ClinicalEvidence

Paracetamol (acetaminophen) poisoning

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B. Kevin Park, James W. Dear, and Daniel J. Antoine

ABSTRACT

INTRODUCTION: Paracetamol directly causes around 150 deaths per year in UK. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of treatments for acute paracetamol poisoning? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 127 studies. After deduplication and removal of conference abstracts, 64 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 46 studies and the further review of 18 full publications. Of the 18 full articles evaluated, one systematic review was updated and one RCT was added at this update. In addition, two systematic reviews and three RCTs not meeting our inclusion criteria were added to the Comment sections. We performed a GRADE evaluation for three PICO combinations. CONCLUSIONS: In this systematic overview we categorised the efficacy for six interventions, based on information about the effectiveness and safety of activated charcoal (single or multiple dose), gastric lavage, haemodialysis, liver transplant, methionine, and acetylcysteine.

QUESTIONS

INTERVENTIONS

TREATING ACUTE PARACETAMOL POISONING

Beneficial

Likely to be beneficial

Unknown effectiveness

Key points

- Paracetamol (acetaminophen) is a common means of self-poisoning in Europe and North America, often taken as an impulsive act of self-harm in young people.

  Mortality from paracetamol overdose is now about 0.4%, although without treatment, severe liver damage would occur in many people depending on their blood paracetamol concentration.

  Ingestion of less than 75 mg/kg is unlikely to lead to hepatotoxicity. However, there are cases of hepatotoxicity with therapeutic doses of paracetamol.

  We found few RCTs, and most were old. The difficulties of undertaking RCTs in this area should not be underestimated; however, high-quality RCTs are possible.

- Standard treatment of paracetamol overdose is acetylcysteine, which, based on animal studies and clinical experience, is widely believed to reduce liver damage and mortality, although few studies have been done.

  Adverse effects from acetylcysteine include rash, urticaria, vomiting, and anaphylactoid reactions, which can (rarely) be fatal.

  One RCT found that side-effects from acetylcysteine were substantially reduced with a novel dosing regimen that reduces the peak plasma acetylcysteine concentration, but further research is needed to confirm efficacy because the RCT was not powered to detect non-inferiority. At the time of publication of this overview, most patients in the UK receive the standard 21-hour intravenous acetylcysteine regimen.

  We don't know what the optimal dose, route, and duration of acetylcysteine treatment should be. However, liver damage is unlikely to occur if treatment is started within 8 to 10 hours of ingestion of a single overdose.

- It is possible that methionine reduces the risk of liver damage and mortality after paracetamol poisoning compared with supportive care, but we don't know for sure.

- We found no direct information from RCTs meeting our inclusion criteria about activated charcoal in the treatment of people following paracetamol poisoning.

  There is some limited evidence from studies not meeting our inclusion criteria, such as non-randomised trials and studies in volunteer participants, that activated charcoal may reduce the absorption of paracetamol, but we don't know if it improves other clinical outcomes (e.g., mortality, hepatotoxicity, or liver failure) in patients following paracetamol poisoning.

- We don't know whether gastric lavage reduce the risks of liver damage after paracetamol poisoning. Gastric lavage is no longer routine clinical practice.
- Liver transplantation may increase survival rates in people with fulminant liver failure after paracetamol poisoning compared with waiting list controls, but which patients benefit most is unclear.
- We found no RCTs on the effects of haemodialysis.

Clinical context

GENERAL BACKGROUND

Paracetamol overdose is one of the most common reasons for emergency hospital admission. Around 100,000 people present to emergency departments each year in the UK with paracetamol overdose, and around half are admitted for antidote therapy with acetylcysteine.

FOCUS OF THE REVIEW

To determine the strength of evidence for current management approaches for paracetamol overdose.

COMMENTS ON EVIDENCE

We found few RCTs, and most were old. The difficulties of undertaking RCTs in this area should not be underestimated; however, high-quality RCTs are possible.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, March 2007, to October 2014. A search dated back from 1966 was performed for the new option added to the scope at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 127 studies. After deduplication and removal of conference abstracts, 64 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 46 studies and the further review of 18 full publications. Of the 18 full articles evaluated, one systematic review was updated and one RCT was included at this update. In addition, two systematic reviews and three RCTs not meeting our inclusion criteria were added to the Comment sections.

ADDITIONAL INFORMATION

An additional area of interest is the widely acknowledged potential of mechanistic biomarkers to improve patient treatment stratification following paracetamol overdose.

