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Efficacy and gastrointestinal risk of aspirin used for the treatment of pain and cold

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Aims: To analyse major sources of evidence-based information on the efficacy and gastrointestinal tolerability of aspirin, used short-term, in over-the-counter (OTC) doses, to relieve acute pain and cold symptoms, including associated feverishness.

Methods: Evidence was largely collected from published meta-analyses and systematic reviews that focused on randomised, controlled, double-blind clinical trials, in which aspirin was compared to placebo and, in some cases also, to active comparators such as OTC doses of paracetamol or ibuprofen.

Results: Across a large number of comparisons, aspirin was superior to placebo in treating pain, cold or fever. Efficacy was essentially similar to that of comparators used in equivalent doses. There was no serious GI adverse event attributed to ASA in any study, but mild-to-moderate dyspepsia in small percentages of cases was commonly reported.

Conclusion: OTC aspirin is safe and effective. Safety concerns should not limit brief use to relieve acute pain, cold or fever.

Introduction

Aspirin (acetylsalicylic acid) was first marketed in 1899, after the German chemist Felix Hoffman, a scientist at Bayer Industries, modified the commonly used sodium salt of salicylic acid by acetylation, in an effort to diminish the digestive side effects that troubled his father who suffered from

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Rheumatoid Arthritis. The medication soon enjoyed explosive growth, establishing Bayer Pharmaceuticals as the first modern pharmaceutical company. However, from the beginning the use of aspirin has been tempered by the occurrence of various side effects, the incidences of which were principally related to the dose of drug and duration of therapy.

Despite any side effects, its use as a household remedy was long established prior to the birth of modern pharmaceutical Regulatory Agencies. Principally because of this, and the fact that it was widely regarded as safe and effective, aspirin was 'grandfathered' into both prescription and over-the-counter use, without the performance of the myriad of pre-and post-marketing, randomised, clinical trials that today would be required for any new drug. While initially helpful, this has left the medical use of aspirin at some informational disadvantages. While there is an abundance of data from randomised, double-blind, clinical trials, of the long-term use of relatively low doses of aspirin in the prophylaxis of thrombotic vascular events, (affecting the heart, brain and other organs), and in the prevention of various cancers, there is a comparative paucity of such information attending the short-term use of often higher doses of aspirin, in what has been its main use, i.e. taking it for short times, usually without prescription, in the relief of acute pain, fever, and the symptoms of the common cold or influenza. This review attempts to gather available evidence about these applications in the context of contemporary use of this old-fashioned but still valuable drug.

Efficacy of aspirin

After over a hundred years of world-wide use, it will not be possible to review every study of the efficacy of aspirin, so this paper will review all the important papers published in the past 35 years, embodying data from trials of more modern design and from systematic reviews. The consensus concerning use of the drug prior to this time for pain, fever, common cold and influenza has been reviewed by others [1–4]. Here the efficacy data are presented, as far as possible, using as sources data from trials conducted for specific indications, and grouped under two main headings, 'Pain Relief' and 'Use in Fever, Common Colds or Influenza'. In contrast, all available will be pooled in analysing data on gastrointestinal tolerability and risks of the drug in various trials. This review will summarise all key results and conclusions as to efficacy and tolerability recorded in the various referenced clinical trials. For specifics as to trial design, data analysis and statistical methodologies, readers should consult the quoted references.

Pain relief

Results of trials will be grouped under uses in treating pain under: Headache including Migraine; Toothache; Sore Throat; Menstrual Pain; Back Pain; and Muscular, Joint and Mild Arthritis Pain. In all these trials, efficacy was assessed by using a set of measurements which have served as relatively standard end-points for measuring pain relief in prospective controlled trials, as used by Cochrane Library authors in compiling systematic reviews [5,6]. Pain Relief (PAR), Summed Total Pain Relief (TOTPAR), Pain Intensity Difference (PID), or Sum of Pain Intensity Differences (SPID) over 4–6 h, are commonly used to calculate the number of participants achieving at least 50% pain relief. These results can then be used to calculate the relative efficacy of aspirin, compared to placebo or a comparator drug, the 95% confidence intervals, and the number-needed-to treat (NNT) for 1 subject to achieve the benefit. Other end-points have included counting the number of subjects in each test group who had to use a rescue medication, and employing a variety of subjective measures of pain intensity or pain relief, with the patient using visual analogue scales (VAS) to record their experiences quantitatively. The emphasis of this review is the efficacy and tolerability of aspirin, and other drugs are mentioned only for comparison.

