

**Supplement, table 1: Search strategy**

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

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

Web of Science

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

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

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

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

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

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

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

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

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

<sup>a</sup> Cross-over trial

<sup>b</sup> No placebo in the control group

<sup>c</sup> Patients were given NAC plus lipoic acid

<sup>d</sup> All patients were treated for PCP with co-trimoxazole

<sup>e</sup> All patients received IFN, patients in the NAC also received sodium selenite

<sup>f</sup> Patients who did not respond to IFN treatment at 3 months were given NAC

<sup>g</sup> No RCT, patients were given an option to take NAC or not

<sup>h</sup> Drug administration 3 times per week

<sup>i</sup> All patients received metformin, no placebo in the control group

<sup>j</sup> Patients in the comparison group received metformin (not placebo)

<sup>k</sup> Comparison group DMSO cream

<sup>l</sup> Patients in the control group took ambroxol or bromhexine or carbocisteine

<sup>m</sup> All patients received omeprazole

<sup>n</sup> Patients in the control group took Vitamin C

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[illegible]



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

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

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

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

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

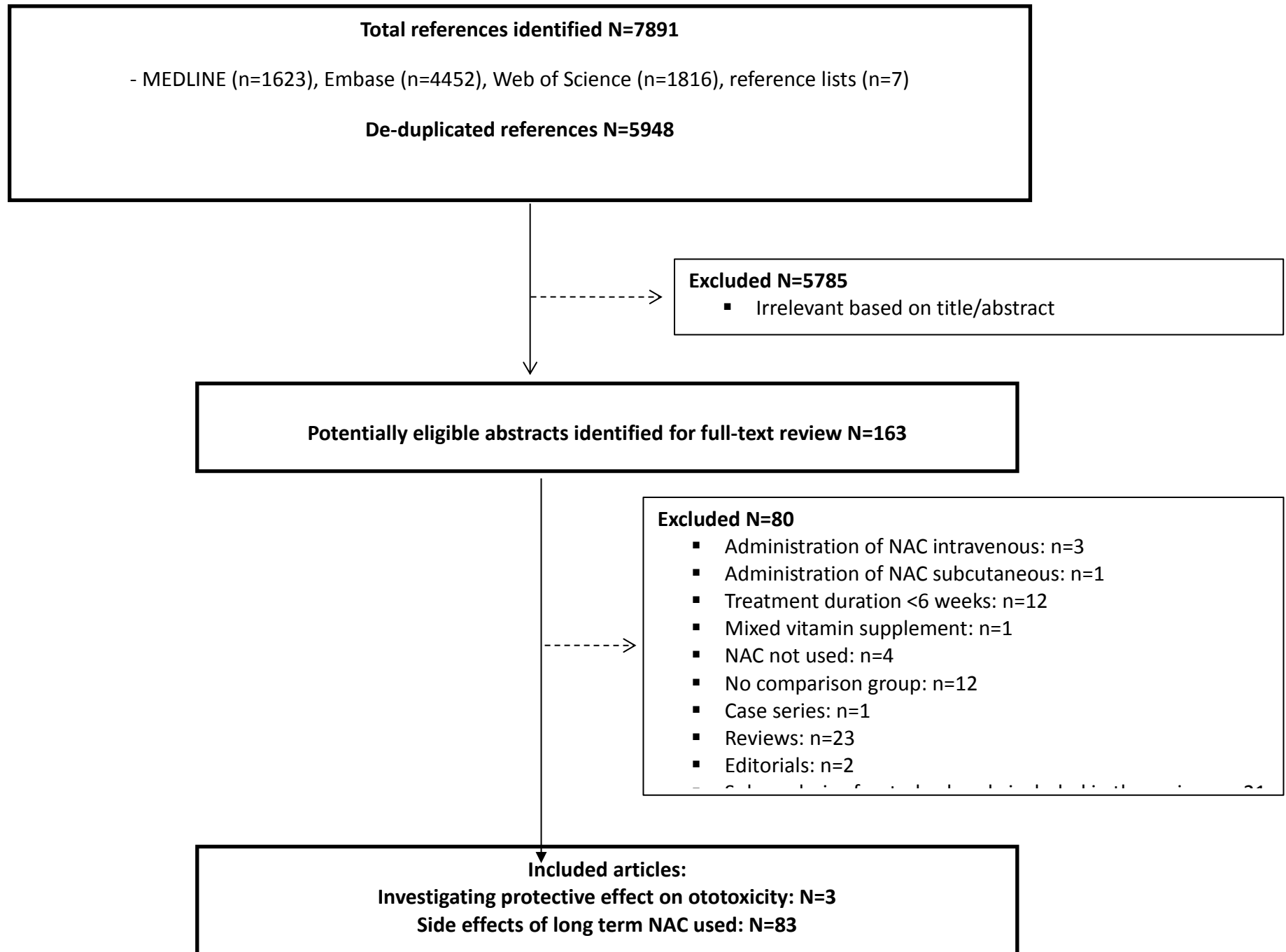
<b>Author, year</b>	<b>Sequence generation</b>	<b>Allocation concealment</b>	<b>Blinding-participant</b>	<b>Blinding-investigator</b>	<b>Complete outcome data - side effect</b>	<b>Complete outcome data - withdraw</b>	<b>Complete outcome data - death</b>	<b>Selective outcome reporting</b>
Lukas, 2005[27]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

