REVIEW ARTICLE

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A Benefit-Risk Assessment of Caffeine as an Analgesic Adjuvant

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Abstract

Caffeine has been an additive in analgesics for many years. However, the analgesic adjuvant effects of caffeine have not been seriously investigated since a pooled analysis conducted in 1984 showed that caffeine reduces the amount of paracetamol (acetaminophen) necessary for the same effect by approximately 40%. *In vitro* and *in vivo* pharmacological research has provided some evidence that caffeine can have anti-nociceptive actions through blockade of adenosine receptors, inhibition of cyclo-oxygenase-2 enzyme synthesis, or by changes in emotion state. Nevertheless, these actions are only considered in some cases. It is suggested that the actual doses of analgesics and caffeine used can influence the analgesic adjuvant effects of caffeine, and doses that are either too low or too high lead to no analgesic enhancement.

Clinical trials suggest that caffeine in doses of more than 65mg may be useful for enhancement of analgesia. However, except for in headache pain, the benefits are equivocal. While adding caffeine to analgesics increases the number of patients who become free from headache [rate ratio = 1.36, 95% confidence interval

(CI) 1.17 to 1.58], it also leads to more patients with nervousness and dizziness (relative risk = 1.60, 95% CI 1.26 to 2.03).

It is suggested that long-term use or overuse of analgesic medications is associated with rebound headache. However, there is no robust evidence that headache after use or withdrawal of caffeine-containing analgesics is more frequent than after other analgesics. Case-control studies have shown that caffeine-containing analgesics are associated with analgesic nephropathy (odds ratio = 4.9, 95% CI 2.3 to 10.3). However, no specific contribution of caffeine to analgesic nephropathy can be identified from these studies. Whether caffeine produces nephrotoxicity on its own, or increases nephrotoxicity due to analgesics, is yet to be established.

Caffeine has been used as an additive to analgesics since it was first isolated and characterised in 1895.[1] Formulations containing caffeine with analgesics such as paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drugs (NSAIDs) have long been available. However, the ability of caffeine to actually increase the analgesic response has not been universally accepted. Clinical studies performed in the 1950s and 1970s yielded results indicating that caffeine-containing analgesics produce analgesic effects similar to those of the analgesics alone.[2-5] Nevertheless, Laska and colleagues[6] found that, when added to paracetamol or aspirin (acetylsalicylic acid), caffeine reduced the amount of analgesic necessary for the same effect by approximately 40%. They pooled results from 30 unpublished clinical trials and obtained a relative potency of 1.4 [95% confidence interval (CI) 1.2 to 1.6].[7] These results were supported by some later studies,[8-11] but not others.[12-16]

While randomised controlled trials have supported the efficacy of caffeine-containing analgesics, they have also detected some adverse effects, such as nervousness and dizziness.[10,11] Epidemiological studies have indicated that analgesics are associated with withdrawal headache[17-20] and nephropathy.[21,22] However, it is still not known whether caffeine-containing analgesics increase the risk of these conditions. This review attempts to assess clinical evidence for both benefit and harm when using caffeine-containing analgesics versus analgesics alone.

1. Pharmacology

1.1 Mechanisms of Action

1.1.1 Interference with Drug Absorption/Metabolism

Since caffeine lowers gastric pH and increases gastric and hepatic blood flows,[23,24] it might improve the absorption of agents whose pk_a renders them non-ionised in an acid environment (e.g. aspirin).[25] However, several animal studies do not support these views, as there was no significant change of NSAID plasma concentrations when caffeine was administered concomitantly, although anti-nociceptive effect was increased.[26-30] Moreover, some reports have shown that caffeine coadministration results in a reduction of paracetamol and aspirin plasma concentrations.[31,32] It is therefore suggested that modification of the antinociceptive effect of analgesics by caffeine is not likely to be due to a pharmacokinetic interaction, but results need to be clarified with human studies.

1.1.2 Antagonism of Adenosine Receptors

Caffeine is a nonselective antagonist of adenosine receptors, and much of its pharmacology is understood in relation to the blockade of adenosine A_1 and A_2 receptors in several physiological systems.[33] In the peripheral nervous system, results from both animal and human studies indicate that adenosine is pro-nociceptive.[17] It is postulated that the analgesic activity of caffeine is due to blockade of peripheral pro-nociceptive actions of adenosine, activation of the central noradenosine pathway (i.e. pain-suppressing systems), and stim-

ulation of the central nervous system with subsequent actions on pain perception.[25] Caffeine is absorbed efficiently from the gastrointestinal tract, and peak plasma concentrations occur 15 to 120 minutes after ingestion. An oral dose of 1 mg/kg in humans (equivalent to a cup of coffee) produces plasma concentrations of 1 to 2 mg/L or 5 to 10 μmol/L. The active plasma concentration of caffeine ranges from 5 to 10 μmol/L for mild central stimulation to about 50 μmol/L for inhibitory effects.[17,25,33] However, the dose-dependent response reaches a maximum at the plasma concentration of 100 μmol/L and then declines as the concentration of caffeine is further increased. Whether this contributes to the discrepancies in clinical effects needs to be determined.

1.1.3 Cyclo-Oxygenase-2 Inhibition

Fiebich and colleagues[34] investigated the inhibitory effects of aspirin, paracetamol and caffeine on lipopolysaccharide (LPS)-induced cyclooxygenase (COX) and prostaglandin (PG) E_2 synthesis in primary rat microglial cells. The results suggested that not only aspirin, but also paracetamol and caffeine, inhibit PGE_2 synthesis in microglial cells and that both paracetamol and caffeine enhance the inhibitory effect of aspirin on microglial PGE_2 synthesis. The synergistic effects of the combinations of aspirin with paracetamol or caffeine were explained by different mechanisms of COX inhibition. The mechanism of action of aspirin-like drugs at the catalytic site of the COX enzyme has been well established.[35] However, paracetamol may act at a different site, such as the peroxidation site of COX, while caffeine may block synthesis of the COX-2 protein, probably at the transcriptional level, providing less enzyme for aspirin to inhibit, and thereby leading to enhanced COX-2 inhibition. Caffeine is a nonselective antagonist of adenosine A_1 and A_2 receptors. Adenosine A_{2a} receptors induce intracellular signalling events that cause an upregulation of the COX-2 gene and the release of PGE_2 in rat microglia.[36] Selective adenosine A_2 receptor antagonism has also been shown to inhibit adenosine-induced COX-2 expression and PEG_2 release in rat microglial cells.[36] Thus, the inhibitory effect of caffeine on COX-2 activity in stimulated microglial cells may be due to adenosine A_2 receptor antagonism. This hypothesis of action needs to be evaluated directly in animal models and clinical trials.

