

N-ACETYLCYSTEINE FOR NON-PARACETAMOL DRUG-INDUCED LIVER INJURY: A SYSTEMATIC REVIEW

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DECLARATION

I, Mohamed Farouk Chughlay, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed on 09 September 2015:

Signed by candidate

DEDICATION

I dedicate this work to my dearest wife, Sameera. Completing this MMED could not have been achieved without your love and support.

ACKNOWLEDGEMENTS

I have been privileged to work with an exceptionally talented and dedicated team. I have learnt something unique from each of them. Special thanks must go to my friend and co-reviewer, Nicky Kramer, for all her hard work and dedication throughout the review process.

ACRONYMS AND ABBREVIATIONS

AASLD: American Association for the Study of Liver Diseases

ALF: Acute Liver Failure

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

DDW: Digestive Diseases Week

DILI: Drug-induced Liver Injury

EASL: European Association for the Study of Liver

ICTRP: International Clinical Trials Registry Platform

INR: International Normalised Ratio

NAC: N-acetylcysteine

NAPQI: N-acetyl-p-benzo-quinone imine

PACTR: Pan African National Clinical Trials Registry

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

RCT: Randomised Controlled Trial

RevMan: Review Manager

WHO: World Health Organisation

PART A: PUBLISHED PEER-REVIEWED PROTOCOL



N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review protocol

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Abstract

Background: Drug-induced liver injury (DILI) refers to acute or chronic liver injury that may occur as a consequence of using drugs and herbal or dietary supplements. Specific therapies for DILI are limited. There is considerable evidence for efficacy and safety of *N*-acetylcysteine (NAC) in management of paracetamol-induced liver injury. More recently, research has explored the use of NAC in non-paracetamol drug-induced liver injury. It is important to summarise the evidence of NAC for non-paracetamol DILI to determine if NAC may be considered a therapeutic option in this condition.

Methods/design: We will conduct a systematic review of the benefit and harm of NAC in non-paracetamol drug-induced liver injury. Primary and secondary outcomes of interest are pre-specified. Primary outcomes include all-cause mortality, mortality due to DILI, time to normalisation of liver biochemistry (e.g. return of alanine transaminase to <100 U/l and/or international normalized ratio (INR) <1.5) and adverse events. Secondary outcomes include transplantation rate, time to transplantation, transplant-free survival and duration of hospitalisation. We will include randomized controlled trials (RCTs) and prospective cohort studies. RCTs will contribute to the evaluation of safety and efficacy of NAC, whereas, the cohort studies will contribute exclusively to the evaluation of safety. We will search several bibliographic databases (including PubMed, Scopus, CINAHL, CENTRAL), grey literature sources, conference proceedings and ongoing trials. Following data extraction and assessment of the risk of bias, we will conduct a meta-analysis if feasible, as well as subgroup analyses. We will assess and explore clinical and statistical heterogeneity.

Discussion: The aim of this review is to provide evidence on the effectiveness and safety of NAC in non-paracetamol DILI. We anticipate that the results could aid health care practitioners, researchers and policymakers in the decision-making regarding the use of NAC in patients with non-paracetamol DILI.

Systematic review registration: PROSPERO CRD42014008771

Keywords: *N*-acetylcysteine, Acetylcysteine, Drug-induced, Hepatitis, Liver, Liver failure, Non-paracetamol, Non-acetaminophen

Background

Drug-induced liver injury (DILI) refers to acute or chronic liver injury that may occur as a consequence of using drugs and herbal or dietary supplements [1, 2]. According to recent estimates, the yearly incidence of DILI is estimated to be between 14–19 cases per 100,000 [3, 4].

While this may suggest that the condition is uncommon, there is still a considerable potential for harm. In the USA, it is the most common cause of acute liver failure, with 11 % of cases due to idiosyncratic DILI [5]. Moreover, the true incidence of DILI may be underestimated due to diagnostic difficulty as well as underreporting [2].

A number of risk factors are thought to be associated with the development of DILI. In general, older age is a risk factor, with DILI occurring more commonly in adults compared with children [6]. While there seems to be a biological basis for age as a risk factor, it may also

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reflect that adults are more frequently exposed to potential hepatotoxins compared with children. However, age as a risk factor does not always hold true, such that for certain drugs, the risk is greater in children e.g. DILI caused by valproic acid is more common in children. Females appear to be at a greater risk compared to their male counterparts [7]. Certain genetic variations place individuals at risk of DILI due to specific drugs e.g. isoniazid DILI and *N*-acetyltransferase 2 gene polymorphism as well as the HLA-^{*}B5701 genotype and flucloxacillin [8]. While these genetic variations have been shown to increase the risk for the development of DILI, they do not predict severity of injury. Pre-existing liver disease is a further independent risk factor, with this being observed in patients coinfecting with viral hepatitis and tuberculosis who develop DILI in response to antiviral and antituberculous drugs [9, 10]. Furthermore, alcohol abuse and malnutrition are also risk factors associated with the development of DILI [2].

The general management of DILI consists of the discontinuation of the offending drug in combination with supportive treatment [2]. Patients often require prolonged hospital stays which may be costly to both patient and health service. Therapeutic re-challenge with the offending drug is generally not recommended but may be attempted in certain instances after a thorough consideration of the risks and potential benefits. There are specific therapies available for DILI caused by certain drugs. However, these are limited to carnitine for valproic acid and *N*-acetylcysteine (NAC) for paracetamol overdose [11, 12]. This limited availability highlights the need for further research into therapies for DILI.

NAC was first used as a treatment for paracetamol overdose in 1979 [13]. Since then, it has been firmly established as an effective and safe treatment for this condition [12]. NAC has also been shown to be safe and effective outside of paracetamol overdose. NAC has been evaluated as a treatment option for non-paracetamol acute liver failure in adults and paediatric patients. In a randomised clinical trial comparing NAC with placebo in adults with non-paracetamol acute liver failure, NAC was associated with an improvement in transplant-free survival in a subgroup of patients with grade 1 and grade 2 encephalopathy [14]. In a prospective study conducted in adults with non-paracetamol acute liver failure at a centre without the facility for transplantation, the use of NAC was associated with a mortality benefit [15]. In a retrospective study in paediatric patients with non-paracetamol acute liver failure, NAC was associated with a shorter hospital stay and improved survival post-transplantation [16]. Furthermore, in a case series of patients with DILI secondary to *Amanita phalloides* mushroom poisoning, 10 out of 11 patients recovered fully after receiving NAC in combination with other therapies [17].

NAC has also been evaluated for non-liver related clinical indications. These indications include its use as a mucolytic agent in pulmonary diseases, in the prevention of radio-contrast associated nephrotoxicity and for the treatment of certain ophthalmic conditions [18–21].

