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

Katharina Kranzer, Wael F Elamin, Helen Cox, James A Seddon, Nathan Ford, Francis Drobniewski

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 I² 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 otoprotection 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.

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. As the sensory epithelium of the mammalian cochlea has little regenerative capacity, this apoptosis leads to irreversible loss of hearing and balance. 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.

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.

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. 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%.

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, but may be less efficacious. Increasing the dose interval to thrice weekly rather than daily has not been shown to have any impact on ototoxicity. 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. Aspirin, an established antioxidant, has been shown to protect against hearing loss in adults treated with gentamicin. 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. 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. Moreover, NAC has been used in both animals and humans to reduce cisplatin- and noise-induced ototoxicity.

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. Intravenous NAC carries a small risk of an anaphylaxis-like reaction, including rash, pruritus, angioedema, bronchospasm and, rarely, hypotension. NAC given orally is associated with low toxicity, with reported non-life-threatening side effects including nausea, vomiting, rhinorhoea, 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. 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.

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. 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.
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=25), and rheumatic conditions (N=4), diabetics (N=6), obstetric and gynaecological conditions (N=5), male infertility (N=2), and blood-borne viruses (N=14), kidney disease (N=6), obstetric complications (N=5), male infertility (N=2), and respiratory (N=26) and rheumatological conditions (N=6), among which only three studies 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 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 MDR-TB were indentified. 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 and 33 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.

Table 1

| Author, year | Condition | AG | N (NAC) | N (P) | Duration of NAC | 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 | Haemodialysis, sepsis | Gentamicin | 53* | 20 | 600 mg twice daily | 14.8±3.8 (NAC), 14.3±5.8 (P) | 0.68 (NAC) | 0.69 (P) | 0.26 (0.06 to 1.04) | 2.0±3.84 | 5.8±5.14 | 2.1±5.24 | 7.0±8.24 |
| Tokgoz, 2011 | CAPD peritonitis | Amikacin | 60 | 30 | 600 mg twice daily | 1.5 (NAC) | 1.25 (P) | 0.08 (0.01 to 0.55) | −4.7±2.9 | 1.1±0.5 | −7.4±4.7 | −6.0±1.5 |
| Kocyigit, 2014 | CAPD peritonitis | Amikacin | 50§ | 23 | 600 mg twice daily | 9 (4–20) | 4–21 (P) | 1.5 (NAC) | 1.2 (P) | 5.4±6.8 | 6.0±1.5 | 16.9±8.11 |

*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.
†1 week 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 Hz.
††1 week after completing gentamicin therapy, at frequency 10 000 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.
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 ran-
domised, placebo-controlled trials (N=52); the remainder were
randomised, placebo-controlled crossover trials (N=11), ran-
domised 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, ome-
prazole, lipoid 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 con-
ducted 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 women, 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 informa-
tion 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 attrib-
utable 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 with-
drawal 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,
and drowsiness were not significantly increased.

Quality assessment was challenging, as procedures for side
effect ascertainment were not reported. Furthermore, the major-
ity of studies failed to report death and discontinuation of treat-
ment because of side effects (see online supplementary table S3).

DISCUSSION

This review identified three randomised trials reporting a pro-
tective effect of NAC in preventing aminoglycoside-induced oto-
toxicity 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 interven-
tion 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 commen-
ted on side effects. Most studies did not report data on discon-
tinuation 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 compar-
able in the few studies that reported deaths stratified by treat-
ment group.

This review provides evidence for the safety of prolonged
NAC administration. However, the reported side effects asso-
ciated with NAC use are potentially additive to those associated
with second-line TB drugs other than the aminoglycosides.61 62
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. 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. Furthermore, a considerable proportion of patients treated for MDR-TB experience depression, or develop hepatic and renal impairment as a result of treatment. Thus, the safety of any adjunctive therapy needs to be considered carefully, weighing risks and benefits.

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

<table>
<thead>
<tr>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman, 2007</td>
<td>Randomised, open-label, controlled, parallel, one centre, duration 50 days, intention to treat analysis</td>
<td>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</td>
<td>NAC 600 mg twice daily</td>
<td>Author’s judgement</td>
</tr>
<tr>
<td>Tokgoz, 2011</td>
<td>Randomised, open-label, controlled, parallel, one centre, duration 28 days, analysis (per protocol or intention to treat) not clarified</td>
<td>60 patients on peritoneal dialysis treated with amikacin for their first episode of peritonitis, excluded if tympanic membrane perforated and admitted after office hours</td>
<td>NAC 600 mg twice daily</td>
<td>Author’s judgement</td>
</tr>
<tr>
<td>Kocyigit, 2014</td>
<td>Randomised, placebo controlled, parallel, one centre, duration 28 days, analysis (per protocol or intention to treat) not clarified</td>
<td>46 patients on peritoneal dialysis treated with amikacin for their first episode of peritonitis, excluded if tympanic membrane perforated and admitted after office hours</td>
<td>NAC 600 mg twice daily or placebo</td>
<td>Author’s judgement</td>
</tr>
</tbody>
</table>

NAC, N-acetylcysteine.
Risk of withdrawals attributable to N-acetylcysteine.