DEFINITION	Paracetamol poisoning occurs as a result of either accidental or intentional overdose with paracetamol (acetaminophen). In this overview, we have included studies in people with paracetamol poisoning from either accidental or intentional overdose. We have excluded studies undertaken in animals or experimental studies undertaken in volunteers.
INCIDENCE/ PREVALENCE	Paracetamol is the most common drug used for self-poisoning in the UK. [1] It is also a common means of self-poisoning in the rest of Europe, North America, and Australasia. In the UK, around 98,000 patients attend emergency departments each year with paracetamol poisoning and around 49,000 are admitted for treatment. [2] Overdoses from paracetamol alone directly result in an estimated 150 to 200 deaths and 15 to 20 liver transplants each year in England and Wales (data from routinely collected health and coronial statistics). [3] [4] Pack-size restrictions instituted in the UK in 1998 resulted in modest reductions in large overdoses, liver transplants, and deaths in England and Wales. In Scotland, the reduction in admissions and mortality from paracetamol overdose was short lived. [3] [4]
AETIOLOGY/ RISK FACTORS	Most cases in the UK are impulsive acts of self-harm in young people. [1] [5] In one cohort study of 80 people who had overdosed with paracetamol, 42 had obtained the tablets for the specific purpose of taking an overdose, and 33 had obtained them less than 1 hour before the act. [5]
PROGNOSIS	The majority of patients present to hospital soon after overdose, a time when subsequent hepatotoxicity cannot be reliably excluded by current liver function tests. The need for treatment is determined by the patient's blood paracetamol concentration, which is interpreted with regard to the time from overdose on a nomogram. In the UK, a line starting at 100 mg/L at 4 hours post overdose determines need for treatment. [6] The position of the line is critical in determining the number of patients treated and the risk of missing a case of treatable hepatotoxicity. The nomogram used in the UK is more conservative when compared with those used in North America or Australia. The

UK position was informed by a comprehensive Medicines and Healthcare products Regulatory Agency (MHRA) review that included data from RCTs, observational studies, and clinical experience. [6] In patients with a staggered overdose (tablets taken repeatedly over more than 2 hours), the nomogram cannot be used and the decision to treat is complex, being based on clinical judgement, reported dose of paracetamol ingested, and blood results. For the majority of patients, treatment with acetylcysteine is successful. However, the prediction of the likely clinical course of the patient remains difficult. This is mainly due to marked inter-individual variation and a lack of sensitivity and specificity, as well as an indirect mechanistic basis of currently used biomarkers to diagnose paracetamol hepatotoxicity and to predict outcome. Recent evidence from both prospective and retrospective studies of paracetamol overdose patients have shown that biomarkers linked to the mechanisms of toxicity can be used to diagnose paracetamol hepatotoxicity (paracetamol-protein adducts), [7] predict the potential to develop acute liver injury at first presentation to hospital (miR-122, Keratin-18, HMGB1), [8] and predict patient outcome (acetyl-HMGB1, KIM-1). [9] [10]

AIMS OF INTERVENTION

To prevent liver failure, liver transplantation, or death, with minimal adverse effects.

OUTCOMES

Mortality, **hepatotoxicity** (most commonly defined by the objective criterion of blood alanine aminotransferase >1000 U/L), **liver failure** (includes liver transplantation [with the exception of our option on liver transplant]). For the option on haemodialysis, we have also reported on **clearance of paracetamol** from the circulation; and **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date October 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to October 2014, Embase 1980 to October 2014, The Cochrane Database of Systematic Reviews 2014, issue 10 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, with no minimum level of blinding (open studies included), and containing more than 20 individuals, of whom more than 80% were followed up. Trials had a minimum length of follow-up of 1 week. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the intervention for ipecacuanha from this overview and added the new intervention for haemodialysis. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included,

in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for acute paracetamol poisoning?

OPTION ACETYLCYSTEINE

- For GRADE evaluation of interventions for Paracetamol (acetaminophen) poisoning, see table, p 15 .
- Standard treatment of paracetamol overdose is acetylcysteine, which, based on animal studies and clinical experience, is widely believed to reduce liver damage and mortality, although few studies have been done.
- Adverse effects from acetylcysteine include rash, urticaria, vomiting, and anaphylactoid reactions, which can (although, rarely) be fatal. These may be reduced by using novel regimens for acetylcysteine treatment. At the time of publication of this overview, the standard regimen in the UK for most patients is 21-hour intravenous acetylcysteine.
- We don't know what the optimal dose, route, and duration of acetylcysteine treatment should be. However, liver damage is unlikely to occur if treatment is started within 8 to 10 hours of ingestion.
- We found no direct information from RCTs comparing acetylcysteine with methionine in the treatment of people with paracetamol poisoning.

Benefits and harms

Acetylcysteine versus no treatment:

RCTs comparing acetylcysteine with no treatment are now likely to be considered unethical.

Acetylcysteine versus placebo:

We found one systematic review (search date 2005), [11] which identified one small RCT in people with established paracetamol-induced liver failure. [12] We found no RCTs in people in the acute phase of paracetamol overdose.

Mortality

Acetylcysteine compared with placebo Acetylcysteine may be more effective than placebo at reducing mortality in people with established paracetamol-induced liver failure and receiving conventional intensive liver care compared with placebo after 21 days (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[12] RCT	50 people with established paracetamol-induced liver failure In review [11]	**Mortality , 21 days** 13/25 (52%) with acetylcysteine 20/25 (80%) with placebo (5% dextrose) Acetylcysteine was continued until death or recovery Everyone also received conventional intensive liver care	ARR 28% 95% CI 3% to 53% P = 0.037 Possible bias due to sealed envelope allocation; for full details, see Further information on studies	◌◌◌	acetylcysteine

Hepatotoxicity

No data from the following reference on this outcome. [11] [12]

Liver failure

No data from the following reference on this outcome. [11] [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] RCT	50 people with established paracetamol-induced liver failure In review [11]	**Adverse effects** with acetylcysteine with placebo (5% dextrose) Acetylcysteine was continued until death or recovery Everyone also received conventional intensive liver care The RCT did not specifically assess adverse outcomes and reported that no adverse effects were seen			

Acetylcysteine versus methionine:

See option on Methionine, p 11 .

