RAPID REVIEW OF NON NHS TREATMENTS FOR SMOKING CESSATION

SEPTEMBER 2007

Authors:

Hayden McRobbie, University of Auckland

Peter Hajek, Queen Mary, University of London

Chris Bullen, University of Auckland

Valery Feigin, University of Auckland

Contributors:

Tim Coleman, University of Nottingham

James Raftery, University of Southampton

Lindsay Stead, University of Oxford

Robert West, University College London

Acknowledgements:

We are grateful to Marta Calonge-Contreras (NICE) and Julie Glanville (Centre for Reviews and Dissemination, University of York) for their assistance in searching some of the literatue databases.

November 2021: NICE guidelines PH10 (February 2008) and PH14 (July 2008) have been updated and replaced by NG209.
The recommendations labelled [2008] or [2008, amended 2021] in the updated guideline were based on these evidence reviews.
See www.nice.org.uk/guidance/NG209 for all the current recommendations and evidence reviews.

CONTENTS

1. EXECUTIVE SUMMARY 6
1.1. Abstract 6
1.2.1 Rationale for this review 12
1.2.2 Selection of interventions to review 12
1.3 METHODOLOGY 13
1.4 SUMMARY OF FINDINGS 15
1.4.1 Acupuncture 15
1.4.2 Allen Carr's Easyway Programme 15
1.5 REFERENCES 19
2 NON-NHS SMOKING CESSATION INTERVENTIONS 22
2.4 Rationale for this review 22
2.5 Objective 23
2.6 Which non-NHS smoking cessation interventions are included? 23
2.7 Which populations are included? 24
2.8 What are the main outcomes? 24
2.9 Structure of this rapid review 26
2.10 References 26
3 METHODOLOGY 28
3.4 Literature Search 28
3.5 Selection of Studies for Inclusion 30
3.6 Quality Appraisal 31
3.7 Study categorisation 34
3.8 Assessing applicability 34
3.9 Statistical evaluation 34
3.10 Synthesis of evidence statements 34
4 ACUPUNCTURE 36
4.4 Background 36
4.5 Methodology 38
4.5.5 Literature Search 38
4.5.6 Selection of Studies for Inclusion 38
4.6 Summary of Findings 39
4.6.5 Summary of studies identified Reviews 39
4.6.6 Evidence of efficacy 43
4.6.7 Effect size 44
4.6.8 Acceptability 44
4.6.9 Cost of treatment 45
4.6.10 Evidence statement 45
4.7 Evidence table 46
4.8 Meta-analysis 47
4.9 References 54
4.9.5 Included reviews and other studies 54
4.9.6 Retrieved references covered within included reviews 55
4.9.7 Additional references 56
5 ALLEN CARR'S EASYWAY PROGRAMME 59
5.4 Background 59
5.5 Methodology 60
5.5.5 Literature Search 60

5.5.6 Selection of Studies for Inclusion 60
5.6 Summary of Findings 61
5.6.5 Summary of studies identified 61
5.6.6 Evidence of efficacy 63
5.6.7 Effect size 64
5.6.8 Acceptability 64
5.6.9 Cost of treatment 65
5.6.10 Evidence statement 65
5.7 Evidence table 66
5.8 Meta-analysis 68
5.9 References 68
5.9.5 Included reviews and other studies 68
5.9.6 Additional references 68
6 HYPNOSIS 70
6.4 Background 70
6.5 Methodology 71
6.5.5 Literature Search 71
6.5.6 Selection of Studies for Inclusion 71
6.6 Summary of Findings 71
6.6.5 Summary of studies identified 71
6.6.6 Evidence of efficacy 75
6.6.7 Effect size 76
6.6.8 Acceptability 76
6.6.9 Cost of treatment 77
6.6.10 Evidence statement 77
6.7 Evidence table 78
6.8 Meta-analysis 81
6.9 References 88
6.9.5 Included reviews and other studies 88
6.9.6 Retrieved references covered within included reviews 88
6.9.7 Additional references 89
7 NICOBLOC 90
7.4 Background 90
7.5 Methodology 91
7.5.5 Literature Search 91
7.5.6 Selection of Studies for Inclusion 91
7.6 Summary of Findings 92
7.6.5 Summary of studies identified 92
7.6.6 Evidence of efficacy 93
7.6.7 Effect size 94
7.6.8 Acceptability 94
7.6.9 Cost of treatment 94
7.6.10 Evidence statement 95
7.7 Evidence table 96
7.8 Meta-analysis 97
7.9 References 99
7.9.5 Included reviews and other studies 99
7.9.6 Additional references 99
8 NICOBREVIN 100
8.4 Background 100

8.5 Methodology....101
8.5.5 Literature Search....101
8.5.6 Selection of Studies for Inclusion....101
8.6 Summary of Findings....101
8.6.5 Summary of studies identified....101
8.6.6 Evidence of efficacy....102
8.6.7 Effect size....103
8.6.8 Acceptability....103
8.6.9 Cost of treatment....104
8.6.10 Evidence statement....104
8.7 Evidence table....105
8.8 Meta-analysis....106
8.9 References....108
8.9.5 Included reviews and other studies....108
8.9.6 Additional references....108
9 RAPID SMOKING....109
9.4 Background....109
9.5 Methodology....111
9.5.5 Literature Search....111
9.5.6 Selection of Studies for Inclusion....111
9.6 Summary of Findings....112
9.6.5 Summary of studies identified....112
9.6.6 Evidence of efficacy....115
9.6.7 Effect size....116
9.6.8 Acceptability....116
9.6.9 Cost of treatment....118
9.6.10 Evidence statement....118
9.7 Evidence table....119
9.8 Meta-analysis....120
9.9 References....123
9.9.5 Included reviews and other studies....123
9.9.6 Retrieved references covered within included reviews....123
9.9.7 Additional references....123
10 CYTISINE....126
10.4 Background....126
10.5 Methodology....127
10.5.5 Literature Search....127
10.5.6 Selection of Studies for Inclusion....128
10.6 Summary of Findings....128
10.6.5 Summary of studies identified....128
10.6.6 Evidence of efficacy....130
10.6.7 Effect size....131
10.6.8 Acceptability....132
10.6.9 Cost of treatment....133
10.6.10 Evidence statement....133
10.7 Evidence table....134
10.8 Meta-analysis....136
10.9 References....139
10.9.5 Included reviews and other studies....139
10.9.6 Additional references....139

