ORIGINAL ARTICLE

A systematic review and meta-analysis of the efficacy and safety of *N*-acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB

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ABSTRACT

Background Ototoxicity is a severe side effect of aminoglycoside antibiotics. Aminoglycosides are recommended for the treatment of multidrug-resistant TB (MDR-TB). *N*-Acetylcysteine (NAC) appears to protect against drug- and noise-induced hearing loss. This review aimed to determine if coadministering NAC with aminoglycoside affected ototoxicity development, and to assess the safety and tolerability of prolonged NAC administration.

Methods Eligible studies reported on the efficacy of concomitant NAC and aminoglycoside administration for ototoxicity prevention or long-term (≥6 weeks) administration of NAC regardless of indication. Pooled estimates were calculated using a fixed-effects model. Heterogeneity was assessed using the I^2 statistic.

Results Three studies reported that NAC reduced ototoxicity in 146 patients with end-stage renal failure receiving aminoglycosides. Pooled relative risk for otoprotection at 4–6 weeks was 0.14 (95% CI 0.05 to 0.45), and the risk difference was −33.3% (95% CI 45.5% to 21.2%). Eighty-three studies (N=9988) described the administration of NAC for >6 weeks. Abdominal pain, nausea and vomiting, diarrhoea and arthralgia were increased 1.4–2.2 times.

Discussion This review provides evidence for the safety and otoprotective effect of NAC when coadministered with aminoglycoside. It represents a strong justification for a clinical trial to investigate the effect of concomitant NAC treatment in patients receiving aminoglycosides as part of MDR-TB treatment.

Key messages

What is the key question?
- Does coadministration of *N*-acetylcysteine (NAC) with aminoglycosides prevent the development of ototoxicity and is it safe?

What is the bottom line?
- Coadministration of NAC reduces the risk of ototoxicity by 80% and was found to be safe.

Why read on?
- NAC may be an effective strategy to reduce ototoxicity in patients treated with aminoglycoside in the context of multidrug-resistant TB.

INTRODUCTION

Ototoxicity is a potentially severe side effect of aminoglycoside antibiotics. Aminoglycosides induce apoptosis of the inner and outer hair cells—the auditory and vestibular sensory receptors within the cochlea. This apoptosis is mediated by disruption of mitochondrial protein synthesis with the subsequent generation of free radicals.[1 2] As the sensory epithelium of the mammalian cochlea has little regenerative capacity,[3] this apoptosis leads to irreversible loss of hearing and balance.[4] Hearing loss, which mainly affects high-frequency tones, may progress even after discontinuation of the drug because of the accumulation of free radicals and is irreversible.[5]

Multidrug-resistant (MDR)-TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other anti-TB drugs. The second-line injectable drugs, including the aminoglycosides (amikacin and kanamycin) and the polypeptides (capreomycin), are among the main anti-TB antibiotics used for the treatment of MDR-TB, with a recommended minimum treatment duration of 8 months.[6] If aminoglycoside-induced hearing loss is detected early, through systematic and regular audiological examination, it may be possible to intervene before the hearing loss reaches the frequencies that might affect communication (mid- and low-frequency ranges). However, audiology assessment is often inadequate in both resource-limited and -rich settings, and even regular assessment may not be timely enough to prevent rapid hearing loss for some patients. In addition, the incidence of, and risk factors for, ototoxicity in patients treated for MDR-TB remain poorly characterised. A recent systematic review identified 35 studies reporting the frequency of ototoxicity in patients receiving MDR-TB treatment, but the majority (86%) of these studies failed to specify the testing and classification methods used. In the five studies that used standardised testing and classification methods, the frequency of ototoxicity ranged from 18% to 62%.[7]

There are limited interventions available to prevent or ameliorate hearing loss in patients

receiving second-line injectable drug treatment for MDR-TB. Streptomycin (an aminoglycoside previously used in retreatment of TB but now rarely used) and capreomycin are thought to be less ototoxic than amikacin or kanamycin,[8 9] but may be less efficacious.[10] Increasing the dose interval to thrice weekly rather than daily has not been shown to have any impact on ototoxicity.[8] Although therapeutic drug monitoring is recommended for amikacin and streptomycin, this is not readily available for capreomycin and kanamycin, particularly in low-resource settings where the majority of MDR-TB is managed. The main options that can be used to prevent the progression of hearing loss once it has been detected include stopping the drug, reducing the dose, or increasing the dose interval. However, none of these strategies has been systematically evaluated, and, to date, evidence of any benefit of alteration in dose and interval is lacking. Furthermore these options may reduce treatment efficacy and lower the chance of cure through compromising the regimen.

As the cochlear hair cell damage is caused by reactive oxygen species, it is theoretically possible to mitigate these effects by coadministration of antioxidants.[11 12] Aspirin, an established antioxidant, has been shown to protect against hearing loss in adults treated with gentamicin.[13] More recently, several studies in patients undergoing dialysis have shown a protective auditory effect of *N*-acetylcysteine (NAC) when coadministered with either gentamicin or amikacin.[14–17] NAC, a thiol-containing antioxidant, is a successful and established treatment which ameliorates hepatic and renal toxicity in acetaminophen (paracetamol) overdose and contrast-induced kidney injury.[18 19] Moreover, NAC has been used in both animals and humans to reduce cisplatin- and noise-induced ototoxicity.[20–26]

NAC has been available in clinical practice for several decades, and is predominantly used to treat acetaminophen intoxication. It can be administered intravenously, orally or by inhalation. Oral bioavailability is 6–10% because of first-pass metabolism.[27] Intravenous NAC carries a small risk of an anaphylaxis-like reaction, including rash, pruritus, angioedema, bronchospasm and, rarely, hypotension.[28] NAC given orally is associated with low toxicity, with reported non-life-threatening side effects including nausea, vomiting, rhinorrhoea, pruritus and tachycardia.

To date, studies investigating whether NAC can prevent aminoglycoside-induced ototoxicity have only evaluated the administration of NAC for short durations (10–14 days), and no studies have evaluated the impact of NAC on the polypeptides. However, if NAC were to be used in the context of MDR-TB to reduce aminoglycoside-induced ototoxicity, it would need to be administered for many months. NAC has been used for prolonged periods in patients with cystic fibrosis, COPD and psychiatric disorders.[29–31] To date, however, studies have not specifically evaluated the safety profile and side effects associated with prolonged NAC use.

In order to assess the potential for NAC use in MDR-TB treatment, this review aimed to determine the effect of NAC on the development of ototoxicity when coadministered with aminoglycosides, as well as the safety and side effect profile of prolonged (>6 weeks) NAC administration.

METHODS

This review was conducted according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group, and a protocol was developed before the review was conducted.[32]

Randomised controlled trials and comparative observational studies were eligible for inclusion if they reported efficacy of concomitant NAC administration on ototoxicity prevention in patients receiving aminoglycoside treatment or if NAC was administered long term (≥6 weeks) regardless of indication. Case reports and case series (<20 patients) were excluded. No date, geographical or language restrictions were applied.

The primary outcome for the efficacy review was ototoxicity (proportion with any hearing loss, proportion with tinnitus and/or vertigo, and degree of hearing loss across different auditory frequencies). The primary outcome measures for the safety review included the number of adverse drug reactions, the number of individuals with an adverse event and/or side effect, and the number of individuals with each specific side effect associated with ≥6 weeks NAC administration. Secondary outcomes included the number of adverse drug reactions resulting in treatment discontinuation and mortality, and the total number of discontinuations and deaths.

Search strategy

A compound search strategy was developed (see online supplementary table S1) to identify all relevant studies regardless of language or publication status. The following electronic databases were searched: Medline (OVID), Embase (OVID), Web of Science, Current Controlled Trials, and the Cochrane database of systematic review. All references were imported into EndNote, and titles and abstracts were examined after duplicates were removed independently by two reviewers (WFE and KK). The full-text articles of all potentially relevant studies were obtained, and the inclusion criteria were applied using a standardised eligibility form. The full text of studies included in 26 previously published reviews investigating the effect of NAC on various chronic conditions was obtained and the studies were screened by two authors (WFE and KK) for inclusion.[29 31 33–57] Reference lists of all studies identified by the above methods and bibliographies of systematic reviews or meta-analyses were examined. Final agreement on study inclusion was determined through consensus (WFE, KK).

Data extraction and management

Data extraction was performed independently, in duplicate, using a standardised data extraction form. Data regarding efficacy included information on the intervention (number of individuals in the intervention (receiving NAC) and control groups, and dose, frequency, duration and serum concentration of aminoglycoside and NAC), outcomes (number of individuals with evidence of ototoxicity per group) and patient characteristics (age, sex and presence of comorbidities). For the review investigating safety, the underlying condition for which NAC was administered, exclusion criteria, age, sex and comorbidities were recorded, as well as NAC dose, frequency and duration, number of adverse events, number of total deaths and withdrawals attributable to NAC.

Quality of included studies

For randomised trials investigating the efficacy of ototoxicity, the Cochrane risk of bias tool for quality assessment of randomised controlled trials was used, and this information was used to inform an overall assessment of quality using GRADE. Studies reporting safety data were assessed taking into account the design (retrospective/prospective), allocation of intervention (randomised, non-randomised), placebo use, blinding of participants and/or investigators, and monitoring strategy.

Data analysis

Relative risk (RR), risk difference and the frequency of events and corresponding 95% CIs for prevention of ototoxicity and side effects/adverse events were calculated. For relative effect measures, the Haldane method was applied in the event of zero outcomes in one arm; for frequencies, data were transformed before pooling using standard methods.[58 59] Data were pooled using a fixed-effects model, and heterogeneity assessed using the I^2 statistic.[60] Pooled frequency estimates, risk ratios, risk difference and corresponding 95% CIs for specific side effect, total withdrawals and death and withdrawals attributable to NAC were calculated. Only placebo-controlled studies and studies in which solely NAC was administered were included to calculate the pooled estimates for side effects. Weighted medians were calculated for dosage and duration of NAC. All data analysis was performed using Stata V.12.0.

