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Long-term Adverse Effects of Paracetamol – a Review

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Abstract

Paracetamol (Acetaminophen) is the most commonly used drug in the world, with a long record of use in acute and chronic pain. In recent years the benefits of paracetamol use in chronic conditions has been questioned, notably in the areas of osteoarthritis and lower back pain. Over the same period, concerns over the long-term adverse effects of paracetamol use have increased, initially in the field of hypertension, but more recently in other areas also.

The evidence base for adverse effects of chronic paracetamol use consists of many cohort and observational studies, with few randomised controlled trials that in many cases contradict each other, so these studies must be interpreted with caution. Nevertheless, there are some areas where the evidence for harm is more robust, and if a clinician is starting paracetamol with the expectation of chronic use it might be advisable to discuss these side effects with patients first. In particular, an increased risk of GI bleeding and a small (~4mmHg) increase in systolic BP are adverse effects for which the evidence is particularly strong, and which show a degree of dose dependence. As our estimation of the benefits decreases, an accurate assessment of the harms is ever more important. This review summarises the current evidence on the harms associated with chronic paracetamol use, focusing on cardiovascular disease, asthma and renal injury, and the effects of *in utero* exposure.

Introduction

Paracetamol (acetaminophen) was first synthesised in 1878 [1], from its precursor phenacetin. Its use was not widespread initially, due to early reports of a link to methaemoglobinaemia [2, 3]. After this association was discredited, it was marketed in the 1950s as a safer alternative to phenacetin, which by then had been found to be nephrotoxic and potentially carcinogenic [4]. In the early 1980s, paracetamol overtook aspirin as the most widely used over-the-counter analgesic in the UK [5]. It is now the most commonly used analgesic in the world [6], and the first step of the World Health Organisation (WHO) analgesic ladder for treatment of cancer pain [7].

Paracetamol is currently marketed as an analgesic and antipyretic, to be used for no more than three days without consulting a doctor [8]. However, due in part to its inclusion in the WHO analgesic ladder, as well as decades of clinical experience, it is also prescribed in chronic conditions such as osteoarthritis and lower back pain. Recently, meta-analyses of the randomised controlled trials covering these conditions have shown the effect sizes to be modest, though still statistically significant, compared with placebo (averaging a 4-5% reduction in pain) [9-12]. Despite this, paracetamol continues to be recommended as first-line treatment in UK guidelines [13], and attempts to remove paracetamol as a recommendation from the UK's National Institute for Health and Care Excellence (NICE)

guidance on osteoarthritis raised considerable concerns amongst medicines regulators and various specialist societies [14], particularly as this would leave opioids as the major alternative. Given the current opioid addiction epidemic ongoing in several US states [15], and a desire not to repeat this in the UK [16, 17], the introduction of opioids earlier in the pain management pathway is unlikely to be viewed favourably.

Paracetamol has less of an analgesic effect in chronic use than previously thought; there needs to be greater emphasis on accurately determining the harms of long-term use at therapeutic doses. This helps clinicians balance harms against likely benefits for individual patients and allows regulators to make recommendations on its availability in over-the-counter preparations. The acute effects of paracetamol ingestion in overdose are well-known [18]. Harms with long-term therapeutic use are less clear. Concerns have been raised over the effects on the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems, as well as potential effects in the offspring of pregnant women ingesting paracetamol.

This review summarises our understanding of the evidence on adverse effects of paracetamol in long-term therapeutic use, informs clinicians of the risks and provides a clearer picture of the underpinning evidence-base. This will, in turn, allow clinicians to discuss with their patients the relative benefits and harms of long-term paracetamol use.

Mechanism of action

The mechanism of action of paracetamol is not completely understood, but likely involves cyclo-oxygenase-2 (COX-2) inhibition. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes, preventing the metabolism of arachidonic acid to prostaglandin (PG) G₂. COX enzymes also have a separate peroxidase function, and metabolise PG-G₂ to PG-H₂, which is in turn converted to several different prostaglandins by local tissues according to their individual needs [2, 19, 20]. Unlike the closely-related NSAIDs, paracetamol interferes with the peroxidase activity of COX isoenzymes, predominantly COX-2, particularly when the cellular environment is low in arachidonic acid and peroxides [2, 19, 20]. This explains paracetamol's apparent 'central' effect in earlier studies (as COX-2 is constitutively expressed in neural tissue) [19, 21], and why it appears to be ineffective in inflamed tissues (where peroxide and arachidonic acid are abundant), seen in conditions such as rheumatoid arthritis. A proposed COX-3 isoenzyme (an exon splice variant of COX-1 seen in insects and rodents) has not been found in humans, and further studies suggest that paracetamol has no clinically significant effects on the COX-1 exon splice variants found so far in humans [19, 21]. Other possible mechanisms of action include the inhibition of anandamide reuptake (and subsequent cannabinoid receptor CB₁ stimulation) by paracetamol metabolite N-arachidonoylphenolamine (AM404), which is produced by the conjugation of arachidonic acid and deacetylated paracetamol [22], and direct activation of the capsaicin receptor TRPV1 by AM404 [23]. TRPA1 activation by paracetamol metabolites has also been suggested [24, 25].