In paracetamol overdose, a form of non-idiosyncratic DILI, the pathogenesis underlying hepatotoxicity is fairly well understood. Here, the metabolism of paracetamol produces an excess of the hepatotoxic metabolite *N*-acetyl-p-benzo-quinone imine (NAPQI). NAPQI is normally inactivated by hepatic glutathione; however, glutathione is depleted in paracetamol overdose. This results in an accumulation of NAPQI with consequent hepatic cell injury and death. NAC is thought to replenish hepatic glutathione stores, which forms the basis for its efficacy in this condition [22]. In contrast, the mechanism underlying hepatotoxicity in idiosyncratic DILI does not involve glutathione depletion. However, the precise pathogenesis in idiosyncratic DILI is not clearly defined [23]. The proposed pathogenic mechanisms in idiosyncratic DILI include direct cell injury, immune mediated damage and mitochondrial injury. These mechanisms, especially those that lead to mitochondrial damage, have significant implications. Mitochondria are involved in protecting hepatocytes against oxidative stress from oxygen-free radicals in the liver. The damage and loss of mitochondria leads to an accumulation of oxygen-free radicals and subsequent oxidative cell damage. NAC may be of benefit in this context through its antioxidant effect [24, 25]. Furthermore, additional benefits of NAC in this context involve the improvement of systemic haemodynamics and tissue oxygen delivery, as well as other favourable effects on the injured liver [26, 27].

The aim of this systematic review is to review the evidence of safety and effectiveness including improvement in time, if any, to normalisation of liver function tests and of NAC in non-paracetamol drug-induced liver injury. NAC has already been established as a safe and effective treatment for paracetamol-induced liver injury. Recently, the research focus has shifted to investigating the use of NAC in non-paracetamol drug-induced liver injury. It is important to review the evidence of NAC safety and efficacy in this setting to determine if NAC may be considered as a treatment option in non-paracetamol drug-induced liver injury. The evidence from this research may then be used to inform the decisions made by policymakers, health care practitioners, as well as researchers in this area.

Methods/design

This review protocol is registered in the PROSPERO International Prospective Register of systematic reviews, registration number CRD42014008771.

Criteria for considering studies for this review**Types of studies**

We will include randomized controlled trials (RCTs) and prospective cohort studies. RCTs will contribute to the evaluation of safety and efficacy of NAC, whereas, the cohort studies will contribute exclusively to the evaluation of safety.

Language and timing

No language and time restrictions will apply.

Types of participants

Human participants of any age diagnosed with non-paracetamol drug-induced liver injury and diagnosed according to recognised diagnostic criteria [28–31].

Types of interventions

Intervention, *N*-acetylcysteine administered intravenously or orally.

Control, placebo or standard of care (as described in the study) or alternative therapy.

There will be no restriction on dose, timing and route of administration of NAC.

Types of outcome measures

Results must include quantitative data for outcomes measured.

Primary outcomes All-cause mortality, mortality due to DILI, time to normalisation of liver biochemistry (e.g. return of alanine transaminase to <100 U/l and/or international normalized ratio (INR) <1.5), adverse events (graded using the Common Terminology Criteria for Adverse Events) [32].

Secondary outcomes Transplantation rate, time to transplantation, transplant-free survival, duration of hospitalisation.

Search methods for identification of studies

We will perform a comprehensive search of databases and conference proceedings to identify all relevant studies available by October 2014, regardless of language or publication status. We will search both peer-reviewed journal articles and grey literature (unpublished, internal or non-reviewed papers and reports).

Electronic searches

We will search the following electronic databases: Cochrane Library, Medline via PubMed, SCOPUS, Web of Science (SciELO), and EBSCO (CINAHL, Africa-Wide, Academic Search Premier). We will use both text words and medical subject heading (MeSH) terms. The literature search strategy will be adapted to suit each

database. Briefly, we will use a combination of the following terms: *N*-acetylcysteine, Acetylcysteine, Drug-induced, Hepatitis, Liver, Liver Failure, Non-paracetamol, Non-acetaminophen.

The detailed search strategy is provided in Additional file 1.

Conference proceedings

We will conduct a manual search of relevant abstracts or proceedings of the following conferences (2000 to present): American Association for the Study of Liver Diseases (AASLD) Drug-Induced Liver Injury Conference, AASLD-FDA-NIH-PhRMA-Hepatotoxicity Special Interest Group Conferences, European Association for the Study of Liver (EASL), The International Liver Congress and Digestive Diseases Week (DDW). If conference abstracts are not adequately comprehensive, we will use the information from these abstracts to search for the full text articles. We will attempt to contact the authors of the conference abstracts if we are unable to track down the full text articles. If we are unable to obtain the full text articles and contact the authors, we will list the studies as potentially relevant.

Manual searches

We will obtain reference lists of relevant studies identified, and the full text articles reviewed for inclusion in the review will be checked for additional information.

Searching other sources

Grey Literature will include Google Scholar, SCOPUS for conference proceedings. www.opengrey.eu and www.greylit.org. For ongoing studies, we will search the Pan African National Clinical Trials Registry (PACTR), World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov and NHS Clinical Trials. Individuals and organisations working in the field of drug-induced liver injury will be consulted for information regarding unpublished data and work in progress.

Data collection and analysis

The methods for data collection and analysis will be based on the Cochrane Handbook of Systematic Reviews for Interventions [33].

Selection of studies

Two review authors (MFC and NK) will independently review all relevant material identified from the above search. After reading the titles and abstracts of the identified articles, we will acquire the full text articles of all citations deemed to meet the inclusion criteria. These articles will be independently inspected to verify that they meet the pre-specified inclusion criteria. We will

resolve disagreements between the two reviewers regarding study eligibility through discussion with a third author (KC). For all studies excluded by the assessors, we will describe the reasons for exclusion.

Data extraction and management

MFC and NK will use a standardised data extraction form to extract data from the included studies and to assess the study quality. Extracted information will include administrative details, verification assessment of the diagnosis of DILI, details of the intervention, details of comparators, details of outcomes and information for assessment of the risk of bias. A pilot data extraction will be performed using the data extraction form, and the form will be modified if required. Any discrepancies will be resolved via discussion of the original articles with a third author (KC). We will request missing data from study authors. References will be managed using Mendeley Desktop reference manager and data will be analysed using Review Manager 5.3 (RevMan5) software. MFC and NK will both enter data and conduct cross-checks to ensure that there are no data entry errors.

Assessment of risk of bias in included studies

MFC and NK will independently assess the risk of bias in each of the included studies. The assessment will include information on the following: sequence generation, allocation concealment, blinding, incomplete outcome data or missing data, selective outcome reporting, other sources of bias and overall risk of bias. Each methodological component will be assessed, and the RCTs will be described as having a low, unclear or high risk of bias, as per the Cochrane Handbook of Systematic Reviews of Interventions [33]. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses tool will be used for assessing the risk of bias of the included cohort studies [34]. More specifically, we will use an adapted version of the modified NOS (see Additional file 2) to assess the risk of bias of the included cohort studies [35]. This modified NOS includes seven questions amongst four domains of risk assessment: methods for selecting study participants (selection bias), methods to control for confounding (performance bias), statistical methods (detection bias) and methods of exposure and outcome assessment (information bias). Risk of bias will be measured using a scale ranging from 0 (high risk of bias) to 3 (low risk of bias), and question-specific descriptions including examples of varying degrees of bias are included. Items from the original NOS pertaining to adequacy of follow-up, selection of participants (representativeness of cohort) and assessment of outcomes will be retained in the adapted modified NOS.