RESULTS

From 5941 unique citations identified, 86 studies were included in this review, among which only three studies reported on the efficacy of NAC to prevent ototoxicity in the context of aminoglycoside use, and 83 reported on long-term (≥6 weeks) NAC use for other purposes (see online supplementary figure S1). No studies assessing the use of NAC together with aminoglycoside for the treatment of MDR-TB were indentified.

Prevention of ototoxicity

Three randomised trials reported on the efficacy of NAC to prevent ototoxicity including a total of 146 patients with end-stage renal disease receiving aminoglycosides for the treatment of bloodstream infections (table 1). Two of these trials were open-label,[14 16] and one was a randomised, placebo-controlled trial.[17] Patients received 600 mg NAC twice daily for the duration of aminoglycoside treatment,[16] for a total of 14 days[17] or for up to 7 days[14] after completion of aminoglycoside treatment. The aminoglycosides used were amikacin (n=2) and gentamicin (n=1). Two of the studies measured the mean hearing loss (in dB) 1–2 and 4–6 weeks after enrolment and found a significant reduction in aminoglycoside-induced hearing loss at both time points.[14 16] The pooled RR for otoprotection at 4–6 weeks was 0.14 (95% CI 0.05 to 0.45) and the pooled risk difference was −33.3% (95% CI −45.5% to −21.2%) (figure 1). One study compared transient-evoked otoacoustic emissions (OAEs) and distortion-product OAEs among 23 patients receiving placebo and 23 receiving NAC. This study reported a significant improvement in patients receiving NAC at 1500 and 2000 Hz when measured using transient-evoked OAEs and at 1000 and 800 Hz in terms of distortion-product OAEs.[17] Overall the aminoglycosides caused the greatest hearing loss at high frequencies, and so it was at these frequencies that the most protective effect of NAC was seen.

The risk of bias was high because two of the three trials were open-label and did not include a control group with placebo (table 2). The overall quality of the evidence was rated as low/very low because of risk of bias and indirectness (different patient population).

Long-term NAC use

We identified a total of 83 studies describing the administration of NAC for >6 weeks. NAC was used for psychiatric (N=15), respiratory (N=26) and rheumatological conditions (N=6), blood-borne viruses (N=14), kidney disease (N=6), obstetric and gynaecological conditions (N=5), male infertility (N=2)

Table 1 Studies investigating the effect of NAC in preventing aminoglycoside-induced ototoxicity

Author, year	Condition	AG	N	N (NAC)	N (P)	NAC dose	Duration of NAC	Duration of AG	Cumulative dose, g	N hearing loss (NAC)	N hearing loss (P)	Risk ratio hearing loss (95% CI)	Mean hearing loss, dB (NAC), early	Mean hearing loss, dB (P), early	Mean hearing loss, dB (NAC), late	Mean hearing loss, dB (P), late
Feldman, 2007[14]	Haemodialysis, sepsis	Gentamicin	53*	20	20	600 mg twice daily	For the duration of gentamicin therapy until 1 week after completing therapy	14.8±3.8 (NAC) 14.3 ±5.8 (P)	0.68 (NAC) 0.69 (P)	2†	11†	0.26 (0.06 to 1.04)	2.0±3.8‡	5.8±5.1‡	2.1±5.2§	7.0±8.2§
Tokgoz, 2011[16]	CAPD peritonitis	Amikacin	60	30	30	600 mg twice daily	For the duration of amikacin therapy		1.5 (NAC) 1.25 (P)	1¶	21¶	0.08 (0.01 to 0.55)	−4.7±7.4**	5.4±8.6**	-6.0±8.9††	16.9±8.1††
Kocyigit, 2014‡‡[17]	CAPD peritonitis	Amikacin	50§§	23	23	600 mg twice daily	2 weeks	9 (4–20) (NAC) 8 (4–21) (P)	1.5 (NAC) 1.2 (P)							

*In the NAC group, 1 died, 3 had airborne discrepancies, 2 were unable to cooperate; in the placebo group, 2 died, 3 had airborne discrepancies, 1 was unable to cooperate, 1 withdrew consent.
†6 weeks after completing gentamicin therapy.
‡1 week after completing gentamicin therapy, at frequencies 6000, 8000, 12 000 Hz.
§6 weeks after completing gentamicin therapy, at frequencies 6000, 8000, 12 000 Hz.
¶4 weeks after starting amikacin therapy.
**1 week after starting amikacin therapy, at frequency 10 000, 12 000, 14 000, 16 000 Hz.
††4 weeks after starting amikacin therapy, at frequency 10 000, 12 000, 14 000, 16 000 Hz.
‡‡No measurement of pure-tone average hearing threshold, but measurement of transient-evoked otoacoustic emissions and distortion-product otoacoustic emissions.
§§In the NAC group, 1 withdrew consent, 1 dropped out; in the placebo group, 1 died, 1 withdrew consent.
AG, aminoglycoside; CAPD, continuous ambulatory peritoneal dialysis; NAC, *N*-acetylcysteine; P, placebo.

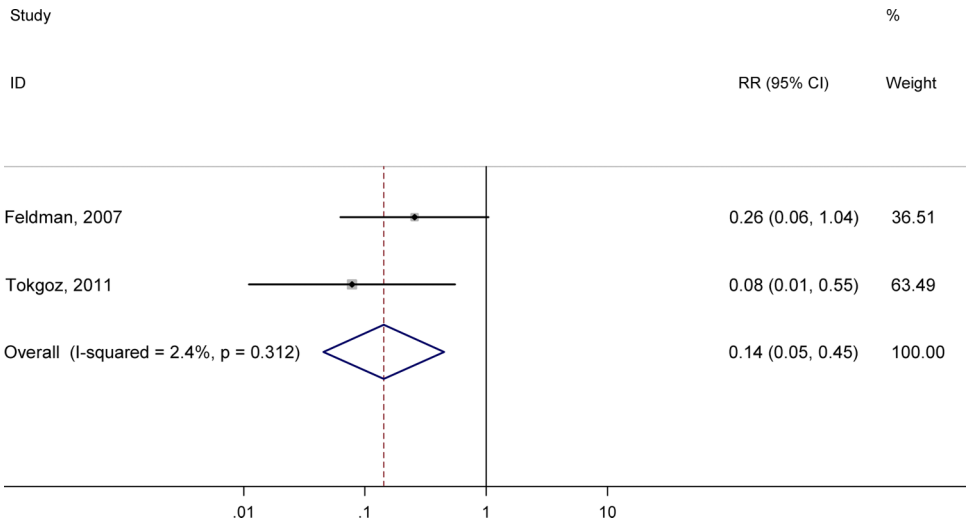

Figure 1 Effect of *N*-acetylcysteine on aminoglycoside-induced ototoxicity.

and other conditions (N=9) such as non-alcoholic fatty liver disease, diabetes mellitus and Alzheimer's disease (see online supplementary table S2). The majority of studies were randomised, placebo-controlled trials (N=52); the remainder were randomised, placebo-controlled crossover trials (N=11), randomised crossover trials without placebo (N=2), randomised trials without administration of a placebo (N=17), and a quasi-experimental study with patients choosing to take NAC (N=1). Six studies described the administration of NAC or placebo in combination with metformin, cotrimoxazole, omeprazole, lipoic acid and interferon. A total of 5014 patients received a median of 1200 mg (IQR 600–1800) of NAC per day over a median of 24 weeks (IQR 12–54), and 4974 patients served as a control group. The majority of studies were conducted in Europe (N=44), and 13 studies were conducted in the USA. The age of participants ranged from 5 to 80 years, and severe liver and renal impairment was common. Two studies were conducted exclusively among pregnant woman, with a total of 220 pregnant woman receiving NAC. Specific side effects were reported in only 23 (28%) studies. A statement regarding adverse drug reactions was included in 32 (39%) studies in the results section (see online supplementary tables S3 and S4). The remaining 28 (34%) studies provided no information on adverse drug reactions.

More than half of the studies (n=49) reported the number of patients withdrawn from the study; of those, 34 reported the reason for withdrawal. No deaths were reported as being attributable to NAC administration. There was no difference in the risk of overall withdrawal with a pooled RR of 1.06 (95% CI 0.96 to 1.17, I^2 0%) and a pooled risk difference of 0.9% (95% CI 0.6% to 2.5%, I^2 0%) in the NAC compared with the control group. Furthermore, there was no increased risk of withdrawal attributable to NAC (pooled RR 0.74 (95% CI 0.59 to 0.93, I^2 31%)) and the pooled risk difference was −1.6% (95% CI −2.8% to 0.0%, I^2 67%) when comparing NAC with placebo or control group (figure 2). The pooled mortality was 1.1 (95% CI 0.91 to 1.31, I^2 0%) across the seven studies reporting data on deaths.

Pooled estimates for specific side effects are presented in table 3. The most commonly reported side effects were abdominal pain, nausea, and vomiting and diarrhoea. The risk of abdominal pain (pooled RR 1.4 (95% CI 1.1 to 2.8)), nausea and vomiting (pooled RR 2.0 (95% CI 1.3 to 3.0)), diarrhoea (pooled RR 1.8 (95% CI 1.0 to 3.2)) and arthralgia (pooled RR 2.2 (95% CI 1.2 to 4.1)) were all significantly increased in patients receiving NAC compared with placebo. However, the pooled risk differences for all these side effects were relatively small, ranging from 1.6% for diarrhoea to 6.1% nausea. The risks of headache, rash, dizziness, cramps and drowsiness were not significantly increased.