Paracetamol is mostly metabolised by the formation of conjugates (with glucuronide and sulphate), and subsequently excreted in urine. In therapeutic dosing, around 10% of paracetamol is metabolised by cytochrome P450 enzymes to form n-acetyl-p-benzylquinoneimine (NAPQI), which is subsequently conjugated with intracellular glutathione, and ultimately excreted as cysteine and mercaptopuric acid conjugates. Less than 5% is excreted unchanged [26].

Search Strategy

We conducted a literature search of PubMed, searching the years 1980 to 2016. An initial Pubmed review of “paracetamol [Title] OR acetaminophen [Title]” with “side effects OR adverse effects” revealed several key interest areas, which were subsequently searched for specifically as follows: we combined “paracetamol [Title] OR acetaminophen [Title]” with: “hypertension OR blood pressure”; “myocardial infarction OR cardiac OR cardiovascular”; “stroke OR CVA OR cerebrovascular accident”; “liver OR hepatic OR transaminase OR aminotransferase”; “gastrointestinal OR bleeding OR anaemia”; “renal OR kidney OR CKD OR chronic kidney disease”; “respiratory OR asthma OR chest”; “reproductive OR maternal OR ADHD OR attention deficit”. Papers were selected with the following criteria: 1) human subjects; and 2) meta-analyses, reviews, randomised controlled trials, prospective studies and cohort studies. English language was not included as a filter but would not have excluded any papers from review. Titles and abstracts were then reviewed, and relevant articles reviewed in full. Key papers identified in references were also reviewed by the authors, where considered relevant. See Figure 1 for our search strategy.

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [27], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [28].

Cardiovascular

Studies examining the effect of paracetamol on the incidence of cardiovascular disease are relatively sparse when compared to those on NSAIDs [29]. Early studies focused on hypertension (which we have reviewed previously [30]), due to the known association of NSAIDs with hypertension, and the similar mechanism of action of paracetamol [31]. One such study was a placebo-controlled crossover study of 20 treated hypertensive patients, where a 4 mmHg rise in blood pressure (BP) was found when paracetamol was administered [32]. Given that a 2mmHg rise in systolic BP is associated with a 7% increase in risk of ischaemic heart disease and a 10% increased risk of stroke [33], this apparently small increase in BP could have serious population-based consequences.

However, both observational and interventional studies examining the effect of paracetamol on hypertension have produced conflicting results [30]. To date, most [34-36], but not all [37, 38], observational studies suggest that long-term paracetamol use increases the risk of developing hypertension. The Nurses' Health Study II, which included 80,020

participants, found that regular NSAID or paracetamol use was associated with an increased risk of developing hypertension [35]: the relative risk of developing hypertension on NSAIDs was 1.86 (95% confidence interval [CI] 1.51-2.28) and on paracetamol was 2.00 (95% CI 1.52-2.62). It also seems that there is some evidence for a dose-response relationship between daily paracetamol dosage and risk of incident hypertension. This was observed not only in the Nurses Health Studies I and II [39], but also by Roberts et al. for overall cardiovascular risk in their systematic review of paracetamol-related adverse effects [6].

In contrast, a retrospective observational study by Dawson et al., with propensity matching, found no impact of paracetamol on BP in a cohort of 2,754 participants with treated hypertension [38]. Although observational studies may find an association between paracetamol use and hypertension, underlying confounders (such as chronic inflammatory conditions) need to be considered. Unfortunately, to date, interventional studies examining the impact of paracetamol on BP have been limited by study design and small sample size. One recent study, by Sudano et al., randomised 33 patients with established coronary artery disease to paracetamol 1g three times per day or placebo in a double-blinded crossover study [40]. Two weeks of treatment with paracetamol significantly increased mean systolic ambulatory BP (from 122 ± 12 to 125 ± 12 mmHg, $p=0.02$) and diastolic ambulatory BP (from 73 ± 7 to 75 ± 8 mmHg, $p=0.02$). Though this difference is unlikely to significantly affect an individual patient's cardiovascular outcomes, it may explain the finding that self-reported frequent paracetamol use in women is associated with an increase in cardiovascular events similar to that seen with frequent NSAID use [41]. Fulton et al. showed no increased risk of

myocardial infarction or stroke in a hypertensive cohort of 4,000 subjects, and no change in BP, which suggests that any increase in risk may be driven by BP alone [42]. Further research in this area is clearly required, and there is currently a suitably-powered double-blind, placebo-controlled, crossover trial from our centre examining the effects of 2 weeks of paracetamol use on BP in hypertensive patients

(<https://clinicaltrials.gov/ct2/show/NCT01997112>), that should report soon.

Respiratory

After aspirin was recognised to cause the rare but serious complication of Reye's syndrome, its use was banned in under-12s, [43, 44]. As aspirin use as an antipyretic waned in developed countries and paracetamol use became more common [45], concerns over paracetamol's association with asthma were raised [46]. Observational and cross-sectional studies demonstrated a connection between paracetamol use and asthma diagnoses or exacerbations [47-54]. However, as for BP, almost all of these studies suffer from confounding by indication: recurrent symptomatic respiratory infections and febrile illnesses are more common in asthmatic patients and contribute to the onset of asthma in childhood [55-57]. In some studies an increased risk/odds for developing asthma with increasing paracetamol use becomes nonsignificant when adjusted for recurrent respiratory tract infection [58-60], though this is not universal [53]. Meta-analyses of these observational studies tend to show only a small effect (e.g. odds ratio [OR] 1.15 for use in infancy), and suffer from considerable heterogeneity [47, 55].

