

# 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,<sup>1,2</sup> Wael F Elamin,<sup>1</sup> Helen Cox,<sup>3</sup> James A Seddon,<sup>4</sup> Nathan Ford,<sup>5</sup> Francis Drobniowski<sup>1,6</sup>

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<sup>1</sup>National Mycobacterium Reference Laboratory, Public Health England, London, UK

<sup>2</sup>Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

<sup>3</sup>Division of Medical Microbiology and Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa

<sup>4</sup>Department of Paediatric Infectious Diseases, Imperial College London, St Mary's Hospital, London, UK

<sup>5</sup>Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa

<sup>6</sup>Department of Infectious Diseases, Imperial College, The Hammersmith Campus, London, UK

## Correspondence to

Dr Katharina Kranzer, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK; [katharina.kranzer@lshtm.ac.uk](mailto:katharina.kranzer@lshtm.ac.uk)

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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 ( $\geq 6$  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.

## 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.<sup>1,2</sup> As the sensory epithelium of the mammalian cochlea has little regenerative capacity,<sup>3</sup> this apoptosis leads to irreversible loss of hearing and balance.<sup>4</sup> 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.<sup>5</sup>

## 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.<sup>6</sup> 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%.<sup>7</sup>

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,<sup>8–9</sup> but may be less efficacious.<sup>10</sup> Increasing the dose interval to thrice weekly rather than daily has not been shown to have any impact on ototoxicity.<sup>8</sup> 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.<sup>11–12</sup> Aspirin, an established antioxidant, has been shown to protect against hearing loss in adults treated with gentamicin.<sup>13</sup> 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.<sup>14–17</sup> 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.<sup>18–19</sup> Moreover, NAC has been used in both animals and humans to reduce cisplatin- and noise-induced ototoxicity.<sup>20–26</sup>

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.<sup>27</sup> Intravenous NAC carries a small risk of an anaphylaxis-like reaction, including rash, pruritus, angioedema, bronchospasm and, rarely, hypotension.<sup>28</sup> 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.<sup>29–31</sup> 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.<sup>32</sup>

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.<sup>29–31–33–57</sup> 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.<sup>58 59</sup> Data were pooled using a fixed-effects model, and heterogeneity assessed using the  $I^2$  statistic.<sup>60</sup> 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 ( $\geq 6$  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 identified.

### 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,<sup>14 16</sup> and one was a randomised, placebo-controlled trial.<sup>17</sup> Patients received 600 mg NAC twice daily for the duration of aminoglycoside treatment,<sup>16</sup> for a total of 14 days<sup>17</sup> or for up to 7 days<sup>14</sup> 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.<sup>14 16</sup> 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.<sup>17</sup> 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 (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 (NAC), late	Mean hearing loss, dB (P), early	Mean hearing loss, dB (P), late
Feldman, 2007 <sup>14</sup>	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 (P) ±5.8 (P)	0.68 (NAC) 0.69 (P)	2†	11†	2.0±3.8†	2.1±5.2§	5.8±5.1†	7.0±8.2§
Tokgoz, 2011 <sup>16</sup>	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**	–6.0±8.9††	5.4±8.6**	16.9±8.1††
Kocigit, 2014 <sup>17</sup>	CAPD peritonitis	Amikacin	50§§	23	23	600 mg twice daily	2 weeks	1.5 (NAC) 1.2 (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.

¶14 weeks after starting amikacin therapy.

\*\*1 week after starting amikacin therapy, at frequency 10 000, 12 000, 14 000, 16 000 Hz.

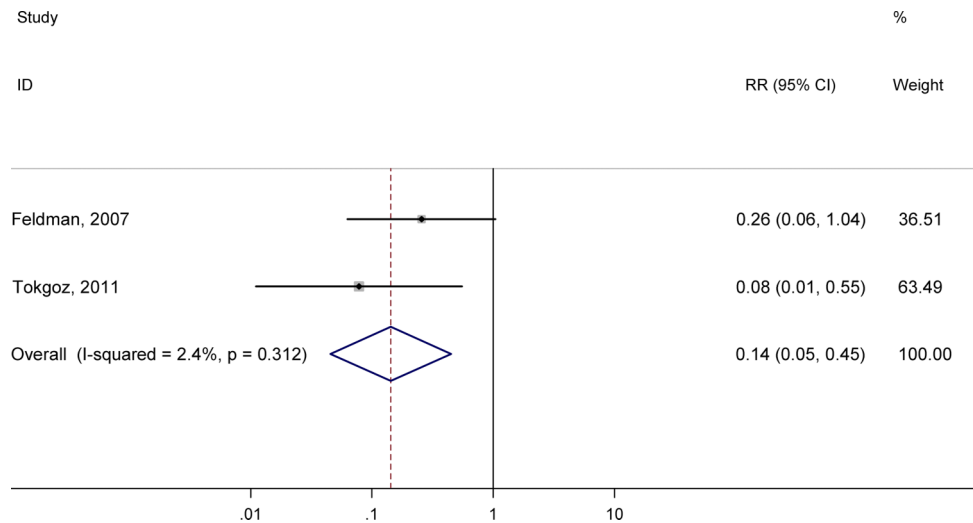
††4 weeks after starting amikacin therapy, at frequency 10 000, 12 000, 14 000, 16 000 Hz.