Intravenous acetylcysteine versus oral acetylcysteine:

We found one systematic review (search date 2005), which found no RCTs. [11] We found no subsequent RCTs.

See Comment section, p 4 .

Intravenous acetylcysteine versus oral acetylcysteine plus intravenous acetylcysteine:

We found one RCT (50 people aged 18 years or older, time of paracetamol ingestion <8 hours), which compared intravenous (iv) acetylcysteine (initial infusion over 30 minutes, followed by 4-hour infusion at another dose, and 16-hour infusion at another dose) with oral and IV acetylcyteine (initial oral dose, then 4-hour infusion at another dose, then 16-hour infusion at another dose). [13] If vomiting occurred 1 hour after the oral ingestion of acetylcysteine, metoclopramide was given intramuscularly and oral acetylcysteine was given again. If time of paracetamol ingestion was less than 4 hours, gastric evacuation and charcoal were also administered. The RCT reported on adverse effects.

Mortality

No data from the following reference on this outcome. [13]

Hepatotoxicity

No data from the following reference on this outcome. [13]

Liver failure

No data from the following reference on this outcome. [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] RCT	50 people with paracetamol (acetaminophen) poisoning	**Proportion of people with no sign or symptom of anaphylactoid reaction (not specifically defined but may have included nausea and vomiting, dyspnoea, flushing, and headache)** 39% with IV acetylcysteine 87% with oral plus IV acetylcysteine Absolute numbers not reported Some participants also received gastric evacuation and charcoal (absolute numbers not reported)	P = 0.004 Result should be interpreted with caution (see Further information on studies)	○○○	oral plus IV acetylcysteine

Further information on studies

[12] Allocation was concealed, but treatment was not blinded. The RCT used a sealed-envelope method to allocate people to treatment, which is considered less effective at concealing allocation than a centralised computer allocation process, and may have increased the risk of bias. There were differences between the groups in prognostic variables (prothrombin time, coma grade) and other treatments, but a possible confounding effect could not be assessed adequately because of the small size of the study.

[13] The RCT did not report the method of randomisation, allocation concealment, or the level of blinding. It reported that 25 people were allocated to each group, but that 10 people in the oral plus intravenous group were excluded from the study. The reason for exclusion was not reported. As only percentages were reported in the RCT, it is unclear whether all participants were included in the final analysis or not. At baseline (before acetylcysteine administration), there was a significant difference between groups in absence of symptoms of poisoning (no sign or symptoms: 11% in IV acetylcysteine group *v* 40% with initial oral plus IV acetylcysteine group, P = 0.04) and in people with more than one sign or symptom (71% in IV acetylcysteine group *v* 27% with initial oral plus IV acetylcysteine group, P = 0.009). The RCT did not report how many people in each group received additional gastric evacuation and charcoal.

Comment: Widespread adoption of IV acetylcysteine for paracetamol poisoning coincided with a marked drop in overall case fatality ratio from around 3% in the early 1970s [14] to 0.4% in the 1980s. [1] There are clear animal data, [15] observational evidence, and clinical experience that the introduction of acetylcysteine has dramatically changed the natural history of paracetamol poisoning favourably. [16] The optimal dose, route, and duration of treatment are unknown, and assessment by RCTs is required.

Adverse effects

Eight studies (population details not reported), including one RCT, found that the incidence of adverse effects from IV acetylcysteine was 4% to 45%. [17] [18] [19] [20] [21] [22] [23] [24] Adverse effects reported were predominantly rash, urticaria, and occasionally more serious anaphylactoid reactions occurring with the initial 'loading' dose. In most or all cases in the studies identified, adverse effects responded to temporary stopping of infusions and symptomatic treatment, and did not recur when treatment recommenced. Adverse reactions were more common in people with asthma and those who had lower paracetamol concentrations. Oral acetylcysteine can also cause hypersensitivity and anaphylactoid reactions.

In two studies (population details not reported) reporting on treatment-related mortality, three deaths were reported; two followed a 10-fold miscalculation of the dose of acetylcysteine, and the other occurred in a person with severe asthma. [25] [26]

In one study (population details not reported), vomiting was common after oral acetylcysteine and was reported to have occurred in 63% of people, despite previous administration of metoclopramide. [20]

One systematic review (search date 2008) examined adverse effects reported in prospective and retrospective studies, and included some of the above studies. [27] It noted that adverse effects to acetylcysteine are common, and are far more frequently detected if looked for prospectively.

One RCT investigated the effect of pre-treatment with ondansetron before IV acetylcysteine therapy. [28] See section below on Duration of infusion for more detail on this trial.

Early versus delayed treatment

One observational study evaluated the effects of IV acetylcysteine in people presenting early to hospital. [29] It found that people treated within 10 hours of ingestion were less likely to develop liver damage than were untreated historical controls (1/62 [2%] with treated people *v* 33/57 [58%] with untreated people).

Pooled analysis of case series [17] and one additional case series [29] suggested that overall hepatotoxicity was worse if treatment was delayed beyond 8 to 10 hours.