A link between paracetamol use and asthma is biologically plausible. Paracetamol metabolism involves the antioxidant glutathione, which is depleted when large doses of paracetamol are taken. There are papers describing glutathione depletion at therapeutic doses of paracetamol [61, 62] and increased oxidative stress could contribute towards either the development of asthma or inflammatory exacerbations in asthmatics [63-67]. Glutathione depletion may also change T helper (Th) physiology towards a Th2 phenotype, which is associated with atopic disease [49]. Paracetamol may also cause an imbalance in lipooxygenase activity, brought about by COX inhibition, resulting in increased leukotriene and decreased prostaglandin E2 production [63, 64, 68]. This latter mechanism has support from studies done in patients with aspirin-associated asthma, where decreases in Forced Expiratory Volume in 1 second (FEV1) following paracetamol administration were observed [69]. In one such study, 34% of aspirin-sensitive participants showed cross-reactivity to paracetamol [70], and in patients with aspirin-associated asthma it is recommended to use the lowest effective dose of paracetamol for analgesia [71, 72]. It should be noted that a later double-blind, randomised controlled trial (RCT) in non-aspirin-sensitive subjects (n=85) taking paracetamol 1g twice daily or placebo for 12 weeks showed no differences in bronchial hyperresponsiveness [73].

A few researchers have attempted to study the effects of paracetamol on asthmatic patients (adult and paediatric) in RCTs. Ioannides et al. randomised adults with mild to moderate asthma to placebo or paracetamol 4g/d for 12 weeks, then submitted them to a

methacholine challenge test. Airway hyper-responsiveness was similar in both groups (amount of methacholine required to reduce FEV₁ by 20%, paracetamol group – placebo was -0.48 mg/ml, 95% CI -1.28 – 0.32) but this study was notably underpowered (n=94; recommended sample size 650) [73]. More recently, Sheehan et al. conducted an RCT where they randomised children aged 0.5 – 5 years to receive either paracetamol or ibuprofen for analgesia/antipyresis over the following 48 weeks. Participants received a mean of 5.5 doses (range 1-15), with no between-group differences. Relative risk for asthma exacerbations was similar between the two groups, and there were no significant differences in secondary outcomes (asthma-controlled days, unscheduled care, use of rescue medication), indicating that, at least in mild to moderately asthmatic children, paracetamol was as safe to use as ibuprofen [74].

Overall, there is evidence of a weak association of paracetamol use with asthma, but causation cannot be established. RCTs are limited, but seem to provide reassurance that paracetamol is safe to use in patients with established asthma [73-75].

Gastrointestinal

The acute effects on the liver of paracetamol in overdose have been well-documented [76-78]. However, the effect of chronic therapeutic-dose paracetamol use on the liver and gastrointestinal (GI) system in general is less clear. Concerns are generally focused around GI blood loss and chronic hepatotoxicity.

Gastrointestinal bleeding

Paracetamol has long been considered the 'safe' analgesic alternative to NSAIDs in patients prone to GI bleeding. Indeed, in studies of the analgesic effects of NSAIDs it is commonly used as a comparator, due to the ethical issues of withholding analgesia [79-81]. There is some evidence to support the safety of paracetamol. Examining adverse events reported in the Spanish drug monitoring system, Carvajal et al. found paracetamol use was associated with nausea (3.3% of all reported adverse events) and dyspepsia (4.2%), but not GI bleeding [82]. Furthermore, a meta-analysis of individual patient data from 3 case-control studies, looking at the risk of GI bleeding with individual NSAIDs, included paracetamol as a comparator and found no increased risk of GI bleeding with increasing daily doses of paracetamol [83].

However, recent epidemiological studies have identified a potential increased risk of upper GI bleeding with doses of paracetamol ≥ 2 -3g/d. In 2001, a case-control study was conducted using the UK's General Practice Research Database (GPRD) [84]. Adults aged 40-79 with no history of prior GI disease or alcohol misuse (n=13,605) were followed up between 1993 and 1998. Incidence of upper GI complications was documented, as was prescription of paracetamol and potentially confounding medications. Compared with nonusers of paracetamol, users of ≤ 2 g/d did not have a significant increase in GI complications. However, use of > 2 g/d had an adjusted relative risk (RR; 95% CI) of 3.6 (2.6 –