Headache

Migraine – the Cochrane analysis [5]

There have been 13 double-blind, controlled clinical trials of the response to 900 mg or 1000 mg doses of aspirin (ASA), given as tablets or as an effervescent solution, alone or in combination with 10 mg of metoclopramide, in the management of 5261 migraine attacks in 4222 patients, with or without an aura.

The majority (>80%) of the patients were females, aged 18–65 years, and had had migraine for at least 12 months prior to the study period, with 1–6 moderate-to-severe attacks/month. The diagnosis of migraine in all cases was in agreement with guidelines issued by the International Headache Society (IHS). Five of the studies used a placebo comparator, four used only an active comparator, and five used both. In most cases the active comparator was sumatriptan 50 mg or 100 mg. The efficacies of all active comparators were superior to placebo. In the case of aspirin, both doses were equally effective, with NNTs of 8.1, 4.9 and 6.6, for 2-h pain-free, 2 h headache relief, and 24-h headache relief, for ASA vs. placebo. There was no additional benefit derived from the addition of 10 mg of metoclopramide (MTC) in relieving headache, but the combination did reduce associated nausea and vomiting compared to ASA alone. Sumatriptan 50 mg did not differ from ASA alone for 2-h pain-free or 2-h headache relief, but sumatriptan 100 mg was better than the combination of ASA + MTC for 2-h pain-free, but not for headache relief: no 24 h-relief data were given. The authors concluded that ASA 1000 mg is effective in treating acute migraine headaches, similar to sumatriptan 50 mg or 100 mg, and that addition of metoclopramide reduces nausea and vomiting but does not increase the relief of pain.

Non-migrainous headaches

These include 'Tension Headaches' (also known as 'Muscle Contraction Headaches', 'Stress headaches', etc.), 'Cluster Headaches' and over a dozen other HIS-designated varieties. These are currently thought due to both peripheral and central mechanisms, although for the most part they are perceived as arising from peripheral sites [7,8].

There are eight placebo-controlled studies of the use of ASA to relieve headache in subjects in whom the diagnosis of migraine has been excluded; six of these include data on effects of an active comparator as well as placebo. The trials are briefly summarised in Table 1 [9–16].

Looking at all the trials, the lowest dose of aspirin significantly superior to placebo in relieving headache was 250 mg. This and all higher doses were significantly superior to placebo, despite fairly high placebo response rates. The efficacy of ASA was broadly similar to that of any of the comparator drugs, but with some evidence of a dose–response effect: effects of increasing ASA dose above 650 mg were observed but not major. There are some differences in efficacy that relate to the severity of the initial headache. In a publication comparing the efficacy of 1000 mg of effervescent ASA with 50 mg of sumatriptan in migraine, a subgroup analysis of 370 patients with severe pain at baseline vs. 564 patients with moderate pain at baseline, showed higher treatment responses to both drugs in those with moderate pain at baseline. Both drugs were significantly better than placebo in both subgroups, but there was no statistically significant difference between the drugs in either group [17]. Aspirin is effective in headache.

Toothache and postoperative dental pain

Pain following dental procedures has long been accepted as a surrogate for toothache, and pain following extraction of an impacted 3rd molar tooth has been quantified in most studies. The analgesic efficacy of a single dose ASA, given for moderate-to-severe pain following extraction of a third molar tooth, has been evaluated in four randomised, double-blind, placebo-controlled studies that are summarised in Table 2.

ASA was clearly effective in relieving dental pain.

Sore throat

The context in which sore throat has been studied is its occurrence during the common cold where a number of other symptoms may also be present: two placebo-controlled studies have assessed relief of sore throat in this setting [22,23]. The first study [22] examined the effect of a single dose of 800 mg of aspirin in 139 patients with a sore throat due to a respiratory infection, compared to the outcome in 139 placebo-treated patients. The primary outcome measure was 2-h Sum of total Pain Intensity Differences (SPID), and ASA was much superior to placebo ($p < 0.0001$). For all secondary end-points, ASA also achieved statistically superiority compared to placebo. In the second similar study [23], 68 patient received ASA 800 mg alone, 70 received ASA 800 mg + 64 mg of caffeine, and 69 received placebo. Under double-blind conditions, during a 2-h evaluation period, patients used different rating

Table 1
Clinical trials of aspirin in non-migrainous headache.