1.1.4 Other Mechanisms of Action

There is fair amount of literature on the intrinsic analgesic actions of caffeine in both animal models and clinical trials.[17,25] These properties should be viewed in context with the multiple actions of adenosine on the transmission of noxious sensory information as described in section 1.1.2. Another recent interesting interpretation of the intrinsic analgesic actions of caffeine is that these actions result from disinhibition of inhibitory adenosine actions on central cholinergic nerve terminals, which leads to increased acetylcholine release and activation of cholinergic mechanisms involved in analgesia.[37]

Since changes in emotional state are known to modify the perception of pain,[38] caffeine-induced changes in mood are also considered as a source of pain relief.[13]

Although there are many studies and hypotheses on the mechanism of action of caffeine as an analgesic or analgesic adjuvant, the specific mechanism still remains unclear. In addition, pain of differing origin has differing pathophysiology. Postlabour pain is tissue pain, tooth extraction pain is partially of neuropathic origin and migraine may relate to vascular function. Whether these differences cause discrepancies in caffeine's analgesic effects is unknown. However, types of pain should at least been considered when the analgesic adjuvant effect of caffeine are discussed.

1.2 Concentration-Response Curve

Granados-Soto et al.[30,39] undertook a study of the modification of the anti-nociceptive effect of paracetamol by caffeine in rats. Sixteen different paracetamol-caffeine combinations were tested (100-10, 100-18, 100-32, 100-56, 178-10, 178-18, 178-32, 178-56, 316-10, 316-18, 316-32, 316-56, 562-10, 562-18, 562-32 and 562-56 mg/kg), and caffeine produced a significant increase in the anti-

nociceptive effect of paracetamol only with certain caffeine-paracetamol combinations. The best enhancement was observed with a ratio of paracetamol 316 mg/kg to caffeine 32 mg/kg. It was postulated that caffeine coadministration produced a parallel shift of the paracetamol sigmoidal concentration-response curve to the left (figure 1).

Given these results, it is possible to understand why caffeine enhances the anti-nociceptive effect of analgesics in some, but not in all, cases. The curves can be divided into three zones. Zone 1 corresponds to low concentrations, at which the anti-nociceptive response of paracetamol, either alone or combined with caffeine, is poor. Therefore, if the paracetamol dose is low and yields effects within zone 1, there will not be any difference in the anti-nociceptive effect when paracetamol is combined with caffeine. However, at higher concentrations, identified as zone 2, there is a quasi-linear concentration-effect relationship, and the shift to the left of the concentration-response curve can be clearly seen. Thus, it is possible to demonstrate differences in the analgesic response between paracetamol alone and the combination of paracetamol with caffeine. In order to effectively observe the enhanced analgesic response, the dose of paracetamol must yield effective-compartment concentrations within the range depicted by zone 2. If the dose of paracetamol is too high, it will yield compartment concentrations within zone 3, where the maximal effect is reached. In such a case, there is a ceiling effect, whereby it is not possible to increase the paracetamol effect any further, either by increasing the paracetamol concentration or by caffeine coadministration.

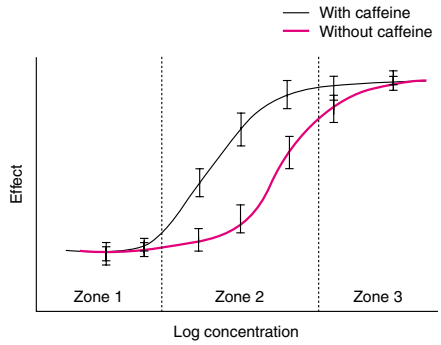

Fig. 1. Hypothetical concentration-response curve of paracetamol (acetaminophen) in the absence and in the presence of caffeine (reproduced from Granados-Soto and Castaneda-Hernandez,[39] with permission).

2. Efficacy

2.1 Headache

There have been a number of studies investigating the analgesic adjuvant action of caffeine in relieving headache (table I). All of them were undertaken with single dose analgesic treatment. One study was excluded because the caffeine/analgesic combination arm contained different analgesics from the monotherapy arm.[2] Assuming aspirin and paracetamol have equal analgesic efficacy, the remaining five studies are useful for determining additional analgesic effects of caffeine, and constitute 10 randomised controlled trials of 3648 patients with headache .[9-11,13,40] The results showed statistically significant differences in pain relief between the caffeine-containing analgesics and analgesic monotherapy (table I). In one study,[13] a difference in pain relief was not found with the low dose (65mg), but was observed with the high dose (130mg) of caffeine.

Sum of pain intensity difference (SPID) or percentage SPID was used as a primary outcome measure in these five studies. Three studies[9-11] also measured total pain relief score (TOTPAR), peak pain relief and peak pain intensity difference (PID). They all showed statistically significant differences between combination therapy and analgesic monotherapy, and the differences were independent of the consumption of caffeine through dietary sources.

Pain intensity is measured using categorical or visual analogue scales. To account for differences in baseline pain intensity among patients in the study, PID is obtained by subtracting pain score at any interview point from that at baseline. Positive scores indicate a reduction in pain, making the PID score analogous to relief scores. PID and relief

Table I. Analgesic adjuvant effect of caffeine in headache pain

Trial	Design	Comparisons	No. of participants	Primary outcome measure	p Value[a]
Currier & Westerberg[2]	DB-C	Aspirin 454mg + phenacetin 320mg + caffeine 64mg *vs* aspirin 640mg	28		>0.05
Wojicki et al.[40]	DB-C	Paracetamol (acetaminophen) 1000mg + caffeine 100mg *vs* paracetamol 1000mg	144	% pain relief	<0.05
Schachtel et al.[9]	DB-P	Aspirin 1000mg + caffeine 64mg *vs* paracetamol 1000mg	302	SPID	<0.05
Ward et al.[13]	DB-C	Paracetamol 648mg + caffeine 65mg *vs* paracetamol 648mg	60	% SPID	>0.05[b]
		Paracetamol 648mg + caffeine 130mg *vs* paracetamol 648mg	60	% SPID	<0.05[b]
Migliardi et al.[10]	4 × DB-C	Paracetamol 500mg + aspirin 500mg + caffeine 130mg *vs* paracetamol 1000mg	1900	% SPID	<0.05
	2 × DB-C	Paracetamol 1000mg + caffeine 130mg *vs* paracetamol 1000mg	911	% SPID	<0.05
Diamond et al.[11]	DB-P	Ibuprofen 400mg + caffeine 200mg *vs* ibuprofen 400mg	331	SPID	<0.05

a For greater effect of caffeine combination.

b % SPID was not reported but can be derived from the original report.

