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Safety of Nortriptyline at Equivalent Therapeutic Doses for Smoking Cessation

A Systematic Review and Meta-Analysis

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Abstract

Background: The limited use of nortriptyline for smoking cessation is likely due to concerns about its serious adverse effects.

Objective: To examine the safety of nortriptyline at doses equivalent to those used in aiding smoking cessation.

Data Sources: A systematic search of relevant articles in MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, CINAHL, PsychINFO, WHO publications and the Clinical Trials database (through November 2008).

Study Selection: All studies of nortriptyline at doses between 75 and 100 mg in any indication were reviewed.

Data Extraction: The quality of included studies was assessed based on the Jadad score. Data were extracted using a data extraction form.

Data Synthesis: From 442 potentially relevant articles identified, 17 studies met our selection criteria and were included for data analysis. Indications for nortriptyline in these studies were smoking cessation (eight studies), depression (five studies), neuropathic pain (three studies) and schizophrenia (one study). 2885 individuals participated in these studies, with exposure time ranging between 4 and 12 weeks. The major comparator used in these trials was placebo. Overall, no life-threatening events occurred in these studies. Orthostatic hypotension was significantly higher in nortriptyline users than in comparator groups (relative risk 2.8; 95% CI 1.4, 5.3). Other adverse events significantly associated with nortriptyline were anticholinergic-related effects including drowsiness, dizziness, gastrointestinal disturbance and dysgeusia.

Conclusions: Current evidence suggests that nortriptyline, at doses between 75 and 100 mg, is not significantly associated with serious adverse events when administered in patients without underlying cardiovascular disease.

Background

Cigarette smoking is well recognized as one of the major causes of diseases and premature death.[1] It is estimated that by the year 2030 smoking will have caused around 8 million deaths per year.[2] Smoking cessation is, therefore, an essential strategy in the prevention of smoking-related health problems and subsequent economic burdens.[3-5] Although many have tried to quit smoking, the success rate appears to be relatively low.[6] Several factors have been associated with this low cessation rate, including limited accessibility to appropriate healthcare interventions and the availability of smoking cessation aids.[7,8] Nicotine replacement therapy (NRT) and bupropion are the first-line medications for smoking cessation recommended by the WHO[9] and the UK Health Education Authority's smoking cessation guidelines for health professionals.[10] The US public health service clinical practice guideline[11] also recommended varenicline as one option for first-line therapy. Nortriptyline and clonidine are the second therapeutic options for patients who do not respond to the first-line regimen.

According to a recent systematic review,[12] nortriptyline and bupropion appear to be equally effective and of similar efficacy to NRT for the treatment of smoking cessation. It should also be noted that nortriptyline is an antidepressant that is available as a generic product, which is far less expensive than bupropion. Nonetheless, the limited use of nortriptyline is likely due to concerns about its serious adverse effects.[13] A number of well known serious adverse effects of nortriptyline are dose-dependent in nature and mostly reported from doses used for the treatment of major depression. The safety profile of nortriptyline at low doses, such as 75–100 mg/day, which is equivalent to doses used for smoking cessation, should be systematically evaluated. Therefore, this systematic review was conducted to evaluate the safety profile of nortriptyline at doses equivalent to those used in smoking cessation therapy. The availability of such information would be useful for clinicians when they decide which pharmacotherapy to select to assist smoking cessation.

Method

Search Strategy

A systematic search of MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, CINAHL and PsychINFO was conducted covering the period from the inception of the database until November 2008. The search term used was 'nortriptyline' with no date restriction. Trials were also retrieved from the WHO publication website (http://www.who.int/publications) and the Clinical Trials database (http://www.clinicaltrials.gov).

Eligibility Criteria and Study Selection

There was no design restriction for studies to be eligible for inclusion in this meta-analysis. The specific inclusion criteria for studies were (i) study participants using nortriptyline at doses between 75 and 100 mg for any indications; (ii) nortriptyline was the intervention drug versus control, which could be placebo or active control; and (iii) the study reported data on the incidence of adverse events or withdrawal from the study because of adverse effects. Only studies reported in the English language were included. Two reviewers independently scanned all titles and abstracts to determine whether a study measured adverse effects of nortriptyline. The eligibility was assessed from full-text articles of studies considered for inclusion by the same reviewers. Disagreements regarding eligibility were resolved by discussions with a third reviewer, if necessary.

Outcome Measures

The outcome measures were death associated with adverse effects, cardiovascular adverse effects, other adverse effects and withdrawal because of adverse effects.

Data Extraction and Quality Assessment

The quality of included studies was assessed based on the Jadad score.[14] Data were extracted using a data extraction form. Both data extraction and quality assessment were independently undertaken by two reviewers (TD, TJ). A third reviewer was consulted to resolve disagreements,

if any, regarding data extraction and quality assessment.