One subsequent systematic review (search date 2009) included retrospective and prospective studies of 20 people or more and examined early versus later treatment. [30] It found studies that provided outcome data stratified by early (949 people) and later (1293 people) treatment. It found seven studies in each group (5 studies with IV acetylcysteine, 2 studies with oral acetylcysteine), six of which were common to both groups. The study designs were not reported. After pooling data, the percentage of people with hepatotoxicity in the early acetylcysteine group (within 10 hours or as defined by trial) was 6% (95% CI 4.3% to 7.4%), compared with 26% (95% CI 23.6% to 29%) of people with later acetylcysteine (>10 hours or as defined by trial). [30] However, it should be noted that these results are based on observational data, as well as indirect comparison, which limits any conclusions that can be drawn.

Oral versus intravenous treatment

We found no RCTs. Pooled analysis of case series comparing oral with IV administration of acetylcysteine, [17] and two subsequent observational studies comparing different protocols for intravenous [31] and oral [32] acetylcysteine, did not find marked differences in outcomes between groups. One subsequent systematic review (search date 2009) included retrospective and prospective studies of 20 people or more. [30] It included 16 articles reporting 5164 people (including [17] [32]). It reported that the overall proportion of people who developed hepatotoxicity in the included studies (early and later treatment included) was 13%. It reported that the percentages of hepatotoxicity were similar when stratified by route (IV or oral). However, the review reported that it found no reports of trials with a direct comparison of oral with IV treatment (the data were based on trials solely with IV or with oral therapy, i.e., indirect comparisons) and the dosages and duration of treatment varied between trials, which limit any conclusions that can be drawn. These findings require confirmation by RCTs.

Duration of infusion

One RCT (223 people, 180 [81%] evaluated; allocation by slips of paper in a closed box) compared rates of drug-related adverse events with IV acetylcysteine infusion over 60 minutes with infusion over the standard 15 minutes. [23] It found limited evidence of no significant difference between groups (drug-related adverse events: 49/109 [45%] with 15 minutes *v* 27/71 [38%] with 60 minutes; mean difference +7, 95% CI −8 to +22), [23] although methodological problems make it difficult to draw any reliable conclusions from these results, and properly conducted RCTs are required. The RCT used a sealed-envelope method to allocate people to treatment, which is considered less effective at concealing allocation than a centralised computer allocation process, and may have increased the risk of bias. Groups were not comparable at baseline, and the 15-minute group was much larger than the 60-minute group (109 people in the 15-minute group *v* 71 people in the 60-minute group).

One RCT (222 people; within 8 hours of paracetamol ingestion; 2 x 2 factorial trial design) compared IV ondansetron pre-treatment plus a shorter IV acetylcysteine regimen (12 hours; 55 people), IV ondansetron and a standard IV acetylcysteine regimen (20.25 hours; 56 people), IV placebo plus a shorter IV acetylcysteine regimen (12 hours; 55 people), and IV placebo plus a standard IV acetylcysteine regimen (20.25 hours; 56 people). [28] The two groups with the shorter regimen and

the two groups with the standard regimen were combined in the analysis. It found that those people allocated to the shorter acetylcysteine group had significantly less vomiting or retching or need for rescue anti-emetic medication than those with the standard regimen within 2 hours of acetylcysteine administration (39/108 [36%] with shorter *v* 71/109 [65%] with standard, OR 0.26, 97.5% CI 0.13 to 0.52, P <0.0001). There was also a significant difference between groups in nausea, vomiting, or retching at up to 12 hours (60/101 [59%] with shorter *v* 80/102 [78%] with standard, OR 0.37, 97.5% CI 0.18 to 0.79, P = 0.003). The RCT found that anaphylactoid symptoms were absent in 50/108 (46%) of people with the shorter acetylcysteine regimen compared with 25/100 (25%) of people with standard regimen (P value not reported). The RCT found that clinically relevant severe (grade 3) reactions needing either drug treatment or interruption of acetylcysteine infusion were significantly lower with the shorter acetylcysteine regimen (5/108 [5%] with shorter *v* 31/100 [31%] with standard, OR 0.23, 97.5% CI 0.12 to 0.43, P <0.0001). The RCT reported that the proportion of people with a 50% increase in alanine aminotransferase activity did not differ significantly between the shorter and standard acetylcysteine groups (OR 0.60, 95% CI 0.20 to 1.83). However, the proportion of people with a 50% increase in alanine aminotransferase activity was significantly higher with ondansetron compared with placebo (OR 3.30, 95% CI 1.01 to 10.72, P = 0.024). The RCT noted that the study was not powered to detect non-inferiority of the shorter protocol versus the standard approach, and that further research was needed to confirm the efficacy of the shorter regimen. [28]

Clinical guide
At the time of publication of this overview, most patients in the UK receive the standard 21-hour intravenous acetylcysteine regimen.

OPTION ACTIVATED CHARCOAL (SINGLE OR MULTIPLE DOSE)

- For GRADE evaluation of interventions for Paracetamol (acetaminophen) poisoning, see table, p 15 .
- We found no direct information from RCTs meeting our inclusion criteria about activated charcoal in the treatment of people following paracetamol poisoning.
- There is some evidence from studies not meeting our inclusion criteria, such as non-randomised trials and studies in volunteer participants, that activated charcoal may reduce the absorption of paracetamol, but we do not know if it improves other clinical outcomes (e.g., mortality, hepatotoxicity, or liver failure) in patients following paracetamol poisoning.