The two authors will resolve disagreements in the assessment of risk of bias by discussion and consensus, consulting KC to resolve any persistent disagreements.

Measures of treatment effect

Data will be analysed using RevMan5. The type of outcomes may include dichotomous, continuous and time-to-event data. For dichotomous data, a summary statistic will be calculated (e.g. odds ratio and risk ratio) with accompanying confidence interval (e.g. 95 % CI). For continuous data, a summary statistic such as a mean difference or standardised mean difference will be calculated. Two methods of summarising the time-to-event data will be considered. The first will use the methods of survival analysis and express the intervention effect as a hazard ratio. For the second method, the time-to-event data may be analysed as dichotomous data if the status of all study participants at a fixed time point are known and further summarised as an odds ratio or risk ratio with accompanying confidence interval. Every effort will be made to contact the original authors or investigators of the selected articles to assist with missing or incomplete data.

Dealing with missing data

In the cases of absent or incomplete evidence found in the included studies, authors will be contacted for further information. We will report unclear issues as presented rather than make assumptions. Should they be necessary, we will be explicit about assumptions made.

Data synthesis, assessment/investigation of heterogeneity

Heterogeneity will be assessed by inspecting forest plots initially then through the Cochran's chi-square test using a 10 % level of significance cut-off (due to the low power of the test) and the I-square statistic (I^2) where values will be evaluated as follows:

- 0–40 % = might not be important
- 30–60 % = moderate
- 50–90 % = substantial
- 75–100 % = considerable

Where heterogeneity is statistically significant, subgroup analysis using the variables of age group, sex and setting (e.g. geographical region), as well as sensitivity analysis, will be conducted to explore the potential sources of heterogeneity. Symmetry of funnel plots will be used to assess for publication or selective reporting bias.

We will attempt primary meta-analyses of the included RCTs for both effectiveness and harm outcomes. If meta-analysis of RCTs is feasible, a random effects model will be constructed. We plan to quantify the statistical reliability of data in the cumulative meta-analysis by undertaking sequential analysis. Should small study effects be found, we

will conduct a meta-regression on small study effects. If the identified RCTs are of substantial heterogeneity rendering meta-analysis not feasible, the findings will be presented in narrative form and will include relevant tables and figures to aid in data presentation. We will consider conducting separate secondary meta-analyses for prospective cohort studies limited to the outcomes of harm. If this is not feasible, the findings from the included cohort studies will be presented in a narrative form. All authors will contribute to the narrative review.

In addition to evaluating all DILI participants, we also plan to explore differences in outcomes between the following subgroups: sex, age strata, geographical region, diagnostic certainty of DILI and exclusion of other possible causes, aetiology of DILI (e.g. antituberculous, HIV antiretrovirals, antiepileptics, herbal supplements), coma grade, severity of DILI (using severity scales such as Drug-Induced Liver Injury Network 5-point scale where severity of liver injury is based upon the presence of jaundice, hospitalisation, signs of hepatic or other organ failure, ultimate outcome and graded as 1+ mild, 2+ moderate, 3+ moderate-severe, 4+ severe, 5+ fatal) and pattern of liver injury (hepatocellular, mixed and cholestatic). For the analyses of outcomes within subgroups, the same methods of analyses for measuring treatment effects as a whole will be applied.

We will use the grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence [36].

Sensitivity analyses

A sensitivity analysis of the findings from primary meta-analysis is planned, and the aim is to determine whether the findings are robust to decisions made during the review process [32]. Amongst others, we will explore the impact of including or excluding particular studies and the chosen method for analysis. Lastly, we will also evaluate the impact of excluding studies deemed as having a high risk of bias.

Presenting and reporting of results

This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [37].

Discussion

This review will provide evidence on the effectiveness and safety of NAC in non-paracetamol DILI. We anticipate that the findings could aid health care practitioners and policymakers in the decision-making regarding the use of NAC in patients with non-paracetamol DILI. Furthermore, the findings may benefit researchers by providing guidance for the focus of future research through the identification of gaps in the existing evidence and advise

on the conduct of future high-quality research through the identification of the shortcomings in previously conducted research.

Additional files

Additional file 1: Electronic search strategy. This describes the electronic search strategy used in searching the electronic databases.

Additional file 2: Modified Newcastle-Ottawa Scale. This describes an adapted version of a modified Newcastle-Ottawa Scale for the risk of bias assessment of included cohort studies.

Abbreviations

ALT: alanine aminotransferase; DDW: Digestive Diseases Week; DILI: drug-induced liver injury; EASL: European Association for the Study of Liver; ICTRP: International Clinical Trials Registry Platform; INR: international normalized ratio; NAC: N-acetylcysteine; NAPQI: N-acetyl-p-benzoquinone imine; PACTR: Pan African National Clinical Trials Registry; RCT: randomized controlled trial; RevMan: Review Manager; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MFC conceived the idea for the review. MFC drafted the written protocol with the support of NK. All authors contributed to the development of the protocol. MW provided input on study methodology. WS served as a content expert in the field of drug-induced liver injury. MEE provided input on study methodology, general study oversight and publication support. KC served as the overall supervisor, content expert and provided input on study methodology. MFC and NK will be involved in data acquisition. All authors will contribute to data analysis and the interpretation of results. MFC will draft the final manuscript intended for publication. All authors have given their approval for publication.

Authors' information

Mohamed Farouk Chughlay (MFC) is a clinical pharmacology registrar in the Department of Medicine, UCT. Nicole Kramer (NK) is a research pharmacist at the Clinical Research Centre, UCT. Wendy Spearman (WS) is a consultant hepatologist and is head of the Division of Hepatology, Department of Medicine, UCT. Mahmoud Werfalli is a PhD Fellow, Division of endocrinology and Diabetes, Chronic Disease Initiative for Africa, (CDIA) Department of Medicine, UCT. Mark Emmanuel Engel (MEE) and is a senior researcher, Department of Medicine, UCT. Karen Cohen is a consultant clinical pharmacologist, Department of Medicine, UCT.

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Additional file 1: Electronic search strategy

Search	Query
#5	Search (#3 AND #4)
#4	Search (acetylcysteine[mh] OR acetylcysteine[tiab] OR n-acetylcysteine[tiab] OR n-acetyl-L-cysteine[tiab] OR n-acetylcystine[tiab] OR acetyl cysteine[tiab] OR n-acetyl cysteine[tiab])
#3	Search (#1 OR #2)
#2	Search (liver failure[mh] OR liver failure[tiab] OR hepatic failure[tiab] OR hepatic injur*[tiab])
#1	Search (chemically-induced liver failure OR drug-induced liver injury[mh] OR drug induced liver injur*[tiab] OR drug induced liver disease*[tiab] OR drug induced hepatitides[tiab] OR drug induced hepatitis[tiab] OR toxic hepatitides[tiab] OR toxic hepatitis[tiab])

(high risk of bias)

(low risk of bias)

Example of low risk of bias: The study identified and adjusted for all possible confounders that may influence estimates of association between exposure and outcome (*i.e. Was the patient being treated for a medical condition such as chronic pain and was being prescribed opioids while on methadone treatment?*)

Example of moderate risk of bias: The study identified and reported possible variables that may influence the outcome but did not explore the interaction.