4 × = 4 trials; **2** × = 2 trials; **DB-C** = double-blind crossover; **DB-P** = double-blind parallel; **SPID** = sum of pain intensity difference; **% SPID** = percentage sum of pain intensity difference.

scores are commonly summed over the observation period, weighted for the time between observations, and the summed scores respectively termed SPID and TOTPAR. SPID and TOTPAR have been widely used because they are relatively sensitive, and often show a statistically significant difference between graded doses of analgesics when peak scores or scores from a single hour do not. However, SPID and TOTPAR scores, like any area under the curve measures, confound onset and duration of analgesic effect with magnitude. A short-acting, highly effective drug cannot be distinguished from a long-acting, marginally effective drug. In addition, patients want to know whether a treatment can provide clinically significant pain relief, not whether it can improve scale scores. In contrast to SPID and TOTPAR scores, measuring the percentage of patients with complete pain relief or more than 50% pain relief has clear-cut clinical significance.[14-16]

Data for percentage of patients with complete pain relief are available from three studies.[9,11,40] The results were re-analysed and a superiority of the caffeine/analgesic combination over analgesic alone was found (table II). Compared with analgesic monotherapy, treating five patients with the combination will lead to one more patient free from headache [number needed to treat (NNT) = 5, 95% CI 4 to 9]. In these studies, only usual doses of analgesics (paracetamol/aspirin 1000mg, ibuprofen 400mg) were used, and doses of caffeine were 65 to 200mg. Laska et al.[7] suggested this dose range of caffeine may be important for adjuvant effects, and recommended that at least 65mg of caffeine should be used.

Two headache studies have also investigated the analgesic effect of caffeine on its own compared with placebo.[11,13] One[13] (paracetamol plus caffeine versus paracetamol versus caffeine versus placebo) detected an independent analgesic effect with caffeine 65mg, which was equivalent to paracetamol 648mg, whereas another [11] (ibuprofen plus caffeine versus ibuprofen versus caffeine versus placebo) did not find any analgesic effect of caffeine 200mg compared with placebo.

2.2 Postpartum Pain

Postpartum pain includes pain due to episiotomy and uterine cramp after childbirth. Pain inten-

Table II. Patients with complete pain relief on a caffeine/analgesic combination versus analgesic monotherapy in headache pain

Study	Patients with complete pain relief		RR (95% CI)	RD (95% CI)	NNT (95% CI)
	Analgesic + caffeine	Analgesic alone			
Wojiki et al.[40]	26/36	13/36	2.00 (1.24 to 3.23)	0.36 (0.15 to 0.58)	3 (2 to 7)
Schachtel et al.[9]	69/101	49/100	1.39 (1.10 to 1.77)	0.19 (0.06 to 0.33)	5 (3 to 17)
Diamond et al.[11]	71/97	58/99	1.25 (1.02 to 1.53)	0.15 (0.02 to 0.28)	7 (4 to 67)
Pooled	166/230	120/235	1.36 (1.17 to 1.58)	0.20 (0.11 to 0.29)	5 (4 to 9)
χ^2_{heter}			3.19	2.83	2.83

χ^2_{heter} = statistic of chi-square test for heterogeneity (with 2 degrees of freedom, the trials were homogeneous, therefore a fixed-effect model was used); **CI** = confidence interval; **NNT** = number needed to treat; **RD** = rate difference; **RR** = rate ratio.

sity is normally moderate to severe. Analgesic actions of many non-narcotic analgesics, such as aspirin and aspirin-like analgesics, are established for this type of pain.[14-16] It was also one of the first pain models used to determine additional analgesia resulting from concomitant caffeine administration. However, not all trials have been designed appropriately for the determination of analgesic adjuvant effects of caffeine (table III).

For example, DeKornfield et al.[41] reported several combinations, but they all contained different analgesics, making comparisons difficult. Although Jain et al.[43] found a difference between the combination of aspirin 800mg plus caffeine 100mg and aspirin 650mg alone, the dose of aspirin in the combination group was higher than that for the analgesic alone. In this case, the extra analgesia could not necessarily be attributed to caffeine. Nevertheless, in their subsequent study[12] with ibuprofen 200mg plus caffeine 100mg versus ibuprofen 400mg, the combination showed similar analgesia compared with the higher dose of ibuprofen. These results were supported by another study,[44] in which the combination of aspirin 800mg with caffeine 65mg had equal analgesia compared with aspirin 648mg plus paracetamol 648mg, and was superior to paracetamol 1000mg alone. Unfortunately, other outcomes such as percentage of patients with complete pain relief were not reported.

Laska et al.[6] undertook four randomised controlled parallel trials comparing different doses of paracetamol-caffeine combinations with paracetamol alone, three in postpartum pain and one in dental pain. With the postpartum trials, 1345 patients were randomly assigned to single doses of either one, two or three tablets of 500mg paracetamol plus 65mg caffeine, 500mg paracetamol alone, or placebo. Pain intensity was measured at baseline, 30 minutes after treatment, and hourly thereafter up to 4 hours using categorical scales. Percentage SPID, SPID, TOTPAR, and time to onset of pain (ONSET) were obtained. Relative potency was derived for each outcome measure using a bioassay analysis approach.[45] The results suggested that the pooled relative potency for percentage SPID was 1.7 with 95% CI 1.1 to 3.1. Therefore, to obtain the same degree of response to paracetamol without caffeine requires a dose that is 70% greater than that needed when caffeine is administered concomitantly.