Benefits and harms

Activated charcoal (single or multiple dose):

We found one systematic review (search date 2005), which found no RCTs that specifically examined clinical outcomes after paracetamol poisoning. [11]

Comment:

Adverse effects
One non-systematic review (population details not reported) found that adverse effects of activated charcoal include aspiration pneumonia, vomiting, diarrhoea, constipation, ileus, and interference with regular medications. [33] One RCT (327 people with medicinal poisoning, 89/327 [27%] with paracetamol poisoning) reported on vomiting and aspiration (vomiting: 15% with activated charcoal *v* 14% with no gastrointestinal decontamination; aspiration: <1% with activated charcoal *v* <1% with no gastrointestinal decontamination; absolute numbers not reported, significance not reported). [34] One retrospective case series (878 people treated with multiple-dose activated charcoal) found pulmonary aspiration in 6/878 (0.6%, 95% CI 0.1% to 1.1%) people with activated charcoal. [35] This large retrospective case series suggested that rates of clinically significant adverse events with multiple-dose regimens are likely to be low.

Single-dose activated charcoal
The systematic review also included simulated overdose studies in volunteers, and found that activated charcoal given within 2 hours of paracetamol ingestion decreased absorption by a variable amount, and that this amount diminished with time. [11]

One prospective cross-over study, published after the search date for the systematic review, [11] also attempted to assess the efficacy of activated charcoal (available in Thailand) by using volunteers to simulate paracetamol poisoning. [36] It did not meet our inclusion criteria because it was in the

wrong population (i.e., volunteers) and was too small, but we include it here for interest. Twelve healthy volunteers were randomly assigned to one of two arms: control followed by experiment or experiment followed by control. Participants each ingested 60 mg/kg of paracetamol and after 0.25 hours were administered either 50 g of activated charcoal plus 250 mL of water (experiment) or 250 mL of water only (control). Serial blood samples were taken measuring paracetamol concentration, and data analysed. It found that there was a statistically significant difference between the means of the area under the time-concentration curve (AUC [0, infinity]) when experiment (activated charcoal plus water) was compared with control (313.7 ± 29.8 and 184.8 ± 91.6 mg-h/ L; P = 0.01). The authors concluded the study demonstrated that the activated charcoal available in Thailand was able to reduce absorption of supratherapeutic doses of paracetamol, such as would be found in cases of paracetamol poisoning.

One cohort study in 450 consecutive people who had taken 10 g or more of paracetamol found that those who had been given activated charcoal were significantly less likely to have high-risk blood paracetamol concentrations than those who had not been given activated charcoal (OR 0.36, 95% CI 0.23 to 0.58). [37] The effect was seen only in those treated within 2 hours, and the study was not large enough to assess the effect of many potential confounders. [37] A single-centre retrospective non-randomised study of 1571 patients reported that activated charcoal treatment reduced the need for acetylcysteine treatment after overdose. [38] One non-systematic review of activated charcoal in all forms of poisoning found no evidence that activated charcoal improved outcome in poisoned people. [33]

Multiple-dose activated charcoal

The review found no studies of simulated overdose that evaluated multiple-dose regimens in paracetamol poisoning. [11] One non-systematic review of case series and reports of multiple-dose regimens in all forms of poisoning found no evidence that multiple-dose regimens improved outcomes in poisoned people. [39]

OPTION GASTRIC LAVAGE

- For GRADE evaluation of interventions for Paracetamol (acetaminophen) poisoning, see table, p 15 .
- We don't know whether gastric lavage reduces the risks of liver damage after paracetamol poisoning.
- Gastric lavage is no longer routine clinical practice.

Benefits and harms

Gastric lavage:

We found one systematic review (search date 2005), which found no RCTs that reported clinical outcomes. [11]

Comment:

Adverse effects

One RCT (876 people with acute oral overdose of a variety of drugs; 136/876 [16%] with paracetamol poisoning) found significantly higher complications rates with gastric emptying plus charcoal compared with charcoal alone (13% with gastric emptying plus charcoal *v* 8% with charcoal alone, absolute numbers not reported, P = 0.43). [40] However, the results may not be generalisable to people undergoing gastric lavage for paracetamol poisoning, as about 50% of people were treated with ipecacuanha, and only 16% of the study population had paracetamol poisoning. Gastric emptying was induced by ipecacuanha in 209 people and by gastric lavage in 220 people. The RCT did not analyse harms data separately for gastric lavage or ipecacuanha. Reported adverse effects included charcoal-induced aspiration, diarrhoea, ileus, arrythmia during vomiting, and haematemesis. Harms with any method of gastric emptying plus charcoal included aspiration 17/459 (4%), diarrhoea (3 people), ileus (3 people), arrhythmia during vomiting (2 people), dystonia from metoclopramide given for vomiting (1 person), and haematemesis (2 people). [40]

General

One cohort study (described previously; see Comment for Activated charcoal, p 8) found that those given activated charcoal were significantly less likely to have high-risk blood paracetamol concentrations than those not given activated charcoal (OR 0.36, 95% CI 0.23 to 0.58). [37] The addition of gastric lavage to activated charcoal regimens did not further decrease the risk (OR 1.12, 95% CI 0.57 to 2.20). [37] One non-systematic review of gastric lavage in all forms of poisoning found no evidence that gastric lavage improved outcome in poisoned people. [41]

Clinical guide
Gastric lavage is no longer routine clinical practice.

