sneezing” is likely spurious, as it occurred for only one out of 13 non-analgesic outcomes, and was based on the 2 problematic trials already described.

Based on these methodological problems, and the serious adverse effects of the drugs, we believe there is no sound basis for recommending NSAIDs for the common cold and urge the authors to present a more balanced view.

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Reply

Thank you for your feedback.
I think that the comments fall into four main areas.

1. Adverse effects.
2. Discrepancy between the protocol and review.
3. The methodological issues of weak studies, and multiple outcomes.
4. The heterogeneity tests used, and the choice of random-effects or fixed-effect model.

We will discuss the feedback according to the four main areas.

1. Adverse effect issues
Safety-related issues of NSAIDs, in particular, the issues of cardiovascular disease and gastrointestinal disease have been reviewed in many studies but no clear conclusion has been drawn on what problems there can be in short-term uses such as the use for a common cold. Of course, the risk of gastrointestinal side effects may increase even in short-term usage.
We agree with the commentators that there have not been many safety-related discussions in the review and the power is not high enough to conclude on the safety of NSAIDs based on trials in this review. We also agree that review of other systematic reviews related to safety issues is necessary.
As for the trial on which the commentators stated that it omitted safety-related results, the trial author mentioned that there was no abnormal adverse events in the trial and the outcomes mentioned by the commentators classified it as effectiveness outcomes.

2. Discrepancy between the protocol and review - search of unpublished trials and publication bias
In the methods, we did make some efforts to search for unpublished trials.
“We searched reference lists of review articles and of all included studies to find other potentially eligible studies. We contacted authors of the included trials to request unpublished studies”. However, we did not find any additional trials.

We did examine publication bias by funnel plot analysis. We omitted them because there were too many funnel plots in our review.

3. The methodological issues of weak studies, and multiple (26) outcomes
As mentioned by the commentators, the number of results may be too large. This problem is mainly because outcomes of trials and duration or dose of therapy were quite diverse, so it was inevitable (in this sense).
The effect of NSAIDs may not be different according to whether a cold is induced experimentally or happens naturally.
A calculation error that the commentators pointed out was corrected.
We added the following to the Discussion:
“Major limitations of this review is that the results of the research are quite diverse and the number of studies for one result is quite small. For this reason, it is somewhat difficult to draw clear conclusions."

4. The heterogeneity tests used, and the choice of random-effects or fixed-effect model
The reason for changing the protocol and review methodology in connection to heterogeneity is because *The Cochrane Handbook* was upgraded from 4.2 to 5.0 during the review and the 5.0 version recommends the use of I^2 statistic and so we added it. In the Chi^2 test, some heterogeneity was observed as I^2 statistic = 58%, although not statistically significant, so in the actual analysis we presented both the fixed-effect model and the random-effects model.
For the above reason, we are going to add new text to the Results, Discussion and Conclusions sections.

Results
Two trials assessed the overall side effects of NSAIDs, and there was moderate heterogeneity. The results of a pooled analysis for overall side effects was significant in the fixed-effect model (risk ratio (RR) 2.88 (95% CI 1.11 to 7.45), (P = 0.03), but not in random-effects model (RR 2.94, 95% CI 0.51 to 17.03).
Three trials reported gastrointestinal adverse effects and found no differences between the groups.
Lethargy/drowsiness, feeling hyperactive, feeling more awake, flushed face, difficulty sleeping, light-headedness and dry mouth were reported in one to two trials and the results were not significantly different between the treatment groups.

Discussion
NSAIDs are drawing attention for their side effects. For some NSAIDs, their long-term use increases the risk of cardiovascular disease and may cause gastrointestinal side effects. The frequency of gastrointestinal side effects increases in proportion to the dose and period of medication with NSAIDs but the risk of gastrointestinal side effects cannot be excluded in short-term use. In trials included in this review, the risk of side effects was not evidently high; it is hard to conclude that they are not different from placebo in terms of side effects.

Conclusion
NSAIDs are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of their effect in easing respiratory symptoms. The use of NSAIDs for a cold should be decided in consideration of side effects.

Contributors

Andreas Lundh, Britta Tendal. The Nordic Cochrane Centre, Rigshospitalet, Dept. 3343, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark

WHAT'S NEW

Date	Event	Description
17 April 2015	New citation required but conclusions have not changed	Our conclusions remain unchanged.
17 April 2015	New search has been performed	Searches updated. We did not identify any new trials for inclusion.

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 3, 2009

Date	Event	Description
17 April 2013	New search has been performed	Searches updated. Two new trials were identified and excluded (Azuma 2010; Azuma 2011). Our conclusions remain unchanged.

CONTRIBUTIONS OF AUTHORS

Soo young Kim (SYK), Yoon-Jung Chang (YJC), Ye-won Hwang (YWH) and Yoo Sun Moon (YSM) were responsible for study selection, methodological quality assessment, data extraction and analyses, and writing the review.
Hye Min Cho (HMC) was responsible for the literature search and writing the review.

DECLARATIONS OF INTEREST

Soo Young Kim: none known.
Yoon-Jung Chang: none known.
Hye Min Cho: none known.
Ye-Won Hwang: none known.
Yoo Sun Moon: none known.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Chills [drug therapy]; Common Cold [complications] [*drug therapy]; Cough [drug therapy]; Headache Disorders, Secondary [drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Adult; Child; Humans