Quality assessment was challenging, as procedures for side effect ascertainment were not reported. Furthermore, the majority of studies failed to report death and discontinuation of treatment because of side effects (see online supplementary table S5).

DISCUSSION

This review identified three randomised trials reporting a protective effect of NAC in preventing aminoglycoside-induced ototoxicity in patients with end-stage renal failure. The short duration of aminoglycoside administration (maximum 3 weeks) and the selected patient population mean that limited inference regarding the applicability of these results to MDR-TB can be made. The overall quality of evidence informing this intervention was rated as low.

The safety of prolonged NAC administration was also addressed in this review, with 83 studies identified in which oral NAC was administered for a minimum of 6 weeks. Specific side effects were only reported in 23 of 83 studies included for review. Pooled RRs for specific adverse side effects showed a 1.4–2.2 times increased risk of abdominal pain, nausea and vomiting, diarrhoea and arthralgia in patients receiving NAC compared with placebo. The proportion of patients developing specific side effects was highly heterogeneous across studies, which is not surprising given the variety of clinical conditions, the wide age ranges, and difference in NAC dosing. The pooled risk difference was highest for nausea and vomiting (6.1%) and lowest for diarrhoea (1.8%). Thirty-two studies commented on side effects and adverse events without providing detailed information on specific adverse side effects. An additional 28 studies administered NAC, but neither reported nor commented on side effects. Most studies did not report data on discontinuation of treatment due to adverse events. However, withdrawal overall and withdrawal attributable to side effects was comparable in patients receiving NAC and placebo or control, where reported. Furthermore, mortality was comparable in the few studies that reported deaths stratified by treatment group.

This review provides evidence for the safety of prolonged NAC administration. However, the reported side effects associated with NAC use are potentially additive to those associated with second-line TB drugs other than the aminoglycosides.[61 62]

Table 2 Quality assessment of studies included to assess the effect of NAC on aminoglycoside-induced ototoxicity

Feldman, 2007[14]		
Methods	Randomised, open-label, controlled, parallel, one centre, duration 50 days, intention to treat analysis	
Participants	53 patients aged 18+ on haemodialysis treated with gentamicin for dialysis catheter-related bacteraemia, excluded if treated with aminoglycosides 3 months before the episode or mechanical occlusion of the external ear or a perforated tympanic membrane	
Interventions	NAC 600 mg twice daily	
Outcomes	Pure-tone audiometry measurements at frequencies 250, 500, 1000, 2000, 3000, 4000, 6000, 8000, 12 000 Hz at 7±3 and 42 ±3 days after completion of gentamicin therapy	
Bias	Author's judgement	Support for judgement
Random sequence generation	Unclear	
Allocation concealment	High risk	No placebo
Blinding of participants and personnel	High risk	No placebo
Incomplete outcome data	Low risk	
Selective reporting	Unclear	Primary outcomes not specifically reported, no protocol available
Other bias	Low risk	
Tokgoz, 2011[16]		
Methods	Randomised, open-label, controlled, parallel, one centre, duration 28 days, analysis (per protocol or intention to treat) not clarified	
Participants	60 patients on peritoneal dialysis treated with amikacin for their first episode of peritonitis, excluded if tympanic membrane perforated and admitted after office hours	
Interventions	NAC 600 mg twice daily	
Outcomes	Pure-tone audiometry measurements at frequencies 250, 500, 1000, 2000, 3000, 4000, 6000, 8000, 10 000, 12 000, 14 000 and 16 000 Hz at 8±2 days and 28±2 days	
Bias	Author's judgement	Support for judgement
Random sequence generation	Low risk	Patients chose an envelop
Allocation concealment	High risk	No placebo
Blinding of participants and personnel	High risk	No placebo
Incomplete outcome data	Low risk	
Selective reporting	Unclear	Primary outcomes not specifically reported, no protocol available
Other bias	Low risk	
Kocyigit, 2014[17]		
Methods	Randomised, placebo controlled, parallel, one centre, duration 28 days, analysis (per protocol or intention to treat) not clarified	
Participants	46 patients on peritoneal dialysis treated with amikacin for their first episode of peritonitis, excluded if tympanic membrane perforated and admitted after office hours	
Interventions	NAC 600 mg twice daily or placebo	
Outcomes	Transient-evoked otoacoustic emissions and distortion-product otoacoustic emissions at 1 and 4 weeks	
Bias	Author's judgement	Support for judgement
Random sequence generation	Low risk	Patients chose an envelop
Allocation concealment	Low risk	Placebo administered
Blinding of participants and personnel	Low risk	Measurements of patients were performed by staff who did not know which patient belonged to which group
Incomplete outcome data	Low risk	
Selective reporting	Unclear	Primary outcomes not specifically reported, no protocol available
Other bias	Low risk	

NAC, *N*-acetylcysteine.

Gastrointestinal side effects, such as nausea and vomiting, are associated with thioamides, para-aminosalicylic acid and fluoroquinolones, and, while not life-threatening, severely affect regimen tolerability and therefore potentially default from MDR-TB treatment. Failure to complete MDR-TB treatment is a significant contributor to poor treatment outcomes and generates further resistance.[63] In addition, the pill burden associated with MDR-TB treatment is considerable and the impact of adding further medication has to be considered carefully, weighing risks and benefits.

Patients receiving prolonged NAC had a variety of clinical conditions including respiratory, renal, liver, infectious (HIV and hepatitis C), obstetric and psychiatric diseases. The severity of diseases and the frequency of other comorbidities, including drug and alcohol misuse, were heterogeneous across studies, with some studies including patients with life-threatening conditions such as idiopathic lung fibrosis, systemic sclerosis and end-stage liver disease. The age of included subjects spanned children less than 1 year of age to patients aged over 80 years. Three studies specifically included pregnant women, with a total of 220 receiving NAC. The safe administration of NAC across such a broad spectrum of patients is reassuring when considering its use as adjuvant treatment in patients with MDR-TB. HIV infection, alcohol and drug misuse, and smoking are common in patients with MDR-TB.[64–66] Furthermore, a considerable proportion of patients treated for MDR-TB experience depression, or develop hepatic and renal impairment as a result of treatment.[67–69] Thus, the safety of any adjunctive therapy needs to

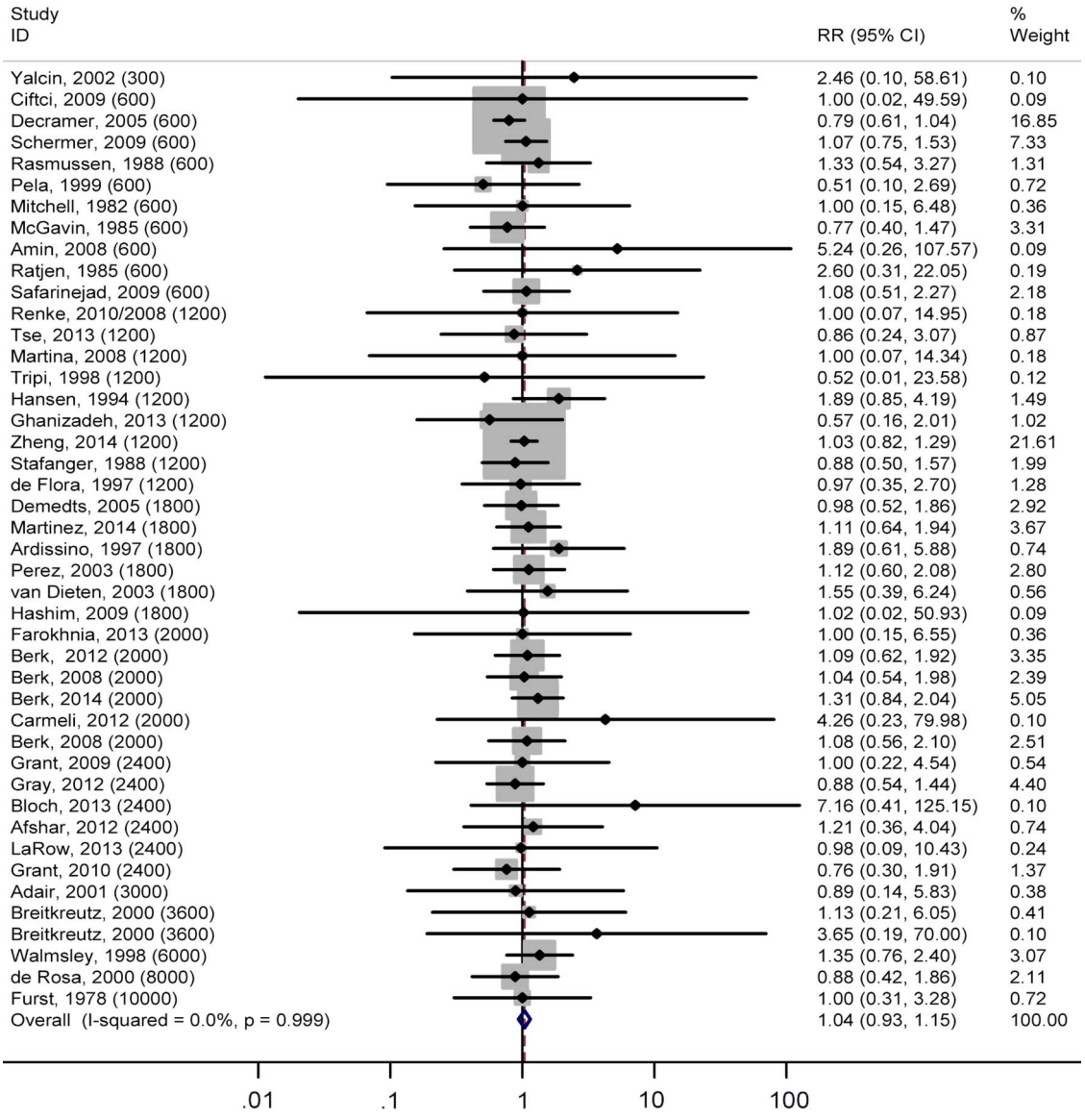

Figure 2 Risk of withdrawals attributable to *N*-acetylcysteine.

be assessed in the context of both the comorbidities and the side effect profile of MDR-TB treatment.