OPTION HAEMODIALYSIS New

- For GRADE evaluation of interventions for Paracetamol (acetaminophen) poisoning, see table, p 15 .
- We found no RCTs on the effects of haemodialysis in people with paracetamol poisoning.
- A clinical working group has provided recommendations regarding haemodialysis. This group suggested that dialysis could be considered in patients with very high blood paracetamol concentrations and evidence of mitochondrial dysfunction (high lactate, metabolic acidosis, coma).

Benefits and harms

Haemodialysis versus placebo or no treatment:

We found one systematic review (search date 2005), which found no RCTs. [11] We found no subsequent RCTs.

Haemodialysis versus methionine, activated charcoal (single or multiple doses), gastric lavage, or liver transplant:

We found one systematic review (search date 2005), which found no RCTs. [11] We found no subsequent RCTs.

Comment:

Clinical guide
An international clinical working group has provided recommendations regarding haemodialysis, based on one systematic review and consensus opinion. This group suggested that dialysis could be considered in patients with very high blood paracetamol concentrations and evidence of mitochondrial dysfunction (high lactate, metabolic acidosis, coma). [42]

OPTION LIVER TRANSPLANT

- For GRADE evaluation of interventions for Paracetamol (acetaminophen) poisoning, see table, p 15 .
- Liver transplantation may increase survival rates in people with fulminant liver failure after paracetamol poisoning compared with waiting list controls.
- Improvements in supportive care create a need for refinement of patient identification tools used to choose those patients to transplant.

Benefits and harms

Liver transplant:

We found one systematic review (search date 2005), which found no RCTs assessing clinical outcomes of liver transplant in people with fulminant hepatic failure after paracetamol poisoning. [11]

Comment:

Short-term outcomes
The largest study (case series, 44 people with orthotopic liver transplant) [43] identified by the review [11] reported that 33/44 (75%) people survived to hospital discharge. The main causes of death were cerebral oedema, multi-organ failure, sepsis, and acute rejection. There were four (9% of total) further deaths after discharge. No information was reported about other long-term adverse effects. [43]

The review found 10 observational studies (mainly retrospective), which compared mortality among people who had liver transplant for fulminant hepatic failure with those that did not, all of which used almost the same criteria (King's College Hospital [KCH] transplant criteria). [11] It pooled data

and reported that 19/67 (28%) of people with transplantation died compared with 121/180 (67%) of those without transplantation. [11] A systematic review of other criteria for transplant found that most criteria have similar (or worse) sensitivity and specificity to the King's criteria. [44] Criteria might be improved with stricter definitions and need to be prospectively validated in a setting of current best supportive care.

Long-term outcomes
The systematic review [11] found no long-term studies of outcomes after liver transplant. Long-term adverse effects may occur from immunosuppressants after liver transplant.

OPTION METHIONINE

- For GRADE evaluation of interventions for Paracetamol (acetaminophen) poisoning, see table, p 15 .
- It is possible that methionine reduces the risk of liver damage and mortality after paracetamol poisoning compared with supportive care, but we don't know for sure.
- We found no direct information from RCTs about methionine compared with acetylcysteine in the treatment of people with paracetamol poisoning.

Benefits and harms

Methionine versus usual care:

We found one systematic review (search date 2005), [11] which identified one small RCT. [45]

Mortality

Methionine compared with usual care We don't know whether methionine is more effective than usual care at reducing mortality in people with paracetamol poisoning, as we found insufficient evidence from one small RCT (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[45] RCT **3-armed trial**	40 people with blood concentrations of paracetamol above the UK standard treatment line at time of study In review [11]	**Mortality** 0/13 (0%) with methionine 1/13 (8%) with usual care Everyone received gastric lavage plus supportive care (usual care) The remaining arm evaluated intravenous mercaptamine	Reported as not significant P value not reported Possible bias due to sealed envelope allocation; for full details, see Further information on studies	⟷	Not significant

Hepatotoxicity

Methionine compared with usual care Methionine may be more effective at reducing hepatotoxicity in people with paracetamol poisoning compared with usual supportive care (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hepatic necrosis					
[45] RCT **3-armed trial**	40 people with blood concentrations of paracetamol above the UK standard treatment line at time of study In review [11]	**Grade III hepatic necrosis** 0/9 (0%) with methionine 6/10 (60%) with usual care The remaining arm evaluated intravenous mercaptamine Everyone received gastric lavage plus supportive care (usual care)	P <0.05 Possible bias due to sealed envelope allocation; for full details, see Further information on studies Interpretation of liver biopsy results was difficult; see Further information on studies for details	○○○	methionine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Liver enzyme levels					
[45] RCT **3-armed trial**	40 people with blood concentrations of paracetamol above the UK standard treatment line at time of study In review [11]	**Peak aspartate aminotransferase greater than 1000 U** 1/13 (8%) with methionine 8/13 (62%) with usual care The remaining arm evaluated intravenous mercaptamine Everyone received gastric lavage plus supportive care (usual care)	RR 0.13 95% CI 0.02 to 0.86 NNT 2 95% CI 2 to 6	●●●	methionine

Liver failure

No data from the following reference on this outcome. [11] [45]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] RCT **3-armed trial**	40 people with blood concentrations of paracetamol above the UK standard treatment line at time of study In review [11]	**Adverse effects** with methionine with usual care Absolute results not reported The remaining arm evaluated intravenous mercaptamine Everyone received gastric lavage plus supportive care (usual care) No serious adverse effects associated with treatment, but vomiting occurred in 8/13 (62%) people after administration of methionine The incidence of adverse effects in the supportive care alone group was not reported			

Methionine versus acetylcysteine:

We found two systematic reviews (search dates 2003 and 2005), which identified no RCTs. [11] [46]

Further information on studies

[45] *Bias* The RCT used a sealed-envelope method to allocate people to treatment, which is considered less effective at concealing allocation than a centralised computer allocation process, and may have increased the risk of bias. *Interpretation of liver biopsy results* Only 27/40 (68%) of people had a liver biopsy, and an intention-to-treat analysis was not possible.