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

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

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

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



**Supplement figure 1: Selection process for the inclusion of studies**

## References

1. Berk M, Dean OM, Cotton SM, et al. Maintenance N-acetyl cysteine treatment for bipolar disorder: A double-blind randomized placebo controlled trial. *BMC Medicine* 2012; 10.
2. Berk M, Copolov DL, Dean O, et al. N-Acetyl Cysteine for Depressive Symptoms in Bipolar Disorder-A Double-Blind Randomized Placebo-Controlled Trial. *Biological Psychiatry* 2008; 64: 468-75.
3. Berk M, Dean OM, Cotton SM, et al. The Efficacy of Adjunctive N-Acetylcysteine in Major Depressive Disorder: A Double-Blind, Randomized, Placebo-Controlled Trial. *Journal of Clinical Psychiatry* 2014; 75: 628-U95.
4. Farokhnia M, Azarkolah A, Adinehfar F, et al. N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. *Clinical Neuropharmacology* 2013; 36: 185-92.
5. Carmeli C, Knyazeva MG, Cuenod M, Do KQ. Glutathione precursor N-acetyl-cysteine modulates EEG synchronization in schizophrenia patients: A double-blind, randomized, placebo-controlled trial. *PLoS ONE* 2012; 7.
6. Lavoie S, Murray MM, Deppen P, et al. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. *Neuropsychopharmacology* 2008; 33: 2187-99.
7. Berk M, Copolov D, Dean O, et al. N-Acetyl Cysteine as a Glutathione Precursor for Schizophrenia-A Double-Blind, Randomized, Placebo-Controlled Trial. *Biological Psychiatry* 2008; 64: 361-8.
8. Afshar H, Roohafza H, Mohammad-Beigi H, et al. N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychopharmacology* 2012; 32: 797-803.
9. Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. *BMC Psychiatry* 2013; 13.
10. Bloch MH, Panza KE, Grant JE, Pittenger C, Leckman JF. N-acetylcysteine in the treatment of pediatric trichotillomania: A randomized, double-blind, placebo-controlled add-on trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2013; 52: 231-40.
11. Grant JE, Odlaug BL, Kim SW, Suck WK. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Archives of General Psychiatry* 2009; 66: 756-63.
12. Grant JE, Kim SW, Odlaug BL. N-Acetyl Cysteine, a Glutamate-Modulating Agent, in the Treatment of Pathological Gambling: A Pilot Study. *Biological Psychiatry* 2007; 62: 652-7.
13. LaRowe SD, Kalivas PW, Nicholas JS, Randall PK, Mardikian PN, Malcolm RJ. A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. *American Journal on Addictions* 2013; 22: 443-52.
14. Gray KM, Carpenter MJ, Baker NL, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *American Journal of Psychiatry* 2012; 169: 805-12.
15. Grant JE, Odlaug BL, Kim SW. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. *European Neuropsychopharmacology* 2010; 20: 823-8.
16. Zheng JP, Wen FQ, Bai CX, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respiratory Medicine* 2014; 2: 187-94.
17. Tse HN, Raiteri L, Wong KY, et al. High-dose N-acetylcysteine in stable COPD: The 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest* 2013; 144: 106-18.
18. De Backer J, Vos W, Van Holsbeke C, et al. Effect of high-dose N-acetylcysteine on airway geometry, inflammation, and oxidative stress in COPD patients. *International Journal of COPD* 2013; 8.
19. Patil AB, Kale AB, Singhal SS, Khan TA. Study of malondialdehyde as an indicator of oxidative stress and its modulation by N-acetylcysteine in chronic obstructive pulmonary disease. *Journal of Clinical and Diagnostic Research* 2011; 5: 48-51.
20. Stav D, Raz M. Effect of N-acetylcysteine on air trapping in COPD: A randomized placebo-controlled study. *Chest* 2009; 136: 381-6.
21. Schermer T, Chavannes N, Dekhuijzen R, et al. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. *Respiratory medicine* 2009; 103: 542-51.
22. Decramer M, Rutten-van Molken M, Dekhuijzen PNR. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial (vol 365, pg 1552, 2005). *Lancet* 2005; 366: 984.
23. De Benedetto F, Aceto A, Dragani B, et al. Long-term oral n-acetylcysteine reduces exhaled hydrogen peroxide in stable COPD. *Pulmonary Pharmacology and Therapeutics* 2005; 18: 41-7.