Example of high risk of bias: The study either did not report any variables of influence or acknowledge variables of influence when it was clear they were present.

Domain of evaluation: Statistical methods (*i.e. Detection bias*)

Did the study use appropriate statistical analysis methods relative to the outcome of interest?

0
(high risk of bias)

1

2

3
(low risk of bias)

Example of low risk of bias: The study reported use of appropriate statistical analysis as required (*i.e. adjusting for an unbalanced distribution of a specific covariate among sexes, or correcting for multiple testing error*)

Example of moderate risk of bias: The study either used correct statistical methods but did not report them well, or used the incorrect methods but reported them in detail.

Example of high risk of bias: The study did not use appropriate statistical analysis as required (*i.e. did not adjust for an unbalanced distribution of a specific covariate among sexes, or correct for multiple testing error when necessary*) or did not report them adequately.

Is there little missing data and did the study handle it accordingly?

0
(high risk of bias)

1

2

3
(low risk of bias)

Example of low risk of bias: The study acknowledged missing data to be less than 10% and specified the method of handling it.

Example of moderate risk of bias: The study either had greater than 15% but they specified the method they used to handle it.

Example of high risk of bias: The study had greater than 15% missing data and did not handle it at all.

Domain of evaluation: Methods for measuring outcome variables (*i.e. Information bias*)

Is the methodology of the outcome measurement explicitly stated and is it appropriate?

0 1 2 3
(high risk of bias) (low risk of bias)

Example of low risk of bias: The study provides a detailed description of the outcome measure(s) which are appropriate for the outcome of interest.

Example of moderate risk of bias: The study provides a somewhat complete description of outcome measurements and they are justified.

Example of high risk of bias: The study provides limited information on the methods of measuring the outcome and the measure is not appropriate considering the outcome.

Is there an objective assessment of the outcome of interest?

0 1 2 3
(high risk of bias) (low risk of bias)

Example of low risk of bias: The study used objective methods to discern the outcome status of participants (*i.e. laboratory measurements, medical records*).

Example of moderate risk of bias: The study relied on subjective data as the primary method to discern outcome status of participants (*i.e. self-report*).

Example of high risk of bias: The study had limited reporting about assessment of outcomes.

PART B: PUBLICATION-READY MANUSCRIPT

N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review

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Structured Summary

Aims: There are limited therapeutic options for drug-induced liver injury (DILI). N-acetylcysteine (NAC) is known to be of benefit in management of DILI due to paracetamol overdose and may also be useful in the management of non-paracetamol DILI. Our objective was to systematically review evidence for the use of NAC as a therapeutic option for non-paracetamol DILI.

Methods: We conducted a systematic review of the benefit and harm of NAC in non-paracetamol DILI. We searched for randomized controlled trials (RCTs) and prospective cohort studies. We searched several bibliographic databases (including PubMed, Scopus, CINAHL, CENTRAL), grey literature sources, conference proceedings and ongoing trials. Our pre-specified primary outcomes were all cause and DILI related mortality, time to normalisation of liver biochemistry and adverse events. Secondary outcomes were proportion receiving liver transplant, time to transplantation, transplant-free survival and hospitalization duration. Two reviewers independently assessed studies for inclusion and quality and extracted data.

Results: We identified one RCT of NAC versus placebo in patients with non-paracetamol acute liver failure. There was no difference in the primary outcomes of overall survival at 3-weeks between NAC [70%, 95% Confidence Interval (CI)= 60% to 81%, n=81] and placebo (66%, 95% CI= 56% to 77%, n=92). NAC

significantly improved the secondary outcomes of transplant-free survival compared with placebo: 40% NAC (95% CI= 28% to 51%) versus 27% placebo (95% CI= 18% to 37%). A subgroup analysis according to aetiology found improved transplant-free survival in patients with non-paracetamol DILI; NAC (58%, n=19) versus placebo (27%, n=26); odds ratio (OR) 0.27 (95% CI= 0.076 to 0.942). Overall survival was similar NAC (79%) versus placebo (65%); OR 0.50 (95% CI= 0.13 to 1.98).

Conclusion: Current available evidence is limited and does not allow for any firm conclusions to be made regarding the role of NAC in non-paracetamol DILI. We therefore highlight the need for further research in this area.

Systematic Review Registration: This review is registered in the PROSPERO International Prospective Register of systematic reviews, registration number CRD42014008771.

Keywords: N-acetylcysteine, Acetylcysteine, Drug-induced, Hepatitis, Liver, Liver Failure, Non-paracetamol, Non-acetaminophen

What is already known about this subject

- N-acetylcysteine is of benefit in the treatment of paracetamol-induced liver injury.
- Recent literature suggests a possible role for N-acetylcysteine in the treatment non-paracetamol drug-induced liver injury.

What this study adds

- We conducted a systematic review of the benefit and harm of NAC in non-paracetamol DILI.
- There is limited evidence supporting the use of N-acetylcysteine in non-paracetamol drug-induced liver injury.
- We therefore highlight the need for further research.

Background

Drug-induced liver injury (DILI) refers to acute or chronic liver injury that may occur as a consequence of using drugs and herbal or dietary supplements [1, 2]. According to recent estimates, In the United States of America (USA), it is the most common cause of acute liver failure (ALF), with 11 % of cases due to idiosyncratic DILI [3]. In South Africa it is the second highest cause of death due to adverse drug reactions in medical wards [4]. Two recent studies estimated incidence at between 14–19 cases per 100,000 persons receiving prescription medication [5, 6]; true incidence of DILI may be underestimated due to diagnostic difficulty as well as underreporting [2].

The general management of DILI consists of the discontinuation of the offending drug in combination with supportive treatment [2]. Patients often require prolonged hospital stays which may be costly to both patient and health service. Therapeutic re-challenge with the offending drug is generally not recommended but may be attempted in certain instances after a thorough consideration of the risks and potential benefits. Specific therapies available for DILI are limited to carnitine for valproic acid and N-acetylcysteine (NAC) for paracetamol overdose [7, 8].

NAC was first used as a treatment for paracetamol overdose in 1979 [9]. Since then, it has been firmly established as an effective and safe treatment for this condition [8]. NAC has also been shown to be safe and effective outside of paracetamol overdose. NAC has been evaluated as a treatment option for non-paracetamol ALF in adults and paediatric patients. In a randomised clinical trial comparing NAC with placebo in adults with non-paracetamol ALF, NAC was associated with an improvement in transplant-free survival, in subgroups of patients with grade 1 and grade 2 encephalopathy [10]. In a cohort study conducted in adults with non-paracetamol ALF at a centre without the facility for transplantation, the use of NAC was associated with a mortality benefit [11]. In a retrospective study in paediatric patients with non-paracetamol ALF, NAC was associated with a shorter hospital stay and improved survival post-transplantation [12]. Furthermore, in a case series of patients with DILI secondary to *Amanita phalloides*

mushroom poisoning, 10 of 11 patients recovered fully after receiving NAC in combination with other therapies [13].