Comment: None.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Haemodialysis New option added. One systematic review found. [11] Categorised as unknown effectiveness.

Acetylcysteine One systematic review updated [11] and one RCT added. [13] Two systematic reviews [27] [30] and one RCT [28] added to the Comment section only. Categorisation unchanged (beneficial).

Activated charcoal One systematic review updated. [11] Two RCTs added to the Comment section only. [36] [38] Categorisation unchanged (unknown effectiveness).

Gastric lavage One systematic review updated. [11] Categorisation unchanged (unknown effectiveness).

Liver transplant One systematic review updated. [11] Categorisation unchanged (unknown effectiveness).

Methionine One systematic review updated. [11] Categorisation unchanged (likely to be beneficial).

REFERENCES

1. Gunnell D, Hawton K, Murray V, et al. Use of paracetamol for suicide and non-fatal poisoning in the UK and France: are restrictions on availability justified? *J Epidemiol Community Health* 1997;51:175–179.[PubMed]
2. Bateman DN, Carroll R, Pettie J,et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. *Br J Clin Pharmacol* 2014;78:610–618.[PubMed]
3. Morgan O, Majeed A. Restricting paracetamol in the United Kingdom to reduce poisoning: a systematic review. *J Public Health* 2005;27:12–18.[PubMed]
4. Morgan O, Griffiths C, Majeed A. Impact of paracetamol pack size restrictions on poisoning from paracetamol in England and Wales: an observational study. *J Public Health* 2005;27:19–24.[PubMed]
5. Hawton K, Ware C, Mistry H, et al. Paracetamol self-poisoning. Characteristics, prevention and harm reduction. *Br J Psychiatry* 1996;168:43–48.[PubMed]
6. Medicines and Healthcare products Regulatory Agency (MHRA). Treating paracetamol overdose with intravenous acetylcysteine: new guidance. Sep 2012. Available at https://www.gov.uk/drug-safety-update/treating-paracetamol-overdose-with-intravenous-acetylcysteine-new-guidance (last accessed 19 June 2015).
7. James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. *Drug Metab Dispos* 2009;37:1779–1784.[PubMed]
8. Antoine DJ, Dear JW, Lewis PS, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. *Hepatology* 2013;58:777–787.[PubMed]
9. Antoine DJ, Jenkins RE, Dear JW, et al. Molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity. *J Hepatol* 2012;56:1070–1079.[PubMed]
10. Antoine DJ, Sabbisetti VS, Francis B, et al. Circulating Kidney Injury Molecule 1 predicts prognosis and poor outcome in patients with acetaminophen-induced liver injury. *Hepatology* 2015 Apr 18 [Epub ahead of print].[PubMed]
11. Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdose. In: The Cochrane Library, Issue 10, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2005.
12. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991;303:1026–1029.[PubMed]
13. Eizadi-Mood N, Sabzghabaee AM, Siadat S, et al. Intravenous acetylcysteine versus oral and intravenous acetylcysteine: Does a combination therapy decrease side effects of acetylcysteine? *Pak J Med Sci* 2013;29(1)Suppl:308–311. Available at http://www.pjms.com.pk/index.php/pjms/article/view/3522 (last accessed 19 June 2015).
14. Clark R, Borirakchanyavat V, Davidson AR, et al. Hepatic damage and death from overdose of paracetamol. *Lancet* 1973;1:66–70.[PubMed]
15. James LP, McCullough SS, Lamps LW, et al. Effect of N-acetylcysteine on acetaminophen toxicity in mice: relationship to reactive nitrogen and cytokine formation. *Toxicol Sci* 2003;75:458–467.[PubMed]
16. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995;346:547–552.[PubMed]
17. Buckley NA, Whyte IM, O'Connell DL, et al. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999;37:759–767.[PubMed]
18. Chan TY, Critchley JA. Adverse reactions to intravenous N-acetylcysteine in Chinese patients with paracetamol (acetaminophen) poisoning. *Hum Exp Toxicol* 1994;13:542–544.[PubMed]
19. Schmidt LE, Dalhoff K. Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Br J Clin Pharmacol* 2001;51:87–91.[PubMed]
20. Wright RO, Anderson AC, Lesko SL, et al. Effect of metoclopramide dose on preventing emesis after oral administration of N-acetylcysteine for acetaminophen overdose. *J Toxicol Clin Toxicol* 1999;37:35–42.[PubMed]
21. Sanaei-Zadeh H, Taghaddosinejad F, Jalali N, et al. Adverse effects of intravenous N-acetylcysteine. *Clin Drug Invest* 2003;23;129–133.
22. Kao LW, Kirk MA, Furbee RB, et al. What is the rate of adverse events after oral N-acetylcysteine administered by the intravenous route to patients with suspected acetaminophen poisoning? *Ann Emerg Med* 2003;42:741–750.[PubMed]
23. Kerr F, Dawson A, Whyte IM, et al. The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* 2005;45:402–408.[PubMed]
24. Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. *J Pediatr* 1998;132:149–152.[PubMed]
25. Mant TG, Tempowski JH, Volans GN, et al. Adverse reactions to acetylcysteine and effects of overdose. *BMJ* 1984;289:217–219.[PubMed]
26. Appelboam AV, Dargan PI, Jones AL, et al. Fatal anaphylactoid reaction to N-acetylcysteine: caution in asthmatics. *J Toxicol Clin Toxicol* 2002;40:366–367.
27. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol (Phila)* 2009;47:81–88.[PubMed]
28. Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. *Lancet* 2014;383:697–704.[PubMed]
29. Prescott LF, Illingworth RN, Critchley JA, et al. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ* 1979;2:1097–1100.[PubMed]
30. Green JL, Heard KJ, Reynolds KM, et al. Oral and intravenous acetylcysteine for treatment of acetaminophen toxicity: A systematic review and meta-analysis. *West J Emerg Med* 2013;14:218–226.[PubMed]
31. Dougherty T, Greene T, Roberts JR. Acetaminophen overdose: comparison between continuous and intermittent intravenous N-acetylcysteine 48-hour protocols. *Ann Emerg Med* 2000;36(4 Suppl 1):S83.
32. Woo OF, Mueller PD, Olson KR, et al. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. *Ann Emerg Med* 2000;35:363–368.[PubMed]
33. Chyka PA, Seger D. Position statement: single-dose activated charcoal. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol* 1997;35:721–741.[PubMed]
34. Cooper GM, Le Couteur DG, Richardson D, et al. A randomized clinical trial of activated charcoal for the routine management of oral drug overdose. *QJM* 2005;98:655–660.[PubMed]
35. Dorrington CL, Johnson DW, Brant R; Multiple Dose Activated Charcoal Complication Study Group. The frequency of complications associated with the use of multiple-dose activated charcoal. *Ann Emerg Med* 2003;41:370–377.[PubMed]
36. Wananukul W, Klaikleun S, Sriapha C, et al. Effect of activated charcoal in reducing paracetamol absorption at a supra-therapeutic dose. *J Med Assoc Thai* 2010;93:1145–1149.[PubMed]
37. Buckley NA, Whyte IM, O'Connell DL, et al. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. *J Toxicol Clin Toxicol* 1999;37:753–757.[PubMed]
38. Duffull SB, Isbister GK. Predicting the requirement for N-acetylcysteine in paracetamol poisoning from reported dose. *Clin Toxicol* (Phila) 2013;51:772–776.[PubMed]
39. American Academy of Clinical Toxicology, European Association of Poison Centres, and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999;37:731–751.[PubMed]
40. Pond SM, Lewis-Driver DJ, Williams GM, et al. Gastric emptying in acute overdose: a prospective randomised controlled trial. *Med J Aust* 1995;163:345–349.[PubMed]