Design	Drugs	*N*	Results	Ref #
DB, R, P-Contr Parallel	500 mg ASA 1000 mg ASA 500 mg Para 1000 mg Para Placebo	126 128 128 128 128	Response Rates were: 70.3%: $p = 0.011$ vs. P; 75.7%: $p = 0.0009$ vs. P; 63.8%: $p = 0.10$ vs. P; 71.2%: $p = 0.007$ vs. P; 54.5%	[9]
Blind, Latin-Square, P-contr, Cross-o	650 mg ASA 325 mg ASA 163 mg ASA Placebo	100 evaluated	Dosages of ASA and % treated with some relief were: 650 mg (81%), 325 mg (68%), 163 mg (57%) and Placebo (57%): only the 650 mg dose was significantly different from placebo	[10]
DB, R, P- contr, Cross -o	650 mg ASA 400 mg IBU Placebo	50	650 mg ASA and 400 mg IBU were both effective compared to placebo, with very little differences between active drugs.	[11]
DB, R, P-contr, Cross-o	1000 mg ASA 500 mg ASA in 4 of 6 studies reported together	24–36 per study	ASA 1000 mg or 500 mg were significantly superior to placebo in SPID and TOTPAR.	[12]
DB, R, P-contr, Cross-o	1000 mg ASA 500 mg ASA 250 mg ASA Dose-ranging study (study 7)	33 more added to previous (above)	7 studies reported together (includes 6 above); in # 7 there was a dose- response relationship for mean PAR, TOTPAR, and SPID over a 3 hr period, with 250 mg significantly more effective than placebo.	[13]
DB, R, P-contr parallel	650 mg ASA 400 mg IBU 800 mg IBU Placebo	29 30 25 24	Patients on IBU (400 mg and 800 mg) and 650 mg ASA had significantly lower pain scores and higher PID scores at 3 h follow-up than did patients on placebo	[14]
DB, R, P-contr parallel	650 mg ASA 1000 mg Para Placebo	90 87 92	ASA 650 mg and paracetamol 100 mg were both significantly superior to placebo, with some minor differences.	[15]
DB, R, P-contr parallel	1000 mg ASA 500 mg metamizol (M) 1000 mg (M) Placebo	102 102 108 105	All active compounds significantly superior to placebo for SPID. Maximum PID, number of patients with >50% pain reduction, maximum PAR and TOTPAR.	[16]

Abbreviations (in order of occurrence): *N* = number of subjects; Ref # = reference number; DB = double blind; R = randomised; ASA = aspirin; P-contr = placebo-controlled; P = placebo; Para = paracetamol; Cross-o = cross-over; IBU = ibuprofen; SPID = sum of total pain intensity difference; TOTPAR = total pain relief; PAR = pain relief; PID = pain intensity difference; M = metamizol. FOR 'PAR', 'TOTPAR', 'PID', 'SPID', see Ref. [8] for details.

scales to assess pain intensity, change in pain, pain relief, and two qualities of throat pain, i.e. how swollen the throat felt, and difficulty in swallowing. Both active treatments were significantly more effective than placebo, for all efficacy measurements, from 30 min through 2 h, and ASA-plus-caffeine was superior to ASA alone. Specifically, in the 2 h SPID dimension, ASA was highly significantly superior to placebo ($p < 0.01$) [23]. Again aspirin was clearly effective. Many patients with sore throat dissolve 2 ASA tablets in warm water, gargle with this solution for 5–10 min, and then swallow the material. Despite its popularity, and that of combining dissolved ASA with topical local anaesthetics, the efficacy of this method of using ASA has not been evaluated.

Other pains

Menstrual pain

The efficacy of ASA in relieving dysmenorrhoea has been documented in earlier literature in one randomised, double-blind, placebo-controlled trial [24], and in two meta-analyses [25,26] involving over 2000 patients. Ninety women, who suffered from pain and cramps during menstruation, participated in a 4-month study, taking no medication for their first two periods. Thereafter, they were

Table 2
Clinical trials of aspirin for acute dental pain.

Design	Drugs	*N*	Main results	Ref #
DB, R, P-contr parallel	1000 mg ASA 650 mg ASA Placebo	71 68 75	ASA 1000 mg and 650 mg were significantly superior to placebo in SPID, PID, TOTPAR & > 50% response rates.	[18]
DB, R, P-contr parallel	650 mg ASA Bromofenac 5 mg 10 mg 25 mg 400 mg IBU Placebo	41 39 43 42 37 39	ASA 650 mg, IBU 400 mg, Bromofenac 5 mg, 10 mg, and 25 mg were all superior to placebo for SPID, PID, TOTPAR and hours of >50% relief. IBU 400 mg & Bromofenac 25 mg were superior to 650 mg ASA ($p< 0.01$)	[19]
DB, R, P-contr parallel	650 mg ASA Diclofenac 25 mg 50 mg 100 mg Placebo	252 Group sizes not given	All active treatments were superior to placebo in their effects on SPID and TOTPAR, over an 8 h period. A 100 mg dose of diclofenac was superior to all other therapies.	[20]
DB, R, P-contr parallel	500 mg ASA 200 mg IBU-Lysine Placebo	65 77 41	For pain intensity, pain relief, time to meaningful pain relief both active treatments were significantly superior to placebo	[21]