‡‡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<sup>2</sup> 0%) and a pooled risk difference of 0.9% (95% CI 0.6% to 2.5%, I<sup>2</sup> 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<sup>2</sup> 31%)) and the pooled risk difference was –1.6% (95% CI –2.8% to 0.0%, I<sup>2</sup> 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<sup>2</sup> 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.<sup>61 62</sup>



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

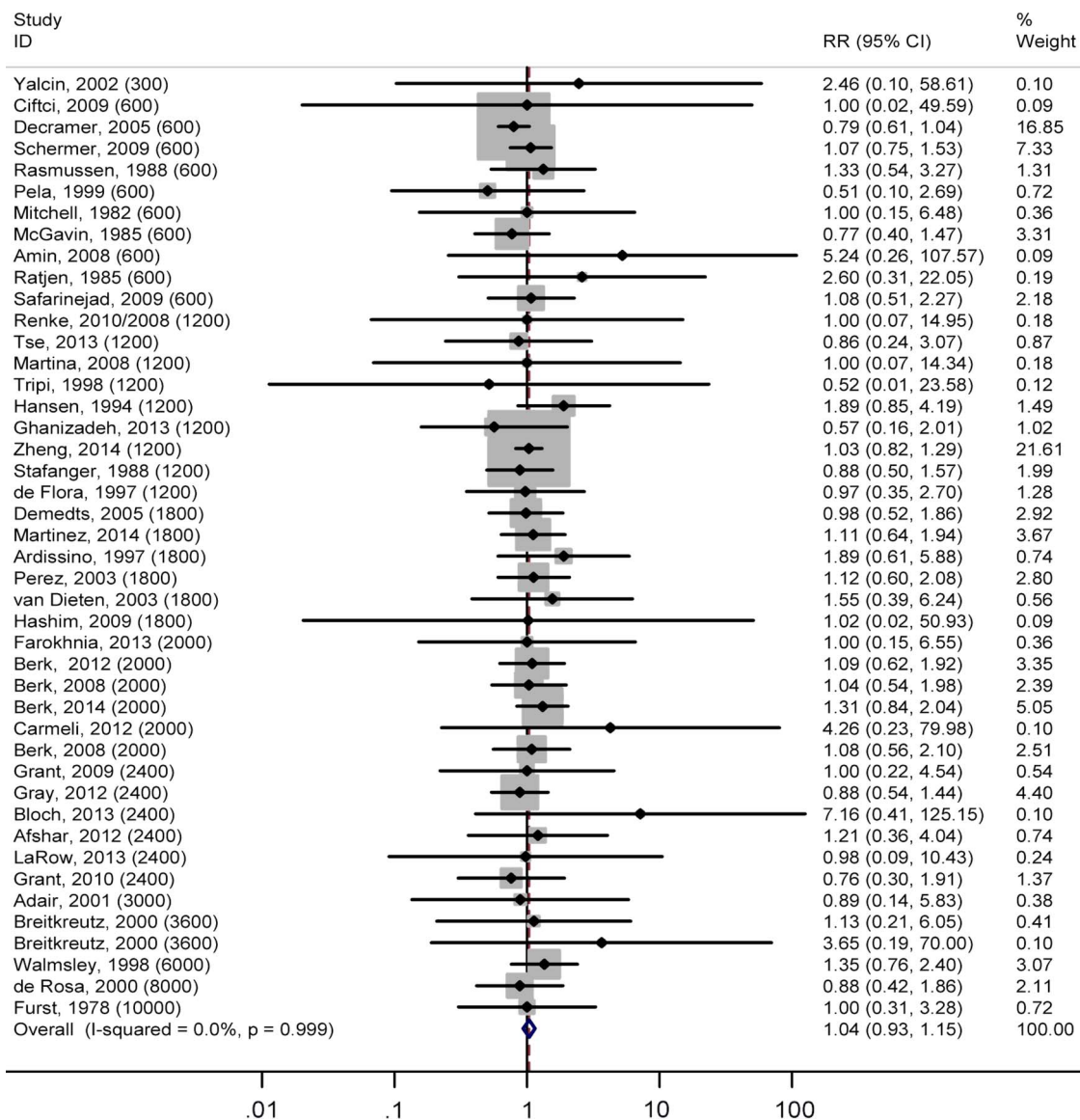
Feldman, 2007 <sup>14</sup>		
Methods	Randomised, open-label, controlled, parallel, one centre, duration 50 days, intention to treat analysis	
Participants	53 patients aged 18+ on haemodialysis treated with gentamicin for dialysis catheter-related bacteraemia, excluded if treated with aminoglycosides 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 <sup>16</sup>		
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 <sup>17</sup>		
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.<sup>63</sup> 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.<sup>64–66</sup> Furthermore, a considerable proportion of patients treated for MDR-TB experience depression, or develop hepatic and renal impairment as a result of treatment.<sup>67–69</sup> 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<sup>70</sup>; 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 <sup>2</sup> , p value	Estimate (95% CI)	I <sup>2</sup> , p value	Estimate (95% CI)	I <sup>2</sup> , p value	Estimate (95% CI)	I <sup>2</sup> , 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.<sup>71</sup> While the desired aim for MDR-TB treatment is to develop shortened, more tolerable and aminoglycoside-sparing regimens,<sup>72</sup> this may be some way from reality. Published studies of novel combinations are promising.<sup>73</sup> Nevertheless, a promising 9-month regimen, piloted in Bangladesh which showed good results in the absence of fluoroquinolone resistance,<sup>74</sup> and which is now being evaluated in the STREAM trial, has aminoglycosides as a key part of the regimen.<sup>75</sup> 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.<sup>75</sup>