NAC has also been evaluated for non-liver related clinical indications. These indications include its use as a mucolytic agent in pulmonary diseases, in the prevention of radio-contrast associated nephrotoxicity and for the treatment of certain ophthalmic conditions [14–17].

In paracetamol overdose, a form of non-idiosyncratic DILI, the pathogenesis underlying hepatotoxicity is fairly well understood. Here, the metabolism of paracetamol produces an excess of the hepatotoxic metabolite N-acetyl-p-benzo-quinone imine (NAPQI). NAPQI is normally inactivated by hepatic glutathione; however, glutathione is depleted in paracetamol overdose. This results in an accumulation of NAPQI with consequent hepatic cell injury and death. NAC is thought to replenish hepatic glutathione stores, which forms the basis for its efficacy in this condition [18]. In contrast, the mechanism underlying hepatotoxicity in idiosyncratic DILI does not involve glutathione depletion. However, the precise pathogenesis in idiosyncratic DILI is not clearly defined [19]. The proposed pathogenic mechanisms in idiosyncratic DILI include direct cell injury, immune mediated damage and mitochondrial injury. These mechanisms, especially those that lead to mitochondrial damage, have significant implications. Mitochondria are involved in protecting hepatocytes against oxidative stress from oxygen-free radicals in the liver. The damage and loss of mitochondria leads to an accumulation of oxygen-free radicals and subsequent oxidative cell damage. NAC may be of benefit in this context through its antioxidant effect [20, 21]. Furthermore, additional benefits of NAC in this context involve the improvement of systemic haemodynamics and tissue oxygen delivery, as well as other favourable effects on the injured liver [22, 23].

The aim of this systematic review was to synthesise the evidence of safety and efficacy including improvement in time, if any, to normalisation of liver function tests and of NAC in non-paracetamol DILI.

NAC has already been established as a safe and effective treatment for paracetamol-induced liver injury. Recently, the research focus has shifted to investigating the use of NAC in non-paracetamol drug-induced liver injury. It is important to review the evidence of NAC safety and efficacy in this setting to determine if NAC may be considered as a treatment option in non-paracetamol DILI. The evidence from this research may then be used to inform the decisions made by policymakers, health care practitioners, as well as researchers in this area.

Methods/Design

This review is registered in the PROSPERO International Prospective Register of systematic reviews, registration number: CRD42014008771. The protocol was peer reviewed [24].

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and prospective cohort studies.

Language and Timing

No language and time restrictions applied.

Types of participants

Human participants of any age diagnosed with non-paracetamol DILI, diagnosed according to recognised diagnostic criteria [25–28].

Types of interventions

Intervention: NAC administered intravenously or orally. Control: placebo or standard of care (as described in the study) or alternative therapy.

There were no restrictions on dose, timing and route of administration of NAC.

Types of outcome measures

Primary outcomes

All-cause mortality, mortality due to DILI, time to normalisation of liver biochemistry (e.g. return of alanine transaminase to < 100 U/l and/or International Normalised Ratio (INR) < 1.5), adverse events (graded using the Common Terminology Criteria for Adverse Events) [29].

Secondary outcomes

Transplantation rate, time to transplantation, transplant-free survival, duration of hospitalisation.

Search Methods for identification of studies

We performed a comprehensive search in June 2015 of electronic databases and conference proceedings to identify all relevant studies, regardless of language or publication status. We searched both peer-reviewed journal articles and grey literature (unpublished, internal or non-reviewed papers and reports).

Electronic Searches

We searched the following electronic databases: Cochrane Library; Medline via PubMed; SCOPUS; Web of Science (SciELO); EBSCO (CINAHL, Africa-Wide, Academic Search Premier). We used both text words and medical subject heading (MeSH) terms. The literature search strategy was adapted to suit each database. Briefly, we used a combination of the following terms: N-acetylcysteine, Acetylcysteine, Drug-induced, Hepatitis, Liver, Liver Failure, Non-paracetamol, Non-acetaminophen.

Conference proceedings

We conducted a manual search of relevant abstracts or proceedings of the following conferences (2000 to 2015): American Association for the Study of Liver Diseases (AASLD) Drug-Induced Liver Injury Conference, AASLD-FDA-NIH-PhRMA-Hepatotoxicity Special Interest Group Conferences, European Association for the Study of Liver (EASL), The International Liver Congress and Digestive Diseases Week (DDW).

Searching other sources

We searched Google Scholar; SCOPUS for conference proceedings; and www.opengrey.eu and www.greylit.org for grey literature. For ongoing studies, we searched the Pan African National Clinical Trials Registry (PACTR); World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP); ClinicalTrials.gov and NHS Clinical Trials. Individuals and organisations working in the field of drug-induced liver injury were consulted for information regarding unpublished data and work in progress.

Data collection and analysis

The methods for data collection and analysis are based on the Cochrane Handbook of Systematic Reviews for Interventions [30].

Selection of studies

Two review authors (MFC and NK) independently reviewed all relevant material identified from the above search. After reading the titles and abstracts of the identified articles, we acquired the full text articles of all citations deemed to meet the inclusion criteria. These articles were independently inspected to verify that they met the pre-specified inclusion criteria. We resolved disagreements between the two reviewers regarding study eligibility through discussion with a third author (KC).

Data extraction and management

Two authors (MFC and NK) used a standardised data extraction form to extract data from the included study and to assess study quality. Any discrepancies were resolved via discussion of the original article with a third author. We requested additional data from study authors. References were managed using Mendeley Desktop reference manager. We prepared our review using Review Manager 5.3 (RevMan5) software [31].

Assessment of risk of bias in included studies

MFC and NK independently assessed the risk of bias in the included study. The assessment included information on: sequence generation, allocation concealment, blinding, incomplete outcome data or missing data, selective outcome reporting, other sources of bias, and overall risk of bias. Each methodological component was assessed and the study was described as having a low, unclear, or high risk of bias, as per the Cochrane Handbook of Systematic Reviews of Interventions [30]. The two authors resolved disagreements in the assessment of risk of bias by discussion and consensus, consulting a third reviewer, KC to resolve any persistent disagreements.

Measures of treatment effect

We planned to conduct our data analysis using Review Manager Version 5.3 [31]. We present the data from the included study with respect to overall survival and transplant-free survival in the overall study population with acute liver failure. We proceeded to calculate the odds ratios and 95% CI for the outcomes of overall survival and transplant-free survival for the DILI subgroup.

Data synthesis, assessment of heterogeneity and sensitivity analyses

In view of limited available data, we could not conduct meta-analysis; assess heterogeneity or sensitivity analyses.

Presenting and reporting of results

This systematic review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [32]. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of the evidence and summarise relevant study outcomes [33].

Results

Results of Search

Figure 1 shows the flow diagram for study inclusion. A total of 691 records were identified through the search until June 2015. After screening titles and abstracts, we excluded 687 records leaving 4 articles for full-text review. We excluded 3 further articles after full-text review, and identified 1 article from which we could extract data for inclusion in a qualitative analysis. We also identified one ongoing placebo-controlled trial of NAC for DILI due to first-line tuberculosis treatment, still recruiting [34].