11 GLUCOSE 140
11.4 Background 140
11.5 Methodology 141
11.5.5 Literature Search 141
11.5.6 Selection of Studies for Inclusion 141
11.6 Summary of Findings 142
11.6.5 Summary of studies identified 142
11.6.6 Evidence of efficacy 146
11.6.7 Effect size 147
11.6.8 Acceptability 147
11.6.9 Cost of treatment 148
11.6.10 Evidence statement 148
11.7 Evidence table 149
11.8 Meta-analysis 151
11.9 References 154
11.9.5 Included reviews and other studies 154
11.9.6 Additional references 154
12 ST JOHNS WORT 156
12.4 Background 156
12.5 Methodology 157
12.5.5 Literature Search 157
12.5.6 Selection of Studies for Inclusion 157
12.6 Summary of Findings 157
12.6.5 Summary of studies identified 157
12.6.6 Evidence of efficacy 159
12.6.7 Effect size 159
12.6.8 Acceptability 159
12.6.9 Cost of treatment 160
12.6.10 Evidence statement 160
12.7 Evidence table 161
12.8 Meta-analysis 162
12.9 References 162
12.9.5 Included reviews and other studies 162
12.9.6 Additional references 162
Appendix A: Search strategies 164
Appendix B: Data extraction form 184
Appendix C: Excluded reviews and studies 186
Appendix D: Evidence tables 192
Acupuncture 192
Allen Carr's Easyway 194
Hypnosis 195
NicoBloc 199
Nicobrevin 200
Rapid smoking 201
Cytisine 202
Glucose 204
St Johns Wort 206

1. EXECUTIVE SUMMARY

1.1. Abstract

The NHS stop smoking service (SSS) which provides evidence based treatment for smokers who seek help is achieving long-term abstinence rates of approximately 15%. There are many commercial smoking cessation treatments available outside SSS that quote success rates many times higher. There are also numerous treatments not yet fully established which may hold promise. This review assesses the current evidence for the effectiveness of nine smoking cessation interventions that are not provided by the NHS: Acupuncture, Allen Carr's Easyway, hypnosis, NicoBloc, Nicobrevin, St. Johns Wort, aversive smoking, cytisine, and glucose.

Because there is variation in the proportions of smokers in different groups that are able to stop smoking without help, demonstration of efficacy of a class of intervention designed to aid smoking cessation requires experimental studies involving a comparison group, ideally with random allocation to the treatment of interest and to the comparison group. In addition, the definition of 'success' can vary widely depending on the criteria adopted, so it is essential to specify clearly the basis on which it is calculated. Finally, for a smoking cessation method to be regarded as effective, it has to increase abstinence over an extended period of time, with 6-months after stopping smoking date considered as the benchmark.

On this basis, this rapid review suggests that acupuncture, St. John's Wort and NicoBloc are probably not effective. There is insufficient evidence to determine the effectiveness of Allen Carr's Easyway Programme and Nicobrevin. Hypnosis has not been found to be more effective than simple advice. Studies of glucose show mixed evidence of efficacy. Rapid smoking may have some efficacy, but its implementation within the contemporary treatment formats is problematic. Cytisine (Tabex) also shows evidence of efficacy. In addition, its pharmacology is understood, there is consistency of evidence with a related compound recently licensed for use in the US, it has been licensed as a smoking cessation treatment in central and eastern

Europe for more than 40 years, and it costs a fraction of other current pharmacotherapies.

SUMMARY TABLE			
DRAFT EVIDENCE STATEMENTS Note: Long-term efficacy is mostly established on the basis of 6-months follow-up			***Cross referencing*** *(page in text and page of evidence table)*
ACUPUNCTURE			
A body of level 1+ evidence from meta-analyses of randomised controlled trials suggests that acupuncture, acupressure, laser therapy and electrostimulation do not improve long-term abstinence rates over that of a placebo effect.	White, A. R., H. Rampes, et al. (2006). "Acupuncture and related interventions for smoking cessation." Cochrane Database of Systematic Reviews (1): CD000009 Docherty, G., D. Gordon, et al. (2003). "Laser and NRT smoking cessation programmes in areas of high social deprivation [Abstract]." Thorax 58(Suppl 3): iii43.	1+ 1+	41, 44
ALLEN CARR'S EASYWAY			
There are no controlled data available on the efficacy of Allen Carr's Easyway Programme. Two of four cohort follow-up studies report high smoking cessation rates but this evidence is weak and further research is needed to determine their effectiveness.	Foulds (1996 a) Foulds (1996b) Csillag et al (2005)/Moshammer & Neuberger 2007[1] Hutter et al. (2006)	2- 2- 2-/2- 2-	60, 63
HYPNOSIS			
A body of level 1+ evidence from a meta-analysis of randomised controlled trials suggests that hypnotherapy does not improve long-	Abbot, N. C., L. F. Stead, et al. (2006). "Hypnotherapy for smoking cessation [Systematic Review]." Cochrane Database of Systematic Reviews (1): 1-15. Carmody, T., C. Duncan, et al.	1+ 1+	71, 74