This review was unable to assess potential drug interactions between NAC and drugs used for the treatment of TB. The trials investigating the otoprotective effects of NAC did not report any drug interactions between NAC and aminoglycosides. However, aminoglycosides and NAC were coadministered for a relatively short duration (2–4 weeks) compared with the 8 months of aminoglycoside that is currently recommended for treatment of MDR-TB. Data on interactions between NAC and other anti-TB drugs are lacking, with only one trial conducted in patients on first-line treatment in Iran[70]; this trial randomised 60 patients being treated with first-line four-drug TB therapy (isoniazid, rifampicin, ethambutol and pyrazinamide) to either receiving 600 mg NAC twice daily for 2 weeks or no additional treatment. The authors hypothesised that NAC would reduce the frequency of drug-induced hepatitis because of its antioxidative properties. The trial reported a significant reduction of alanine aminotransferase and aspartate aminotransferase after 2 weeks of treatment, but drug interactions were not specifically reported.

The strengths of this review include a broad compound search strategy across five different databases and no restrictions with regards to date of publication, language and setting. The safety review included studies administering oral NAC for a minimum of 6 weeks regardless of the disease studied. This permitted the assessment of safety across a broad range of diseases and severity.

This review served to identify a number of important limitations to the existing evidence base. Notably, no studies were identified that investigated the otoprotective potential of NAC in patients receiving aminoglycosides for the treatment of MDR-TB. Furthermore, most studies identified in the safety review failed to provide sufficient information on specific side effects, resulting in a poor quality rating for the purpose of the safety review. The frequency of investigations carried out to assess side effects was only reported in a minority of studies. Thus, the ascertainment of side effects might have been of different quality within and across studies. The review was unable to establish the quality of ascertainment systematically because of lack of information.

Notwithstanding these limitations, the results of this review together with recent findings explaining the mechanism of

Table 3 Pooled estimates of the frequency of specific side effects with risk ratios and risk differences

Side effect	Number of studies	Frequency (NAC)		Frequency (placebo)		Pooled risk ratio		Pooled risk difference	
		Estimate (95% CI)	I^2, p value	Estimate (95% CI)	I^2, p value	Estimate (95% CI)	I^2, p value	Estimate (95% CI)	I^2, p value
Abdominal pain	14	11.8% (8.0% to 15.6%)	93.4%, <0.01	6.1% (3.5% to 8.7%)	88.6%, <0.01	1.4 (1.1 to 1.8)	41.8%, 0.05	2.6% (0.1% to 4.4%)	77.3%, <0.01
Nausea	8	17.6% (9.7% to 25.4%)	91.6%, <0.01	8.1% (3.6% to 12.5%)	61.6%, <0.01	2.0 (1.3 to 3.0)	54.9%, 0.03	6.1% (2.8% to 9.3%)	86.9%, <0.01
Diarrhoea	10	4.2% (1.6% to 6.8%)	66.5%, <0.01	1.8% (0.4% to 3.2%)	38.1%, 0.10	1.8 (1.0 to 3.2)	0%, 0.87	1.6% (0.1% to 3.0%)	27.7%, 0.19
Headache	6	14.4% (6.4% to 22.4%)	81.8%, <0.01	8.6% (5.2% to 12.0%)	0%, 0.78	1.4 (0.8 to 2.4)	0%, 0.47	3.2% (1.4% to 7.9%)	44.2%, 0.11
Arthralgia	7	6.8% (2.6% to 10.9%)	80.4%, <0.01	0.6% (0.4% to 1.5%)	54.3%, 0.04	2.2 (1.2 to 4.1)	0%, 0.67	1.8% (0.4% to 3.2%)	72.3%, <0.01
Rash	7	5.2% (2.1% to 8.2%)	25.8%, 0.23	2.0% (0.2% to 4.3%)	40.3%, 0.12	1.2 (0.6 to 2.4)	0%, 0.56	1.2% (−3.1% to 5.4%)	0%, 0.59
Dizziness	4	6.1% (−0.5% to 12.7%)	78.7%, <0.01	2.9% (−0.5% to 6.3%)	45.2%, 0.14	1.0 (0.5 to 1.8)	20.5%, 0.29	−0.1% (−0.2% to 1.7%)	27.7%, 0.25
Cramps	3	3.4% (−1.7% to 8.5%)	81.8%, <0.01	4.3% (1.8% to 10.5%)	76.5%, 0.01	1.2 (0.5 to 3.1)	39.9%, 0.19	0.7% (−2.4% to 3.8%)	54.3%, 0.11
Drowsiness	3	19.4% (9.5% to 37.8%)	81.6%, 0<0.01	12.5% (5.4% to 19.6%)	0%, 0.66	1.3 (0.62 to 2.7)	0%, 0.42	3.2% (−0.6% to 12.0%)	19.9%, 0.29

NAC, *N*-acetylcysteine.

aminoglycoside-induced ototoxicity and the established antioxidative properties of NAC provide a strong justification for a clinical trial to investigate the effect of concomitant NAC treatment in patients receiving aminoglycosides as part of MDR-TB treatment. The roll-out of the Xpert MTB/RIF (a test to detect TB and rifampicin resistance directly from sputum) in countries with limited laboratory capacity is likely to increase the number of MDR-TB diagnoses and consequently those receiving aminoglycoside therapy, many in areas with limited capacity to monitor ototoxicity.[71] While the desired aim for MDR-TB treatment is to develop shortened, more tolerable and aminoglycoside-sparing regimens,[72] this may be some way from reality. Published studies of novel combinations are promising.[73] Nevertheless, a promising 9-month regimen, piloted in Bangladesh which showed good results in the absence of fluoroquinolone resistance,[74] and which is now being evaluated in the STREAM trial, has aminoglycosides as a key part of the regimen.[75] While we await the incorporation of bedaquiline and delamanid, two newly registered second-line anti-TB drugs, into recommended second-line treatment regimens, it is likely that aminoglycosides will remain a key pillar of MDR-TB treatment, albeit potentially for shortened periods.[75]

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Supplement, table 1: Search strategy

Set	Topic	Medline	Embase
Set 1	N-acetylcysteine	ACETYLCYSTEINE	ACETYLCYESTEINE or ACEYTLCYSTEINE DERIVATE
Set 2		n-acetylcysteine or acetylysteine	Aceytlcysteine
Set 3	Ototoxcicity	HEARING LOSS	HEARING IMPAIRMEN
Set 4		COCHLEA	OTOTOXICITY
Set 5		ototoxicity or cochleotoxic or ototoxic	ototoxicity
Set 6		(hearing adj1 loss)	(hearing adj1 loss)
Set 7		(hearing ajd1 impairment)	(hearing ajd1 impairment)
Set 8	Long term administration	RADOMIZED CONTROLLED TRIAL	RADOMIZED CONTROLLED TRIAL
Set 9		CLINICAL TRIAL	CLINICAL TRIAL
Set 10		OBSERVATIONAL STUDY	OBSERVATIONAL STUDY
Set 11		LONGITUDINAL STUDY	LONGITUDINAL STUDY
Set 12		COHORT STUDY	COHORT ANALYSIS
Set 13		(observational adj1 study)	(observational adj1 study)
Set 14		(longitudinal adj1 study)	(longitudinal adj1 study)
Set 15		(clinical adj1 trial)	(clinical adj1 trial)
Set 16		combine set1 and set 2 with “or”	
Set 17		combine set3-7 with “or”	
Set 18		combine set8-15 with “or”	
Set 19		combine set16-18 with “and”	
Set 20		Limit set19 to human	

Words in capital letters were searched as MESH terms and as free text terms.

Web of Science
Combination of “acetylcysteine” “ototoxic” “vertigo” “longitudinal” “randomized controlled” “clinics trial”