5.1). When this analysis was confined to those patients with no prior NSAID prescription or antecedents of GI disorders (e.g. dyspepsia), the adjusted RR was 5.7 (2.0 – 16.4). When combined with NSAID, the risk increased to 13.2 (9.2 – 18.9), indicating a substantial interaction. It is important to recognise the potential influence of channelling bias in this instance (NSAIDs are not prescribed to those at risk of upper GI bleeding unless necessary, so high-risk patients may be disproportionately prescribed paracetamol). The authors tried to compensate for this by excluding a history of Mallory-Weiss tear, cancer, oesophageal varices, coagulopathy or alcohol-related disease, and adjusting the relative risk for age, smoking, upper GI risk factors and concomitant medications, but this (they admitted) cannot exclude all bias. Additionally, the study was of prescriptions, not ‘real-world’ use. The authors had no data on over-the-counter (OTC) use of paracetamol by patients, and the daily dosage was calculated from prescription frequencies; both of which have the potential to confound the results (though would not explain the apparent dose-response relationship found). The same group later published a follow-up examination of the link between GI complications and paracetamol in the GPRD [85], and found a pooled RR of 1.3 (1.1 – 1.5). Furthermore, in users of $\geq 2\text{g/d}$, the RR was 3.6 (2.6 – 5.1). They did not detect evidence of heterogeneity or publication bias.

In 2008, a study of elderly patients in Quebec examined the relation of NSAIDs paracetamol $\leq 3\text{g/d}$, paracetamol $>3\text{g/d}$, and proton pump inhibitors (PPI) [86]. Using paracetamol $\leq 3\text{g/d}$ as the reference population, they found hazard ratios (HR) for GI-related hospitalisation of 1.2 (95% confidence interval [95% CI] 1.03 – 1.40) for paracetamol $>3\text{g/d}$, 1.63 (95% CI 1.44

– 1.85) for NSAID, and 2.55 (95% CI 1.98 – 3.28) for combined usage. With the use of a PPI the hazards became nonsignificant except in the combined usage group (Hazard Ratio 2.15 [95% CI 1.35 – 3.40]). These data would suggest that elderly patients taking paracetamol with or without concomitant NSAID are at risk of GI-related hospitalisation. The authors hypothesise that the additional, weak, nonspecific COX inhibition from paracetamol could have an additive effect to that of NSAIDs, creating an increased risk of gastric mucosal injury when used together.

Early RCTs in this area appeared to give reassuring results: One crossover study examining the effects of 7 days of paracetamol, ketoprofen or placebo on endoscopic appearances found no acute effects of paracetamol on the GI mucosa [87]. However, more recent RCTs have been less reassuring. In 2011, Doherty et al. examined the effects of paracetamol (3g/d), ibuprofen (1200mg/d) or a combination of the two (ibuprofen 600mg / paracetamol 1.5g daily, or twice this dosage) for chronic knee pain in a parallel-group RCT of 892 patients [79]. Though the study was powered to detect differences in analgesic effect (a 5.5 point reduction in the WOMAC pain scale), they also collected data on adverse events. After 13 weeks, they examined the proportion of the groups that had a decrease in haemoglobin of $\geq 1\text{g/dl}$. This was 19.6% in the ibuprofen group, 20.3% for paracetamol, 24.1% for the low-dose combination and 38.4% for the high-dose combination, which was significantly different to the other three groups. As there was also a small but significant drop in platelet count, and an increase in mean cell volume, the authors suggested that the haemoglobin decrease was likely due to occult GI blood loss. They concluded that paracetamol 3g/d and

ibuprofen 1200mg/d were associated with similar amounts of occult blood loss, and that there was an additive effect in the higher-dose combination. More recently, in 2016, the authors of the PERFORM trial examined the effects of paracetamol and ibuprofen on cardiovascular effects and bleeding using a nested case-control study within their cohort of 19,120 participants with recent ischaemic stroke [88]. A total of 800 cases were paired with 1600 controls, and incidence of bleeding (in general, but including intracerebral haemorrhage or intraocular bleed) was recorded. They found that use of $\geq 3\text{g/d}$ was associated with bleeding events (OR 3.72 [95% CI 1.58 – 8.75]). Dosages of $\leq 3\text{g/d}$ were not associated with significant risk, but the trend test was significant ($p=0.02$), indicating a dose-response relationship.

Based on these data, it seems that when taken regularly in dosages of $>2\text{-}3\text{g/d}$ (i.e. at daily doses normally seen in chronic use) there is a significant risk of GI bleeding with paracetamol. The dose-response relationship seen in some of the studies would indicate that something in the mechanism of action of paracetamol can cause GI bleeding as an adverse effect, and that this effect is additive when combined with NSAIDs.

Hepatotoxicity

Over the past few decades there have been several case reports and small studies implying a connection between the ingestion of therapeutic dosages of paracetamol and liver injury [89]. It has been known for many years that therapeutic paracetamol use ($\leq 4\text{g/d}$) has been

associated with subclinical rises in liver injury markers [77]. However, transient rises in alanine aminotransferase (ALT) can be secondary to many factors, such as exercise, vitamin intake, congestive heart failure, diabetes and medications such as aspirin, heparins and statins [90, 91]. Whether such an enzyme rise results in clinically-significant liver injury is less clear. Heard et al. looked at this issue with healthy volunteers in an RCT of long-term paracetamol ingestion (dose 4g/d). They found that ~50% of the paracetamol group experienced no ALT rise, ~25% had a transient rise gone by day 16, and ~25% had ALT normalise by day 40 [92]. These findings agree with Dart and Bailey's review of >40,000 patients' worth of observational data showing a low incidence of transaminitis (0.4-1.0%) and no progression to hepatotoxicity [93].