Abbreviations (in order of occurrence): *N* = number of subjects; Ref # = reference number; DB = double blind; R = randomised; ASA = aspirin; P-contr = placebo-controlled; P = placebo; SPID = sum of total pain intensity difference; PID = pain intensity difference; TOTPAR = total pain relief; IBU = ibuprofen FOR 'TOTPAR', 'PID', 'SPID', see Ref. [8] for details.

randomised for their next two periods to receive identical-appearing tablets, containing either ASA 650 mg (30 subjects), or paracetamol 650 mg (30 subjects), or placebo (30 subjects). Pain scores were rated on a 4-point scale for the four menstruations. ASA and paracetamol were found to be equally, and significantly, more effective than placebo [24].

In a meta-analysis of 56 controlled trials of four common NSAIDS used in the treatment of primary dysmenorrhoea [25], the efficacy of ASA could be assessed by various methods in 11 studies, encompassing outcomes in 486 patients given 650 mg ASA 4 times/day, compared to placebo. The response rate ratio (RRR), for ASA achieving at least moderate pain relief compared to placebo, was 1.6 (95% CI: 1.12, 2.29), though data were not easily combined. In an even earlier study published in 1982 [26], an analysis was made of data relating to pain of female genital origin from over 4000 post-surgical, post-episiotomy patients, and those with uterine cramping from any cause, who had received 325 mg, 650 mg, 1300 mg of ASA or placebo for pain. Despite the analysis of a mixed bag of patients, statistically significant benefits compared to placebo were apparent for single doses of ASA from 325 mg to 1300 mg, and for a daily dose of 2600 mg [26]. Additional studies of more modern design and execution would be helpful in determining the magnitude of the benefit of ASA, and the correct dose for optimal OTC use. Despite scarcity of data, ASA appears effective in the treatment of dysmenorrhoea.

Back pain, muscular and joint pain, minor arthritis and joint pain

Despite common use, there are no adequate well-controlled studies in the published literature of the effects of ASA on these pains. In the case of back pain, there is no proper efficacy trial of ASA vs. placebo. A meta-analysis of 26 trials of the efficacy of NSAIDs in general [27] yielded mixed results when the drugs were used short-term for low-back pain of unknown cause. In the presence of sciatica or those with nerve root symptoms, ASA/NSAIDs were generally ineffective.

Fever, common colds and influenza-like illnesses

The 'common cold' (also known as 'Rhinitis acuta catarrhalis', 'cold', 'coryza', or 'nasopharyngitis') is an upper respiratory tract infection (URTI), most commonly by a rhinovirus or corona virus, but 10–15% of colds are caused by influenza viruses: over 200 different viruses have been linked to these

'influenza-like' illnesses, so ASA trials in 'cold' include patients with a variety of different illnesses. A 'cold' typically presents with runny nose, cough, sore throat and chills. Occasionally there may be other accompanying symptoms such as fever, conjunctivitis, headache, muscle aches, fatigue and other vague symptoms. The condition has been reviewed in depth by Eccles [28]. While a cold is 'influenza-like', and may be accompanied by 'chills' or a real sensation of 'chilliness', fever is mild, uncommon and transient. In true influenza the symptoms are generally more severe, with prominent cough, sustained fevers, and onset of gastrointestinal symptoms. However, the conditions are often confused at the onset. There is no cure for the common cold but, unlike influenza, the symptoms are mild and usually treated with over-the-counter remedies. Among these is aspirin, a drug believed to reduce symptoms although it cannot shorten or prevent the disease. Getting 'a cold' is one of the most frequent reasons for patients to consult a physician. Two studies done in the setting of 'cold' have already been quoted in the section on 'sore throat', and ASA was clearly effective [22,23]. There are three additional controlled trials of ASA use in treating colds and fever, in one of which ASA treatment was compared to placebo, and in two of which it was compared to another active treatment. These studies are summarised in Table 3.

The agents causing these illnesses were not identified, so 'cold' groups are probably heterogeneous, and may include influenza virus illnesses as well as 'colds'.

Two studies [30,31] are from 1986. However, the 2005 study from Bachert et al [29] is worth careful examination. This was a multicenter, randomised, double-blind, double-dummy, placebo-controlled, parallel group trial that admitted only patients with URTI and Acute Fever $\geq$38.5 °C. This made it well suited to evaluating the anti-pyrexial effects of the 'cold' drugs, unlike other trials that included afebrile patients.