[1] These two papers report on the same study

term continuous abstinence rates over that of attention control. A body of level 1- evidence suggests that hypnotherapy may be more effective than no treatment.	(2006). Self-hypnosis for smoking cessation: A randomised controlled trial. Society for Research on Nicotine & Tobacco, 12th Annual Meeting, Orlando, Florida. Tindel, H., N. Rigotti, et al. (2006). Guided imagery for smoking cessation: A pilot randomised trial. Society for Research on Nicotine & Tobacco, 12th Annual Meeting, Orlando, Florida. Casmar, P. V. (2003). "Hypnosis and smoking cessation: Anesthetization of craving." Dissertation Abstracts International: Section B: The Sciences and Engineering **63**(11-B): 5507. Valbo, A. and T. Eide (1996). "Smoking cessation in pregnancy: the effect of hypnosis in a randomized study." Addictive Behaviors **21**(1): 29-35.	1- 1- 1+	
NICOBLOC			
One good quality trial (level 1+) indicates that NicoBloc has no effect on long-term smoking cessation rates.	Gariti, P., A. I. Alterman, et al. (2004). "Adding a nicotine blocking agent to cigarette tapering." J Subst Abuse Treat **27**(1): 17-25.	1+	89, 92
NICOBREVIN			
There is level 1-evidence that Nicobrevin may have a short-term effect but no data are available on its long-term efficacy.	Dankwa, E., L. Perry, et al. (1988). "A double-blind, placebo-controlled study to determine the efficacy of Nicobrevin anti-smoking capsules." Br J Clin Pract **42**(9): 359-63. Schmidt, F. (1974). "Drug support during breaking of smoking habit - report about experiment with over 5000 smokers (double blind experiment)." Munchener Medizinsicher Wochenschrift	1- 1-	98, 101

	116(11): 557-564.		
RAPID SMOKING			
A body of level 1+ evidence from meta-analyses of randomised controlled trials suggests that rapid smoking improves 6-month abstinence rates.	Hajek, P. and L. F. Stead (2006). "Aversive smoking for smoking cessation [Systematic Review]." Cochrane Database of Systematic Reviews **1**:1.	1+	111, 115
CYTISINE			
Level 1+ evidence from one randomised controlled trial shows that cytisine improves 6-month abstinence rates.	Scharfenberg, G., S. Benndorf, et al. (1971). "[Cytisine (Tabex) as a pharmaceutical aid in stopping smoking]." Deutsche Gesundheitswesen **26**(10): 463-5. Paun, D. and J. Franze (1968). "[Breaking the smoking habit using cytisin containing "Tabex" tablets]." Deutsche Gesundheitswesen **23**(44): 2088-91. Schmidt, F. (1974). "Drug support during breaking of smoking habit - report about experiment with over 5000 smokers (double blind experiment)." Munchener Medizinsicher Wochenschrift **116**(11): 557-564	1+- 2- 1-	126, 130
GLUCOSE			
A body of level 1+ evidence from one randomised controlled trial shows that glucose on its own does not increase long-term abstinence rates. Post hoc analyses suggest that it may increase the efficacy of other smoking cessation medications.	West, R. and N. Willis (1998). "Double-blind placebo controlled trial of dextrose tablets and nicotine patch in smoking cessation." Psychopharmacology **136**(2): 201-4. West, R., S. May, et al. (Unpublished [a]). "A randomised trial of glucose tablets to aid smoking cessation."	1+ 1+	142, 145
ST JOHNS WORT			

There are no data available on long-term effects of SJW, but level 1- evidence from one randomised controlled trial shows lack of efficacy at one month.	Becker, B., B. Bock, et al. (2003). "St. John's Wort oral spray reduces withdrawal symptoms during quitting smoking (POS4-82)." Society for Research on Nicotine and Tobacco 9th Annual Meeting February.	1-	154, 157

1.2 BACKGROUND

The National Institute for Health and Clinical Excellence (NICE) is undertaking a series of rapid reviews on the evidence behind smoking cessation treatments. This is to identify the optimal provision of smoking cessation services to all smokers, but in particular to specific population groups (manual working groups, pregnant smokers and hard to reach communities) and contribute to guidance on the provision of smoking cessation treatment. The present review of the evidence of the effectiveness of non-NHS treatments for smoking cessation is a part of this project.

1.2.1 Rationale for this review

The NHS Stop Smoking Service (SSS) typically combines behavioural support, delivered in a group or individual setting, with pharmacotherapy (nicotine replacement therapy or bupropion) and achieves 4-week abstinence rates of between 50% and 60% and 1-year abstinence rates of around 15% (Ferguson, Bauld et al. 2005). These are respectable success rates compared with the estimated 1-year abstinence rate without support of less than 4% (Royal College of Physicians 2000).

However, numerous commercial smoking cessation treatments are widely available, some of which quote success rates many times higher. Although these claims may be of questionable validity, some treatments may be effective. Other treatments not yet fully established may also be effective. The objective of this review was to assess nine such smoking cessation interventions.

1.2.2 Selection of interventions to review

Despite the promotion of a very large number of smoking cessation treatments only a few are available on NHS. Within the limited resources and time available a choice had to be made as to which non-NHS treatments should be included in the review. There exists no list of such treatments and so the selection was based on the expertise available within the consortium.

The consortium comprises academic researchers in the field of smoking cessation with expertise in treatment, training and guidance development.

Treatments were included in the review based on awareness among the consortium of the existence of reviewable literature, and their knowledge of the literature. We included all three best known and most widely advertised treatment approaches commercially available within the UK (hypnosis, acupuncture, and Allen Carr's Easy Way). We also included commercial medications and devices where we were aware there is at least some published research available on their effects (NicoBloc, Nicobrevin, and St. John's Wort), pharmacological treatments not commercially disseminated in the UK but considered promising by the consortium members (cytisine and glucose) and the behavioural treatment with the largest volume of controlled trials which also has some evidence of efficacy (rapid smoking). Ideally we would have reviewed a wider range of methods, but time constraints did not allow this. The selection was the first venture into the largely uncharted territory and the expert view of the consortium is that these interventions are the most promising of those that are not routinely available on the NHS. However there remain several other methods and approaches which may deserve similar treatment.

1.3 METHODOLOGY

The evidence base for this review was sourced from reviews and trials published between 1990 and 2005 in the English language. The searchable databases included Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, ASSIA, AMED, British Nursing Index, Embase, Cinahl, PsycINFO, Sociological Abstracts, and Controlled Clinical Trials. Google Scholar was also used where there was paucity of data from these sources. Unpublished data were also considered. Where limited evidence was available the search limits were removed to include all literature contained in the databases that were searched. A systematic search of the 'Grey' literature was not undertaken due to the time constraints.