Of those case reports of liver injury in patients taking therapeutic doses, additional factors such as alcohol abuse, nutritional deficiency or concurrent febrile illness are usually present [94]. As the toxic metabolite of paracetamol NAPQI is produced via Cytochrome P450 metabolism (predominantly the CYP2E1 isoenzyme), clinicians have hypothesised that induction of these enzymes through alcohol misuse might predispose patients to liver injury. This appeared to be supported by animal studies showing that CYP2E1 was induced by ethanol in rodents, and that levels of NAPQI and hepatotoxicity were increased when paracetamol was administered [89]. However, researchers have failed to replicate this finding in humans, and have found evidence of the opposite: CYP2E1 appears to increase only modestly with short-term alcohol use, reversing soon after abstinence [89], and one examination of cirrhotic livers found them to have 59% *less* CYP2E1 than control samples

[95]. In addition, NAPQI levels are not increased in chronic alcoholics taking paracetamol and, although the drug's half-life is prolonged in chronic liver disease, this does not significantly affect metabolism or lead to NAPQI accumulation/hepatotoxicity [89, 96]. Similarly, taking cytochrome P450 enzyme-inducing medication (such as rifampicin and P450 enzyme-inducing anticonvulsants) does not seem to lead to an increased production of NAPQI when paracetamol is taken at therapeutic doses [97]. This has led some researchers to hypothesise that glutathione depletion may be the causal factor in those few cases where therapeutic-dosage paracetamol has resulted in liver injury [94]. Glutathione must be >70% depleted before NAPQI starts to accumulate, but in a starvation state (such as that seen in some alcoholics) this could occur. Indeed, it is known that chronic alcohol misuse is associated with glutathione deficiency [98]. Despite these concerns, due to its lack of a direct effect on coagulation (though there is evidence that a dose of 4g/day taken for two weeks raises the INR of patients taking warfarin by ~0.8 [99]) and (apparent) GI safety profile, paracetamol remains the first-line analgesic of choice for patient with chronic liver disease [100]. There does not seem to be evidence for therapeutic paracetamol treatment causing hepatotoxicity, either in healthy individuals or chronic liver disease patients, with the exception of those in a poor nutritional state [101, 102].

Hepatotoxicity in children

Children metabolise paracetamol differently from adults [103], and there is some concern that children may also suffer as a result of ingestion of therapeutic dosages of paracetamol. This prompted Lavonas et al. to perform a systematic review in 2010, examining 62 studies

and >32,000 children receiving therapeutic-dosage paracetamol ($\leq 75\text{mg/kg/d}$, up to a maximum of 4g/d) for an average of 3-5 days [90]. The range of settings (inpatient, outpatient, primary care, developed & developing world) and indications for paracetamol (infective illness, postoperative pain) was comprehensive. In their analysis, no child showed symptoms of liver disease, and only 10 showed any hepatic adverse events at all (incidence 0.031%, 95% CI 0.015 – 0.057%). They concluded that short-term, therapeutic dose paracetamol is not associated with significant hepatotoxicity.

Renal

Acute kidney injury (AKI) is said to occur in 1-2% of patients with paracetamol overdose [104] and most commonly occurs in the setting of severe paracetamol-induced hepatotoxicity [105]. Renal biopsy, while not often performed, shows evidence of acute tubular necrosis, particularly of the proximal tubule [104]. While the explanation for hepatotoxicity is well known [18], the causes of renal toxicity are less clear: possible reasons include the local generation of NAPQI or other toxic metabolites from paracetamol by cytochrome P450 or COX enzymes [106]. Administration of N-acetylcysteine has no effect on peak creatinine concentration, suggesting that depletion of glutathione stores is not the sole cause of renal toxicity [107, 108]. The clinical outcome from paracetamol-induced nephrotoxicity in the absence of concomitant liver failure is good, with only 1% of patient needing temporising dialysis and most patients returning to baseline renal function by one month [104].

Analgesic nephropathy is characterised by interstitial nephritis and progressive reduction in renal size due to repeated episodes of papillary necrosis. The association between the analgesic phenacetin and nephropathy was first described in 1953 [109] and by the 1970s analgesic nephropathy was reported to be responsible for at least 10-20% of cases of chronic renal failure in the UK and Australia [109]. Despite phenacetin's withdrawal from sale in the 1980s, analgesic nephropathy has not been eradicated, suggesting other agents may also be responsible [110, 111]. As the major active metabolite of phenacetin is paracetamol [112], some questioned whether chronic paracetamol use might also cause chronic kidney disease. In 1994, Perneger et al. studied 716 subjects with end-stage renal disease (ESRD) and found that ESRD was associated with an increase of paracetamol use in a dose-dependent fashion, with ~10% of the overall incidence of ESRD attributable to paracetamol use [113]. The study unfortunately failed to adjust for possible previous use of phenacetin and NSAIDs, bringing its results into question. A large review in 2000, requested by the regulatory authorities of Germany, Switzerland and Austria, examined all published data on non-phenacetin analgesic nephropathy [114]. Overall, its findings were that there was insufficient evidence to claim non-phenacetin-containing analgesics were causally associated with nephropathy, suggesting further research was required [114].