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>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yalcin, 2002 (300)</td>
<td>2.46 (0.10, 58.61)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cifci, 2009 (600)</td>
<td>1.00 (0.02, 49.95)</td>
<td>0.09</td>
</tr>
<tr>
<td>Decramer, 2005 (600)</td>
<td>0.79 (0.61, 1.04)</td>
<td>16.85</td>
</tr>
<tr>
<td>Schermer, 2009 (600)</td>
<td>1.07 (0.75, 1.53)</td>
<td>7.33</td>
</tr>
<tr>
<td>Rasmussen, 1988 (600)</td>
<td>1.33 (0.54, 3.27)</td>
<td>1.31</td>
</tr>
<tr>
<td>Pela, 1999 (600)</td>
<td>0.51 (0.10, 2.69)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mitchell, 1982 (600)</td>
<td>1.00 (0.15, 6.48)</td>
<td>0.36</td>
</tr>
<tr>
<td>McGavin, 1985 (600)</td>
<td>0.77 (0.40, 1.47)</td>
<td>3.31</td>
</tr>
<tr>
<td>Amin, 2008 (600)</td>
<td>5.24 (2.26, 107.57)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ratjen, 1983 (600)</td>
<td>2.60 (0.31, 22.05)</td>
<td>0.19</td>
</tr>
<tr>
<td>Safranenjad, 2009 (600)</td>
<td>1.08 (0.51, 2.27)</td>
<td>2.19</td>
</tr>
<tr>
<td>Renke, 2010/2008 (1200)</td>
<td>1.00 (0.07, 14.95)</td>
<td>0.18</td>
</tr>
<tr>
<td>Tse, 2013 (1200)</td>
<td>0.86 (0.24, 3.07)</td>
<td>0.87</td>
</tr>
<tr>
<td>Martina, 2008 (1200)</td>
<td>1.00 (0.07, 14.34)</td>
<td>0.18</td>
</tr>
<tr>
<td>Trip, 1998 (1200)</td>
<td>0.52 (0.01, 23.58)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hansen, 1994 (1200)</td>
<td>1.89 (0.85, 4.19)</td>
<td>1.49</td>
</tr>
<tr>
<td>Ghanizadaeh, 2013 (1200)</td>
<td>0.57 (0.16, 2.01)</td>
<td>1.02</td>
</tr>
<tr>
<td>Zheng, 2014 (1200)</td>
<td>1.03 (0.82, 1.29)</td>
<td>21.61</td>
</tr>
<tr>
<td>Stafanger, 1988 (1200)</td>
<td>0.88 (0.50, 1.57)</td>
<td>1.99</td>
</tr>
<tr>
<td>de Flora, 1997 (1200)</td>
<td>0.97 (0.35, 2.70)</td>
<td>1.29</td>
</tr>
<tr>
<td>Demedts, 2005 (1800)</td>
<td>0.98 (0.52, 1.86)</td>
<td>2.92</td>
</tr>
<tr>
<td>Martinez, 2014 (1800)</td>
<td>1.11 (0.64, 1.94)</td>
<td>3.67</td>
</tr>
<tr>
<td>Ardissino, 1997 (1800)</td>
<td>1.89 (0.81, 5.88)</td>
<td>0.74</td>
</tr>
<tr>
<td>Perez, 2003 (1800)</td>
<td>1.12 (0.60, 2.08)</td>
<td>2.80</td>
</tr>
<tr>
<td>van Dieten, 2003 (1800)</td>
<td>1.55 (0.39, 6.24)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hashim, 2009 (1800)</td>
<td>1.02 (0.02, 50.93)</td>
<td>0.09</td>
</tr>
<tr>
<td>Farokhnia, 2013 (2000)</td>
<td>1.00 (0.15, 6.55)</td>
<td>0.38</td>
</tr>
<tr>
<td>Berk, 2012 (2000)</td>
<td>1.09 (0.62, 1.92)</td>
<td>3.35</td>
</tr>
<tr>
<td>Berk, 2008 (2000)</td>
<td>1.04 (0.54, 1.98)</td>
<td>2.39</td>
</tr>
<tr>
<td>Berk, 2014 (2000)</td>
<td>1.31 (0.84, 2.04)</td>
<td>5.05</td>
</tr>
<tr>
<td>Carmeli, 2012 (2000)</td>
<td>4.26 (0.23, 79.98)</td>
<td>0.10</td>
</tr>
<tr>
<td>Berk, 2008 (2000)</td>
<td>1.08 (0.56, 2.10)</td>
<td>2.51</td>
</tr>
<tr>
<td>Grant, 2009 (2400)</td>
<td>1.00 (0.22, 4.54)</td>
<td>0.54</td>
</tr>
<tr>
<td>Gray, 2012 (2400)</td>
<td>0.88 (0.54, 1.44)</td>
<td>4.40</td>
</tr>
<tr>
<td>Bloch, 2013 (2400)</td>
<td>7.18 (0.41, 125.15)</td>
<td>0.10</td>
</tr>
<tr>
<td>Afsar, 2012 (2400)</td>
<td>1.21 (0.36, 4.04)</td>
<td>0.74</td>
</tr>
<tr>
<td>LaRow, 2013 (2400)</td>
<td>0.98 (0.09, 10.43)</td>
<td>0.24</td>
</tr>
<tr>
<td>Grant, 2010 (2400)</td>
<td>0.78 (0.30, 1.91)</td>
<td>1.37</td>
</tr>
<tr>
<td>Adair, 2001 (3000)</td>
<td>0.89 (0.14, 5.83)</td>
<td>0.38</td>
</tr>
<tr>
<td>Breitkreutz, 2000 (3600)</td>
<td>1.13 (0.21, 6.05)</td>
<td>0.41</td>
</tr>
<tr>
<td>Breitkreutz, 2000 (3600)</td>
<td>3.65 (0.19, 70.00)</td>
<td>0.10</td>
</tr>
<tr>
<td>Wielmsley, 1998 (6000)</td>
<td>1.35 (0.76, 2.40)</td>
<td>3.07</td>
</tr>
<tr>
<td>de Rosa, 2000 (8000)</td>
<td>0.88 (0.42, 1.86)</td>
<td>2.11</td>
</tr>
<tr>
<td>Furst, 1978 (10000)</td>
<td>1.00 (0.31, 3.28)</td>
<td>0.72</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.999)</td>
<td>1.04 (0.93, 1.15)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
### Table 3