Statistical Analyses

Studies were categorized according to the indication for nortriptyline treatment and adverse event outcomes were measured. All studies were pooled in the main analysis regardless of the control used. Relative risks (RR) were calculated as the measure of association. The Q-statistics and I^2 for test of heterogeneity were performed to evaluate heterogeneity. The I^2 statistic[15] was used to determine the percentage of total variation across studies that was due to heterogeneity rather than chance; I^2 values of 50% or more indicate a substantial level of heterogeneity. The DerSimonian and Laird[16] random effects models were employed to pool data across studies. In addition to the main analysis, a series of sensitivity analyses were also undertaken by pooling only studies that compared nortriptyline with placebo and only those that compared it with an active control group. All analyses were conducted using STATA version 10.0 (STATACorp, College Station, TX, USA).

Results

A total of 442 potentially relevant articles were identified (figure 1). Of the 78 articles considered for inclusion, 61 were excluded based on dosage of nortriptyline studied (<75 mg/day or >100 mg/day), lack of information on dosage used, missing adverse outcome reports, report was in non-English language and the comparator group was a combination regimen. The 17 remaining studies consisted of studies on smoking cessation,[17-24] depression[25-29] and other indications, including schizophrenia[30] and pain reduction[31-33] (table I). Sixteen studies were randomized controlled trials (RCTs), whilst one[25] was a non-randomized, comparative, placebo-controlled trial.

Overall, 2885 patients were included in the meta-analysis (1426 participants received nortriptyline and 1459 received control treatment). Ten studies[17,18,20-26,32] reported an average age of participants in the range of 30–60 years, and

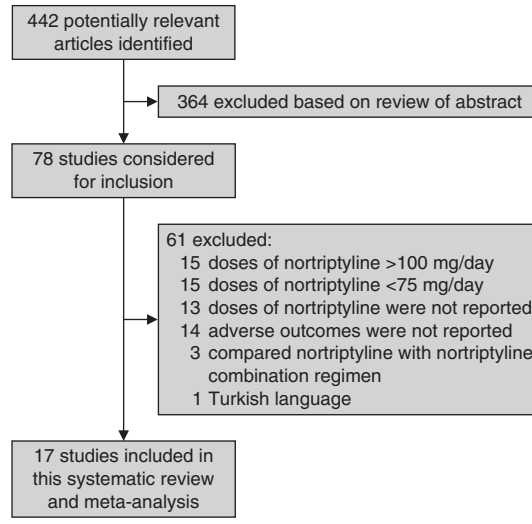

Fig. 1. Study selection process.

four trials[27-29,31] were conducted in participants with a mean age of over 60 years, whilst the remaining trials[19,30,33] did not report the average age of the patients. Most (>60%) participants were male in two studies[17,20] and female (>60%) in four trials,[23,27,32,33] and the sex of participants was balanced (40–60% of participants were male) in five other studies.[18,21,22,24,28] The sex of participants was not reported in five trials[19,25,26,30,31] or reported as a mix of sex proportion in the nortriptyline and comparator groups in another trial.[29] The majority of participants in smoking cessation trials were healthy individuals. Patients with depression were included in the other five studies.[25-29] Patients with various pre-existing medical conditions, i.e. cancer,[31] post-herpetic neuralgia[32] and lumbar root pain,[33] were studied in trials evaluating nortiptyline use for pain reduction. The duration of treatment ranged from 4–12 weeks in 16 studies. Only one trial evaluated the effects of nortriptyline treatment for more than 12 weeks, i.e. comparing brief (12 weeks) and extended (up to 52 weeks) treatment.[20] Nortriptyline was compared with placebo in 13 trials,[17-25,27,29,31,33] although five of these[18,22,23,25,29] studied nortriptyline in comparison with placebo and other medicines. Active comparators included fluoxetine,[26] sertraline,[28] amitriptyline[30] and