Pregnancy

Paracetamol is administered to pregnant women as an anti-pyretic agent and for the management of mild to moderate pain. The presumed safety of this agent has resulted in paracetamol becoming one of the most common prescriptions in pregnancy: ~50-60% of pregnant women in North and Western Europe self-report using this medication [115]. Its

popularity is mainly due to the recommendation of paracetamol over other analgesics, with NSAIDs having a less favourable risk profile in pregnant women, and use of aspirin limited due to concerns over its effect on the fetus [116, 117].

In recent years, the safety of paracetamol in pregnancy has come under increasing scrutiny. Paracetamol and its metabolites cross the placenta [118] and undergo different PK/PD processes in neonates than in adults: an immature glucuronide conjugation system makes the sulfation pathway the major route of metabolism in neonates [119]. Paracetamol has been postulated to cause a diverse range of embryo-fetal and neonatal adverse effects, dependent on dose, duration of treatment and the trimester of exposure. However, large cohort studies have not found an association between maternal paracetamol use in the first trimester and either adverse pregnancy outcomes or congenital malformations [120, 121]. Nevertheless, there is some evidence of increased risk with paracetamol use in pregnancy and neurodevelopmental disorders, respiratory illness and reproductive toxicity.

Neurodevelopmental

The association between paracetamol exposure *in utero* and the risk of long-term neurological disorders has been the focus of several controversial pharmaco-epidemiological studies. Brandlistuen et al. (2013) suggested maternal paracetamol use for >28 days during pregnancy was associated with problems in gross motor development, communication, externalising and internalising behaviour, and higher activity levels, when

compared to controls [122]. These data were obtained from a Norwegian sibling-controlled study (n=2919) and based on parental reports of child behaviour at 18 and 36 months. Notably, the group also reviewed ibuprofen exposure, to control for possible confounders arising from paracetamol indication, and concluded ibuprofen exposure was not associated with adverse neurodevelopmental outcomes. There was no relation between trimester of exposure to paracetamol and any of the above outcomes.

Maternal paracetamol use was later linked to a neurodevelopmental clinical outcome in the Danish National Cohort Study. Liew et al. suggested that maternal paracetamol use during pregnancy was associated with a higher risk of receiving a hospital diagnosis of hyperkinetic disorder (HR 1.37, 95% CI, 1.19-1.59), use of ADHD medications (HR 1.29, 95% CI 1.15-1.44), or having ADHD-like behaviors at age 7 years (HR 1.13, 95% CI, 1.01-1.27) [123]. The strengths of this flagship study lie in its large sample size (n=64,322) and adjustment for a large number of potential confounders. Notably, these associations were stronger with increased frequency of paracetamol use and were not confounded by maternal inflammation and infection during pregnancy. Using hospital outcome coding data in the same patient cohort, the group later identified an association between prenatal paracetamol use and an increased risk of autistic spectrum disorder (ASD) accompanied by hyperkinetic symptoms (HR 1.51, 95% CI 1.19–1.92), but not with other ASD cases [124]; other studies have suggested an association with ASD symptoms in male offspring only, with associations dependent on the frequency of exposure [125].

The mechanism by which paracetamol and its metabolites may impact on neurological development is poorly understood. Animal studies have reported behavioural and cognitive changes in mice given paracetamol during neonatal brain development, specifically locomotor activity and attainment of spatial learning [126]. Levels of brain-derived neurotrophic factor (BDNF) in the neonatal brain were affected (significantly increased in the frontal, and decreased in the parietal, cortices), postulating this may be the mechanism of action. The role of BDNF in development and brain maturation has been extensively reviewed elsewhere [127].

In conclusion, on the basis of these studies, only weak associations between paracetamol exposure and neurodevelopmental issues are identified, and no causal link can be inferred.

The epidemiological studies that support a link are subject to confounding by unmeasured environmental factors, recall bias, diagnostic inaccuracy (most rely on coding data or parental recall for their outcomes), and differences in drop-out rates. Notably, few studies confirm the effect of duration and timing of paracetamol exposure, details critical in the assessment of toxicological risk in pregnancy.

Asthma

The potential mechanisms by which paracetamol may contribute to the development/exacerbation of asthma are detailed earlier. How paracetamol exposure *in utero* could cause asthma is less clear, unless glutathione levels are lowered in the fetus sufficient to affect lung development. Some support for maternal intake of paracetamol

affecting offspring comes from mouse studies, where adult mice exposed to paracetamol *in utero* underwent an allergic airway challenge [128]. Increased airway infiltration by leukocytes (notably eosinophils) was observed, suggesting an increased susceptibility to asthma, but this finding has not been consistently reproduced [129].