The main search strategy combined terms relevant to smoking cessation with terms to capture each of the non-NHS smoking cessation interventions being assessed. The titles and abstracts returned in the search were screened by one of the reviewers who identified those that were potentially relevant. Full papers were also obtained where there was no abstract and the relevance could not be assessed by the title alone. The numbers (n) identified in this way for each topic were: acupuncture (n= 40), Allen Carr's Easyway programme (n= 9), aversive smoking (n=9), cytisine (n=16), glucose (n=14), hypnosis (n= 30), NicoBloc (n=4), Nicobrevin (n= 3), and St. Johns Wort (n= 3). These papers were then independently assessed by two other reviewers for their relevance to this review (except for Nicobrevin and NicoBloc where only one reviewer made the assessment). Each reviewer also assessed the quality and criteria for inclusion into the review. Trials were excluded if they did not report the results of a randomised trial unless only co-hort studies were available, in which case these are described but not included in meta-analysis (e.g. Allen Carr's method).Trials included in relevant reviews were not reassessed. Other relevant publications were considered where no controlled trials were available.

Trials included in reviews were not reassessed for inclusion/exclusion criteria.

Data from included reviews, and trials not already included in reviews, were extracted into evidence tables. The quality of the included trials and reviews was assessed using criteria outlined in NICE guidance. Any data relating to sub-populations of smokers were also summarised.

To summarise the findings of each treatment the following evidence statements were used: (1) *'There is robust evidence from randomised controlled trials with biochemical verification of abstinence that 'intervention X' improves/does not improve 6-month continuous abstinence rates.'* (2) *'There is evidence from one randomised controlled trial that 'intervention X' improves/does not improve 6-month continuous abstinence rates.'* (3) *'There is insufficient evidence concerning whether 'intervention X' improves 6-month continuous abstinence rates but evidence from short-term studies/studies with no biochemical verification suggests that definitive trials are warranted.'* (4)

'There is mixed or inconsistent evidence on whether 'intervention X' improves 6-month continuous abstinence rates.' and (5) *'There is insufficient evidence on 'intervention X' to draw any conclusions.'* These evidence statements differ from the standard statements used by NICE. However, given the very different nature of the treatments being reviewed they provide more meaningful conclusions to the existing evidence.

1.4 SUMMARY OF FINDINGS

1.4.1 Acupuncture

1.4.1.1 Evidence of efficacy

A comprehensive Cochrane meta-analysis ((White, Rampes et al. 2006) and one randomised controlled trial (Docherty et al. 2003).

1.4.1.2 Evidence statement

A body of level 1+ evidence suggests that acupuncture, acupressure, laser therapy and electrostimulation do not improve long-term abstinence rates over that of a placebo effect.

1.4.2 Allen Carr's Easyway Programme

1.4.2.1 Evidence of efficacy

There are no adequate controlled data available to ascertain the efficacy of the Allen Carr method.

Four cohort follow-up studies reported a range of abstinence rates (Foulds 1996a and b; Csillag, Feuerstein et al. 2005/ Moshammer and Neuberger 2007; Hutter, Moshammer et al. 2006;)

1.4.2.2 Evidence statement

There are no controlled data available on the efficacy of Allen Carr's Easyway Programme. Two cohort studies suggest that it may have an effect on smoking cessation rates but this evidence is weak and further research is needed to determine their effectiveness.

1.4.3 Hypnosis

1.4.3.1 Evidence of efficacy

A comprehensive Cochrane meta-analysis (Abbot, Stead et al. 2006) and two recent randomised controlled trials (Carmody, 2006; Tindel, Rigotti et al. 2006).

1.4.3.2 Evidence statement

A body of level 1+ evidence suggests that hypnotherapy does not improve long-term abstinence rates over that of simple advice or when added to other interventions. A body of level 1- evidence suggests that hypnotherapy may be more effective than no treatment.

1.4.4 NicoBloc

1.4.4.1 Evidence of efficacy

One well designed but small randomised double blind placebo controlled trial (Gariti, Alterman et al. 2004).

1.4.4.2 Evidence statement

One trial (level 1-) indicates that NicoBloc has no effect on long-term smoking cessation rates.

1.4.5 Nicobrevin

1.4.5.1 Evidence of efficacy

No data are available on the effects of Nicobrevin on long-term smoking cessation. Two trials suggest that Nicobrevin may have an effect on short-term outcome but both studies have methodological problems (Schmidt 1974; Dankwa, Perry et al. 1988).

1.4.5.2 Evidence statement

There is level 1- evidence that Nicobrevin may have a short-term effect but no data are available on its long-term efficacy.

1.4.6 Rapid smoking

1.4.6.1 Evidence of efficacy

A comprehensive Cochrane meta-analysis (Hajek and Stead 2006) and three new studies of effects of rapid smoking on urge to smoke (Houtsmuller and Stitzer 1999; Dallery, Houtsmuller et al. 2003; McRobbie and Hajek 2005).

1.4.6.2 Evidence statement

A body of level 1+ evidence suggests that rapid smoking improves long-term abstinence rates. The method could be implemented within the UK specialist services at almost no additional cost, but it is likely to be impracticable in most settings.

1.4.7 Cytisine

1.4.7.1 Evidence of efficacy

One unpublished meta-analysis (Etter 2006) and our own meta-analysis of three early trials (Paun and Franze 1968; Scharfenberg et al 1971; Schmidt 1974) reporting 2-6 month outcomes.

1.4.7.2 Evidence statement

Level 1+ evidence from one randomised controlled trial suggests that cytisine improves six month abstinence rates. Evidence from studies with shorter follow-ups and recent highly positive results of a similar medication corroborate the verdict.