Table I. Main characteristics and quality scores of included studies

Study (y)	Treatment duration (wk)	Nortriptyline dose [mg]	Comparator	No. in group (mean age [y])		Jadad score	Method of AE monitoring
				nortriptyline	control		
Cigarette smoking							
Prochazka et al.[17] (1998)	8	75	Placebo	108 (47)	106 (47)	3	Not stated
Hall et al.[18] (2002)	12	75 (36%)[a] 100 (34%)[a]	Placebo	73 (38, 41)[b]	73 (43, 40)[b]	4	Checklist
da Costa et al.[19] (2002)	6	75	Placebo	68 (NA)	76 (NA)	3	Spontaneous report
Hall et al.[20] (2004)	12 and up to 52	75–100[c]	Placebo	79 (36, 40)[d]	81 (39, 39)[d]	2	Checklist
Prochazka et al.[21] (2004)	12	75	Placebo	79 (44)	79 (45)	3	Not stated
Wagena et al.[22] (2005)	12	75	Placebo	80 (51)	89 (51)	5	Routine monitor
Haggstram et al.[23] (2006)	9	75	Placebo	52 (44)	51 (42)	4	Routine monitor
Aveyard et al.[24] (2008)	8	75	Placebo	445 (43)	456 (44)	4	Questionnaire
Depression							
Georgotas et al.[25] (1987)	8	79 ± 13.8	Placebo	25 (≥55)	28 (≥55)	1	Routine monitor for BP
Fabre et al.[26] (1991)	5	84 (mean)	Fluoxetine	102 (38)	103 (36)	4	Routine monitor
Nair et al.[27] (1995)	7	75	Placebo	38 (71)	35 (71)	4	Routine monitor, spontaneous and checklist
Bondareff et al.[28] (2000)	12	78 (mean)	Sertraline	105 (68)	105 (68)	4	Routine monitor
Robinson et al.[29] (2000)	12	100	Placebo	31 (64, 65)[e]	33 (73, 67)[e]	3	Not stated
Others							
Haider[30] (1966)	4	75	Amitriptyline	20 (NA)	20 (NA)	2	Not stated
Hammack et al.[31] (2002)	9	75–100 (76%)[a]	Placebo	51 (60)	51 (63)	3	Routine monitor
Chandra et al.[32] (2006)	8	75	Gabapentin	36 (52)	34 (56)	5	Spontaneous and checklist
Khoromi et al.[33] (2007)	9	84 (mean)	Placebo	34 (NA)	39 (NA)	3	Routine monitor

a Percent of patients receiving the dose indicated.

b Studied in two groups: (i) with medical management; and (ii) with psychological intervention.

c Increased to 100 mg if therapeutic level was not achieved with nortriptyline 75 mg.

d Studied in two groups: (i) brief (12 wk); and (ii) extended treatment (up to 52 wk).

e Studied in two groups: (i) depressed; and (ii) non-depressed patients.

AE = adverse events; **BP** = blood pressure; **NA** = not available.

gabapentin.[32] Death or life-threatening adverse events associated with nortriptyline were not reported in any of the studies reviewed.

The methodological quality of trials reviewed was generally high, as shown by the Jadad score (scale range from 0–5). Among the 17 studies, three[20,25,30] had a Jadad score below 3. The study by Hall et al.[20] was given a Jadad score of 2 since it was not described as a double-blind trial and the randomization was not appropriately described. A study by Georgotas and colleagues[25] received a Jadad score of 1 as it was a non-randomized comparative trial. The Haider study[30] had a Jadad score of 2 as it failed to describe the detail of randomization and method of double blinding, as well as reasons for withdrawals and dropouts. All studies had clearly defined eligibility criteria and reasons for patient exclusion. The randomization in 14 trials[17-21,23,25-31,33] was not described nor was it appropriate based on the CONSORT (CONsolidated Standards of Reporting Trials) Statement, which covers the following topics: (i) sequence generation; (ii) allocation concealment mechanism; and (iii) implementation. Although all, except one,[20] were described as double-blind trials, the method of double blinding was adequately

described in only eight studies.[18,23,26-28,32-34] Trials were diverse in terms of included patients and treatment duration.

Considering the methods used for monitoring adverse effects, a study by da Costa et al.[19] required patients to spontaneously report on any adverse effects, whilst another four studies[17,21,29,30] failed to clearly describe how adverse effects were measured, although it is likely that spontaneous reporting was also applied in these studies. The majority of studies routinely monitored adverse effects by making inquiries with healthcare professionals[22,23,26-28,31,33] using a checklist[18,20] or questionnaire[24] at each visit, or combining the use of spontaneous reporting and a checklist.[27,32] The Georgotas et al.[25] study regularly monitored patients' blood pressure (BP) as the aim of the study was to examine the effect of nortriptyline on orthostatic hypotension.

Cardiovascular Adverse Effects

Cardiovascular adverse effects were identified in five trials and reported as orthostatic adverse events,[25,27,32] asymptomatic prolonged QT interval,[21] subjective elevated heart rate[17,21] and non-specific cardiovascular adverse effects.[27] Of note is that the characteristics of the latter two outcomes were not defined. Evidence of heterogeneity of orthostatic adverse events reported in three trials[25,27,32] was identified ($I^2 = 66.7\%$; $p = 0.05$) [table II and figure 2]. The pooled RR for orthostatic adverse events in patients using nortriptyline was 3.2 (95% CI 1.9, 5.4). In the sensitivity analyses, the association of nortriptyline for orthostatic adverse events in studies comparing nortriptyline with placebo or with active control groups remained unchanged.