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Frequency (NAC)</th>
<th>Frequency (placebo)</th>
<th>Pooled risk ratio</th>
<th>Pooled risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>Estimate (95% CI)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>11.8% (8.0% to 15.6%)</td>
<td>98.6%, &lt;0.01</td>
<td>6.1% (3.5% to 9.7%)</td>
</tr>
<tr>
<td></td>
<td>1.4 (1.1 to 1.8)</td>
<td>1.8 (1.3 to 2.3)</td>
<td>0.078</td>
<td>0.076</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>17.6% (9.7% to 25.4%)</td>
<td>91.6%, &lt;0.01</td>
<td>8.1% (3.6% to 12.5%)</td>
</tr>
<tr>
<td></td>
<td>2.0 (1.3 to 2.0)</td>
<td>0.8% (0.1% to 2.0%)</td>
<td>0.047</td>
<td>0.047</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>5.2% (2.1% to 10.9%)</td>
<td>25.8%, 0.23</td>
<td>2.9% (0.5% to 6.3%)</td>
</tr>
<tr>
<td></td>
<td>6.5 (4.2 to 10.5)</td>
<td>5.3% (3.1% to 9.4%)</td>
<td>0.061</td>
<td>0.061</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>6.5% (4.2% to 10.5)</td>
<td>43.3%, 0.12</td>
<td>2.9% (0.5% to 6.3%)</td>
</tr>
<tr>
<td></td>
<td>5.3% (3.1% to 9.4%)</td>
<td>7.3% (4.8% to 11.7)</td>
<td>0.061</td>
<td>0.061</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>4.3% (1.2% to 10.5)</td>
<td>25.3%, 0.23</td>
<td>2.9% (0.5% to 6.3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>4.3% (1.2% to 10.5)</td>
<td>75.3%, 0.01</td>
<td>7.0% (1.4% to 18.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>19.4% (9.5% to 37.8%)</td>
<td>19.4%</td>
<td>12.5% (5.4% to 23.9%)</td>
</tr>
</tbody>
</table>

**References**


Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;8:CD001287.