24. Van Overveld FJ, Demkow U, Gorecka D, De Backer WA, Zielinski J. New developments in the treatment of COPD: Comparing the effects of inhaled corticosteroids and N-acetylcysteine. *Journal of Physiology and Pharmacology* 2005; 56: 135-42.
25. Kasielski M, Nowak D. Long-term administration of N-acetylcysteine decreases hydrogen peroxide exhalation in subjects with chronic obstructive pulmonary disease. *Respiratory medicine* 2001; 95: 448-56.
26. Pela R, Calcagni AM, Subiaco S, Isidori P, Tubaldi A, Sanguinetti CM. N-acetylcysteine reduces the exacerbation rate in patients with moderate to severe COPD. *Respiration* 1999; 66: 495-500.
27. Lukas R, Scharling B, Schultze-Werninghaus G, Gillissen A. Administration of N-acetylcysteine and Vitamin C to augment antioxidant protection in patients with chronic bronchitis. [German]. *Deutsche medizinische Wochenschrift* 2005; 130: 563-7.
28. Hansen NCG, Skriver A, Brorsen-Riis L, et al. Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. *Respiratory medicine* 1994; 88: 531-5.
29. Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. *European Respiratory Journal* 1988; 1: 351-5.
30. Poder G, Puskas J, Kelemen J. Acetylcysteine in chronic obstructive bronchitis. [German]. *Therapiewoche* 1984; 34: 7047-52.
31. Anonymous, McGavin CR, Prescott RJ, Nariman S, Macfarlane JT. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. *Thorax* 1985; 40: 832-5.
32. Stafanger G, Koch C. N-acetylcysteine in cystic fibrosis and *Pseudomonas aeruginosa* infection: clinical score, spirometry and ciliary motility. *European Respiratory Journal* 1989; 2: 234-7.
33. Stafanger G, Garne S, Howitz P, Morkassel E, Koch C. The clinical effect and the effect on the ciliary motility of oral N-acetylcysteine in patients with cystic fibrosis and primary ciliary dyskinesia. *European Respiratory Journal* 1988; 1: 161-7.
34. Ratjen F, Wonne R, Posselt HG, Stover B, Hofmann D, Bender SW. A double-blind placebo controlled trial with oral ambroxol and N-acetylcysteine for mucolytic treatment in cystic fibrosis. *European Journal of Pediatrics* 1985; 144: 374-8.
35. Mitchell EA, Elliott RB. Controlled trial of oral N-acetylcysteine in cystic fibrosis. *Australian Paediatric Journal* 1982; 18: 40-2.
36. Martinez FJ, de Andrade JA, Anstrom KJ, King TE, Raghu G, Idiopathic Pulm Fibrosis C. Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis. *New England Journal of Medicine* 2014; 370: 2093-101.
37. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *New England Journal of Medicine* 2005; 353: 2229-42.
38. Ghanei M, Shohrati M, Jafari M, Ghaderi S, Alaeddini F, Aslani J. N-acetylcysteine improves the clinical conditions of mustard gas-exposed patients with normal pulmonary function test. *Basic and Clinical Pharmacology and Toxicology* 2008; 103: 428-32.
39. van Zandwijk N, Dalesio O, Pastorino U, de Vries N, van Tinteren H. EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. For the European Organization for Research and Treatment of Cancer Head and Neck and Lung Cancer Cooperative Groups. *Journal of the National Cancer Institute* 2000; 92: 977-86.
40. Van Schooten FJ, Nia AB, De Flora S, et al. Effects of oral administration of N-Acetyl-L-cysteine: A multi-biomarker study in smokers. *Cancer Epidemiology Biomarkers and Prevention* 2002; 11: 167-75.
41. Milazzo L, Menzaghi B, Caramma I, et al. Effect of antioxidants on mitochondrial function in HIV-1-related lipoatrophy: A pilot study. *AIDS Research and Human Retroviruses* 2010; 26: 1207-14.
42. Spada C, Treitinger A, Reis M, et al. The effect of N-acetylcysteine supplementation upon viral load, CD4, CD8, total lymphocyte count and hematocrit in individuals undergoing antiretroviral treatment. *Clinical Chemistry & Laboratory Medicine* 2002; 40: 452-5.
43. Breitzkreutz R, Pittack N, Nebe CT, et al. Improvement of immune functions in HIV infection by sulfur supplementation: Two randomized trials. *Journal of Molecular Medicine* 2000; 78: 55-62.
44. De Rosa SC, Zaretsky MD, Dubs JG, et al. N-acetylcysteine replenishes glutathione in HIV infection. *European Journal of Clinical Investigation* 2000; 30: 915-29.
45. Walmsley SL, Khorasheh S, Singer J, Djurdjev O. A randomized trial of N-acetylcysteine for prevention of trimethoprim- sulfamethoxazole hypersensitivity reactions in pneumocystis carinii Pneumonia prophylaxis (CTN 057). *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1998; 19: 498-505.
46. Look MP, Rockstroh JK, Rao GS, et al. Sodium selenite and N-acetylcysteine in antiretroviral-naïve HIV-1-infected patients: a randomized, controlled pilot study. *European Journal of Clinical Investigation* 1998; 28: 389-97.