The risk of a subjective increase in heart rate in nortriptyline-treated patients was not significantly different from that in the control groups (RR 3.0; 95% CI 0.3, 28.3), with no evidence of heterogeneity ($I^2 = 0.0\%$; $p = 0.99$). Outcome measures from other cardiovascular adverse effects could not be combined and are presented as risk ratios for individual studies. The presence of an asymptomatic prolonged QT interval in patients treated with nortriptyline was not statistically different to that observed in patients in the control group (RR 3.0; 95% CI 0.1, 72.5).[21] The risk of developing unspecified cardiovascular adverse events with nortriptyline treatment did not differ from that with placebo (RR 1.8; 95% CI 0.5, 6.8).[27] None of the other studies provided an appropriately detailed description of each adverse outcome, such as orthostatic hypotension, subjective increased heart rate and non-specific cardiovascular adverse effects.

Other Adverse Effects

The pooled analyses indicated that patients treated with nortriptyline were more likely to experience adverse events related to its anticholinergic effects, i.e. dry mouth (RR 2.3; 95% CI 2.1, 2.5), constipation (RR 2.1; 95% CI 1.8, 2.4),

Table II. Results of studies reporting cardiovascular adverse effects

Outcomes, study (y)	No. of events/no. of pts in nortriptyline group (%)	No. of events/no. of pts in control group (%)	Relative risk (95% CI)	Weight (%)	I^2 (%)	p-Value for heterogeneity
Orthostatic hypotension						
Overall	43/99 (43.4)	13/97 (13.4)	3.2 (1.8, 5.4)	100.0	66.7	0.05
Georgotas et al.[25] (1987)	15/25 (60.0)	4/28 (14.3)	4.2 (1.6, 11.0)	27.6		
Nair et al.[27] (1995)	16/38 (42.1)	9/35 (25.7)	1.6 (0.8, 3.2)	68.6		
Chandra et al.[32] (2006)	12/36 (33.3)	0/34 (0.0)	23.6 (1.4, 384.5)	3.8		
Subjective increased heart rate						
Overall	2/187 (1.1)	0/185 (0.0)	3.0 (0.3, 28.3)	100.0	0.0	0.99
Prochazka et al.[17] (1998)	1/108 (0.9)	0/106 (0)	2.9 (0.1, 71.5)	50.3		
Prochazka et al.[21] (2004)	1/79 (1.3)	0/79 (0)	3.0 (0.1, 72.5)	49.7		

I^2 = test for heterogeneity; **pts** = patients.

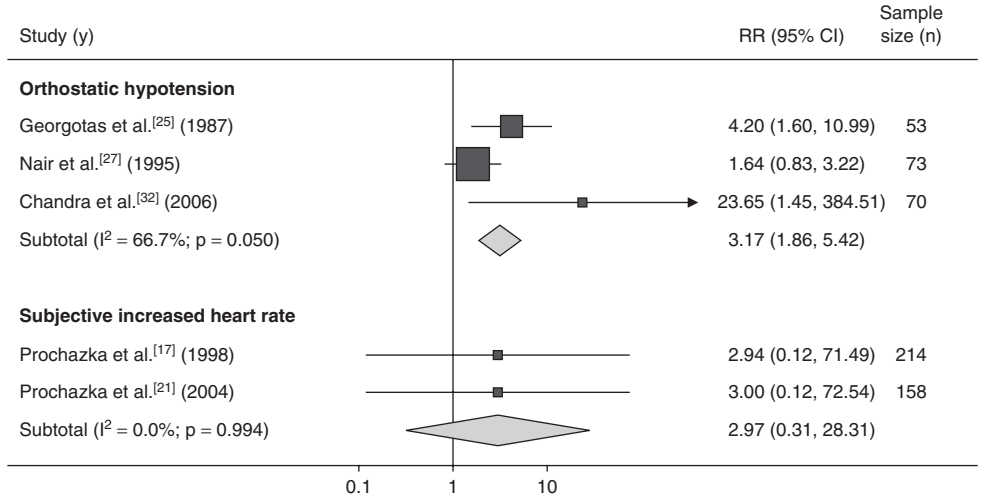

Fig. 2. Cardiovascular adverse effects of nortriptyline vs control groups. The diamond indicates the summary relative risk (RR) and 95% CI. Studies are ordered chronologically. The size of squares is proportional to the reciprocal of the variance of the studies.

blurry vision (RR 1.9; 95% CI 1.4, 2.6), light headache (RR 1.4; 95% CI 1.1, 1.8) and shaky hands (RR 4.1; 95% CI 2.8, 5.8) [table III]. Other adverse effects associated with nortriptyline included drowsiness (RR 1.9; 95% CI 1.4, 2.6), dizziness (RR 1.8; 95% CI 1.3, 2.4), gastrointestinal