Here Fig. 1A (reproduced by permission [29]) clearly shows the time courses of temperature alterations in response to single doses of 500 mg or1000 mg of either ASA or paracetamol, with approximately 80 patients in each group. The primary measure of efficacy was the AUC for the change in body temperature, from the time of drug administration to 4 h post-dose. All of the differences between groups shown in Fig. 1B were statistically significant ($p < 0.001$). Significant reductions were also seen in the intensity of headache, 'achiness', and 'feverish discomfort', but not in sinus sensitivity to percussion or sore throat. These data (Fig. 1A and B) provide unequivocal evidence of the efficacy of single doses of ASA (and paracetamol) in lowering body temperature in this setting. Similar time courses of temperature change were also observed in the active comparator studies [30,31].

Table 3
Clinical trials of aspirin in fever, common cold/influenza.

Design	Drugs	*N*	Results	Ref #
DB, R, P-contr parallel	ASA 500 mg ASA 1000 mg Para 500 mg Para 1000 mg placebo	78 78 79 79 78	ASA and paracetamol equally more effective against fever and other symptoms of URTI than placebo: both active treatments showed dose-related efficacy, with no differences between equal doses of the 2 agents.	[29]
DB, R, Act-contr parallel, for 4 days	ASA 500 mg Twice daily Flurbiprofen 100 mg bid	15 15	ASA and flurbiprofen both lowered fever effectively with similar antipyretic effects; URTI, GI, articular and muscular pains and asthenia were also relieved by both drugs.	[30]
R, active, parallel, for 2 days	ASA 500 mg × 4 daily. Diclofenac 25 mg twice/day.	60 60	ASA and diclofenac lowered fever effectively; Mean temperature changes over 2 days and overall assessments of antipyretic effects were good in all cases, and similar for both drugs.	[31]

Conclusion on efficacy

From the materials listed and summarised in this paper it is clear that even a single dose of ASA possesses the ability to relieve, and sometimes completely abolish, pain of a variety of types and severities. It also lowers pyrexia, and relieves many of the vague but troubling symptoms that attend the common cold, and does so to an extent comparable to similar doses of competing OTC products. Efficacy in relieving migraine headache seems generally underrated: it appears to be just as effective as the more expensive sumatriptan.

The amount of credible data for all OTC products is greatest in documenting pain relief. Although the amount of evidence supporting ASA use to treat fever and influenza-like illnesses is less, it nevertheless demonstrates efficacy of the drug. One limitation is that the data are mainly derived from subjects over 18 years of age: though causality remains unproven, the widely held suspicion that ASA may be involved in the pathogenesis of Reye's Syndrome, in recent years has greatly limited paediatric use of the drug [32]. Unanswered is whether use of any of the newer marketed forms of aspirin (effervescent tablets, dry granules, chewable tablets, caplets, or carbasalate calcium tablets) will prove, in head-to-head comparison trials, to have any significant clinical advantage over each other, or over currently available plain tablets. Similarly, there is a scarcity of valuable information on the value of

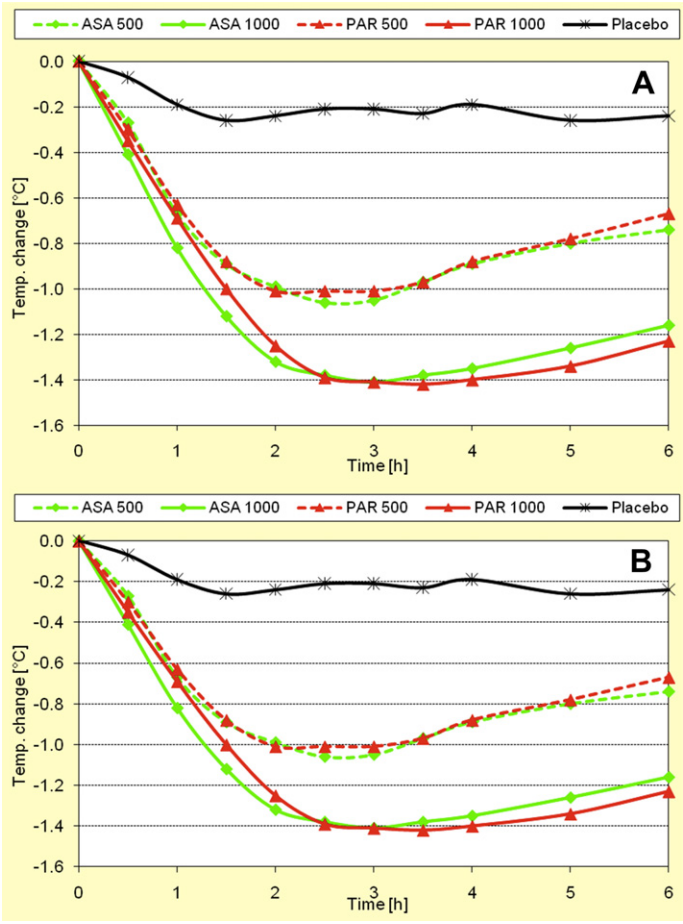

Fig. 1. Mean temperatures recorded for 6 h (A) following time of administration of medication and (B) from time of administration of medication, for all five treatment groups.