47. Grant PR, Black A, Garcia N, Prieto J, Garson JA. Combination therapy with interferon-alpha plus N-acetyl cysteine for chronic hepatitis C: A placebo controlled double-blind multicentre study. *Journal of Medical Virology* 2000; 61: 439-42.
48. Neri S, Ierna D, Antoci S, Campanile E, D'Amico RA, Noto R. Association of alpha-interferon and acetyl cysteine in patients with chronic C hepatitis. *Panminerva medica* 2000; 42: 187-92.
49. Look MP, Gerard A, Rao GS, et al. Interferon/antioxidant combination therapy for chronic hepatitis C--a controlled pilot trial. *Antiviral Research* 1999; 43: 113-22.
50. Ideo G, Bellobuono A, Tempini S, et al. Antioxidant drugs combined with alpha-interferon in chronic hepatitis C not responsive to alpha-interferon alone: A randomized, multicentre study. *European Journal of Gastroenterology & Hepatology* 1999; 11: 1203-7.
51. Cimino L, Belisario MA, Intrieri M, et al. Effect of N-acetyl-cysteine on lymphomonocyte glutathione and response to interferon treatment in C-virus chronic hepatitis. *Italian Journal of Gastroenterology and Hepatology* 1998; 30: 189-93.
52. Tripi S, Di Gaetano C, Soresi M, et al. Acetylcysteine therapy for chronic hepatitis C. Are its effects synergistic with interferon alpha? A pilot study. *Clinical Drug Investigation* 1998; 16: 297-302.
53. Bernhard MC, Junker E, Hettinger A, Lauterburg BH. Time course of total cysteine, glutathione and homocysteine in plasma of patients with chronic hepatitis C treated with interferon-alpha with and without supplementation with N-acetylcysteine. *Journal of Hepatology* 1998; 28: 751-5.
54. Purwanto B, Prasetyo DH. Effect of oral N-acetylcysteine treatment on immune system in continuous ambulatory peritoneal dialysis patients. *Acta medica Indonesiana* 2012; 44: 140-4.
55. Hashemi SR, Noshad H, Tabrizi A, et al. Angiotensin receptor blocker and N-Acetyl Cysteine for reduction of proteinuria in patients with type 2 diabetes mellitus. *Iranian Journal of Kidney Diseases* 2012; 6: 39-43.
56. Renke M, Tylicki L, Rutkowski P, et al. The effect of N-acetylcysteine on proteinuria and markers of tubular injury in non-diabetic patients with chronic kidney disease: A placebo-controlled, randomized, open, cross-over study. *Kidney and Blood Pressure Research* 2008; 31: 404-10.
57. Renke M, Tylicki L, Rutkowski P, et al. The effect of N-acetylcysteine on blood pressure and markers of cardiovascular risk in non-diabetic patients with chronic kidney disease: A placebo-controlled, randomized, cross-over study. *Medical Science Monitor* 2010; 16: 13-8.
58. Nascimento MM, Suliman ME, Silva M, et al. Effect of oral N-acetylcysteine treatment on plasma inflammatory and oxidative stress markers in peritoneal dialysis patients: A placebo-controlled study. *Peritoneal Dialysis International* 2010; 30: 336-42.
59. Hsue PY, Hunt PW, Wu Y, et al. Association of abacavir and impaired endothelial function in treated and suppressed HIV-infected patients. *AIDS* 2009; 23(15): 2021-7.
60. Tepel M, van der Giet M, Statz M, Jankowski J, Zidek W. The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. *Circulation* 2003; 107(7): 992-5.
61. Porpora MG, Brunelli R, Costa G, et al. A promise in the treatment of endometriosis: An observational cohort study on ovarian endometrioma reduction by N-acetylcysteine. *Evidence based Complementary and Alternative Medicine* 2013; 240702.
62. Abu Hashim H, Anwar K, Abd El-Fatah R, et al. N-acetyl cysteine plus clomiphene citrate versus metformin and clomiphene citrate in treatment of clomiphene-resistant polycystic ovary syndrome: a randomized controlled trial. *Journal of Women's Health* 2013; 19: 2043-8.
63. Elnashar A, Fahmy M, Mansour A, Ibrahim K. N-acetyl cysteine vs. metformin in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective randomized controlled study. *Fertil Steril* 2007; 88(2): 406-9.
64. Shahin AY, Hassanin IMA, Ismail AM, Kruessel JS, Hirchenhain J. Effect of oral N-acetyl cysteine on recurrent preterm labor following treatment for bacterial vaginosis. *International Journal of Gynecology and Obstetrics* 2009; 104: 44-8.
65. Amin AF, Shaaban OM, Bediawy MA. N-acetyl cysteine for treatment of recurrent unexplained pregnancy loss. *Reproductive BioMedicine Online* 2008; 17: 722-6.
66. Safarinejad MR, Safarinejad S. Efficacy of Selenium and/or N-Acetyl-Cysteine for Improving Semen Parameters in Infertile Men: A Double-Blind, Placebo Controlled, Randomized Study. *Journal of Urology* 2009; 181: 741-51.
67. Ciftci H, Verit A, Savas M, Yeni E, Erel O. Effects of N-acetylcysteine on Semen Parameters and Oxidative/Antioxidant Status. *Urology* 2009; 74: 73-6.