Table III. Results of studies reporting other adverse effects

Outcomes (no. of studies)	No. of events/no. of pts in nortriptyline group (%)	No. of events/no. of pts in control group (%)	Pooled relative risk (95% CI)	I^2 (%)	p-Value for heterogeneity
Anticholinergic effects					
Dry mouth (14)[17-24,26,28,30-33]	847/1326 (63.9)	370/1352 (27.4)	2.3 (2.1, 2.5)	42.7	0.04
Constipation (12)[18-21,23,24,26,28,31-33,35]	432/1152 (37.5)	208/1171 (17.8)	2.1 (1.8, 2.4)	0.0	0.89
Blurry vision (5)[20,22,24,33,36]	92/657 (14.0)	50/684 (7.3)	1.9 (1.4, 2.6)	32.2	0.21
Urinary retention (2)[32,33]	2/70 (2.9)	0/73 (0.0)	3.1 (0.3, 29.2)	0.0	0.93
Light headache (2)[20,24]	151/524 (28.8)	109/537 (20.3)	1.4 (1.1, 1.8)	58.5	0.12
Shaky hand (2)[20,24]	127/524 (24.2)	32/537 (6.0)	4.1 (2.8, 5.8)	89.8	0.00
Various effects					
Drowsiness (9)[17,21,23,26,28-30,32,33]	93/566 (16.4)	48/569 (8.4)	1.9 (1.4, 2.6)	35.2	0.14
Dizziness (8)[17,22,23,26,30-33]	88/483 (18.2)	51/493 (10.3)	1.8 (1.3, 2.4)	0.0	0.55
Insomnia (8)[17,19,21,22,26,28,31,33]	114/678 (16.8)	126/698 (18.1)	0.9 (0.7, 1.2)	54.9	0.02
Headache (7)[17,19,22,23,28,30,33]	83/466 (17.8)	78/485 (16.1)	1.1 (0.8, 1.4)	0.0	0.59
Fatigue (5)[17,21,22,32,33]	43/337 (12.8)	36/347 (10.4)	1.2 (0.8, 1.9)	10.3	0.35
GI disturbance (4)[17,20,22,23]	121/319 (37.9)	74/327 (22.6)	1.7 (1.3, 2.1)	66.0	0.03
Sweating (2)[28,30]	13/124 (10.5)	14/124 (11.3)	0.9 (0.5, 1.9)	0.0	0.50
Abdominal pain (2)[23,33]	3/86 (3.5)	9/90 (10.0)	0.4 (0.1, 1.2)	58.1	0.12
Diarrhoea (2)[28,30]	12/124 (10.5)	25/124 (20.2)	0.5 (0.3, 0.9)	0.0	0.97
Dysgeusia (2)[17,21]	32/187 (17.1)	16/185 (8.6)	2.0 (1.1, 3.5)	40.9	0.19
Irritation (2)[19,21]	16/147 (10.9)	23/155 (14.8)	0.8 (0.4, 1.4)	0.0	0.92
Nausea (2)[26,28]	27/206 (13.1)	24/207 (11.6)	1.1 (0.7, 1.9)	90.0	0.00
Weight gain (2)[19,33]	12/102 (11.8)	18/115 (15.7)	0.8 (0.4, 1.4)	51.2	0.15

GI = gastrointestinal; **I^2** = test for heterogeneity; **pts** = patients.

Table IV. Results of studies reporting dropout associated with adverse events

Outcomes, study (y)	No. of events/no. of pts in nortriptyline group (%)	No. of events/no. of pts in control group (%)	Relative risk (95% CI)	Weight (%)	I^2 (%)	p-Value for heterogeneity
Overall	28/356 (7.9)	13/367 (3.5)	2.2 (1.2, 4.2)	100.0	9.8	0.35
Prochazka et al.[17] (1998)	5/108 (4.6)	1/106 (9.4)	4.9 (0.6, 41.3)	7.8		
Robinson et al.[29] (2000)	5/31 (16.1)	5/33 (15.2)	1.1 (0.3, 3.3)	37.2		
da Costa et al.[19] (2002)	5/68 (7.4)	5/76 (6.6)	1.1 (0.3, 3.7)	36.3		
Prochazka et al.[21] (2004)	10/79 (12.6)	1/79 (1.3)	10.0 (1.3, 76.3)	7.7		
Chandra et al.[32] (2006)	1/36 (2.7)	0/34 (0.0)	2.8 (0.1, 67.4)	3.9		
Khoromi et al.[33] (2007)	2/34 (5.9)	1/39 (2.6)	2.3 (0.2, 24.2)	7.1		

I^2 = test for heterogeneity; **pts** = patients.

disturbance (RR 1.7; 95% CI 1.3, 2.1) and dysgeusia (RR 2.0; 95% CI 1.1, 3.5).

Dropouts

In pooled results from six studies,[17,19,21,29,32,33] the reported dropout rates associated with adverse effects revealed that patients treated with nortriptyline were significantly more likely to dropout from the studies than those in the control groups (RR 2.2; 95% CI 1.2, 4.2) [table IV and figure 3]. Reasons for dropout included dry mouth, constipation, indigestion, abdominal pain, trouble urinating, micturition syncope and fractured humerus, hot flashes, headache, sedation, sleep disturbance, rash, subjective increased heart rate and asymptomatic prolonged QT interval.