short-term use of aspirin in combination with other drugs, e.g. metoclopramide, pseudoephedrine, lidocaine, dextromethorphan, Vitamin C and caffeine, all of which combinations are sold OTC. Evaluation of these efficacies is beyond the scope of this review. Nevertheless, the efficacy of ASA can be regarded as established in all of the ailments reviewed.

Tolerability of aspirin – what are the gastrointestinal risks

Background

From the beginning of their medicinal use it has been recognised that some side effects attended the consumption of aspirin or salicylates, the gastrointestinal (GI) effects probably being the most frequently experienced. In 1938, the first description of the finding of ulcers and other gastric lesions in the stomachs of aspirin users at gastroscopy, led to the realisation that gastrointestinal symptoms attending the use of aspirin might be accompanied by frank mucosal injury [33]. As later emerged from largely observational studies, use of aspirin or other NSAIDs was also occasionally associated with serious gastrointestinal complications such as perforation, haemorrhage, obstruction and even death, although the majority of the deaths have occurred in elderly patients with serious co-morbid conditions [34]. For this reason, the numbers of deaths or complications solely attributable to aspirin or NSAIDs remains undetermined, but is probably quite small [35].

Some GI complications arise from lesions actually caused by these drugs, but others arise from the anti-platelet effects of the drugs on a variety of GI lesions, causing them to bleed, especially when the drugs are used in combination with each other, in higher doses, for longer periods of time, or in co-use with steroids, anti-coagulants or other anti-platelet medications [35]. Detailed accounting for many of these factors is commonly lacking in epidemiological studies. The incidence of GI symptoms is usually ignored. Because of the large number of additional factors which attend the outcome of aspirin use in individuals or in specific groups, the exact risk of a dose of aspirin causing an Adverse Effect (AE) in any particular situation is quite variable. The GI recently reviewed safety of cyclo-oxygenase inhibitor drugs in general, pertains mainly to serious events, long-term use, in chronic conditions, and is limited to outcomes attributed to ulcers [36]. These data have no direct relevance to this paper, but furnish a background as to why some vague concerns among physicians and members of the public, about the GI safety and tolerability of ASA, may spill over into limiting short-term use of an effective compound in very different settings, i.e. to relieve the acute symptoms of pain, fever or a 'cold', in otherwise healthy adults.

Adverse events in acute short-term studies

Aspirin is marketed OTC in different forms and various doses (300 mg, 325 mg, 500 mg, etc.), in different countries, but for most acute, short-term use, a recommended one-time dose of between 300 mg and 1000 mg is employed, and up to daily doses of 3000–4000 mg. Marketing studies and clinical trial data both indicate that most users take a single dose, and few use ASA for more than one day. In comparison to the large amount of largely epidemiological data on the safety and tolerability of aspirin use in chronic diseases, relatively few studies have examined outcomes in the setting of acute short-term use. Many of the trials reported are small and of questionable quality, so the current discussion will focus on published reviews and meta-analyses where, with careful pooling of results of comparable studies carried out in similar circumstances, conclusions can be drawn based on results from fairly large numbers of subjects.

(1) An early publication from Oxford examined the adverse effects of a single dose of aspirin ($N = 3253$) compared with placebo $N = 3297$), in 72 randomised trials that met inclusion criteria [37]. Some studies also included the comparators paracetamol or ibuprofen. Although no adverse effects were reported in 6 trials, overall 12% of patients on aspirin and 10% of patients on placebo reported at least one adverse effect (AE) with Number-Needed-To-Harm (NNTH) of 44 for aspirin compared to placebo. With aspirin doses of 600/650 mg, significantly higher incidences of drowsiness and 'gastric irritation' were reported than with placebo, with NNTHs of 28 and 38, respectively.