Characteristics of included study (See Table 1)

The included study was a randomised, double-blind, placebo-controlled trial investigating a 72-hour intravenous infusion of NAC as treatment for adults with non-paracetamol ALF, at multiple sites in the USA [10]. ALF was defined in the study as encephalopathy with accompanying coagulopathy. Randomisation was stratified by hepatic encephalopathy grade (1-2 versus 3-4) and study site. The study enrolled 173 participants and randomly assigned 81 participants to receive NAC and 92 participants to receive placebo. After randomisation, an infusion of either 5% dextrose with NAC or 5% dextrose only (placebo) was administered. The primary outcome was overall survival at 3 weeks. Although not listed as an outcome of interest, the study did report on rates of adverse events in study participants.

Effect of NAC on outcomes in overall study population (participants with non-paracetamol ALF): Overall survival at 3 weeks was similar for the NAC and placebo groups; 57/81 (70%; 95% CI 60% to 81%); versus 61/92 (66%; 95% CI 56% to 77%), Chi squared $p = 0.283$. In contrast, transplant-free survival was greater in the NAC group than the placebo group; 32/81 (40%; 95% CI 28% to 51%); versus 25/92 (27%; 95% CI 18% to 37%), Chi squared $p=0.043$. In a secondary analysis, transplant-free survival was stratified by coma grade. In patients with coma grade I-II survival was higher in the NAC group than the placebo group; 30/58 (52%; 95% CI= 38% to 65%); versus 17/56 (30%; 95% CI 17% to 43%), $p=0.010$, with an odds ratio (OR) of 2.46 (95% CI= 1.14 to 5.30). In contrast in participants with coma grades III-IV transplant-free survival was lower

in the NAC group but this did not reach statistical significance; 2/23 (9%; 95% CI 0% to 22%); versus 8/36 (22%; 95% CI 7% to 37%), $p=0.912$, OR 0.33 (95% CI= 0.06 to 1.74). The difference in odds ratios according to coma grade was statistically significant ($p=0.012$). Transplantation rates were 26/81 (32%; 95% CI= 21% to 43%) in the NAC group and 41/92 (45%; 95% CI 34% to 55%) in the placebo group, $p=0.09$. Rates of adverse events were similar between groups; nausea and vomiting was more common in the NAC than the placebo group, 11/81 (14%; 95% CI 6% to 22), versus 4/92 (4%; 95% CI 0%, 9%), $p=0.031$. In total, there were 5 early discontinuations of therapy due to side-effects possibly due to the drug, 4 due to NAC.

Effect of NAC on outcomes in subgroup with ALF due to non-paracetamol DILI: A subgroup analysis by aetiology of ALF was conducted. Non-paracetamol DILI was the largest aetiological subgroup with 45 participants, of which 19 received NAC and 26 received placebo. Outcome data on the 45 DILI participants were limited to overall survival and transplant-free survival. There were 4 deaths in the NAC arm compared with 9 deaths in the placebo arm, which corresponded with an overall survival of 79% ($n=15$) in the NAC arm and 65% ($n=17$) in the placebo arm, with an odds ratio of 0.50 (95% CI= 0.13, 1.98, $p=0.33$), and risk ratio for death of 0.61 (95% CI= 0.22 to 1.68, $p=0.34$). Transplant-free survival was higher in the participants with non-paracetamol DILI treated with NAC than those treated with placebo; 58% ($n=11$) versus 27% ($n=7$), with an odds ratio of (95% CI: 0.076 to 0.942, $p=0.04$), and risk ratio for death of 0.57 (95% CI 0.32 to 1.03, $p=0.06$). The study was not powered to detect differences within the DILI subgroups.

Risk of Bias in included study

We graded the overall risk of bias in the study as “unclear”. See Table 2 for further details regarding risk of bias assessment.

Quality of the Evidence

The GRADE assessment of the quality of the evidence indicated that the evidence for the various outcomes to be of “very low” or “low” quality. See Table 3 for the details of the GRADE assessment.

Characteristics of excluded studies (See Table 3)

The first excluded study was a small open-label RCT conducted in Iran that investigated the hepatoprotective effect of NAC in antituberculous DILI [35]. This study was excluded on the basis that it investigated the use of NAC in the prevention of DILI, as opposed to the treatment of DILI.

The second excluded study was a multicentre, randomised, double masked, placebo-controlled trial investigating NAC as treatment for non-paracetamol ALF in paediatric participants [36]. Of relevance to our review is that this study included a subgroup analysis according to the aetiology of ALF. Non-paracetamol DILI was included in the aetiology of ALF and although there were 3 cases of ALF secondary to non-paracetamol DILI in the placebo group, there were no cases of ALF secondary to non-paracetamol DILI amongst those who received NAC. Therefore, we excluded this study on the basis that it could not provide evaluable data for our review.

The third excluded study was a cohort study investigating NAC as treatment in non-paracetamol ALF [11]. This study was excluded on the basis that it included a comparison with retrospective controls, and therefore did not meet our inclusion criteria of being a prospective cohort study.

Discussion

After systematic review of published and unpublished literature, we identified only one study addressing efficacy and safety of NAC in non-paracetamol DILI. Participants with non-paracetamol DILI were a subgroup in this randomized controlled trial. This subgroup analysis only addressed one of our primary endpoints (overall survival) and found no difference in this subgroup, but was underpowered for this comparison. Additionally, GRADE assessment indicated the evidence for this endpoint to be of “very low” quality. Based on this study’s findings NAC may be of benefit in treatment of non-paracetamol DILI in improving the secondary endpoint of transplant free survival. Thus, we cannot draw firm conclusions on the efficacy of NAC in management of non-paracetamol DILI, on the basis of limited low quality outcome

data confined to this small subgroup. Findings may not be generalizable to patients with less severe forms of liver injury. Patients with DILI present on a spectrum from mild liver injury to severe liver injury (ALF). We found no studies exploring the benefit of NAC in patients with less severe forms of liver injury. A final limitation concerns the methodological quality, with the study deemed as having an overall “unclear” risk of bias.

The strengths of our review include the use of a comprehensive search, thereby limiting the likelihood that we missed any potentially relevant studies. In addition, eligibility for study inclusion, data extraction and the risk of bias assessment was carried out by two authors independently, thereby reducing the chances of bias in our review process.

This review has highlighted the need for further research to investigate the role of NAC in non-paracetamol DILI. There is a clear need for prospective studies with sufficient sample sizes that enrol participants with varying grades of severity of DILI. However, there may be certain challenges in undertaking these studies such as the difficulty in enrolling sufficient numbers of participants as a consequence of diagnostic difficulty and underreporting of DILI [2].

We found an ongoing placebo-controlled RCT currently enrolling in South Africa attempting to address this research gap, by investigating the role of NAC in participants with antituberculous DILI [34]. Low-resource settings such as South Africa have a high prevalence of tuberculosis with accompanying high rates of antituberculous DILI between 5-33% of patients [37]. Death may be a consequence of DILI and this was highlighted in a recently published cross-sectional survey in hospitalised patients, which found DILI to be the second most common adverse drug reaction contributing to death, with antituberculous drugs being implicated in the majority of DILI cases [4].