Sensitivity Analyses

The pooled RR estimates for each outcome were presented separately for studies comparing nortriptyline with placebo and for those comparing nortriptyline with active control[22,26,28,30,32] (table V). Compared with the main analysis, changes were found in sensitivity analyses of active control studies for the following outcomes: dizziness (RR 1.8; 95% CI 1.3, 2.4 vs RR 1.2; 95% CI 0.8, 1.8) and dropout due to adverse effects (RR 2.2; 95% CI 1.2, 4.2 vs RR 2.8; 95% CI 0.1, 67.4). Results of other adverse outcomes, including orthostatic hypotension, in sensitivity anal-

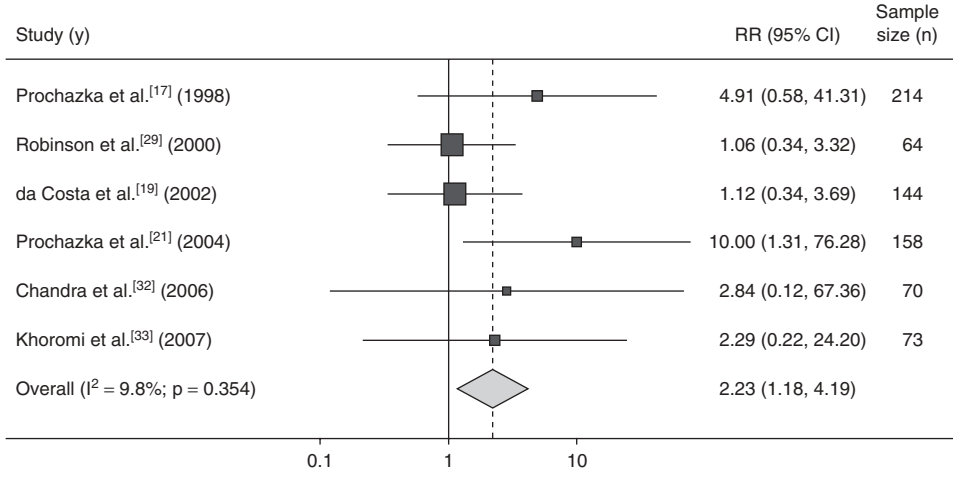

Fig. 3. Dropout from trials of nortriptyline vs control groups. The diamond indicates the summary relative risk (RR) and 95% CI. Studies are ordered chronologically. The size of squares is proportional to the reciprocal of the variance of the studies.

Table V. Results of studies reporting adverse effects derived from different comparators

Outcomes (no. of studies)	No. of events/total no. of pts in nortriptyline groups (%)	No. of events/total no. of pts in control groups (%)	Pooled relative risk (95% CI)	I^2 (%)	p-Value for heterogeneity
Placebo-control studies					
Orthostatic hypotension (2)[25,27]	31/63 (49.2)	13/63 (20.6)	2.4 (1.4, 4.1)	60.2	0.11
Dry mouth (10)[17-24,31,33]	693/1064 (65.1)	301/1091 (27.6)	2.3 (2.1, 2.6)	24.1	0.22
Constipation (9)[18-21,23,24,31,33,35]	70/325 (21.5)	40/336 (11.9)	2.0 (1.8, 2.4)	0.0	0.96
Drowsiness (5)[17,21,23,29,33]	55/304 (18.1)	17/308 (5.5)	3.2 (1.9, 5.2)	0.0	0.47
Dizziness (5)[17,22,23,31,33]	70/325 (21.5)	40/336 (11.9)	1.8 (1.3, 2.6)	6.9	0.37
Insomnia (6)[17,19,21,22,31,33]	75/364 (20.6)	64/385 (16.6)	1.0 (0.8, 1.3)	54.5	0.04
Headache (5)[17,19,22,23,33]	39/342 (11.4)	41/361 (11.4)	1.0 (0.6, 1.4)	0.0	0.41
Fatigue (4)[17,21,22,33]	43/301 (14.3)	35/313 (11.2)	1.3 (0.8, 1.9)	19.4	0.29
Dropout (5)[17,19,21,29,33]	27/320 (8.4)	13/333 (3.9)	2.2 (1.2, 4.2)	26.9	0.24
Active-control studies					
Orthostatic hypotension (1)[32]	12/36 (33.3)	0/34 (0.0)	23.6 (1.4, 384.5)	NA	
Dry mouth (6)[22,23,26,28,30,32]	238/394 (60.4)	120/400 (30.0)	2.0 (1.7, 2.4)	68.1	0.01
Constipation (4)[23,26,28,32]	74/294 (25.2)	34/294 (11.6)	2.2 (1.5, 3.1)	44.8	0.14
Drowsiness (5)[23,26,28,30,32]	48/314 (15.3)	31/314 (9.9)	1.5 (1.0, 2.3)	40.6	0.15
Dizziness (5)[22,23,26,30,32]	48/290 (16.6)	40/296 (13.5)	1.2 (0.8, 1.8)	0.0	0.50
Insomnia (4)[22,23,26,28]	49/338 (14.5)	90/346 (26.0)	0.6 (0.4, 0.8)	69.7	0.02
Headache (4)[22,23,28,30]	53/256 (24.6)	60/263 (22.8)	1.1 (0.8, 1.4)	38.3	0.18
Fatigue (2)[22,32]	16/116 (13.8)	8/120 (6.7)	2.0 (0.9, 4.5)	34.3	0.22
Dropout (1)[32]	1/36 (2.8)	0/34 (0.0)	2.8 (0.1, 67.4)	NA	