Supplement Table 2: Studies reporting on long-term NAC use

Author, year	Country	Disease or Condition	NAC dose (mg)	Frequency of dosing	Duration (weeks)	N (NAC)	N (placebo)	Age - NAC	N men - NAC	Age - Placebo	N men - Placebo
Psychiatric disease											
Berk, 2012[1]	Australia	Bipolar disorder	1000	2	12	76	73	47.1	16	44.4	32
Berk,2008[2]	Australia	Bi-polar disorder	1000	2	24	38	37	44.6	15	46.6	15
Berk, 2014[3]	Australia	Major depressive disorder	1000	2	12	135	134	49.9	46	50.5	54
Farokhnia, 2013[4]	Iran	Schizophrenia	1000	2	8	23	23	32.2	11	33.4	13
Carmeli, 2012[a] [5]	Switzerland	Schizophrenia	2000	1	8	11	11	31.9	9	31.9	9
Lavoie, 2008[a] [6]	Switzerland	Schizophrenia	1000	2	8	7	7	31.9	5	31.9	5
Berk, 2008[7]	Australia	Schizophrenia	1000	2	24	69	71	37.2	48	36.1	50
Afshar, 2012[8]	Iran	Obsessive compulsive disorder	600, 1200, 2400		12	24	24	30.6	6	31.3	6
Ghanizadeh, 2013[9]	Iran	Autistic disorder	600	2	8	20	20	8.8	13	7.9	12
Bloch,2013[10]	USA	Trichotillomania	1200	2	12	20	19	14	3	13.1	2
Grant, 2009[b] [11]	USA	Trichotillomania	1200 (6wks), 2400 (6wks)	1	12	25	25	32.7	4	35.8	
Grant, 2007[12]	USA	Pathological gambling	600	2-3	6	6	7				
LaRow, 2013[13]	USA	Cocaine Dependence	600-1200	2	8	78	38	43.5	58	43.3	25
Gray, 2012[14]	USA	Cannabis dependency	1200	2	8	58	58	18.9	39	18.8	45
Grant,2010[15]	USA	Methamphetamine dependence	600, 1200, 1800, 2400		8	14	17	37.2	8	36.1	14
Respiratory disease											
Zheng, 2014[16]	China	COPD	600	2	52	504	502	66.2	415	66.4	409
Tse, 2013[17]	Hong Kong	COPD	600	2	52	58	62	71	54	70.8	58
de Backer, 2013[a] [18]	Belgium	COPD	600	3	12	12	12	65	9	65	9
Patil, 2011[19]	India	COPD	600	1,2	8	54	23				
Stav, 2009[a] [20]	Israel	COPD	1200	1	6	24	24	66		66	
Schermer, 2009[21]	Netherlands	COPD	600	1	24	96	96	59.2	75	59.6	65
Decramer, 2005[22]	Europe	COPD	600	1	156	256	267	62	204	62	210
de Benedetto, 2005[23]	Italy	COPD	600	2	8	32	23	66.2		66.3	
van Overveld, 2005[a,b] [24]	Poland	COPD	600	1	10	20	20		16		16
Kasielski, 2001[25]	Poland	COPD	600	1	52	22	22	61	10	60	11
Pela, 1999[b] [26]	Italy	COPD	600	1	24	85	84	66	60	66	68
Lukas, 2005[27]	Germany	Chronic bronchitis	600	2	12	15	17	53.6	9	58.0	8

Supplement Table 2: Studies reporting on long-term NAC use – con't

Author, year	Country	Disease or Condition	NAC dose (mg)	Frequency of dosing	Duration (weeks)	N (NAC)	N (placebo)	Age - NAC	N men - NAC	Age - Placebo	N men - Placebo
Hansen, 1994[28]	Denmark	Chronic bronchitis	600	2	22	75	78	51.1	30	51.7	36
Rasmussen, 1988[29]	Sweden	Chronic bronchitis	300	2	24	59	57	58.8	31	58.9	35
Poder, 1984[b] [30]	Hungary	Chronic bronchitis	10mg/kg	2-3	12	27	18	0.5-3		0.5-3	
McGavin, 1985[31]	UK	Chronic bronchitis	200	3	20	85	96	64.3	75	62	80
Stafanger, 1989[a] [32]	Denmark	Cystic fibrosis with *P. aeruginosa* infection	200 (<30kg), 400 (>30 kg)	3	12	52	52	15.8	17	15.8	17
Stafanger, 1988[a] [33]	Denmark	Cystic fibrosis	200/400	3/2	12	22	22	9.5	23	9.5	23
Ratjen, 1985[34]	Germany	Cystic fibrosis	200	3	10	12	12	13.9	10	13.9	10
Mitchell, 1982[a] [35]	New Zealand	Cystic fibrosis	200	3	12	20	20	10.8	10	10.8	10
Stafanger, 1988[a] [33]	Denmark	Primary ciliary dyskinesia	200/400	3/2	12	8	8	29.7	6	29.7	6
Martinez, 2014[36]	USA	Idiopathic pulmonary fibrosis	600	3	60	133	131	68.3	107	67.2	98
Demedts, 2005[37]	Europe	Idiopathic pulmonary fibrosis	600	3	52	92	90	62	69	64	75
Ghanei, 2008[38]	Iran	Chronic lung disease due to mustard gas exposure	600	2	16	72	72	44.9	32	46.7	37
Van Zandwijk, 2000[b] [39]	Multicentre Europe	Non-small-cell lung cancer, pT1-2, N0-1, T2N0 or cancer of the larynx	600	2	104	642	641	61	556	60	559
Van Schooten, 2002[40]	Netherlands	Smoker	600	2	24	21	20	42	6	44	8
Blood born viruses											
Milazzo, 2010[c] [41]	Italy	HIV, lipoatrophy	2000	1	48	20	20	45	7	44	9
Spada, 2002[42]	Brazil	HIV	600	1	24	10	10				
Breitkreutz, 2000[43]	Germany	HIV, not on ART	600	6, 4, 2, 1	28	16	13		8		8
Breitkreutz, 2000[43]	Germany	HIV, ART	600	6, 4, 2, 1	28	21	16		11		10
de Rosa, 2000[44]	USA	HIV	8000	1	8	41	42	38	41	38	42
Walmsley, 1998[d] [45]	Canada	HIV, PCP	3000	2	8	96	102	38.1	83	38.6	100
Look, 1998[a,b] [46]	Germany	HIV	1200	1	12	24	24	36.5	17	36.5	17
Grant, 2000[47]	Spain/Italy	HCV	600	3	24	73	74	39.1	51	40.9	53
Neri, 2000[b] [48]	Italy	HCV	1200	2	64	38	39				
Look, 1999[b, e] [49]	Germany	HCV	1800	1	24	8	8	35.7	6	38.7	3
Ideo, 1999[b,e,f] [50]	Italy	HCV	1200	1	24	58	62	48.3	33	46.9	37
Cimino, 1998[b,f] [51]	Italy	HCV	1200	1	12	12	13	30-62	8	23-57	8
Tripi, 1998[b] [52]	Italy	HCV	600	2	24	14	7	53.8	6	46.5	5
Bernhard, 1998[53]	Switzerland	HCV	600	3	24	19	17				

Supplement Table 2: Studies reporting on long-term NAC use – con't

Author, year	Country	Disease or Condition	NAC dose (mg)	Frequency of dosing	Duration (weeks)	N (NAC)	N (placebo)	Age - NAC	N men - NAC	Age - Placebo	N men - Placebo
Kidney disease											
Purwanto, 2012[54]	Indonesia	Peritoneal dialysis	600	2	8	16	16	45.8	10	42.5	11
Hashemi, 2012[b] [55]	Iran	Proteinuria, diabetes mellitus type 2	600	2	8	35	35	60.2	19	63.4	20
Renke, 2010/2008[a] [56-57]	Poland	Non diabetic chronic kidney disease	600	2	8	20	20	39.4	12	39.4	12
Nascimento, 2009[58]	Brazil	Peritoneal dialysis	600	2	8	12	10	57	5	54	4
Hsu, 2009[g] [59]	Taiwan	Hemodialysis	200	3	12	38	227	57.9	20	61.3	107
Tepel, 2003[60]	Germany	Hemodialysis	600	2	58	64	70	63	33	62	43
Obstetric and gynaecology conditions											
Popora, 2013[h] [61]	Italy	Endometriosis	600	3	12	45	47	32.9	0	32.5	0
Hashim, 2009[i] [62]	Egypt	Polycystic Ovary Syndrome	600	3	6	95	97	27.3	0	26.8	0
Elnashar, 2007[j] [63]	Egypt	Polycystic Ovary Syndrome	600	3	6	30	31	26.7	0	27.3	0
Shahin, 2009 [64]	Egypt	Preterm labour	600	1	>12	140	140	26.5	0	25.9	0
Amin,2008[b] [65]	Egypt	Recurrent pregnancy Loss	600	1	20	80	86	26.2	0	25.2	0
Male infertility											
Safarinejad, 2009[66]	Iran	Male infertility	600	1	26	118	118	32	118	31	118
Ciftci,2009[67]	Turkey	Male infertility	600	1	12	118	60	33.1	60	32.8	60
Rheumatological conditions											
Lai, 2012[68]	USA	Lupus erythematosus	600, 1200, 2400	3	12	18	9				
van Dieten,2003[69]	Netherlands	Reflex sympathetic dystrophy	600	3	54	67	64	48	34	52	39
Perez, 2003[k] [70]	Netherlands	Regional pain syndrome	600	3	17	74	71	50	29	49	20
Yalcin, 2002[b] [71]	Turkey	Blepharitis	100	3	8	43	36	42.9	8	43.7	4
Currie, 1988[a,l] [72]	UK	Young syndrome	200	3	8	8	8	37	8	37	8
Furst, 1978[73]	USA	Systemic sclerosis	10000		8	11	11	55.1	1	60.1	2
Others											
Kasperczyk, 2014[b] [74]	Poland	Lead exposure	200	1, 2, 3	12	120	49				
Dabirmoghaddam, 2013[m] [75]	Iran	Laryngopharyngeal Reflux	600	1	12	30	30				
Khoshbaten, 2010[n] [76]	Iran	Non-alcoholic fatty liver	600	2	12	15	15	40.1	6	46.8	5
Martina, 2008[77]	Italy	Diabetes mellitus II	600	2	24	12	12	62.5	12	67	12
Pace, 2003[78]	USA	Sickle cell disease	200, 400, 800	3	28	16	5		8		3
Adair, 2001[79]	USA	Alzheimer disease	50 mg/kg/day	3	24	25	22				

Supplement Table 2: Studies reporting on long-term NAC use – con't

Author, year	Country	Disease or Condition	NAC dose (mg)	Frequency of dosing	Duration (weeks)	N (NAC)	N (placebo)	Age - NAC	N men - NAC	Age - Placebo	N men - Placebo
Estensen, 1999[80]	USA	Adenomatous colonic polyps	400	2	12	34	30				
de Flora, 1997[81]	Italy	Chronic degenerative disease (other than chronic respiratory disease)	600	2	24	133	129	69	60	68	48
Ardissino, 1997[82]	Italy	Unstable angina	600	3	16	45	46	58	32	58	32