Conclusion

Our review has highlighted a paucity of data, limited to a single RCT in non-paracetamol ALF suggesting a trend for improved transplant and overall survival in a subgroup of participants with non-paracetamol DILI. However, the evidence was graded as “low” or “very low” quality, and the study was not powered to detect differences in this subgroup with DILI. Therefore, due to the limited available evidence, we are unable to conclusively determine if there is a role for NAC in patients with non-paracetamol DILI. Thus, we are unable to make recommendations for clinical practice and emphasise the need for high quality prospective RCTs in this area.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Author’s contributions

MFC conceived the idea for the review and drafted the manuscript. MFC and NK were involved in data acquisition. All authors contributed to the final manuscript. WS served as a content expert in the field of drug-induced liver injury. MW provided input on methodology. KC served as the overall supervisor, content expert and provided input on methodology, data analysis and interpretation. All authors have given their approval for publication.

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Figure 1: Flow diagram of screened, excluded and included publications

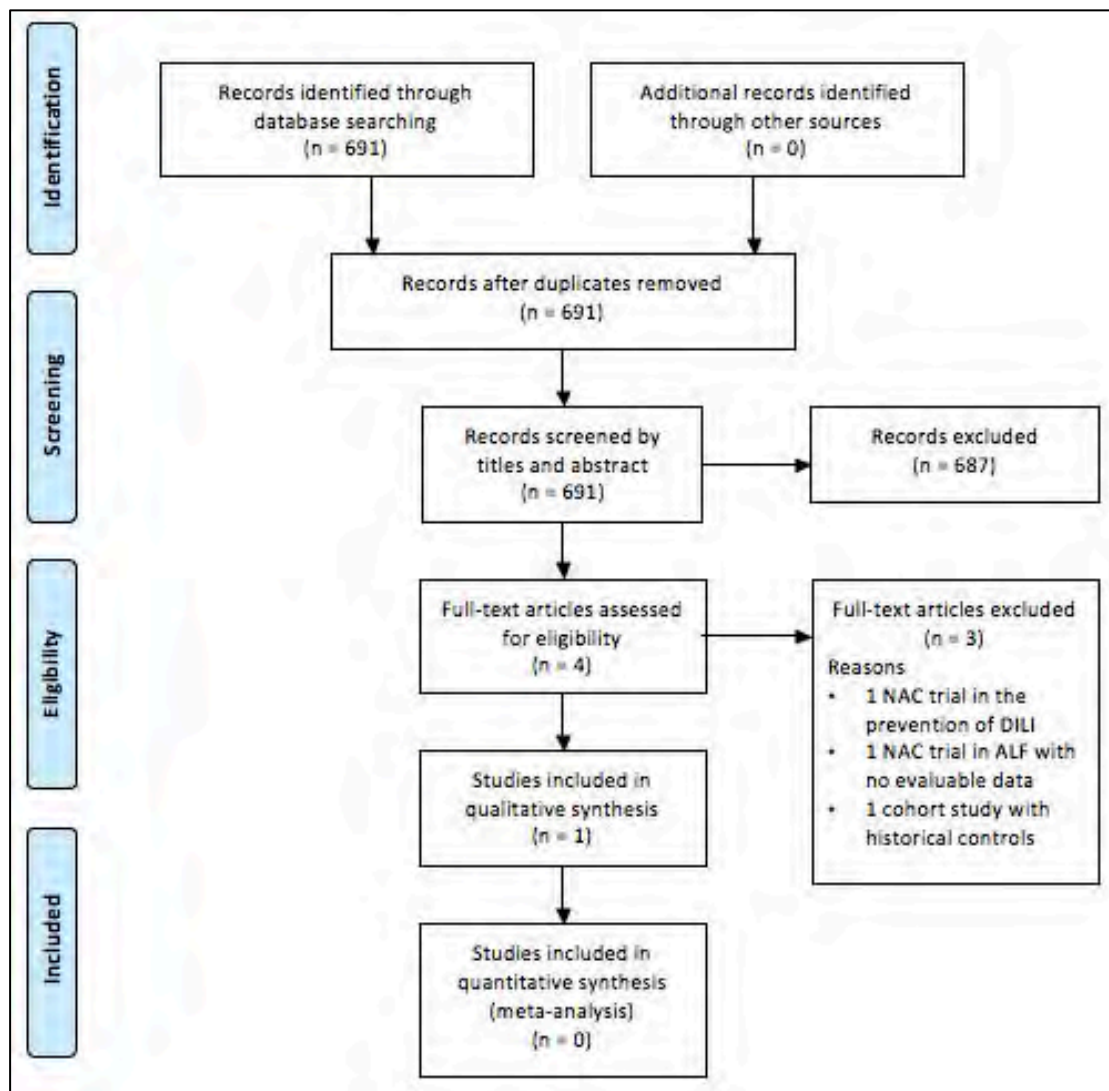


Table 1: Characteristics of included study

Lee et al. 2009 [10]

Methods		Randomised, Double-blind, Placebo-controlled Trial
Participants		173 patients with non-paracetamol ALF
Interventions		Intravenous NAC or Placebo infused for 72 hours. The NAC regimen was as follows: initial loading dose of 150 mg/kg/h of NAC over 1 hour, followed by 12.5 mg/kg/h for 4 hours, then continuous infusions of 6.25 mg/kg/hr NAC for the remaining 67 hours.
Outcomes		Primary outcome was overall survival at 3 weeks Secondary outcomes included transplant-free survival, rate of transplantation, length of hospital stay and number of organ systems failing
Results	Overall study population	Overall survival at 3 weeks: 70% (95% CI= 60%, 81%) NAC group versus 66% (95% CI= 56%, 77%) placebo group, p = 0.283. Transplant-free survival at 3 weeks: 40% NAC group (95% CI= 28%, 51%) versus 27% placebo group (95% CI= 18%, 37%), p=0.043.
	DILI subgroup	Overall survival at 3 weeks: 79% (95% CI= 58% to 100%) NAC group versus 65% (95% CI= 45% to 86%) in the placebo group, odds ratio = 0.50 (95 % CI= 0.13, 1.98, p=0.33). Transplant-free survival at 3 weeks: 58% (95% CI= 33% to 83%) NAC group versus 27% (95% CI= 8% to 46%) placebo group, odds ratio = 0.27 (95 % CI: 0.076 to 0.942, p=0.04).
Notes		Subgroup of 45 patients with non-paracetamol DILI provided data specific to our review question. Nineteen patients received NAC and 26 patients received placebo.