1.4.8 Glucose

1.4.8.1 Evidence of efficacy

One good quality UK trial with long-term outcome (West, May et al. Unpublished [a]), one trial with a short-term outcome (West and Willis 1998) and a series of studies looking at effects of glucose on withdrawal syndrome (West, Hajek et al. 1990; Helmers and Young 1998; Jarvik et al. 1998; West and Willis 1998; West, Courts et al. 1999; Harakas and Foulds 2002; McRobbie and Hajek 2004; Berlin, Vorspan et al. 2005; West, Maini et al. Unpublished [b])

1.4.8.2 Evidence statement

A body of level 1+ evidence suggests that glucose on its own does not increase long-term abstinence rates. A body of level 1- evidence suggests that glucose may increase efficacy of other smoking cessation medications

1.4.9 St. Johns Wort

1.4.9.1 Evidence of efficacy

One randomised study tested its short-term (one-month) effect when added to nicotine patch (Becker, Bock et al. 2003), and another study compared long-term effects of two different doses of the drug (Barnes, Barber et al. 2006).

1.4.9.2 Evidence statement

There are no placebo controlled trials available on long-term effects of SJW, but two grade 1- studies suggest indirectly that it lacks efficacy when added to nicotine patches or used on its own.

1.5 REFERENCES

Abbot, N. C., L. F. Stead, et al. (2006). "Hypnotherapy for smoking cessation [Systematic Review]." Cochrane Database of Systematic Reviews (1): 1-15.

Barnes, J., N. Barber, et al. (2006). "A Pilot Randomised, Open, Uncontrolled, Clinical Study of Two Dosages of St John's Wort (Hypericum perforatum) Herb Extract (LI-160) as an Aid to Motivational/Behavioural Support in Smoking Cessation." Planta Med **72**(4): 378-82.

Becker, B., B. Bock, et al. (2003). "St. John's Wort oral spray reduces withdrawal symptoms during quitting smoking (POS4-82)." Society for Research on Nicotine and Tobacco 9th Annual Meeting February.

Csillag, H., A. Feuerstein, et al. (2005). "The long term success of occupational non-smoking seminars." Sichere Arbeit: 28-34.

Dankwa, E., L. Perry, et al. (1988). "A double-blind, placebo-controlled study to determine the efficacy of Nicobrevin anti-smoking capsules." Br J Clin Pract **42**(9): 359-63.

Etter, J.-F. (2006). Cytisine for smoking cessation: a literature review and a meta-analysis (RPOS3-59). Society for Research on Nicotine and Tobacco, 12th Annual Meeting, Orlando, Florida.

Ferguson, J., L. Bauld, et al. (2005). "The English smoking treatment services: one-year outcomes." Addiction **100 Suppl 2**: 59-69.

Foulds, J. (1996). Brief evaluation of the "Easy Way To Stop Smoking" Clinic, Raynes Park. London, St George's Hospital Medical School**:** 1-7.

Gariti, P., A. I. Alterman, et al. (2004). "Adding a nicotine blocking agent to cigarette tapering." J Subst Abuse Treat **27**(1): 17-25.

Hajek, P. and L. F. Stead (2006). "Aversive smoking for smoking cessation [Systematic Review]." Cochrane Database of Systematic Reviews **1**: 1.

Hutter, H. P., H. Moshammer, et al. (2006). "Smoking cessation at the workplace: 1 year success of short seminars." International Archives of Occupational & Environmental Health **79**(1): 42-48.

Judge, K., L. Bauld, et al. (2005). "The English smoking treatment services: short-term outcomes." Addiction **100 Suppl 2**: 46-58.

Leahy, M. (2003). Stop smoking gradually with NicoBloc. The 2003 National Conference on Tobacco or Health, Boston, USA.

Moshammer, H., Neuberger, M. (2007). "Long term success of short smoking cessation seminars supported by occupational health care." Addictive Behaviors **32** (7): 1486-93.

NicoBloc (2003). Summary of data available. Available online: http://www.stopsmokingnow.co.uk/nicobloc/research.pdf (Accessed: 09/05/06).

Royal College of Physicians (2000). Nicotine Addiction in Britain. London, Royal College of Physicians.

Scharfenberg, G., S. Benndorf, et al. (1971). "[Cytisine (Tabex) as a pharmaceutical aid in stopping smoking]." Deutsche Gesundheitswesen **26**(10): 463-5.

Schmidt, F. (1974). "Drug support during breaking of smoking habit - report about experiment with over 5000 smokers (double blind experiment)." Munchener Medizinsicher Wochenschrift **116**(11): 557-564.

Valbo, A. and T. Eide (1996). "Smoking cessation in pregnancy: the effect of hypnosis in a randomized study." Addictive Behaviors **21**(1): 29-35.

West, R., S. May, et al. (Unpublished [a]). "A randomised trial of glucose tablets to aid smoking cessation."

White, A. R., H. Rampes, et al. (2006). "Acupuncture and related interventions for smoking cessation." Cochrane Database of Systematic Reviews(1): CD000009.

Yiming, C., Z. Changxin, et al. (2000). "Laser acupuncture for adolescent smokers--a randomized double-blind controlled trial." The American journal of Chinese medicine **28**(3-4): 443-9.

2 NON-NHS SMOKING CESSATION INTERVENTIONS

This review assesses the evidence on the effectiveness of nine non-NHS smoking cessation interventions. It has been commissioned by the National Institute of Clinical Excellence (NICE) to inform the production of guidance for the optimal provision of smoking cessation services.

2.1 Rationale for this review

Smoking cessation treatments are life-saving and very cost-effective interventions. As part of the Government commitment to addressing the burden of disease associated with smoking a national smoking cessation service that can be accessed free of charge by any smoker, or tobacco user, who wishes to use it was established (Department of Health 1998). The UK now has a world-leading service. The NHS Stop Smoking Service (SSS) typically combines behavioural support, delivered in a group or individual setting, with pharmacotherapy (nicotine replacement therapy or bupropion) and achieves 4-week abstinence rates of between 50 and 60% and 1-year abstinence rates of around 15% (Ferguson, Bauld et al. 2005; Judge, Bauld et al. 2005). These are respectable success rates compared with the underlying spontaneous long-term quit rates of 1-3% (Royal College of Physicians 2000).