The Avon Longitudinal Study of Parents and Children was one of the first epidemiological studies to examine the causal link between paracetamol exposure during pregnancy and childhood asthma [130]. Frequent paracetamol use in late pregnancy (20–32 weeks) was associated with an increased risk of wheezing in the offspring at 30–42 months (adjusted OR 2.10, 95% CI 1.30 to 3.41), particularly if wheezing started before 6 months (termed ‘persistent wheezers’ – OR 2.34, 95% CI 1.24 to 4.40). Two further cohort studies suggested paracetamol use during any time of pregnancy was associated with a small increased risk of asthma or bronchitis among children at 18 months (RR 1.17, 95% CI 1.13–1.23) and 7 years (RR 1.15, 95% CI 1.02–1.29) [131, 132]. Interestingly, maternal pain showed a positive association with asthma development without the use of paracetamol [132].

However, maternal infections, including respiratory infections, are already associated with an increase in childhood asthma [133, 134]. Paracetamol use may simply be a surrogate for these disease states. Notably, maternal paracetamol use for non-infectious disorders revealed no increased risk of wheezing in children [135]. Further studies expanded on this theme of confounding by paracetamol indication and have highlighted that the increased risk of asthma diagnosis in children exposed to paracetamol prenatally (unadjusted OR 1.36, 95% CI 1.14-1.61) drops significantly (OR 1.26, 95% CI 1.02-1.58) when adjusted for potential

confounders [136]. For an in-depth review of paracetamol exposure and asthma in children, and the issue of confounding, see elsewhere [63]. Further clarification of this issue will be difficult, as RCTs would be both unethical and impractical [55].

Endocrine & Reproductive toxicity

The incidence of cryptorchidism is reportedly increasing, which is particularly concerning given its association with early adulthood disorders such as low sperm count and testicular germ cell cancers [137]. When considered together, these conditions represent a testicular dysgenesis syndrome, a disorder related to androgen disruption during the fetal programming window [138]. Experimental data have shown reduced testicular prostaglandin and testosterone production and reduced ano-genital distance (a marker for androgen action) in rats prenatally exposed to paracetamol [139]. Prenatal paracetamol exposure likely results in reduction of key steroidogenic enzymes (Cyp11a1, Cyp17a1), implicated in the reduced fetal plasma testosterone (45% reduction; $P = 0.025$) and seminal vesicle weight (18% reduction; $P = 0.005$) [140]. These changes were noted in castrated host mice bearing human fetal testis xenografts following exposure to therapeutic doses of paracetamol for 7 days. Notably, however, exposure for 1 day had no effect [140]. Another recent study has linked reduced germ cell development in human fetal testes and ovary xenografts when exposed to paracetamol; this effect was linked to PGE_2 -mediated alterations in epigenetic regulatory genes, indicating that the effect of paracetamol on the fetus may affect the genetics of subsequent generations [141].

Several clinical studies associate paracetamol exposure during pregnancy with increased occurrence of cryptorchidism, particularly when used in for >2 weeks in the second trimester [139, 142, 143]. Few of these studies considered indication for paracetamol use in their analyses, and latterly, reanalysis of these data sets showed slightly lower hazard ratios for paracetamol exposure during weeks 8–14 among women who did not report an illness that would trigger weak analgesic use [144]. This is an interesting paradoxical observation given this time frame represents the human fetal programming window, disruption of which has previously been linked to reduced male infant ano-genital distance [138, 145]. However, we should also note that several large cohort studies have not identified any association between paracetamol and cryptorchidism [120, 146-148]. Indeed, the use of paracetamol may decrease the risk of selected congenital abnormalities when used for febrile illness [147].

The continuing search for evidence that paracetamol causes harm in pregnancy clearly highlights the difficulty in implying causation from pharmaco-epidemiological studies.

Extrapolation of pre-clinical toxicology data to humans may suggest associations with

asthma, ADHD and androgen disruption but the small associations seen in clinical cohort studies may be explained by various confounders and biases inherent in the study designs.

Confidently teasing apart these issues would require randomised control trials, which would be difficult to perform ethically in pregnant populations. Carefully designed, long-term, sibling- and sex-matched cohort studies are more ethically acceptable, and would further

our understanding of the risks. Whilst the evidence-base is uncertain, care should be taken to avoid raising poorly founded concerns among pregnant women because of the risk of switching to other analgesic/ antipyretic drugs with less favourable risk profiles [116].

Untreated febrile illness is associated with severe harm to both mother and child, posing a far greater risk than that postulated for paracetamol exposure [133, 149-151]. Practical advice would be to avoid protracted use of paracetamol for non-febrile illness, a view shared by many study authors [140, 152].

Discussion

Clearly, there remains considerable uncertainty regarding the chronic adverse effects of paracetamol usage. The evidence base in each of the above sections relies mostly on observational and cohort studies, and so is prone to inherent biases. The positive associations found in these studies are generally weak, and often contradictory. Few RCTs have been performed, but, when undertaken, usually give reassuring results. Further studies are required in many areas, but RCTs may be difficult to perform, either because they would need to be very large to detect the modest increases in risk seen in the observational studies, or because of the significant ethical issues of using placebo in patients in pain, as well as of conducting trials in children and pregnant women.

The two areas where the evidence is most convincing are hypertension and gastrointestinal bleeding. A small BP rise of 4 mmHg would be clinically important at the population level, and the outcome of ongoing RCTs should clarify the reliability of this estimate. This may be particularly important in patients with angina or pre-existing hypertension. The fairly consistent evidence for GI bleeding associated with paracetamol use, along with its additive effect when combined with NSAIDs, may be less well known but similarly important. When considering prescribing paracetamol in the chronic setting it would seem wise to consider these adverse effects, based on current data, and discuss them with the patient.