68. Lai ZW, Hanczko R, Bonilla E, et al. N-Acetylcysteine Reduces Disease Activity by Blocking Mammalian Target of Rapamycin in T Cells From Systemic Lupus Erythematosus Patients A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis and Rheumatism* 2012; 64: 2937-46.
69. Van Dieten HEM, Perez RSGM, Van Tulder MW, et al. Cost effectiveness and cost utility of acetylcysteine versus dimethyl sulfoxide for reflex sympathetic dystrophy. *Pharmacoeconomics* 2003; 21: 139-48.
70. Perez RSGM, Zuurmond WWA, Bezemer PD, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain* 2003; 102: 297-307.
71. Yalcin E, Altin F, Cinhuseyinoglu F, Arslan MO. N-acetylcysteine in chronic blepharitis. *Cornea* 2002; 21: 164-8.
72. Currie DC, Greenstone M, Pavia D, et al. Efficacy of 'mucoregulatory' agents in Young's syndrome. *Thorax* 1988; 43: 480-1.
73. Furst DE, Clements PJ, Harris R, Ross M, Levy J, Paulus HE. Measurement of clinical change in progressive systemic sclerosis: a 1 year double-blind placebo-controlled trial of N-acetylcysteine. *Annals of the Rheumatic Diseases* 1979; 38: 356-61.
74. Kasperczyk S, Dobrakowski M, Kasperczyk A, et al. Effect of treatment with N-acetylcysteine on non-enzymatic antioxidant reserves and lipid peroxidation in workers exposed to lead. *Annals of Agricultural and Environmental Medicine* 2014; 21: 272-7.
75. Dabirmoghaddam P, Amali A, Langroudi MM, Fard MRS, Hejazi M, Razavi MS. The effect of N-acetyl Cysteine on laryngopharyngeal reflux. *Acta Medica Iranica* 2013; 51: 757-64.
76. Khoshbaten M, Aliasgarzadeh A, Masnadi K, et al. N-acetylcysteine improves liver function in patients with non-alcoholic fatty liver disease. *Hepatitis Monthly* 2010; 10: 12-6.
77. Martina V, Masha A, Gigliardi VR, et al. Long-term n-acetylcysteine and l-arginine administration reduces endothelial activation and systolic blood pressure in hypertensive patients with type 2 diabetes. *Diabetes Care* 2008; 31: 940-4.
78. Pace BS, Shartava A, Pack-Mabien A, Mulekar M, Ardia A, Goodman SR. Effects of N-acetylcysteine on dense cell formation in sickle cell disease. *American Journal of Hematology* 2003; 73: 26-32.
79. Adair JC, Knoefel JE, Morgan N. Controlled trial of N-acetylcysteine for patients with probable Alzheimer's disease. *Neurology* 2001; 57: 1515-7.
80. Estensen RD, Levy M, Klopp SJ, et al. N-Acetylcysteine suppression of the proliferative index in the colon of patients with previous adenomatous colonic polyps. *Cancer Letters* 1999; 147: 109-14.
81. De Flora S, Grassi C, Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. *European Respiratory Journal* 1997; 10: 1535-41.
82. Ardissino D, Merlini PA, Savonitto S, et al. Effect of transdermal nitroglycerin or N-acetylcysteine, or both, in the long-term treatment of unstable angina pectoris. *Journal of the American College of Cardiology* 1997; 29: 941-7.