However, there also exist numerous commercial smoking cessation treatments quoting success rates many times higher. Although the basis for these claims may be questionable, some treatments may hold promise. There are also treatments not yet fully established which may nevertheless be effective. UK smoking cessation guidelines discuss interventions with a firm evidence base (West, McNeill et al. 2000), but do not comment on other interventions that are often popular with smokers such as acupuncture and hypnosis. Smoking cessation specialists require information about these interventions to be able to adequately inform smokers wanting advice on how to quit.

2.2 Objective

The objective of this evidence review is to assess the available evidence for the effectiveness of nine smoking cessation interventions not currently used within the NHS SSS.

2.3 Which non-NHS smoking cessation interventions are included?

There are dozens of commercial and alternative smoking cessation methods and the review had to be selective. We selected nine non-NHS approaches based on three criteria: (1) Popularity, as assessed by expert members of the consortium; (2) some empirical evidence of an active ingredient, and (3) volume of reviewable literature. The list of the selected methods include

1. Acupuncture
2. Allen Carr's Easyway programme
3. Hypnosis
4. NicoBloc
5. Nicobrevin
6. Aversive smoking
7. Cytisine
8. Glucose
9. St. Johns Wort

The first three Interventions, i.e. acupuncture, Allen Carr, and hypnosis, are the main commercial alternatives to SSS. In a large UK cohort, hypnosis, books (where Allen Carr dominates the market), herbal remedies (a category combining many different treatments including Nicobrevin and St. Johns Wort included in this review) and acupuncture were the main commercial treatments used (West, 2006). This applies not just for the UK. A Google Search (undertaken on 23 Mar. 06) showed 3,580,000 hits for 'hypnosis and smoking', 2,800,000 for 'acupuncture and smoking', and 2,140,000 for 'Carr and smoking' with other methods much less prominent.

NicoBloc, Nicobrevin and St Johns Wort are less popular but also readily available alternative smoking cessation treatments promoted within the UK and there exist at least some scientific literature evaluating their effects.

Cytisine and glucose appear promising in that they have good hypotheses about a possible active ingredient, have generated scientific literature testing these notions, are inexpensive and appear safe.

Finally, aversive smoking is included to examine a non-SSS behavioural approach. Among individual behavioural methods (such as cue exposure, response substitution, contingency management, coping skills training, stress management, nicotine fading, etc.). rapid smoking has shown the most promising results and generated the largest volume of experimental literature.

There are dozens of other approaches, although not many have generated any reviewable literature. The time constraints limited the number of methods we were able to cover and some subjective judgements based on the expertise of the consortium members had to be taken. Other candidates such as oxytocine, 5-day Plan, Nicogel, homeopathy, a range of gradual reduction methods other than Nicobloc etc. await a review.

2.4 Which populations are included?

The review covers all smokers seeking help with stopping smoking. The literature on these methods is sparse and generally insufficient to allow sub-analyses looking at specific subgroups. However, we attempted to look at priority subgroups wherever possible.

2.5 What are the main outcomes?

For a smoking cessation method to be seen as effective it has to increase abstinence rates over an extended period of time, with the minimum of 6-months from the stop smoking date considered a benchmark (Pierce and Gilpin 2003, West, Hajek et al., 2005). As longer follow-up data (e.g. 1 or 2 years) are much less frequently reported than 6-months follow-ups, we have used 6-month data wherever possible to allow comparisons between studies. However, where no long-term data are available, where long-term results are

negative and where studies were excluded from systematic reviews for only reporting short-term outcomes, short-term abstinence data are examined as well. This is made clear in each section.

In accordance with current best practice, for example by Cochrane reviews, continuous abstinence rates are used in meta-analyses in preference to point prevalence data, and validated smoking cessation outcomes (typically measured using carbon monoxide in expired air or cotinine in plasma or saliva) are used in preference to unconfirmed self-reported abstinence.

2.6 What questions are to be answered in this review?

This review attempts to answers the question of efficacy of the nine reviewed methods. Within each of the nine reviews, the following questions are posed as dictated by NICE review requirements:

1. What is the aim of the treatment?
2. What is the content of the treatment?
3. Does the treatment have any effect on at least 6 months continuous abstinence?

If there is an effect on abstinence:

4. What is the estimated effect size?
5. What is the estimated cost of the treatment?
6. How does the structure and content of the treatment/intervention influence effectiveness?
7. Does effectiveness vary with site/setting or intensity/duration of the intervention?
8. What are the views of those receiving and delivering the intervention?
9. Is there evidence of unintended or harmful effects?

10. Are there barriers to replication of effective interventions?

The brief for the review also required that wherever possible, the issue is addressed as to whether effectiveness vary by gender, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention. The limited literature available did not allow such sub-analyses for any of the treatments reviewed.

2.6 Structure of this rapid review

Each of the interventions assessed in this review is presented in its own section, detailing methodology, summarising the findings, and presenting evidence tables and meta-analyses.

2.7 References

Department of Health (1998). Smoking Kills: A White Paper on Tobacco. London, The Stationary Office.

Ferguson, J., L. Bauld, et al. (2005). "The English smoking treatment services: one-year outcomes." Addiction **100 Suppl 2**: 59-69.

Judge, K., L. Bauld, et al. (2005). "The English smoking treatment services: short-term outcomes." Addiction **100 Suppl 2**: 46-58.

Pierce, J. and E. Gilpin (2003). A minimum 6-month prolonged abstinence should be required for evaluating smoking cessation trials. Nicotine Tob Res 5(2): 151-153

Royal College of Physicians (2000). Nicotine Addiction in Britain. London, Royal College of Physicians.

West, R. (2005). Smoking: Prevalence, Mortality and Cessation in Great Britain. http://www.rjwest.co.uk/smokingcessationgb.pdf. Date last updated 9 October 2005. Accessed 10 May 2006.