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## REFERENCES

- Segal JA, Skolnick P. Polyamine-like actions of aminoglycosides and aminoglycoside derivatives at NMDA receptors. *Eur J Pharmacol* 1998;347:311–17.
- Chang J, Yang JY, Choi J, et al. Calcium imaging in gentamicin ototoxicity: increased intracellular calcium relates to oxidative stress and late apoptosis. *Int J Pediatr Otorhinolaryngol* 2011;75:1616–22.
- Santaolalla F, Salvador C, Martinez A, et al. Inner ear hair cell regeneration: A look from the past to the future. *Neural Regen Res* 2013;8:2284–9.
- Selimoglu E. Aminoglycoside-induced ototoxicity. *Curr Pharm Des* 2007;13:119–26.
- Black FO, Pesznecker S, Stallings V. Permanent gentamicin vestibulotoxicity. *Otol Neurotol* 2004;25:559–69.
- WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update*. Geneva, Switzerland: World Health Organization, 2011.
- Seddon JA, Godfrey-Faussett P, Jacobs K, et al. Hearing loss in patients on treatment for drug-resistant tuberculosis. *Eur Respir J* 2012;40:1277–86.
- Peloquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clin Infect Dis* 2004;38:1538–44.
- Sturdy A, Goodman A, Jose RJ, et al. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. *J Antimicrob Chemother* 2011;66:1815–20.
- Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012;9:e1001300.
- Darrat I, Ahmad N, Seidman K, et al. Auditory research involving antioxidants. *Curr Opin Otolaryngol Head Neck Surg* 2007;15:358–63.
- Sinswat P, Wu WJ, Sha SH, et al. Protection from ototoxicity of intraperitoneal gentamicin in guinea pig. *Kidney Int* 2000;58:2525–32.
- Sha SH, Qiu JH, Schacht J. Aspirin to prevent gentamicin-induced hearing loss. *N Engl J Med* 2006;354:1856–7.
- Feldman L, Efrati S, Eviatar E, et al. Gentamicin-induced ototoxicity in hemodialysis patients is ameliorated by N-acetylcysteine. *Kidney Int* 2007;72:359–63.