At the same time, the authors also compared original outcome measures such as percentage SPID between the two treatment groups directly using routine statistical testing. The p values for three of the studies were 0.01, 0.25 and 0.53, respectively. Only one study identified differing levels of analgesia between the caffeine/paracetamol combination and paracetamol alone. Similar results were shown with SPID, TOTPAR and ONSET.[6] Two other studies also noted a controversy between the relative potency and the original outcome measures.[8,46] Laska et al.[7] pooled 30 trials with over 10 000 subjects regardless of types of analgesics used, and suggested that caffeine-containing analgesics were superior to analgesic monotherapy. The pooled relative potency for percentage SPID was 1.41, with 95% CI 1.23 to 1.63.

Relative potency has been defined as the ratio of doses between test drug (e.g. caffeine plus analgesic combination) and standard drug (e.g. analge-

sic alone) to produce the same response.[47] It has been calculated from the dose-response curve where a linearity of logarithm of dose against pain intensity, and parallelism of response between the combination and analgesic alone were assumed.[47] Using these assumptions, one can draw two parallel lines, one for the combination and another for the analgesic alone to present the dose against response (e.g. pain intensity), and generate the relative potency, as the difference between two lines. Since this is a regression analysis, the sensitivity for detecting a difference is high. However, as the analgesic effect is, in fact, not linear (figure 1) and outcome measures such as percentage SPID, SPID, and TOTPAR are not continuous variables but ordinal data, the fit of these variables to the model would be poor. As a result, the argument of whether caffeine has an analgesic adjuvant effect turns into an argument of whether the methods chosen by investigators to detect such effects are appropriate. While a more sensitive method is preferred, the appropriateness of the method is essential.

Recently, a standard method using rate ratio (RR), rate difference (RD) and NNT for patients with moderate to excellent pain relief was developed.[14-16] The advantages of using this method are that it is: (i) more clinically meaningful; (ii) easily measured; (iii) more applicable for pooling; and (iv) flexible for modelling. However, few trials in postpartum pain determined discrete outcome measures, and a post-hoc assessment is not possible.

In summary, there is some evidence of additional efficacy of caffeine when combined with analgesics in postpartum pain. Unlike headache pain,

Table III. Analgesic adjuvant effect of caffeine in postpartum pain

Trial	Design	Comparisons	No. of participants	Primary outcome measure	p Value[a]
DeKornfield et al.[41]	DB-P	Aspirin 325mg + phenacetin 300mg + caffeine 23.5mg *vs* aspirin 225mg + phenacetin 225 + salicylamide 200mg + caffeine 100mg *vs* aspirin 500 mg	298	Mean pain relief score	>0.05
Bauer et al.[42]	DB-P	Aspirin 454mg + phenacetin 320mg + caffeine 60mg *vs* aspirin 454mg + phenacetin 320mg	122	SPID	>0.05
Jain et al.[43]	2 × DB-P	Aspirin 800mg + caffeine 100mg *vs* aspirin 650mg	140	PID	<0.05 for episiotomy pain >0.05 for uterine pain
Laska et al.[6]	3 × DB-P	Paracetamol (acetaminophen) 500mg + caffeine 65mg (1, 2, or 3 tablets) *vs* paracetamol 500mg (1, 2, or 3 tablets)	1345	Relative potency	<0.05
Laska et al.[7]	30 × DB-P	Analgesic with caffeine *vs* analgesic without caffeine	10 000	Relative potency	<0.05
Rubin & Winter Jr[44]	DB-P	Aspirin 800mg + caffeine 65mg *vs* paracetamol 1000mg *vs* paracetamol 648mg + aspirin 648mg	500	% SPID	<0.05
Jain et al.[12]	DB-P	Ibuprofen 200mg + caffeine 100mg *vs* ibuprofen 400mg	989	PID	>0.05
Sunshine et al.[8]	DB-P	Ibuprofen 100mg + caffeine 100mg *vs* ibuprofen 200mg + caffeine 100mg *vs* ibuprofen 50, 100, 200mg	787	Relative potency	<0.05
Zhang & Li Wan Po[14]b	Meta-analysis of 4 trials	Paracetamol 500mg + caffeine 65mg (1, 2, 3 tablets) *vs* paracetamol 500mg (1, 2, 3 tablets)	1285	% TOTPAR	<0.05
Zhang & Po [15]b	Meta-analysis of 3 trials	Aspirin 650/800mg + caffeine 65mg *vs* aspirin 650/1000mg	319	% TOTPAR	>0.05

a For greater effect of caffeine combination.

b Includes trials in dental pain and other postoperative pain.

2 × = 2 trials; **3** × = 3 trials; **30** × = 30 trials; **DB-P** = double-blind parallel; **SPID** = sum of pain intensity difference; **PID** = pain intensity difference; **% SPID** = percent sum of pain intensity difference; **% TOTPAR** = percent total pain relief score.

Table IV. Analgesic adjuvant effect of caffeine in dental pain

Trial	Design	Comparisons	No. of participants	Primary outcome measure	p Value[a]
Winter et al.[48]	DB-P	Paracetamol (acetaminophen) 1000mg + caffeine 130mg *vs* paracetamol 1000mg	164	SPID	>0.05
Forbes et al.[49]	DB-P	Aspirin 650mg + caffeine 65mg *vs* aspirin 650mg	350	SPID	>0.05
Forbes et al.[46]	DB-P	Ibuprofen (100, 200mg) + caffeine 100mg *vs* ibuprofen (100, 200mg)	298	SPID relative potency	>0.05 <0.05
McQuay et al.[50]	DB-P	Ibuprofen 200mg + caffeine (50, 100, 200mg) *vs* ibuprofen (200, 400mg)	161	SPID	>0.05 with 50mg caffeine <0.05 with 100 or 200mg caffeine
Li Wan Po & Zhang[16]b	Meta-analysis of 3 trials	Ibuprofen (100, 200mg) + caffeine 100mg *vs* ibuprofen (100, 200, 400mg)	331	%TOTPAR	>0.05 with 100 + 100 and 200 + 100 *vs* 400 <0.05 with 200 + 100 *vs* 200

a For greater effect of caffeine combination.

b Includes trials in dental pain and other postoperative pain.