41. Vale JA. Position statement: gastric lavage. American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol* 1997;35:711–719.[PubMed]
42. Gosselin S, Juurlink DN, Kielstein JT, et al; EXTRIP Workgroup. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)* 2014;52:856–867.[PubMed]
43. Bernal W, Wendon J, Rela M, et al. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. *Hepatology* 1998;27:1050–1055.[PubMed]
44. Bailey B, Amre DK, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: a systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. *Crit Care Med* 2003;31:299–305.[PubMed]
45. Hamlyn AN, Lesna M, Record CO, et al. Methionine and cysteamine in paracetamol (acetaminophen) overdose, prospective controlled trial of early therapy. *J Int Med Res* 1981;9:226–231.[PubMed]
46. Alsalim W, Fadel M. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. Oral methionine compared with intravenous n-acetyl cysteine for paracetamol overdose. *Emerg Med J* 2003;20:366–367.[PubMed]

B. Kevin Park
Professor of Pharmacology
MRC Centre for Drug Safety Science
University of Liverpool
Liverpool
UK

James W. Dear
Consultant Clinical Pharmacologist and Toxicologist
Edinburgh Royal Infirmary
University of Edinburgh
Edinburgh
UK

Daniel J. Antoine
Lecturer in Pharmacology and Wellcome Trust Research Fellow
MRC Centre for Drug Safety Science
University of Liverpool
Liverpool
UK

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Disclaimer

GRADE **Evaluation of interventions for Paracetamol (acetaminophen) poisoning.**

Important outcomes				Hepatotoxicity, Liver failure, Mortality					
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for acute paracetamol poisoning?									
1 (50) [12]	Mortality	Acetylcysteine versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and methodological flaws (allocation and concealment); directness point deducted for differences between the groups (prognostic)
1 (26) [45]	Mortality	Methionine versus usual care	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, weak methods (allocation and concealment), and incomplete reporting of results; directness point deducted for small number of events (total of 1 event)
1 (19) [45]	Hepatotoxicity	Methionine versus usual care	4	–3	0	–1	+2	Low	Quality points deducted for sparse data, and for weak methods (allocation and concealment) and no intention-to-treat analysis; directness point deducted for differences between the groups (liver biopsy); effect size points added for RR less than 0.2

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.