West, R., Hajek, P., et al. (2005) Outcome criteria in smoking cessation trials: proposal for the common standard. Addiction 100, 299-303.

West, R., A. McNeill, et al. (2000). "Smoking cessation guidelines for health professionals: an update. Health Education Authority." Thorax 55(12): 987-99.

3 METHODOLOGY

This section provides an overview of the methodology used in this review. Details relating to the methodology of the review for each individual topic are contained in the individual sections.

3.1 Literature Search

Literature was sourced from reviews and trials published in English between January 1990 and December 2005. Unpublished data were also considered. Where only limited evidence was available, the search limits were relaxed to included *all* literature contained in the databases that were searched. A systematic search of the Grey Literature was not undertaken due to the time constraints.

3.1.1 Databases searched

The following databases were searched.

MEDLINE
Cochrane Database of Systematic Reviews
Cochrane Controlled Trials Register (CENTRAL)
DARE
AMED
ASSIA
British Nursing Index
Embase
Cinahl
PsycINFO
Sociological Abstracts
Controlled Clinical Trials (<http://controlled-trials.com>)

Google Scholar was also used where there was a paucity of data available from these sources.

3.1.2 Search strategy

As this rapid review consists of nine distinct interventions separate searches were undertaken for each intervention. Each search strategy combined the intervention specific terms with smoking specific terms. The terms used for the

searches of MEDLINE are given here. Full search strategies for all databases are provided in Appendix A.

Smoking specific terms:

((smoking cessation.mp.) or (smoking cessation/) or ("tobacco use cessation"/) or (stopping smoking.mp.) or (Smoking/pc [Prevention & Control]))

OR

((exp Tobacco/) or (tobacco.mp.) or (nicotine/) or (nicotine.mp.) or (cigarette$.mp.) or (smoking.mp.)) and ((withdraw$.mp.) or (quit$.mp.) or (stop$.mp.))

Intervention specific terms

Acupuncture: ((Acupuncture Therapy/ or Acupuncture Points/ or Acupuncture/ or Acupuncture, Ear/ or acupuncture.mp.) or (acupressure.mp. or Medicine, Chinese Traditional/ or Acupressure/) or transcranial.mp. or transcutaneous.mp. or (Electric Stimulation/ or Electric Stimulation Therapy/ or electrostimulation.mp.) or electric stimulation.mp. or (electroacupuncture.mp. or Electroacupuncture/) or neuroelectrotherapy.mp. or laser therapy.mp.))

Allen Carr's Easyway: ((allen carr$.mp.) or (easy way.mp.))

Hypnosis: ((hypnosis.mp. or Hypnosis/) or hypnotherapy.mp.)

NicoBloc: (nicobloc.mp. or (accu drop.mp.) or (take-out.mp.))

Nicobrevin: Nicobrevin.mp

Aversive smoking: ((Aversive Therapy/ or aversive.mp.) or avers$.mp. or rapid.mp)

Cytisine: (tabex.mp. or (golden rain.mp.) or (cytisus laburnum.mp. or Laburnum/) or cytisine.mp.)

Glucose: ((glucose.mp. or Glucose/) or sweet$.mp. or dextrose.mp. or (Carbohydrates/ or carbohydrate.mp.) or sugar.mp. or (Sucrose/ or sucrose.mp.) or (Fructose/ or fructose.mp.))

St Johns Wort: ((exp Hypericum Perforatum/) or st john$ wort.mp. or hypericum.mp.))

Database searches were undertaken by one reviewer (HM) except of the ASSIA and BNI databases which were carried out by NICE and the Centre for Reviews and Dissemination, University of York.

3.2 Selection of Studies for Inclusion

The process for selecting reviews and trials for this review is shown in Figure 3.1. The titles and abstracts of papers identified from the literature search were screened by one reviewer (HM) to assess their potential relevance to the review. The relevant references were downloaded into EndNote™, a reference management database. This process was undertaken to screen out papers that had no relevance to the review, for example papers that did not primarily address smoking cessation or the specific intervention being assessed. The selected papers were then independently assessed for inclusion by two other reviewers (CB and VF) (except for Nicobrevin and NicoBloc where only one reviewer made the assessment). Literature written in German and Eastern European languages was assessed by PH. No discrepancies in identifying relevant papers occurred between the reviewers.

Reviews were excluded if they were not conducted systematically. Where there was uncertainty the full paper was obtained and its inclusion resolved by discussion. Trials were excluded if they did not report the results of a randomised trial unless only non-randomised controlled trials were available, in which case these are described but not included in meta-analysis.Trials included in relevant reviews were not reassessed. Other relevant publications were considered where no controlled trials were available.

A critical appraisal form was completed for each review and trial. Data were extracted using a standardised data extraction sheet (see Appendix B). Data

were extracted about the intervention/programme's: aim, objectives, setting, target population, intervention, content, method and duration.

The completed critical appraisal and data extraction forms were used to produce evidence tables.

The returned search results were also screened for reference to particular groups and settings (including: pregnant smokers as well as smokers from lower socio-economic groups/ areas, unemployed, black and minority ethnic groups, homeless, travellers, refugees or asylum seekers, and young people under 18 years of age). Details of the search strategy and results are shown in Appendix A.

For controlled trials, data regarding the interventions aims, objectives, setting, target population, intervention, content, method and duration, and outcome were extracted from papers not already included in the Cochrane Reviews. This information was used to compose the evidence tables.

3.3 Quality Appraisal

Studies were evaluated by assessing the methods used in relation to the research question(s) being addressed. They were assessed for their methodological rigour and quality against a number of criteria using the critical appraisal checklists provided by NICE (Appendix B of the *Public Health Guidance. Methods Manual – version 1).* As noted, studies already included in reviews that met the inclusion criteria were not reassessed for quality and are not included separately in the evidence tables.