- 15 Feldman L, Sherman RA, Weissgarten J. N-acetylcysteine use for amelioration of aminoglycoside-induced ototoxicity in dialysis patients. *Semin Dial* 2012;25:491–4.
- 16 Tokgoz B, Ucar C, Kocyigit I, et al. Protective effect of N-acetylcysteine from drug-induced ototoxicity in uraemic patients with CAPD peritonitis. *Nephrol Dial Transplant* 2011;26:4073–8.
- 17 Kocyigit I, Vural A, Unal A, et al. Preventing amikacin related ototoxicity with N-acetylcysteine in patients undergoing peritoneal dialysis. *Eur Arch Otorhinolaryngol* Published Online First: 30 Jul 2014. doi:10.1007/s00405-014-3207-z
- 18 Yarema MC, Johnson DW, Berlin RJ, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. *Ann Emerg Med* 2009;54:606–14.
- 19 Weisbord SD, Gallagher M, Kaufman J, et al. Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial. *Clin J Am Soc Nephrol* 2013;8:1618–31.
- 20 Bielefeld EC, Kopke RD, Jackson RL, et al. Noise protection with N-acetyl-L-cysteine (NAC) using a variety of noise exposures, NAC doses, and routes of administration. *Acta Oto-Laryngologica* 2007;127:914–19.
- 21 Coleman J, Huang XY, Liu JZ, et al. Random study on the effectiveness of salicylate/ N-acetylcysteine for prevention of noise-induced hearing loss. *Noise Health* 2010;12:159–65.
- 22 Ewert DL, Lu JZ, Li W, et al. Antioxidant treatment reduces blast-induced cochlear damage and hearing loss. *Hear Res* 2012;285:29–39.
- 23 Lorito G, Giordano P, Petruccioli J, et al. Different strategies in treating noise-induced hearing loss with N-acetylcysteine. *Med Sci Monit* 2008;14:BR159–64.
- 24 Lin CY, Wu JL, Shih TS, et al. N-Acetyl-cysteine against noise-induced temporary threshold shift in male workers. *Hear Res* 2010;269:42–7.
- 25 Yoo J, Hamilton SJ, Angel D, et al. Cisplatin ototoxicity using transtympanic L-N-acetylcysteine: a pilot randomized study in head and neck cancer patients. *Laryngoscope* 2014;124:E87–94.
- 26 Riga MG, Chelis L, Kakolyris S, et al. Transtympanic injections of N-acetylcysteine for the prevention of cisplatin-induced ototoxicity: a feasible method with promising efficacy. *Am J Clin Oncol* 2013;36:1–6.
- 27 Samuni Y, Goldstein S, Dean OM, et al. The chemistry and biological activities of N-acetylcysteine. *Biochim Biophys Acta* 2013;1830:4117–29.
- 28 Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol (Phila)* 2009;47:81–8.
- 29 Cheng K, Smyth RL, Motley J, et al. Randomized controlled trials in cystic fibrosis (1966–1997) categorized by time, design, and intervention. *Pediatr Pulmonol* 2000;29:1–7.
- 30 Poole P, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2010;(2):CD001287.
- 31 Asevedo E, Mendes AC, Berk M, et al. Systematic review of N-acetylcysteine in the treatment of addictions. *Revista Brasileira De Psiquiatria* 2014;36:168–75.
- 32 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- 33 van Dalen EC, Caron HN, Dickinson HO, et al. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev* 2011;(6):CD003917.
- 34 Rothbart R, Amos T, Siegfried N, et al. Pharmacotherapy for trichotillomania. *Cochrane Database Syst Rev* 2013;11:CD007662.
- 35 Albers JW, Chaudhry V, Cavaletti G, et al. Interventions for preventing neuropathy caused by cisplatin and related compounds. *Cochrane Database Syst Rev* 2014;3: CD005228.
- 36 Showell MG, Brown J, Clarke J, et al. Antioxidants for female subfertility. *Cochrane Database Syst Rev* 2013;8:CD007807.
- 37 Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;8:CD001287.
- 38 Atkins CP, Loke YK, Wilson AM. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. *Respir Med* 2014;108:376–87.
- 39 Sutherland ER, Crapo JD, Bowler RP. N-acetylcysteine and exacerbations of chronic obstructive pulmonary disease. [Review] [38 refs]. *COPD* 2006;3:195–202.
- 40 Boogaard R, de Jongste JC, Merkus PJFM. Pharmacotherapy of impaired mucociliary clearance in non-CF pediatric lung disease. A review of the literature. [Review] [93 refs]. *Pediatr Pulmonol* 2007;42:989–1001.
- 41 Block KI, Koch AC, Mead MN, et al. Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials. *Cancer Treat Rev* 2007;33:407–18.
- 42 Brown KK, Wells AU. Recent clinical trials in idiopathic pulmonary fibrosis and the BUILD-1 study. *Eur Respir J* 2008;17:116–22.
- 43 Yancy WS Jr, McCrory DC, Coeytaux RR, et al. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. *Chest* 2013;144:1827–38.