[a] Cross-over trial
[b] No placebo in the control group
[c] Patients were given NAC plus lipoic acid
[d] All patients were treated for PCP with co-trimoxazole
[e] All patients received IFN, patients in the NAC also received sodium selenite
[f] Patients who did not respond to IFN treatment at 3 months were given NAC
[g] No RCT, patients were given an option to take NAC or not
[h] Drug administration 3 times per week
[i] All patients received metformin, no placebo in the control group
[j] Patients in the comparison group received metformin (not placebo)
[k] Comparison group DMSO cream
[l] Patients in the control group took ambroxol or bromhexine or carbocisteine
[m] All patients received omeprazole
[n] Patients in the control group took Vitamin C

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Total Withdrawn (NAC)	Total Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Berk, 2012[1]	76	73	Systemic medical disorder, respiratory insufficiency, pregnancy, breastfeeding	49% smokers, 47% alcohol use, 21% alcohol abuse	No side effects reported	21	18	1	0		Not reported	Not reported
Berk,2008[2]	38	37	Respiratory disease, PUD, pregnancy, breastfeeding	79% alcohol use, 45% smokers	Side effects in text	14	13	Not reported	Not reported		Not reported	Not reported
Berk, 2014[3]	135	134	PUD, pregnancy, breastfeeding	22% CVS, 19% GI, 19% smokers, 60% alcohol use	Side effects in text	38	27	2	1		Not reported	Not reported
Farokhnia, 2013[4]	23	23	Serious medical or neurological disorders, alcohol or substance abuse, pregnancy, lactation, hepatic and kidney disease		Side effects reported	2	2	0	0		Not reported	Not reported
Carmeli, 2012[a] [5]	11	11			No side effects reported	2	0	0	0		Not reported	Not reported
Lavoie, 2008[a] [6]	7	7			No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Berk, 2008[7]	69	71	Abnormal renal, hepatic, thyroid or haematological findings, pregnancy	16% substance abuse, 53% alcohol use	Side effects in text	15	14	Not reported	Not reported	"There were no significant effects of NAC on safety parameters or reported adverse events"	Not reported	Not reported
Afshar, 2012[8]	24	24	Substance abuse, pregnancy, breastfeeding, convulsive disorder, suicidal		Side effects in text	5	4	3	0		Not reported	Not reported
Ghanizadeh, 2013[9]	20	20	Psychotic disorder, substance abuse, liver disease, seizures, hypertension, cardiac disease, unstable asthma, kidney disease		Side effects reported	3	6	1	0		Not reported	Not reported

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Total Withdrawn (NAC)	Total Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Bloch, 2013[10]	20	19	Bipolar, psychotic, substance abuse, development disorder, mental retardation, pregnancy		Side effects in text	4	0	1	0		Not reported	Not reported
Grant, 2009[11]	25	25	Unstable medical disease, abnormal laboratory tests, pregnancy, breastfeeding	60% psychiatric co-morbidity	Side effects reported	3	3	Not reported	Not reported		Not reported	Not reported
Grant, 2007[12]	6	7	Abnormal physical examination		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
LaRow, 2013[13]	78	38	Substance abuse, pregnancy, breastfeeding, serious medical condition, asthma	36% alcohol abuse,	Side effects reported	38	17	3	0		Not reported	Not reported
Gray, 2012[14]	58	58	Co-morbid substance abuse, unstable psychiatric disease, pregnancy	14% psychiatric co-morbidity	Side effects in text	21	25	Not reported	Not reported	"There were no FDA-defined serious adverse events and there were no significant differences between the two treatment groups in the occurrence of any adverse events (38 adverse events in 24 participants receiving NAC, 46 adverse events in 27 participants receiving placebo)"	Not reported	Not reported
Grant, 2010[15]	14	17	Medical disease, pregnancy, suicidal, bipolar disorder, dementia, psychotic disorder, abnormal liver function tests, substance abuse		Side effects in text	5	9	Not reported	Not reported	"Rates of side effects did not significantly differ between groups (57.1% NAC vs 41.5% placebo)	Not reported	Not reported

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Zheng,, 2014[16]	504	502	Asthma, long term oxygen	18% smokers	Side effects reported	124	119	32	24		Not reported	Not reported
Tse, 2013[17]	58	62	Co-exiting pulmonary disease, severe dyspnoea		Side effects in text	4	5	0	0	"No major adverse effects occurred in either group. There was no increase in incidence of minor adverse effects with NAC (3/58, 5%) vs placebo (5/62, 8%)"	2	1
de Backer, 2013[18]	12	12	Exacerbation during the last 8 weeks, PUD, steroids, pregnancy, breastfeeding		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Patil, 2011[19]	54	23	Decompensated cardiovascular, endocrine, hepatic or renal function, parenchymal lung pathology, active infection due to M tuberculosis, gastric or duodenal ulcer		Side effects in text	Not reported	Not reported	Not reported	Not reported	"Nausea and stomatitis were the most common adverse reactions"	Not reported	Not reported
Stav, 2009[20]	24	24	Asthma, long term oxygen		Side effects in text	Not reported	Not reported	Not reported	Not reported	"Apart from mild epigastric discomfort that was reported by a few patients in the treated group, no other complaints or findings were recorded"	Not reported	Not reported
Schermer, 2009[21]	96	96	Asthma, allergic rhinitis, eczema		No side effects reported	44	40	4	4		1	3

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Decramer, 2005[22]	256	267	Long term, PUD, congestive heart failure, oral steroids, cystic fibrosis, bronchiectasis, past history of TB		Side effects in text	70	99	19	26	"1428 adverse events in NAC group, 1381 adverse events in placebo group, no adverse events were thought to be drug-related"	Not reported	Not reported
de Benedetto, 2005[23]	32	23	Neoplasma, DIP, pulmonary disease		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
van Overveld, 2005[24]	20	20	Atopy, asthma, hepatic or renal failure, cystic fibrosis, CVS		No side effects reported	not reported	not reported	Not reported	Not reported		Not reported	Not reported
Kasielski, 2001[25]	22	22	Alcohol or substance abuse		Side effects in text	not reported	not reported	Not reported	Not reported	"The number of adverse events was low: two in the NAC group and three in the placebo group"	Not reported	Not reported
Pela, 1999[26]	85	84	Lung cancer, cardiomyopathy, metabolic disease, chronic renal disease	28% smokers	Side effects in text	2	3	1	0	"NAC was well tolerated. There was no difference in side effects reported in both groups"	0	1
Lukas, 2005[27]	17	15			No side effects reported	8	10	Not reported	Not reported		Not reported	Not reported
Hansen, 1994[28]	75	78	Eosinophilia, positive skin test to allergens, long term antibiotic treatment		Side effects in text	16	8	Not reported	Not reported	"There were no serious adverse events during the study"	Not reported	Not reported
Rasmussen, 1988[29]	59	57	Pregnancy, antibiotics		Side effects reported	10	7	10	7		Not reported	Not reported
Poder, 1984[30]	27	18			Side effects in text	Not reported	Not reported	Not reported	Not reported	"No side effects were observed"	Not reported	Not reported
McGavin, 1985[31]	85	96	Bronchiectasis, insulin dependent DM, PUD, pregnancy	27% smokers	Side effects reported	13	20	1	2		3	2

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Stafanger, 1989[32]	52	52	PUD, liver of kidney disease, pregnancy		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Stafanger, 1988[33]	22	22	PUD, liver of kidney disease, pregnancy		Side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Ratjen, 1985[34]	12	12	Atopy, bronchodilators		Side effects in text	3	1	Not reported	Not reported	"No side effects of active therapy were noted"	Not reported	Not reported
Mitchell, 1982[35]	20	20			Side effects in text	2	2	0	0	"No side effects were noticed for either placebo or NAC"	Not reported	Not reported
Stafanger, 1988[33]	8	8	PUD, liver of kidney disease, pregnancy		Side effects reported	9	12	1	1		Not reported	Not reported
Martinez, 2014[36]	133	131	Non-idiopathic fibrotic lung disease, coexisting medical disease, on the waiting list of a lung transplant	23% CVS, 19% diabetes, 61% GERD	Side effects reported	23	20	1	4		Not reported	Not reported
Demedts, 2005[37]	92	90	Prednisolone dose >0.5mg/kg		Side effects reported	16	16	2	2		7	8
Ghanei, 2008[38]	72	72	Pneumonia, history of TB, smoking, substance abuse		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Van Zandwijk, 2000[39]	642	641	Recurrent disease, synchronous multiple tumours, previous malignant disease, abnormal LFTs, abnormal renal function, DM, HTN, PUD	93% smokers	Side effects reported	115	Not applicable	Not reported	Not reported	"No comparison of side effects to the non-treatment groups (the control group did not receive any placebo), GI and skin side effects were similar in the groups receiving NAC, NAC+Retinyl and Retinyl alone."	167	147
Van Schooten, 2002[40]	21	20			No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Milazzo, 2010[41]	20	20	Neoplastic disease, alcohol abuse	Median CD4 count 490 (NAC) and 524 (placebo)	Side effects in text	Not reported	Not reported	Not reported	Not reported	"Two patients reported insomnia one in the NAC and one in the control group."	Not reported	Not reported
Spada, 2002[42]	10	10			No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Breitkreutz, 2000[43]	21	16	CD4 >200, endocrine disease, liver cirrhosis, serum creatine >1.5 mg/dl, cardiorespiratory insufficiency, substance or alcohol abuse		No side effects reported	3	2	0	0		Not reported	Not reported
Breitkreutz, 2000[43]	16	13	CD4 200-500, endocrine disease, liver cirrhosis, serum creatine >1.5 mg/dl, cardiorespiratory insufficiency, alcohol or drug abuse		No side effects reported	2	0	0	0		Not reported	Not reported
de Rosa, 2000[44]	41	42	CD4>500	Mean CD4 count 203 (NAC), 160 (placebo)	Side effects in text	10	12	Not reported	Not reported	"No evidence of toxicity associated with NAC administration was found"	Not reported	Not reported
Walmsley, 1998 [45]	96	102	CD4>200	Concurrent cotrimoxazole use, mean CD4 count 148 (NAC) and 160 (control)	Side effects reported	23	17	11	Not reported		Not reported	Not reported
Look, 1998[46]	24	24	CD4<200, opportunistic infection, abnormal laboratory findings		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Grant, 2000[47]	73	74	HIV/HBV co-infection		No side effects reported	not reported	not reported	Not reported	Not reported		Not reported	Not reported