I^2 = test for heterogeneity; **NA** = not applicable; **pts** = patients.

yses of active control studies showed a similar pattern to those from the main analyses, although the intensity of RR did differ for some parameters.

Of the eight trials on smoking cessation, three[18,22,23] investigated the clinical effects of nortriptyline, bupropion and placebo. However, our present review evaluated adverse outcomes of nortriptyline in comparison with bupropion based on the results of two trials,[22,23] as quantitative data of the adverse outcomes on the bupropion arm were not presented in the study by Hall et al.[18] The pooled analysis revealed that dry mouth was the only outcome that was reported significantly more often in nortriptyline-treated patients than in those receiving bupropion (RR 1.7; 95% CI 1.3, 2.2).

One of the studies reviewed was non-RCT[25] and scored only 1 on the Jadad scale, which reflected its relatively low quality. We therefore considered conducting further examinations to remove this particular study from the pooled analyses. There was only one outcome parameter derived from this study, i.e. orthostatic hypotension. It was found that orthostatic adverse outcomes remained unchanged after excluding the result from this study (RR 2.8; 95% CI 1.4, 5.3). This suggests the risk of orthostatic hypotension associated with nortriptyline is well established.

Discussion

To the best of our knowledge, this report is the first systematic review and meta-analysis conducted to evaluate the adverse effects of nortriptyline at equivalent therapeutic doses for smoking cessation (75–100 mg). There were no reports of death or serious cardiovascular events among those receiving nortriptyline. Our findings indicate that nortriptyline is significantly associated with orthostatic hypotension but not with other cardiovascular adverse events. The orthostatic hypotension effect associated with nortriptyline is probably related to its anti-α_1 adrenergic actions.[37] Other adverse events that were evident among nortriptyline users included anticholinergic-related effects (dry

mouth, constipation, blurry vision, light headache and shaky hand), drowsiness, dizziness, gastrointestinal disturbance and dysgeusia. Overall, results from the present study are consistent with published reviews.[12,34]

The strength of our study is that all studies of nortriptyline for any indications were included. Instead of focusing only on trials evaluating nortriptyline for smoking cessation, like other previous systematic reviews,[12,34] our study expanded inclusion criteria to allow a higher number of nortriptyline users to be included, which could provide more meaningful information such as cardiovascular adverse events. This extension of inclusion criteria is justified by our assumption that the adverse effects of concern are directly related to the dose used. Regardless of indications used, all studies evaluating nortriptyline at doses of 75–100 mg were included in this systematic review and meta-analysis. In fact, this broader inclusion improved the generalizability of our findings considering the diversity of indications for nortriptyline use, the participants' underlying medical conditions and comparators available.

The quality of the trials reviewed based on the Jadad score was generally high despite the fact that the randomization use in many of them was not well described. It should be noted, however, that the absence of information reported in clinical trials is a common limitation seen in a systematic review. Although this could be addressed by asking authors to provide missing or incomplete data, some suggested that there was a poor success rate in the acquisition of essential information from such an approach.[38] We therefore believed that failure to contact authors for clarification of randomization may not have had much effect on the overall evaluation of the quality of the trials in the present review.

The relatively low level of side effects and lack of serious adverse events uncovered by this systematic review may be explained by several reasons. One reason is that the doses of nortriptyline used in the included trials were 75–100 mg, whilst serious adverse events have been reported in patients receiving nortriptyline at higher doses.[13,39] It is well recognized that tricyclic antidepressants, including nortriptyline, have direct cardiac-depressing actions such as those associated with class I antiarrhythmics, which are related to actions at fast Na^+ channels.[37] However, cardiovascular effects (including orthostatic hypotension, sinus tachycardia and variable prolongation of cardiac conduction times with the potential for arrhythmias) tend to be dose-related and are most often observed after overdose.[37] Another reason is the majority of participants included in the trials reviewed had no co-morbidities. Some trials enrolled patients with depression, neurological symptoms and cancer, but none included patients with underlying cardiovascular diseases, whose risk of serious cardiovascular events is high. The absence of patients with underlying cardiovascular disease might explain the relatively low number of cardiovascular adverse events reported following nortriptyline use. The heterogeneity observed in the pooled analysis for orthostatic hypotension may be caused by differences in the following factors: (i) the comparators used (placebo in two studies[25,27] and active control in the remaining study[32]); (ii) the study designs (RCT in two trials[27,32] and cohort in the remaining study[25]); and (iii) the regularity and method used to monitor BP (BP measurement every week in two studies[25,27] and not described in the other study[32]). Another postulated reason for low serious adverse events is that the number of trials available for analysis is small. This may preclude ability to detect such events. Caution should also be exercised when interpreting subjective outcomes, specifically subjective increased heart rate, since the definition of such adverse outcomes was not described.