Table 2: Risk of bias in included study

Lee et al. 2009 [10]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not mentioned in detail. Randomisation was stratified by encephalopathy grade with a blocking factor of 4.
Allocation concealment (selection bias)	High risk	Not mentioned
Blinding of participants and personnel (performance bias)	Low risk	Double-blind. Participants and all study personnel, except biostatisticians and site pharmacist were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Double-blind. All study personnel except biostatisticians and site pharmacist were blinded.
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis. All participants analysed in the group they were randomised to. No missing data.
Selective reporting (reporting bias)	Low risk	No
Other bias	Low risk	No

Table 3: GRADE Summary

Lee et al. 2009 [10]

No of studies	Study design	No of patients		Effect		Quality	Importance
		N-acetylcysteine	placebo	Relative (95% CI)	Absolute (95% CI)		
Survival in Overall Study Population							
1 (n=173)	randomised trials	57/81 (70.4%)	61/92 (66.3%)	p = 0.283		⊕○○○ VERY LOW	IMPORTANT
Transplant-free survival in Overall Study Population							
1 (n=173)	randomised trials	32/81 (39.5%)	25/92 (27.2%)	p=0.043		⊕○○○ VERY LOW	IMPORTANT
Adverse events (Nausea and Vomiting) in Overall Study Population							
1 (n=173)	randomised trials	11/81 (13.6%)	4/92 (4.3%)	p= 0.031		⊕⊕○○ LOW	CRITICAL
Transplantation Rates in Overall Study Population							
1 (n=173)	randomised trials	26/81 (32.1%)	41/92 (44.6%)	p= 0.09		⊕○○○ VERY LOW	IMPORTANT
Odds of Death in subgroup of study population with Drug-induced ALF							
1 (n=45)	randomised trials	15/19 (78.9%)	17/26 (65.4%)	OR 0.50 (0.13 to 1.98)	168 fewer per 1,000 (from 135 more to 457 fewer)	⊕○○○ VERY LOW	CRITICAL
Odds of Death without transplant in subgroup of study population with Drug-induced ALF							
1 (n=45)	randomised trials	11/19 (57.9%)	7/26 (26.9%)	OR 0.27 (0.07 to 0.94)	179 fewer per 1,000 (from 12 fewer to 242 fewer)	⊕⊕○○ LOW	CRITICAL

CI: Confidence interval; OR: Odds ratio

1. Study population includes only patients with severe liver injury i.e Acute Liver Failure (ALF). Furthermore, the aetiology of ALF is not specific to drug-induced liver injury (DILI) only
2. Wide 95% CI for of the point estimate
3. Results derived from small subgroup based on aetiology
4. Small subgroup includes only patients with severe DILI i.e. ALF

Table 4: Excluded studies with rationale

Study	Reason for exclusion
Baniasadi et al. 2010 [34]	Investigated the use of NAC in the prevention of DILI
Squires et al. 2013 [35]	No evaluable data in patients with non-paracetamol DILI
Mumtaz et al. 2009 [11]	Not a prospective cohort study

Baniasadi et al. 2010 [35]

Methods	Randomised, Open-label Trial
Participants	60 patients with tuberculosis commencing antituberculous therapy
Interventions	Oral NAC for initial 2 weeks of antituberculous therapy versus no NAC
Outcomes	Primary outcome was incidence of DILI* *DILI defined as: <ol style="list-style-type: none"> 1. ALT / AST \geq 5 times upper limit of normal 2. Raised serum total bilirubin > 1.5 mg/dl 3. Any increase in AST and/or ALT above the pretreatment levels together with the hepatitis symptoms
Reason for Exclusion	Investigated the use of NAC in the prevention of DILI

Squires et al. 2013 [36]

Methods	Randomised, Adaptive allocation, Doubly mask, Placebo-controlled Trial
Participants	184 paediatric patients with non-paracetamol ALF
Interventions	Intravenous NAC or Placebo infused for up to 7 days
Outcomes	Primary outcome was one year survival Secondary outcomes included liver transplantation, survival without liver transplantation, length of hospital stay, maximum degree of hepatic encephalopathy and number of organ systems failing
Reason for Exclusion	No evaluable data in patients with non-paracetamol DILI

Mumtaz et al. 2009 [11]

Methods	Retrospective cohort study
Participants	91 Patients with non-paracetamol ALF
Interventions	Oral NAC versus no NAC
Outcomes	Primary outcome was overall survival Secondary outcomes included evaluation of factors related to survival and safety of NAC
Reason for Exclusion	Not a prospective cohort study

ETHICS APPROVAL



UNIVERSITY OF CAPE TOWN
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05 September 2014

Dr MF Chuglay
Clinical Pharmacology
K Floor
OMB

Dear Dr Chuglay

RE: A SYSTEMATIC REVIEW OF N-ACETYLCYSTEINE IN THE MANAGEMENT OF PATIENTS WITH NON-PARACETOMOL DRUG-INDUCED LIVER INJURY

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 04 September 2014.

The HREC notes your systematic review. This type of research does not need ethical approval from the HREC.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

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When a drug can exist as stereoisomers or diastereomers (for example geometrical isomers), the form of compound studied must be designated as follows in the methods section.

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Some mediators with well established common names (*e.g.* prostacyclin) are also prescribed as licensed preparations with an rINN (*e.g.* epoprostenol). In such cases the rINN should be used in the context of therapeutic use. Sometimes English and American usage varies, as with adrenaline / epinephrine and noradrenaline / norepinephrine. "Adrenaline / noradrenaline" relate clearly to terms such as "noradrenergic", "adrenergic" and "adrenal gland" but we will accept the term preferred by authors.

Units

SI units (mass or molar units) should be used. If other units are used, a conversion factor should be included in the **Methods** section.

Symbols

A set of standard symbols in pharmacokinetics and pharmacodynamics can be found here.

Structure

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The title page should include:

- the title giving an informative and accurate indication of the content of the paper. It should be no longer than 150 characters, including spaces;
- the names, positions, and addresses of the authors;
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The text must be preceded by a structured summary, including the following headings:

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- Conclusions

The summary should be a maximum of 250 words; abstracting services truncate summaries that are longer. It should be couched in terms that will be understood by most readers of the Journal.

Analytical methods

Authors should include details of the precision, accuracy, sensitivity, and specificity of an analytical method used to measure drugs, metabolites or biomarkers or refer to other publications in which the information is given.

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- **Accuracy** is a measure of systematic error, also called bias; it can be expressed as the percentage difference between the result for a test sample and the reference value for that compound.
- **Sensitivity** or lower limit of quantification.
- **Specificity** is the extent to which the method does not detect compounds other than those intended.

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In the **Methods** section statistical methods should be described clearly, with references when appropriate. Editors and referees will be particularly concerned that any study described had sufficient statistical power for its purpose; when appropriate, the power of the study and its calculation should be described in the Methods section.

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2. Metters J (editor). Independent Steering Committee Report of an Independent Review of Access to the Yellow Card Scheme. London: The Stationery Office, 2004.
3. Hoffman BB, Lefkowitz RJ. Beta-adrenergic receptor antagonists. In: *The Pharmacological Basis of Therapeutics*, Eighth Edition, eds Gilman AG, Rail TW, Nies AS, New York: Pergamon Press, 1990: 229-43.

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Acknowledgements

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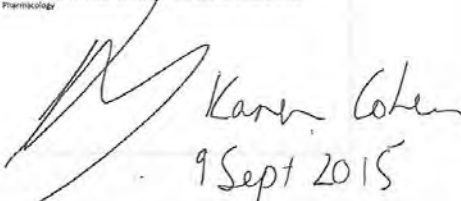
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**N-ACETYLCYSTEINE FOR NON-PARACETAMOL
DRUG-INDUCED LIVER INJURY:
A SYSTEMATIC REVIEW**

Student name: Dr Mohamed Farouk Chughlay
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