(2) About the same time, from France appeared the first version of a study of unusual design [38] that directly compared the tolerabilities of aspirin, paracetamol and ibuprofen, but not placebo, in 8233 subjects, recruited by 1108 general practitioners. The study relied almost entirely on data recorded by the patients. Although at least four subsequent publications of data extracted from this same study calculated similar total AE rates [39–42], estimates of the relative safety and GI tolerability of the three compounds were not closely comparable. The findings from two of these publications are summarised in Table 4, furnishing different estimates of Serious GI Adverse Events (SGAE), for example dyspepsia, making clear conclusions elusive [41,42].

These estimates are higher than those reported in other trials reported here. This might be due in part to the trial being carried out over a 7-day period. Furthermore, during the 7-day period, individual patients may have consumed at different rates, different numbers of the 42 tablets supplied: less than 50% of patients completed 7 days of treatment, and results were not adjusted for consumption or compliance. Another factor relates to a similar trend observed in an unrelated study that also used patient-reported data [43]. The authors of that study, commenting on patient reporting, wrote that the 'method generates an excessively strong tendency to report those adverse clinical effects suspected to be drug-related'.

(3) A third attempt, to address gastrointestinal tolerability of ASA directly, came from a study that took only closely comparable, randomised, controlled, double-blind, placebo-controlled trials, all done for pain relief (>75% of patients had migraine), and for whom all individual patient data (IPD) were on file with the sponsor of the trials – Bayer GmbH, Leverkusen, Germany [44]. Data from 9 trials, 1 of which was of cross-over design and 8 of which were parallel group studies, was included in the IPD database; all trials compared 1000 mg ASA to placebo. Data retrieval, statistical analysis and preparation of tables were done by an independent contract company, ClinResearch GmbH of Cologne, Germany.

Among 2852 cases included, 1581 received ASA and 1271 placebo. Overall AE rates were 14.9% and 11.1% for ASA and placebo, respectively (NNH: 26). Among all AEs, the organ system most affected was the gastrointestinal tract (5.9% for ASA and 3.5% for placebo: NNH: 42). Adverse Drug Reactions (ADRs) for the GI system were lower (ASA: 3.1% and placebo 2.0%): even these rates may be overestimates because many of the ADRs were nausea or vomiting, possibly due to migraine itself (the majority of subjects included) rather than to drug. Results of this analysis bore a striking resemblance to those of the earlier-quoted Oxford study [37] though drowsiness was not observed. The term 'gastric irritability', previously reported as 3.7% [37] could not be used for direct comparison with the figures reported here, 5.9% gastrointestinal adverse events (GIAEs) or 3.1% gastrointestinal adverse drug reactions (GIADRs). Nevertheless, placebo AE rates were almost identical (11.0% [37] and 11.1% [44])

Table 4
Significant adverse events in PAIN study, variously sampled/reported.

Year	Drug	SAE (%)	GI SAE	Ref #
1999	ASA	18.7	Dyspepsia: 7.1% Abdominal pain: 6.8%	[41]
	Para	14.5	Dyspepsia: 5.3% Abdominal pain: 3.9%	
	IBU	13.7	Dyspepsia: 4.0% Abdominal pain: 2.8%	
2002(1)	ASA	16.8	Abdominal pain: 5.6% Digestive system: 5.7% Dyspepsia: 2.3%	[42]
	Para	12.0	Abdominal pain: 2.9% Digestive system: 4.1% Dyspepsia: 1.3%	
	IBU	12.3	Abdominal pain: 2.4% Digestive system: 3.6% Dyspepsia: 1.1%	

and the very slightly different AE rates for ASA were 13.0% for 600/650 mg [37] and 14.9% for 1000 mg [44] doses, possibly a dose effect.

(4) The recent Cochrane analysis [5] pertaining to migraine headache was primarily concerned with the efficacy of ASA in relieving the headache caused by migraine, and made no attempt to deal with the issue of GI tolerability. Nevertheless, an attached appendix summarising AEs in 13 published studies, reports some analysable data on GIAEs for 7 of the studies, yielding a rough estimate of GIAE incidence of 72 in a total of 1321 cases, 5.45%: no estimate of a placebo GI AE rate is possible, but the crude incidence rate is quite similar to the 5.9% rate in the Bayer IPD study [44]. Looking at many papers, 'somnolence' occurs as an AE only in studies involving migraine.
(5) Most recently, an extensive detailed study of the incidence of all ASA-associated adverse effects has been completed [45]. This study was commissioned and supported by Bayer HealthCare, but not executed by them. A panel of 4 independent university professors, with combined expertise in Gastroenterology, Pharmacology, Clinical Trial Design, Data Collection/Analysis, Statistics, and clinical medicine in general, was commissioned by Bayer to execute the study, with no restriction of their access to any company data. In addition, one clinical scientist and one statistician, employed by Bayer, facilitated the panel's access to company records, and aided in locating relevant study details/results and clarifying in-house statistical analysis. A detailed account of the elaborate methodology has been published [45]. Individual patient data obtained from the records of all clinical trials involving ASA conducted by Bayer prior to March 31, 2008, was entered into a new (IPD) database designed for the study. After establishment of clear inclusion criteria, 67 trials were considered suitable for objective analysis. Some studies that compared aspirin with either paracetamol or ibuprofen were also included because of relevance to widespread OTC use.