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Neri, 2000[48]	39	38	Renal insufficiency, cancer, respiratory distress, alcohol abuse, obesity, DM		Side effects in text	Not reported	Not reported	Not reported	Not reported	"No adverse reaction to, nor side effects of, treatment, necessitated suspension of IFN or NAC"	Not reported	Not reported
Look, 1999 [49]	8	8	Cirrhosis, prior IFN treatment, renal disorder, HIV/HBV coinfection, other causes of chronic liver disease, contraindication against IFN-therapy		Side effects in text	Not reported	Not reported	0	0	"The medication was well tolerated by all patients and no patient stopped therapy due to side effects"	Not reported	Not reported
Ideo, 1999[50]	58	62	Decompensated cirrhosis, steroid therapy, HIV co-infection, drug addiction, psychosis, malignancy		Side effects reported	9	10	9	10		Not reported	Not reported
Cimino, 1998[51]	12	13			No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Tripi, 1998 [52]	14	7			No side effects reported	0	0	0	0	"No serious side effects were observed"	Not reported	Not reported
Bernhard, 1998[53]	19	17			No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Purwanto, 2012[54]	16	16	Stage V diabetic nephropathy, steroids, malignancy, obstructive uropathy		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Hashemi, 2012[55]	35	35	Creatinine > 1.8mg/dl		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Renke, 2010/2008 [56-57]	20	20	Steroids or immunosuppressive therapy		Side effects in text	1	1	Not reported	Not reported	"NAC therapy was well tolerated by all patients. Adverse effects were not reported"	Not reported	Not reported

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Nascimento, 2009[58]	12	10	Chronic inflammatory disease, DM, active infection, hepatitis B or C		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Hsu, 2009[59]	38	227	Vitamin C, malignancy, active infections, haematological disorders, recent blood transfusion or surgery, renal transplantation	44% diabetic nephropathy	No side effects reported	14	not reported	Not reported	Not reported		Not reported	Not reported
Tepel, 2003[60]	64	70		31% DM	Side effects in text	Not reported	Not reported	Not reported	Not reported	"Five patients (8%) reported GI discomfort during treatment with NAC. No major side effects were observed"	14	14
Popora, 201[61]	45	47	Steroids		Side effects in text	Not reported	Not reported	Not reported	Not reported	"NAC was well tolerated by all patients and no adverse reactions were reported"	Not reported	Not reported
Hashim, 2009[62]	95	97	Other causes of infertility, DM, smoking, alcohol use, age>40		No side effects reported	0	0	0	0		Not reported	Not reported
Elnashar, 2007[63]	30	31	History of pelvic pelvic surgery, infertility other than anovulation, endocrine disorders		No side effects reported	2	1	2	1		Not reported	Not reported
Shahin, 2009[64]	140	140	>35 years, <20 years, threatened abortion in the current pregnancy	Pregnant (mean gestational age 17wks)	Side effects reported	16	0	16	10		Not reported	Not reported
Amin, 2008[65]	80	86	Consanguineous marriage, uterine anatomic abnormality, positive antibodies for antiphospholipid syndrome, endocrine abnormality	Pregnant (treatment started once pregnancy confirmed)	Side effects in text	2	0	Not reported	Not reported		Not reported	Not reported

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Safarinejad, 2009[66]	118	118	History of cancer, genital disease, STI, smokers, hepatobiliary disease, renal disease, neurological or psychiatric disease		Side effects in text	13	12	0	0		Not reported	Not reported
Ciftci, 2009[67]	60	60	Varicocele, leukospermia, hormonal abnormalities, obstruction		Side effects in text	0	0	0	00	"None of the patients in the present study reported any side effects with use of the drug"	Not reported	Not reported
Lai, 2012[68]	18	9	Pregnancy, breastfeeding, chronic infection, serious co-morbidities (e.g. diabetes)		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
van Dieten, 2003[69]	67	64			No side effects reported	5	3	Not reported	Not reported		Not reported	Not reported
Perez, 2003[70]	74	71	More than one limb involved, surgery, pregnancy	37% smokers	Side effects in text	18	15	Not reported	Not reported	"The most prominent side effects were sulphur like taste and stomach reaction"	Not reported	Not reported
Yalcin, 2002[71]	43	36			Side effects in text	1	0	1	0	"In one patient oral NAC was discontinued because of diarrhoea. Other side effects of the drug included minor nausea in one patient and minor nasal leak in another"	Not reported	Not reported
Currie, 1988[72]	8	8			No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Furst, 1978[73]	11	11	Malignant hypertension, acute renal failure		Side effects in text	4	4	3	1		Not reported	Not reported

Supplement table 3: Co-morbidities, side effects, withdrawals and death in studies reporting long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Exclusion criteria	Co-morbidities	Side effects reported	Withdrawn (NAC)	Withdrawn (placebo)	Attributable Withdraw (NAC)	Attributable Withdraw (Placebo)	Side effects	Death (NAC)	Death (placebo)
Kasperczyk, 2014[74]	120	49		55% smokers	No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Dabirmoghaddam, 2013[75]	30	30	<12, positive history of drug reaction to NAC, history of previous reflux treatment, laryngeal cancer		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Khoshbaten, 2010[76]	15	15			No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Martina, 2008[77]	12	12	Women, smokers, secondary hypertension, cancer, hepatic, pulmonary, renal disease, psychiatric disorder		Side effects in text	1	1	Not reported	Not reported	"No adverse events were noted during the treatment"	Not reported	Not reported
Pace, 2003[78]	16	5	<15, pregnancy, history of stroke, HIV		No side effects reported	Not reported	Not reported	Not reported	Not reported		Not reported	Not reported
Adair, 2001[79]	25	22	Dementia, alcohol or substance abuse, major depressive disorder, Hachinski ischemic score >4		Side effects reported	2	2	0	0		Not reported	Not reported
Estensen, 1999[80]	34	30			Side effects in text	1	1	1	0	"Only one patient reported an adverse reaction (headaches)"	Not reported	Not reported
de Flora, 1997[81]	133	129	Chronic respiratory disease	11% smokers	Side effects reported	7	7	1	1		Not reported	Not reported
Ardissino, 1997[82]	45	46	>75, coronary artery bypass, valvular heart disease, congenital heart disease, symptomatic cerebrovascular disease, anaemia, fever, infections, hypertension, thyrotoxicosis	30% smokers, 5% diabetics, 53% hypertension	Side effects reported	8	4	Not reported	Not reported		Not reported	Not reported

Supplement table 4: Specific side effects in studies reporting on long-term NAC use

Author, year	Total (NAC)	Total (placebo)	Abdominal pain (NAC)	Abdominal pain (Placebo)	Nausea vomiting (NAC)	Nausea vomiting (Placebo)	Diarrhea (NAC)	Diarrhea (Placebo)	Headache (NAC)	Headache (Placebo)	Arthralgia (NAC)	Arthralgia (Placebo)	Rash (NAC)	Rash (Placebo)	Dizziness (NAC)	Dizziness (Placebo)	Cramps (NAC)	Cramps (Placebo)	Drowsiness (NAC)	Drowsiness (Placebo)
Adair, 2001[79]	22	25					4	3	9	3	4	0	3	0	4	1	7	3		
Afshar, 2012[8]	24	24			8	2	4	0												
Amin, 2008[65]	80	86	10	5																
Berk,2008[2]	38	37	6	3					7	3	6	3								
Berk, 2014[3]	135	134	43	23							4	0					1	0		
Bloch, 2013[10]	20	19			6	12	1	1					1	0						
de Flora, 1997[81]	133	129	3	4	1	1	3	2												
Demedts, 2005[37]	80	75	12	7					3	6	6	5					1	4		
Farokhnia, 2013[4]	23	23			11	5	6	3	5	3					6	4			7	4
Furst, 1978[73]	11	11	2	1									1	0						
Ghanizadeh, 2013[9]	20	20	1	0			0	1			2	0	0	0	0	0			5	2
Grant, 2009[11]	25	25			0	1	0	2												
Grant,2010[15]	14	17			6	5														
Martinez, 2014[36]	133	131	0	6																
McGavin, 1985[31]	85	96	3	5	7	6	4	2												

Supplement table 4: Specific side effects in studies reporting on long-term NAC use, con't

Author, year	Total (NAC)	Total (placebo)	Abdominal pain (NAC)	Abdominal pain (Placebo)	Nausea vomiting (NAC)	Nausea vomiting (Placebo)	Diarrhoea (NAC)	Diarrhoea (Placebo)	Headache (NAC)	Headache (Placebo)	Arthralgia (NAC)	Arthralgia (Placebo)	Rash (NAC)	Rash (Placebo)	Dizziness (NAC)	Dizziness (Placebo)	Cramps (NAC)	Cramps (Placebo)	Drowsiness (NAC)	Drowsiness (Placebo)
Pela, 1999[26]	85	84	2	2			1	0					0	1						
Rasmussen, 1988[29]	59	57	10	6									5	4						
Shahin, 2009[64]	140	140	28	0	26	0														
Stafanger, 1989[32]	52	52	1	1									1	0						
Walmsley, 1998[45]	96	102			4	1							20	25						
Zheng, 2014[16]	504	502	15	17			5	3			2	0			4	9				
Ardissino, 1997[82]	45	46	5	0			4	0	1	2										
LaRowe, 2013[13]	78	33	31	19					12	3	6	2	5	5					4	3