- 44 Coombes JS, Fassett RG. Antioxidant therapy in hemodialysis patients: a systematic review. *Kidney Int* 2012;81:233–46.
- 45 Berk M, Malhi GS, Gray LJ, et al. The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol Sci* 2013;34:167–77.
- 46 Grandjean EM, Berthet P, Ruffmann R, et al. Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials. *Clinical Ther* 2000;22:209–21.
- 47 Duijvestijn YCM, Brand PLP. Systematic review of N-acetylcysteine in cystic fibrosis. *Acta Paediatrica* 1999;88:38–41.
- 48 Davies L, Calverley PMA. The evidence for the use of oral mucolytic agents in chronic obstructive pulmonary disease (COPD). *Br Med Bull* 2010;93:217–27.
- 49 Mecocci P, Polidori MC. Antioxidant clinical trials in mild cognitive impairment and Alzheimer's disease. *Biochim Biophys Acta* 2012;5:631–8.
- 50 Musso G, Gambino R, Cassader M, et al. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. *Hepatology* 2010;52:79–104.
- 51 Qureshi NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: a literature review. *Neuropsychiatr Dis Treat* 2013;9:639–58.
- 52 Poole C. Low P-values or narrow confidence intervals: which are more durable?. *Epidemiology* 2001;12:291–4.
- 53 Dean OM, Bush AI, Copolov DL, et al. Effects of N-acetyl cysteine on cognitive function in bipolar disorder. *Psychiatry Clin Neurosci* 2012;66:514–17.
- 54 Schloss JM, Colosimo M, Airey C, et al. Nutraceuticals and chemotherapy induced peripheral neuropathy (CIPN): A systematic review. *Clin Nutr* 2013;32:888–93.
- 55 Stey C, Steurer J, Bachmann S, et al. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. *Eur Respir J* 2000;16:253–62.
- 56 Sommer IE, van Westrhenen R, Begemann MJH, et al. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. *Schizophr Bull* 2014;40:181–91.
- 57 Shen Y, Cai W, Lei S, et al. Effect of high/low dose N-acetylcysteine on chronic obstructive pulmonary disease: a systematic review and meta-analysis. *COPD* 2014;11:351–8.
- 58 Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Inst Stat Math* 1950;21:607–11.
- 59 Miller J. The inverse of the Freeman-Tukey double arcsine transformation. *Am Stat* 1978;32:138.
- 60 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- 61 Isaakidis P, Varghese B, Mansoor H, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. *PLoS ONE* 2012;7:e40781.
- 62 Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis* 2004;8:1382–4.
- 63 Tozcek A, Cox H, du Cros P, et al. Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2013;17:299–307.
- 64 Flor de Lima B, Tavares M. Risk factors for extensively drug-resistant tuberculosis: a review. *Clin Respir J* 2014;8:11–23.
- 65 Cavanaugh JS, Kazenny BY, Nguyen ML, et al. Outcomes and follow-up of patients treated for multidrug-resistant tuberculosis in Orel, Russia, 2002–2005. *Int J Tuberc Lung Dis* 2012;16:1069–74.
- 66 Isaakidis P, Das M, Kumar AM, et al. Alarming levels of drug-resistant tuberculosis in HIV-infected patients in metropolitan Mumbai, India. *PLoS ONE* 2014;9:e110461.
- 67 Das M, Isaakidis P, Van den Bergh R, et al. HIV, multidrug-resistant TB and depressive symptoms: when three conditions collide. *Glob Health Action* 2014;7:24912.
- 68 Baghaei P, Tabarsi P, Dorriz D, et al. Adverse effects of multidrug-resistant tuberculosis treatment with a standardized regimen: a report from Iran. *Am J Ther* 2011;18:e29–34.
- 69 Wu S, Zhang Y, Sun F, et al. Adverse events associated with the treatment of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Am J Ther* Published Online First: 26 Nov 2013. doi:10.1097/01.mjt.0000433951.09030.5a
- 70 Baniyadi S, Filik L. Protective effect of N-acetyl cysteine on antituberculosis drug-induced hepatotoxicity. *Eur J Gastroenterol Hepatol* 2011;23:193; author reply.
- 71 Creswell J, Codlin AJ, Andre E, et al. Results from early programmatic implementation of Xpert MTB/RIF testing in nine countries. *BMC Infect Dis* 2014;14:2.
- 72 Brigid G, Nyang'wa BT, du Cros P, et al. Principles for designing future regimens for multidrug-resistant tuberculosis. *Bull World Health Organ* 2014;92:68–74.
- 73 Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012;380:986–93.
- 74 Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis* 2014;18:1180–7.
- 75 Nunn AJ, Rusen ID, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials* 2014;15:353.