Whether paracetamol usage in the chronic setting should be restricted is doubtful, given the alternatives are NSAIDs and opioids. Indeed, in patients intolerant of NSAIDs their next option would be opioid medication, which come with risks of addiction, drowsiness and fatal accidental overdose.

In summary, the average therapeutic effect for chronic pain syndromes is small, but there is accumulating evidence of clinically significant adverse effects in chronic use. Despite this, for patients who derive clear symptomatic benefit, or only take occasional therapeutic doses, the risks are probably very small. For this reason, paracetamol can be seen as the 'least-worst' option – which likely means it will remain, for now at least, the first-line analgesic of choice.

Conclusion

This review is designed to provide an objective summary of the evidence-base for chronic adverse effects of paracetamol use. We hope that by highlighting the key epidemiological studies, RCTs, meta-analyses and reviews we have provided a valuable summary of knowledge in this field. We hope this work will help clinicians and their patients make an evidence-based, informed decision regarding their chronic pain management, based on the likelihood of clinically-relevant adverse effects.

Accepted Article

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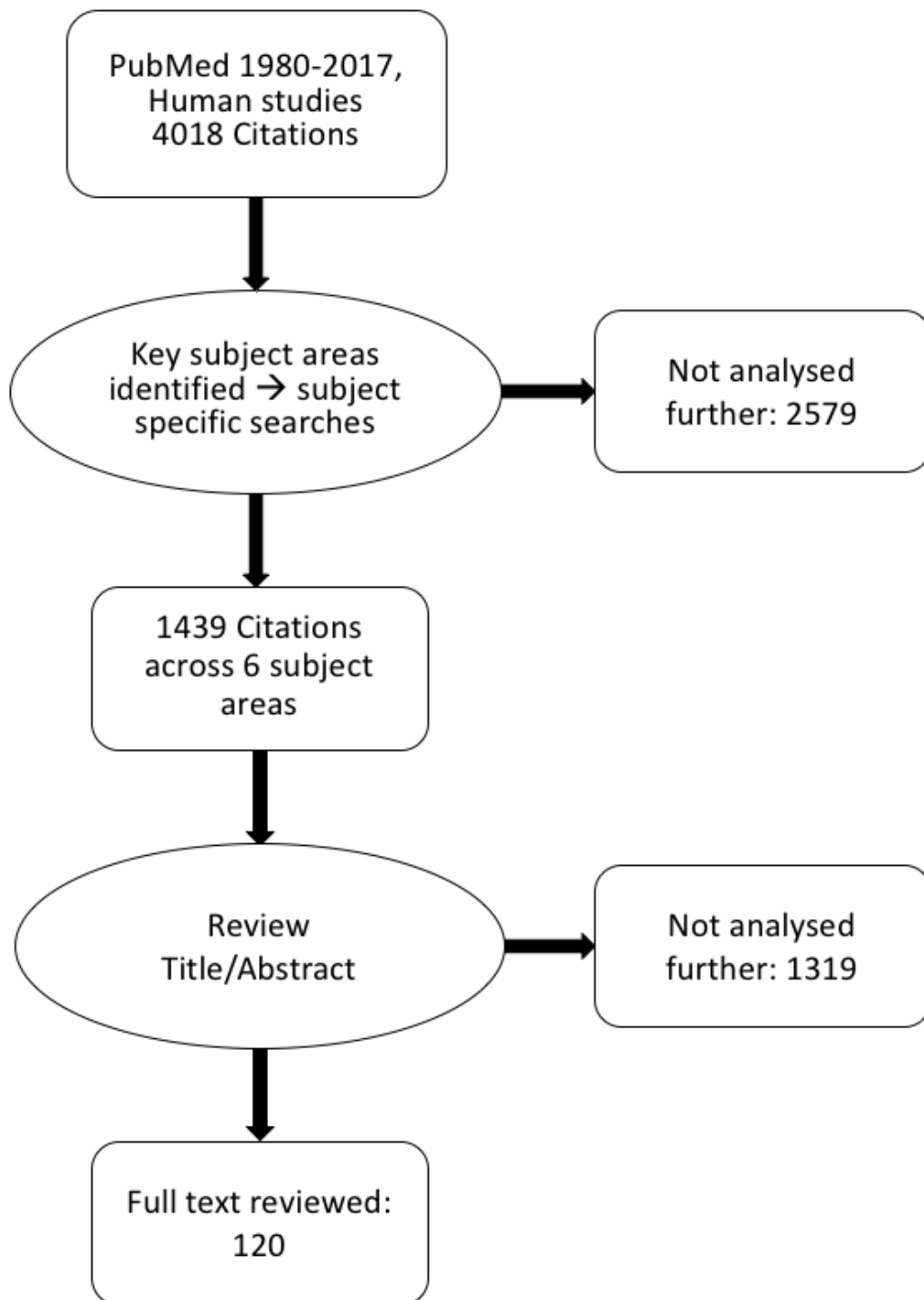


Figure 1: Outline of search strategy