Supplement table 5: Risk of bias assessment for studies reporting on long-term NAC use

Author, year	Sequence generation	Allocation concealment	Blinding-participant	Blinding-investigator	Complete outcome data - side effect	Complete outcome data - withdraw	complete outcome data - death	Selective outcome reporting
Berk, 2012[1]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Berk,2008[2]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Berk, 2014[3]	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear
Farokhnia, 2013[4]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk
Carmeli, 2012 [5]	Unclear	Unclear	Low risk	Low risk	High risk	Unclear	Unclear	Unclear
Lavoie, 2008 [6]	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Berk, 2008[7]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
Afshar, 2012[8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Ghanizadeh, 2013[9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Bloch,2013[10]	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear
Grant, 2009 [11]	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear
Grant, 2007[12]	High risk	High risk	High risk	High risk	Unclear	Unclear	Unclear	Unclear
LaRow, 2013[13]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear
Gray, 2012[14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Grant,2010[15]	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear
Zheng, 2014[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Tse, 2013[17]	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear
de Backer, 2013 [18]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Patil, 2011[19]	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Stav, 2009[a] [20]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schermer, 2009[21]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear
Decramer, 2005[22]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk
de Benedetto, 2005[23]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
van Overveld, 2005[24]	High risk	High risk	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Kasielski, 2001[25]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Pela, 1999 [26]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear

Supplement table 5: Risk of bias assessment for studies reporting on long-term NAC use, con't

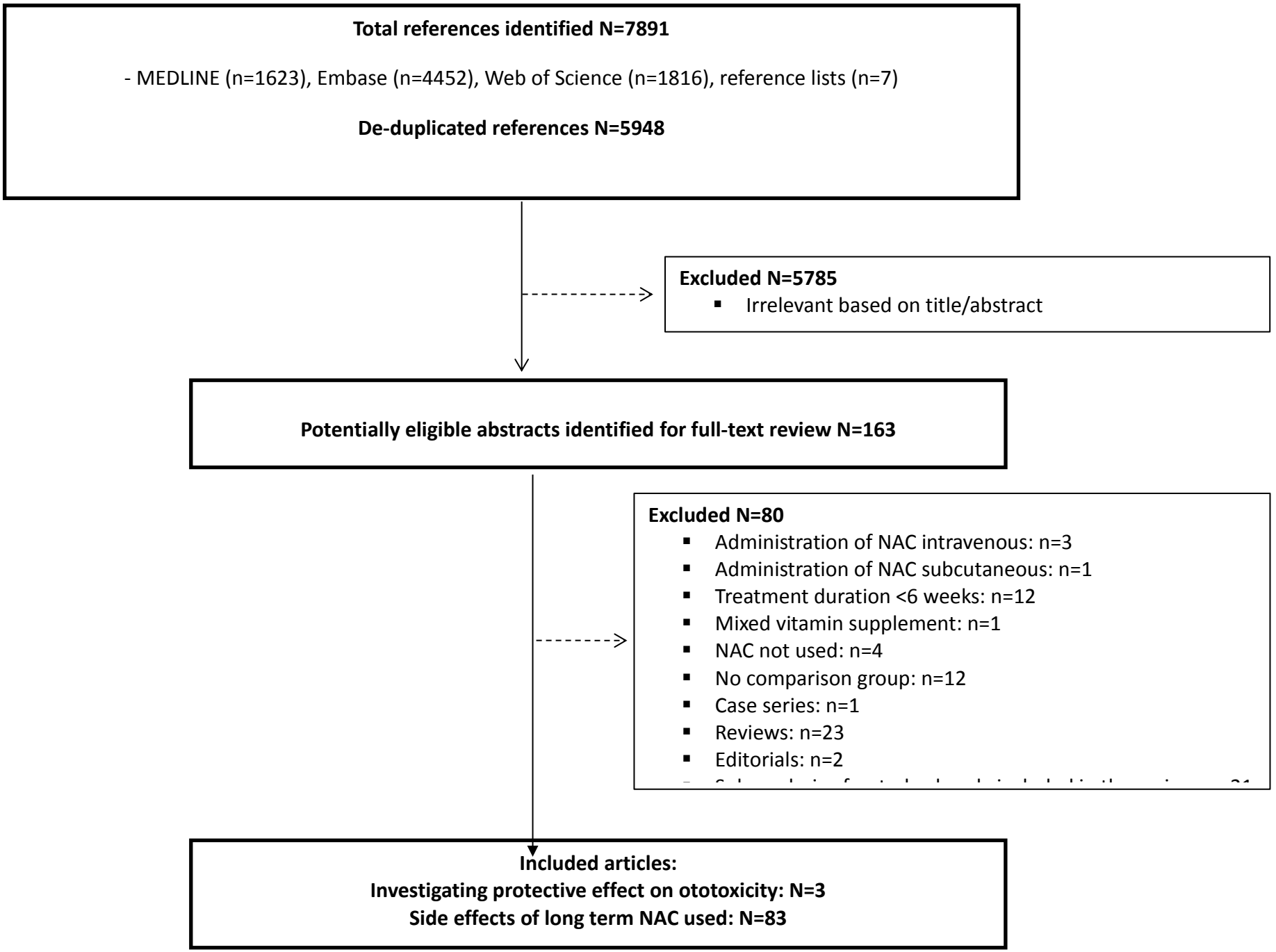
Author, year	Sequence generation	Allocation concealment	Blinding-participant	Blinding-investigator	Complete outcome data - side effect	Complete outcome data - withdraw	Complete outcome data - death	Selective outcome reporting
Lukas, 2005[27]	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Hansen, 1994[28]	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear
Rasmussen, 1988[29]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear
Poder, 1984[30]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
McGavin, 1985[31]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Unclear
Stafanger, 1989[32]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Stafanger, 1988[33]	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Ratjen, 1985[34]	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Mitchell, 1982[35]	Unclear	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Stafanger, 1988[33]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Martinez, 2014[36]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Demedts, 2005[37]	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk
Ghanei, 2008[38]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Van Zandwijk, 2000[39]	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear
Van Schooten, 2002[40]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Milazzo, 2010[41]	High risk	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Spada, 2002[42]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Breitkreutz, 2000[43]	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Breitkreutz, 2000[43]	Unclear	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear
de Rosa, 2000[44]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear	Unclear
Walmsley, 1998 [45]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Look, 1998[46]	Unclear	Unclear	Low risk	Unclear	High risk	Unclear	Unclear	Unclear
Neri, 2000[48]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Look, 1999 [49]	Unclear	Unclear	High risk	High risk	Unclear	Unclear	Unclear	Unclear
Ideo, 1999[50]	Unclear	Unclear	High risk	High risk	Low risk	Unclear	Unclear	Unclear
Cimino, 1998[51]	High risk	High risk	High risk	Unclear	Unclear	Unclear	Unclear	Unclear

Supplement table 5: Risk of bias assessment for studies reporting on long-term NAC use, con't

Author, year	Sequence generation	Allocation concealment	Blinding-participant	Blinding-investigator	complete outcome data - side effect	complete outcome data - withdraw	complete outcome data - death	Selective outcome reporting
Tripi, 1998 [52]	Low risk	Unclear	High risk	Unclear	Unclear	Unclear	Unclear	Unclear
Bernhard, 1998[53]	Unclear	Unclear	Unclear	Unclear	High risk	High risk	Unclear	Unclear
Purwanto, 2012[54]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Hashemi, 2012[55]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Renke, 2010/2008 [56-57]	Low risk	Low risk	High risk	High risk	Unclear	Low risk	Unclear	Unclear
Nascimento, 2009[58]	High risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Hsu, 2009[59]	High risk	High risk	High risk	High risk	Unclear	Low risk	Unclear	Unclear
Tepel, 2003[60]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Low risk	
Popora, 201[61]	High risk	High risk	High risk	Unclear	Unclear	Unclear	Unclear	Unclear
Hashim, 2009[62]	Low risk	Low risk	High risk	High risk	Unclear	Unclear	Unclear	Unclear
Elnashar, 2007[63]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Shahin, 2009[64]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Amin, 2008[65]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Safarinejad, 2009	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Safarinejad, 2009[66]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ciftci, 2009[67]	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Lai, 2012[68]	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
van Dieten, 2003[69]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear
Perez, 2003[70]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Yalcin, 2002[71]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Currie, 1988[72]	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Kasperczyk, 2014[74]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Dabirmoghaddam, 2013[75]	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Unclear
Khoshbaten, 2010[76]	Unclear	Low risk	High risk	High risk	Unclear	Unclear	Unclear	Unclear

Supplement table 5: Risk of bias assessment for studies reporting on long-term NAC use, con't

Author, year	Sequence generation	Allocation concealment	Blinding-participant	Blinding-investigator	Complete outcome data - side effect	Complete outcome data - withdraw	Complete outcome data - death	Selective outcome reporting
Martina, 2008[77]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Pace, 2003[78]	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear
Adair, 2001[79]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear
Estensen, 1999[80]	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear
de Flora, 1997[81]	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear
Ardissino, 1997[82]	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear



Supplement figure 1: Selection process for the inclusion of studies

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