DB-P = double-blind parallel; **SPID** = sum of pain intensity difference; **% TOTPAR** = percentage total pain relief score.

the studies lack transparent methods, and relative potency is yet to be reassessed. The following points may be useful for future research:

- Both standard outcome measures such as percentage SPID, and more clinical meaningful outcome measures such as percentage of patients with moderate to excellent pain relief, are recommended.
- Unless the trials are similar in terms of analgesic comparisons, types of pain, outcome measures and are statistically homogeneous, pooling may not be appropriate.

2.3 Dental Pain

Several randomised controlled trials have been undertaken in dental pain to determine the analgesic adjuvant effect of caffeine. Table IV lists the trials comparing caffeine combinations with analgesics alone. There is no consensus among the studies even with the same outcome measure (SPID).

Three trials provided data for percentage patients with more than 50% pain relief, and these data were re-analysed (table V). Although there was no analgesic difference between the combinations and analgesics alone for each individual trial ($p > 0.05$), the overall pooling showed a superiority of the caffeine-containing analgesics over the analgesic monotherapy. Treating every 9 patients with the caffeine-analgesic combinations would lead to one more patient with more than 50% pain relief compared with the analgesics alone (NNT = 9.0, 95% CI 5 to 93).

The weakness of this overall pooling strategy was that different analgesics were used in the trials, aspirin and ibuprofen. While the overall pooling showed a significant result, the pooling based on two ibuprofen trials[46,50] did not produce a significant difference between the combination and ibuprofen alone (RR = 1.46, 95% CI 0.92 to 2.32, RD = 0.13, 95% CI -0.02 to 0.27). Unlike in headache pain, where results from individual trials and pooling showed evidence of additional analgesia with caffeine, the results in the dental pain are controversial. In addition, two trials[48,49] which compared caffeine 65mg and 130mg with placebo found that caffeine had no analgesic effect when given as monotherapy in patients with in dental pain.

In summary, analgesic adjuvant effects of caffeine are inconclusive in dental pain. This may be due to small sample size in individual trials, or pooling based on few studies, where the statistical power is insufficient. Further well-designed studies are therefore needed.

2.4 Other Conditions

A number of clinical trials have been undertaken with other types of pain, including pain due to cancer, surgery, orthopaedic events, rheumatoid arthritis, etc. (table VI).

Before the 1970s, when phenacetin was banned in many countries, two clinical trials were undertaken to determine whether caffeine-containing phenacetin and aspirin was superior to aspirin alone. Marrs et al.[3] reported the inferior analgesia of the aspirin-phenacetin-caffeine combination compared with aspirin alone in patients with pain from various surgeries or rheumatoid arthritis (table VI). The proportion of patients with good to excellent pain relief was 13 of 53 (25%) with the combination and 24 of 53 (45%) with aspirin monotherapy ($p < 0.05$). Aspirin monotherapy was therefore recommended.

Cass and Frederick[4] undertook a clinical trial to detect effects of multiple doses of analgesics and their combinations in chronic pain. However, they did not report the types of pain. Every patient in the trial received three treatments, the combination (aspirin 325mg plus phenacetin 325mg plus caffeine 30mg), aspirin 650mg alone, and placebo, in a random sequence. Patients received each treatment 4 times daily for 6 days. Pain relief was recorded every day by a 5-point scale. The results showed that both the combination therapy and aspirin monotherapy were superior to placebo, and there was no significant analgesic difference between the active treatments. However, as analgesic components (aspirin 325mg plus phenacetin 325mg) in the combination were different from the analgesic alone (aspirin 650mg), the effect of caffeine alone cannot be identified.

Amongst the trials which are appropriate for determining analgesic adjuvant effects of caffeine, Moertel et al.[5] did not detect additional analgesia with caffeine 64mg, whereas Wallenstein[51] found that caffeine 60mg, but not 30mg, potentiated analgesia in patients with cancer pain. Additional pain relief was found with orthopaedic pain[40] and sore throat[52] when caffeine was added. Pooling is not possible as the trials used different outcome measures and types of pain.

In summary, analgesic adjuvant effects of caffeine have also been investigated in chronic pain such as cancer pain and rheumatoid arthritis with multiple dose treatments. However, results are inconclusive.

3. Adverse Effects

Consumption of caffeine in high doses (>600 mg/day) can cause acute adverse effects, such as anxiety, panic attacks and sleep disorders.[17] Long-term ingestion of caffeine in the form of coffee has been suggested to have various adverse effects on human health, such as cardiovascular diseases and cancer.[17] Adverse effects discussed here are restricted to the comparative effects of caffeine-containing analgesics versus analgesics alone. Other

Table V. Patients with more than 50% pain relief on a caffeine/analgesic combination versus analgesic monotherapy in dental pain

Study	Comparisons	Patients with complete pain relief		RR (95% CI)	RD (95% CI)	NNT (95% CI)
		analgesic + caffeine	analgesic alone			
Forbes et al.[49]	Aspirin 650mg + caffeine 65mg *vs* aspirin 650mg	16/66	10/68	1.65 (0.81 to 3.37)	0.10 (-0.04 to 0.23)	
Forbes et al.[46]	Ibuprofen 200mg + caffeine 100mg *vs* ibuprofen 200mg	17/44	11/48	1.69 (0.89 to 3.19)	0.16 (-0.03 to 0.34)	
McQuay et al.[50]	Ibuprofen 200mg + caffeine 100mg *vs* ibuprofen 200mg	12/30	10/31	1.24 (0.63 to 2.43)	0.08 (-0.16 to 0.32)	
Pooled		45/140	31/147	1.51 (1.02 to 2.23)	0.11 (0.01 to 0.21)	9 (5 to 93)
χ^2_{heter}				0.50	0.36	0.36

χ^2_{heter} = statistic of chi-square test for heterogeneity (with 2 degrees of freedom, the trials were homogeneous, therefore a fixed-effect model was used); **CI** = confidence interval; **NNT** = number needed to treat; **RD** = rate difference; **RR** = rate ratio.

adverse effects due to caffeinated beverage drinks and other caffeine products can be seen in Sawynok's review.[17]

3.1 Short-Term Use

Short-term use of non-opioid analgesics and their combinations may cause gastrointestinal (e.g. nausea, vomiting and stomach pain) and central nervous symptoms (drowsiness, dizziness and headache).[14] These have been found in caffeine-containing analgesic as well. The data have been extracted and reanalysed (table VII).