Most of the results that were revealed by a series of sensitivity analyses are consistent with the main analyses findings. There were no differences in cardiovascular effects between the analyses of studies with placebo and those trials with active control. For some outcomes (i.e. drowsiness, dizziness and dropout due to adverse effect), the magnitude of association in the analyses of studies using active control was less prominent and significant. The lower strength and magnitude of association was likely due to the higher frequency of adverse events associated with the use of active product in the control group. On the other hand, the magnitude of association of

adverse outcomes in the nortriptyline groups compared with placebo groups was larger, with a higher level of significance.

Dropout due to adverse effects is one of the indicators to determine the tolerability of drugs in clinical trials. Although serious adverse events related to nortriptyline use were not identified, mild to moderate adverse effects were shown to have an impact on the patients' decision to withdraw from the studies. However, the dropout rates associated with nortriptyline treatment at doses used to aid smoking cessation did not significantly differ from those of active controls. This potentially suggests that the tolerability profile of nortriptyline, based on dropout rates, may be relatively similar to that of other drugs. It should be noted that active comparators used in the trials evaluated in our study varied widely and were not limited to antidepressants or drugs used for smoking cessation. It is of interest to compare the safety of nortriptyline and bupropion as these drugs share similar profiles, i.e. both are antidepressants and are indicated to aid smoking cessation. Our review showed that adverse outcomes from nortriptyline, except dry mouth, were not significantly different from bupropion. The most recent review by Hughes et al.[12] also showed that typical dropout rates in clinical trials due to adverse events range from 7% to 12% in those receiving bupropion and 4% to 9% in nortriptyline-treated patients. Although these data suggested that the safety profile of nortriptyline appeared to be similar to that of bupropion, a comprehensive systematic review examining the safety of nortriptyline and bupropion is warranted.

The lack of adverse events reported in clinical trials cannot guarantee that the adverse outcomes do not exist. Ioannidis and Lau[40] have empirically shown that adverse events were underreported by 13.5% in most RCTs. The readers should be cautious in interpreting any studies reporting adverse events as the outcome reporting bias has been noted more recently in the literature.[41] Other specific factors that may have an impact on the adverse effects data of the studies reviewed include methods for monitoring and detecting adverse effects, and selective outcome reporting.

Despite our belief of a low risk of serious adverse events associated with nortriptyline 75–100 mg, we still encourage that future trials on nortriptyline state the exact dose used, especially those titrating the dose of the drug to achieve the target therapeutic concentration, as well as reporting all adverse outcomes that may occur, particularly cardiovascular adverse events.

This systematic review used rigorous criteria and review procedures to exclude studies that could potentially be a cause of heterogeneity; however, statistical heterogeneity was found in 6 of 22 outcomes, i.e. orthostatic hypotension (3 studies), dry mouth (14 studies), shaky hand (2 studies), insomnia (8 studies), gastrointestinal disturbance (4 studies) and nausea (2 studies). Although use of the random-effects model is not a remedy of heterogeneity,[42] it can be used to pool studies with heterogeneity when such heterogeneity is due to the true differing effects. We therefore believe that use of the random-effects model is a reasonable choice in this study.

A previous review by Hughes et al.[13] pointed out that one of the major limitations to considering nortriptyline as a first-line treatment for smoking cessation was its safety profile. Although findings from their recent work[12] and others[34] consistently showed that nortriptyline was safe and not associated with serious adverse events, these were derived from a relatively low number of participants treated with nortriptyline (<1000 in both studies) and were deemed as inadequate to establish safety of the drug.[13] Our finding may, in part, address the concern raised as we evaluated the adverse effects of nortriptyline in nearly 3000 subjects and combined studies with different patient populations, different patient ages and various co-existing medical conditions, including depression. It should, however, be noted that the present study did not cover special patient groups, such as those with underlying cardiovascular diseases and pregnant women.

Conclusions

Our systematic review has not uncovered any evidence of mortality and serious adverse events associated with nortriptyline use at doses between

75 and 100 mg. However, nortriptyline use by patients without underlying cardiovascular diseases was significantly associated with orthostatic hypotension, while the risks of developing other cardiovascular adverse events were not established. The most common adverse effects associated with nortriptyline use related to its anticholinergic properties. Given the extent of the safety profile of nortriptyline, policy makers and guideline developers may consider nortriptyline as a safe therapeutic option for smoking cessation management.

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