The primary end-points were GI adverse events. Bayer assigned the appropriate MedDRA terms to each selected AE, but the academic authors also defined additional groups: 'Combined Preferred Terms per System Organ Class', that combined 38 MedDRA terms into 7 clinically relevant designations: GI bleeding, any dyspepsia, minor dyspepsia, severe dyspepsia, abdominal pain, gastro-esophageal reflux disease (GERD)-related symptoms, and oral complications. The search identified 6181 IPD records suitable for analysis. Of these 5099 (82.5%) received a single dose, 1082 (17.5%) a multiple dose regimen, and 188 (3%) were treated for over 5 days. Over half (54%; 3337 patients) took a daily dose of ASA between 500 mg and 1000 mg. Doses of paracetamol of 300 mg (31%), 500 mg (16.6%) and 1000 mg (52.3%) and ibuprofen 200 mg (45%) and 400 mg (55%) were used in comparison studies. Patients were 18–65 years of age, with only 1% older, limiting generalisation of the findings.

Aspirin vs. placebo

The overall incidence of all adverse events was low and similar among those treated with ASA (741/4884: 15.2%) or placebo (580/3731: 15.5%) with (OR 1.1; 95%CI: 0.96, 1.2). The overall incidence of all GIAEs (adding a large number of terms) was also low, with ASA 9.9% vs. placebo 9.0% (OR 1.3: 95%CI: 1.1, 1.5, a slight increase with ASA). There was also a slight increase in Minor Dyspepsia, ASA: 5% vs. placebo: 4% (OR 1.4: 95% CI: 1.1, 1.8), but no significant increase in major dyspepsia or any other symptom. There were very few serious GI events, one GI bleed on ASA and two on placebo, none of which were considered drug-related by the original investigators. More patients (18.1%) on ASA $>$1000 mg/day had AEs than did those on ASA $<$500 mg/day (15.1%), or on placebo (13.5%); and multiple dose administration was also associated with an increase in AEs (16.2%) compared to single dose (12.8%): placebo rates were similarly affected. There was no interaction by age or gender. When events were expressed as ADRs, findings were essentially similar (not published).

Aspirin vs. comparator

There were no statistically significant differences between ASA and either active treatment for the 'Combined Term' Dyspepsia, although ORs were greater than 1.0 for the comparisons with ibuprofen. For ASA vs. paracetamol, the risk of dyspepsia with ASA was slightly increased when the MedDRA term

but not the 'Combined Term' (defined a priori by the academic panel) was examined. A small non-significant increase in ASA dyspepsia, compared to ibuprofen was noted, but there were no important statistically or clinically significant differences in tolerability between the three OTC compounds tested. The use evaluated here was very brief and mostly single dose, although OTC market surveys suggest that 92.4% of aspirin users take only 1 or 2 tablets per month [46].

Summary

The most important finding is that across all studies there was not one serious GIAE, e.g. haemorrhage, perforation, obstruction or death, attributed to ASA. Although total AE rates for ASA were between 0% and 5.9% higher than placebo, such differences were between 1% and 3% in most studies. Across studies, only an increase in mild-to-moderate dyspepsia achieved statistical significance but appeared dose-dependent. 'Gastric irritation' could not be evaluated but appeared minor. There was no increase in severe dyspepsia. There were no significant increases in abdominal pain in most analyses: in the large IPD study [45], there were small, non-significant increases in incidences of abdominal pain and GERD-related symptoms (all of $<0.1\%$). On the basis of these extensive analyses, ASA appears quite effective, well tolerated by the GI tract, and risks of GIAEs attending brief use appear minor.

However, this conclusion is based on data from short-term, low-dose use in apparently healthy adults, between ages 18 and 65 yrs, with all serious co-morbid illnesses and hazardous co-therapies excluded before entry into trials. Unless much larger numbers of patients were included, the serious AEs seen in population studies would not have been detected. In such studies, brief or modest doses of ASA have been hazardous in some high-risk situations. How closely conclusions presented here reflect actual consequences of OTC use of ASA in the general population, awaits the results of larger surveys, but these findings suggest that safety concerns should not limit brief, symptomatic, use of this very effective drug.

Conflict of interest statement

None declared.

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