Caffeine combination caused more patients to report nervousness and dizziness. Pooled relative risks were 4.90 (95% CI 2.75 to 8.75) and 2.36 (95% CI 1.38 to 4.02), respectively. Although there was no difference between the two groups for nausea and headache, the overall safety profile was in favour of analgesic monotherapy. With the caffeine combination, a patient would have 48% greater risk of any adverse effect than with analgesic alone (relative risk = 1.48, 95% CI 1.26 to 1.79).

Pooling was undertaken regardless of the type of pain and dose of analgesic and caffeine. The results are therefore nonspecific. In a large-scale study including 6 sub-trials involving a total of 2810 patients with tension-type headache,[10] the combination of paracetamol 1000mg and caffeine 130mg resulted in more patients with any adverse effect than paracetamol alone (144/692 versus 90/691). The relative risk was 1.60 with 95% CI 1.26 to 2.03.

Table VIII shows further details of the large-scale study[10]. The risk for any adverse effect, stomach discomfort, nervousness or dizziness was increased from placebo to the single analgesic, and then again with combinations. Paracetamol alone had the most favourable safety profile. However, whether or not the benefit derived outweighs the risk depends on type of pain (acute or chronic), patient sensitivity, doctor's perspectives and patients' preferences among the treatment groups. For example, for acute headache with short-term treatment, one may prefer the caffeine/paracetamol combination to paracetamol alone as this would bring an enhancement of pain relief without extra risks of adverse effects. For chronic headache, however, a single agent may be recommended. In any case, patients should be provided with full information

Table VI. Analgesic adjuvant effect of caffeine in other types of pain

Trial	Design	Type of pain	Comparisons	No. of participants	Primary outcome measure	p Value (primary outcome)
Marrs et al.[3]	DB-C	Various	Aspirin 227mg + phenacetin 162mg + caffeine 32.4mg *vs* aspirin 333mg	54	% of patients with good to excellent relief	<0.05 for greater effect of aspirin monotherapy
Cass & Frederick[4]	DB-C	Chronic	Aspirin 325mg + phenacetin 325mg + caffeine 30mg, qid × 6 days, *vs* aspirin 650mg, qid × 6 days	25		no p value provided, but stated no difference between groups
Moertel et al.[5]	DB-C	Cancer	Aspirin 650mg + caffeine 65mg *vs* aspirin 650 mg	100	% of patients with >50% pain relief	>0.05
Wallestein[51]		Cancer	Paracetamol (acetaminophen) 210mg + aspirin 150mg + caffeine 30mg (1 or 2 tablets) *vs* paracetamol 210mg + aspirin 150mg (1 or 2 tablets)		SPID	>0.01 with 1 caffeine tablet <0.01 with 2 tablets for greater effect of caffeine combination
Wojicki et al.[40]	DB-C	Orthopaedic	Paracetamol 1000mg + caffeine 100mg *vs* paracetamol 1000mg	72	% of patients with complete pain relief	<0.05 for greater effect of caffeine combination
Schachtel et al.[52]	DB-P	Sore throat	Aspirin 800mg + caffeine 64mg *vs* aspirin 800mg	207	SPID	<0.01 for greater effect of caffeine combination

DB-C = double-blind crossover; **DB-P** = double-blind parallel; **qid** = 4 times daily; **SPID** = sum of pain intensity difference.

Table VII. Adverse effects of caffeine-containing analgesics (combination) versus analgesics alone, results from randomised controlled trials

Trial	Any adverse effect		Nervousness		Dizziness		Nausea		Headache	
	combination	analgesic	combination	analgesic	combination	analgesic	combination	analgesic	combination	analgesic
Crude rate (number of patients with the event/number of patients treated)										
Case & Frederick[4]	8/25	12/25	3/25	0/25	NA	NA	2/25	2/25	NA	NA
Moertel et al.[5]	14/100	11/100	NA	NA	NA	NA	NA	NA	NA	NA
Rubin & Winter[44]	6/121	6/123	NA	NA	2/121	2/123	1/121	0/123	NA	NA
Jain et al.[12]	5/50	4/48	NA	NA	0/50	1/49	NA	NA	NA	NA
Forbes et al.[49]	8/78	8/78	NA	NA	2/78	2/78	2/78	3/78	1/78	0/78
Forbes et al.[46]	8/58	6/60	2/58	1/60	2/58	0/60	2/58	0/60	2/58	2/60
Migliardi et al.[10]	144/692	90/691	50/692	10/691	34/692	11/691	NA	NA	NA	NA
McQuay et al.[50]	2/30	4/31	NA	NA	NA	NA	NA	NA	1/30	0/31
Diamond et al.[11]	37/110	15/105	12/110	2/105	7/110	3/105	8/110	2/105	2/110	2/105
Pooling [a]										
RR (95% CI)	1.48 (1.26 to 1.79) [b]		4.90 (2.75 to 8.75)[b]		2.36 (1.38 to 4.02)[b]		1.81 (0.74 to 4.43)		1.35 (0.42 to 4.33)	
RD (95% CI)	0.04 (-0.005 to 0.08)		0.06 (0.04 to 0.76)[b]		0.02 (0.007 to 0.035)[b]		0.01 (-0.005 to 0.032)		0.007 (-0.015 to 0.030)	
NNH (95% CI)	NA		17 (13 to 26)		47 (29 to 134)		NA		NA	

a A random-effect model was used to pool risk differences (RDs) for any adverse effect as heterogeneity was detected. A fixed-effect model was used for other pooling, as trials were homogeneous.

b $p < 0.01$.

CI = confidence interval; **NA** = not available or not appropriate; **NNH** = number needed to harm; **RD** = risk difference; **RR** = relative risk.

about the benefits and risks of the treatments and shared decision making should be exercised.[53]

The fundamental rationale for using combination analgesics is to reduce the single doses of the analgesic and hence reduce adverse effects without affecting analgesic efficacy. However, caffeine combinations have not satisfactorily achieved this target. Two studies in dental pain[46,50] compared lower doses of ibuprofen plus caffeine with higher doses of ibuprofen alone, i.e. ibuprofen 100mg plus caffeine 100mg versus ibuprofen 200mg,[46] and ibuprofen 200mg plus caffeine 100mg versus ibuprofen 400mg.[47] Although the authors suggested that some outcome measures such as SPID and TOTPAR were in favour of the combination, this does not necessarily translate into clinically meaningful outcomes. The pooled RR of patients with more than 50% pain relief for the combination therapy versus ibuprofen monotherapy was 1.27 (95% CI 0.93 to 1.75, $p > 0.05$) and the relative risk of patients with any adverse effect was 1.80 (95% CI 0.79 to 4.10, $p > 0.05$). Lower doses of ibuprofen in the combination with caffeine did not significantly increase analgesic effect, nor did they decrease the incidence of adverse effects.

3.2 Long-Term Use

3.2.1 Analgesic-Induced and Withdrawal Headache

A high percentage of patients with drug-induced headache has been reported with combined analgesics.[18-20] However, this finding is likely to have been confounded by the analgesics available for headache treatment and does not necessarily reflect a causal relationship between the use of combinations and drug-induced headache. Results from

randomised controlled trials did not show any more patients with headache among those administered caffeine-containing analgesics versus those given analgesic alone (table VII). There is no robust evidence that caffeine plays a distinctive role in drug-induced headache.

Similarly, there is some evidence for the occurrence of withdrawal headache after intake of single or combined analgesics.[54] Caffeine is suspected to have an add-on effect to analgesic withdrawal headache. This is because on its own, caffeine has significant withdrawal symptoms including headache and fatigue.[17] However, there is no evidence that headache after withdrawal of caffeine-containing analgesics is more severe than after analgesic monotherapy. Indeed, it would be particularly difficult to distinguish the effects of caffeine since in headache medications caffeine is virtually always used in combination with analgesics. In addition, it would be important to consider the influence of dietary caffeine in all patients studied, in both those using analgesics with caffeine, and those using headache medication without caffeine, as it is not known whether on-going dietary intake of caffeine masks the withdrawal effects of caffeine. This should taken into account in future studies to produce robust evidence.

The mechanisms of both drug-induced and withdrawal headaches are unclear. Since they are more likely to occur in patients with pre-existing headache, a special underlying mechanism may be involved.[18-20]

3.2.2 Analgesic Nephropathy

Analgesic nephropathy is a chronic renal disease due to analgesic overuse or abuse, generally defined as daily use of analgesics ≥1 g/day for at least 1 year, or cumulative amounts of 1 to 3kg or more.[22] Epidemiological evidence shows that analgesic nephropathy is associated with any analgesic or analgesic combination. In nearly all early reports of analgesic nephropathy, the patients had taken large amounts of products containing phenacetin, which led to the hypothesis that phenacetin was nephrotoxic. Consequently, phenacetin was removed from analgesic combinations in some European countries and Australia. This resulted in a reduction in the incidence of analgesic nephropathy in both areas.[55] Nevertheless, the role of other analgesics and combinations in analgesic nephropathy cannot be ruled out. Figure 2 shows results from seven case-controlled studies,[56-63] comparing the regular use of analgesics between patients with chronic renal diseases (cases) and patients with other diseases or healthy individuals (controls). The details of these studies were reviewed by Delzell and Shapiro.[22] The results were heterogeneous because of differing definitions of regular analgesic use. The relative risk (odds ratio) of analgesic nephropathy varied depending upon types of analgesics used and studies conducted. However, most of them showed associations between analgesics and chronic renal diseases.

Some of these studies also provided data to compare risks of regular users with heavy users. Figure

Table VIII. Relative risk of adverse effects (treatment versus placebo)

Treatment	RR (95% CI)[a]			
	Any adverse effect	Stomach discomfort	Nervousness	Dizziness
Placebo	1	1	1	1
Paracetamol (acetaminophen) 1000mg	1.10 (0.88 to 1.38)	1.05 (0.31 to 0.77)	1.89 (0.77 to 4.63)	1.49 (0.76 to 2.95)
Paracetamol 1000mg + caffeine 130mg	1.73 (1.25 to 2.39)[b]	1.30 (0.78 to 2.16)	12.32 (3.02 to 50.33)[b]	4.19 (1.50 to 11.71)[b]
Paracetamol 500mg + aspirin 500mg + caffeine 130mg	1.98 (1.52 to 2.58)[b]	1.92 (1.33 to 2.77)[b]	7.65 (2.79 to 20.94)[b]	4.15 (1.91 to 9.05)[b]

a Relative risk was calculated by comparing each treatment with placebo based on the data available from Migliardi et al.[10]

b $p < 0.01$.

RR = relative risk; **CI** = confidence interval.

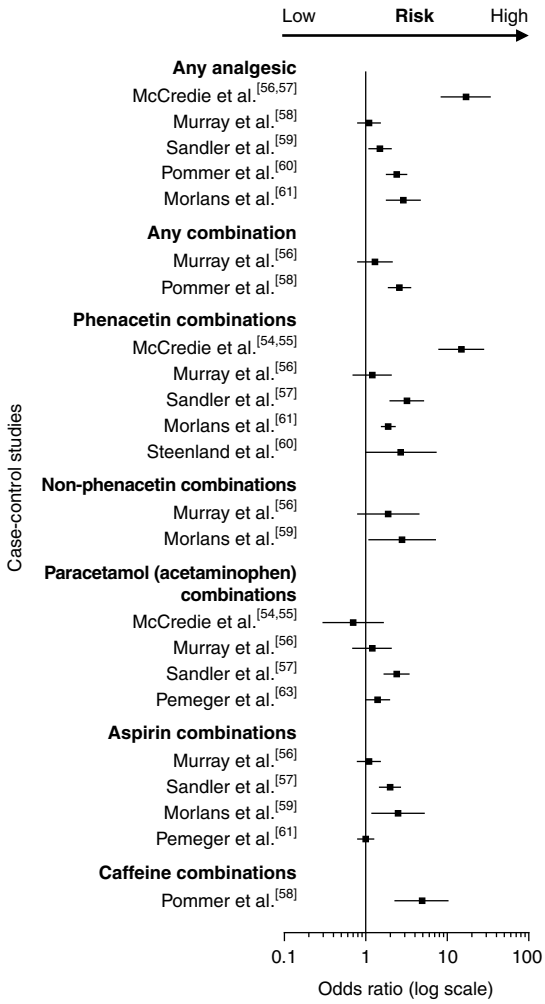

Fig. 2. Odds ratios for chronic renal disease associated with the regular use of analgesics: results from case-control studies.

3 shows pooled odds ratios. The results indicated that: (i) all analgesics and combinations were associated with analgesic nephropathy; (ii) heavy use was in general associated with higher risk. However, this risk could not be attributed to a specific analgesic, as there was no clear-cut information for analgesic components in each combination. For example, for phenacetin combinations, it is not known what other analgesics had been included except for phenacetin. Although the authors had included the non-phenacetin group, there is no reason to assume that other components between groups were the same. Therefore the extra risk (e.g. odds ratio = 6.58 for phenacetin combinations versus 1.32 for non-phenacetin combinations) cannot be completely attributed to phenacetin. For other combinations, the attribution is even more difficult. For example, for regular use of caffeine combinations, the odds ratio was 4.9 (95% CI 2.3 to 10.3), while for the heavy use, the odds ratio increased to 53 (95% CI 6.8 to 403). There is no reason to attribute this risk to caffeine as it is not known what else was contained in the combinations. In addition to the confounding bias, case-controlled study only provides association rather than causality – it is not known whether analgesics caused nephropathy or *vice versa*.

Two cohort studies attempted to provide further evidence of the association between analgesic abuse and analgesic nephropathy.[64,65] The relative risk of developing analgesic nephropathy was 6 (95% CI 1.4 to 26) in individuals who had used analgesics daily for 8 years.[65] The relative risk increased up to 23 (95% CI 6.6 to 79) in those who had abused phenacetin combinations for 20 years.[64] Unfortunately, these two studies did not identify caffeine as a component, so it is not possible to know the role of caffeine in analgesic nephropathy.

So far, it is clear that the long-term daily use or abuse of analgesics and analgesic combinations increases the risk of analgesic nephropathy. The argument is whether this risk can be attributed to a specific analgesic, such as phenacetin. Although some evidence indicates that phenacetin produces nephrotoxicity, neither epidemiological nor experimental studies have been able to rule out the nephrotoxicity of other analgesics, such as paracetamol and aspirin. Although the ban of phenacetin has led to a reduction in the incidence of analgesic nephropathy, we are still not assured whether a ban of paracetamol would also lead to a reduction.

While considerable literature on the effects of caffeine in a dietary context provides some evidence of increased risks of cardiovascular diseases,[66] the evidence for caffeine as a nephrotoxin on its own is absent. Whether it increases nephro-

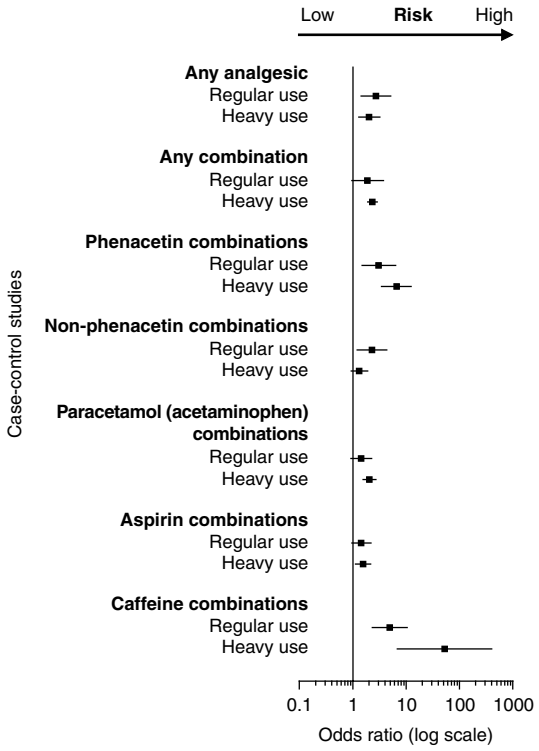

Fig. 3. Pooled odds ratios for chronic renal disease associated with analgesics: results from case-control studies.

toxicity when co-formulated with analgesics is yet to be established. Caffeine can antagonise adenosine receptors and cause medullary imbalance between the demand for transport work and available oxygen supply, promoting cell death.[67] In rodents, NSAIDs cause papillary necrosis, which may be increased by caffeine.[68] However, in rats, the nephrotoxicity of the combination of aspirin, paracetamol and caffeine is similar to that induced by analgesics alone or aspirin plus paracetamol.[69]

It has been well established that NSAIDs inhibit PG synthesis via suppression of COX-1 and COX-2. Caffeine may also play a role in suppression of COX-2 as discussed in section 1.1.3. In the kidney, PGs are involved in renal haemodynamic autoregulation and salt and water homoeostasis.[70] Inhibition of PG synthesis may thereby result in a reduction of glomerular filtration rate, and salt and water retention. This provides some pharmacological basis for renal toxicity of NSAIDs and caffeine. However, clear-cut evidence of caffeine in the development of nephropathy is still needed.

Does caffeine promote analgesic dependence, and then indirectly increase the risk of nephropathy? Studies performed with caffeinated beverages have shown a dose-independent response and time-limited dependence.[54] However, this may be due to the taste of coffee or features of caffeinated beverages other than caffeine itself, as in a double-blind study, no caffeine withdrawal symptoms were noted.[71] In a review of data from double-blind, placebo-controlled trials on ibuprofen and caffeine administered either alone or in combination, the group receiving caffeine-containing capsules was not found to have discernible overuse.[72] Therefore, although caffeine has dependence potential, it may not play a significant role in stimulating or sustaining analgesic intake.

In summary, analgesic nephropathy is associated with long-term overuse of any single or combined analgesics. While phenacetin-containing analgesics have been identified as a risk factor for this disease, other combined analgesics cannot be ruled out, including paracetamol and/or aspirin combinations. Evidence of caffeine increasing the risk of analgesic nephropathy either directly or indirectly is lacking.

4. Conclusion

Caffeine has been used as analgesic adjuvant for many years. A number of randomised controlled trials and observational studies have been undertaken in order to identify its benefits and adverse effects. Caffeine enhances pain relief in headache, as well as increases the risk of nervousness and dizziness. In other types of pain such as postpartum pain, dental pain, postoperative pain, rheumatic and cancer pain, the analgesic adjuvant effects of caffeine are inconclusive.

There is some epidemiological evidence regarding increased risks of drug-induced headache, withdrawal headache and nephropathy associated with long-term overuse of analgesics, particularly

phenacetin combinations. However, little is known about caffeine effects in the development of these conditions except for that it is widely co-formulated with analgesics.

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