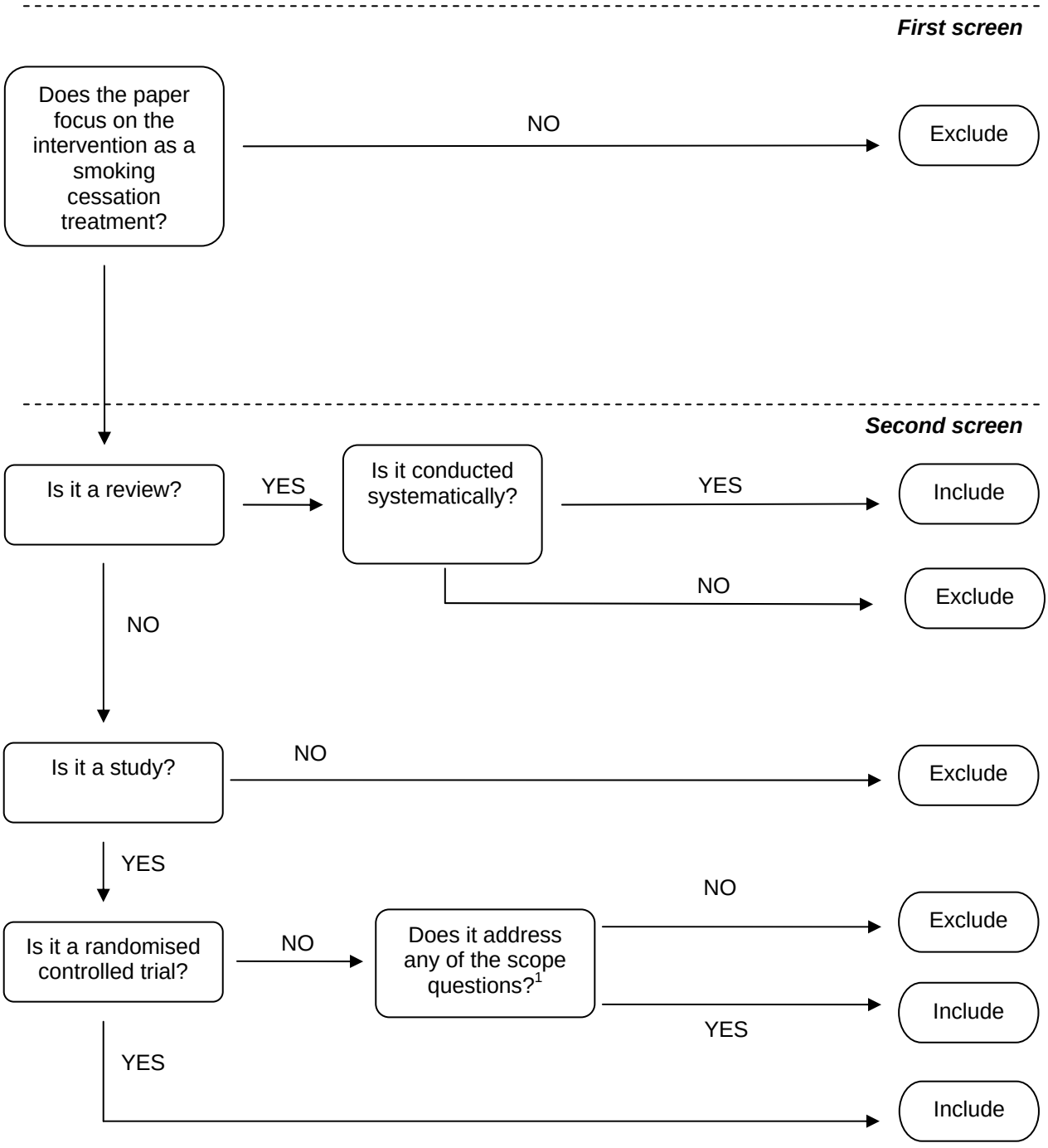
Each study was then graded using a code '++', '+' or '–', based on the extent to which the potential sources of bias have been minimised (see Table 3.1).

Table 3.1	
++	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described

	are thought unlikely to alter the conclusions.
–	Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

NICE Guideline Development Methods, Appendix B
(www.nice.org.uk/pdf/GDM_AppendixB.pdf)

Figure 3.1: Process for selecting reviews, trials and other study types



1. The scope questions regard specific evidence for the effectiveness on the intervention in different sex, age, ethnic, social or professional groups. They also relate to the site or setting and intensity or duration of treatment. Where there were no randomised controlled trails, non-randomised controlled trials and cohort-follow up are described.

3.4 Study categorisation

Studies were categorised as: systematic reviews; randomised controlled trials (RCTs); controlled non randomised trials (CCTs), controlled before & after (CBA), interrupted time series (ITS); and other studies.

3.5 Assessing applicability

All studies were assessed for their applicability to UK population.

3.6 Statistical evaluation

Data extracted from the included studies were entered into the RevMan software programme. We calculated a pooled odds ratio using a fixed effects model. Where there was significant heterogeneity a random effects model was used.

Where appropriate the effect size metric (Cohen's *d*) was calculated from the Chi-square test using the following formula: d = SQRT((4 × Chi-square) ÷ (N - Chi-square)).

3.7 Synthesis of evidence statements

Evidence statements were produced for each question relating to the efficacy of the intervention. The level of evidence was classified according to NICE guidelines (see Table 3.2).

Table 3.2: Levels of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a high risk of bias*
2++	High-quality systematic reviews of, or individual, non-randomised controlled trials, case–control studies, cohort

	studies, controlled before-and-after (CBA), interrupted time series (ITS), correlation studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted non-randomised controlled trials, case–control studies, cohort studies, controlled before-and-after (CBA), interrupted time series (ITS), correlation studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Non-randomised controlled trials, case–control studies, cohort studies, controlled before-and-after (CBA), interrupted time series (ITS), correlation studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence '–' should not be used as a basis for making a recommendation (see section 7.4) NICE Guideline Development Methods: Chapter 7 Reviewing and grading the evidence (www.nice.org.uk/pdf/GDM_Chapter7_0305.pdf)	

4 ACUPUNCTURE

4.1 Background

Acupuncture is one of the most widely used complementary treatments. It has been estimated that approximately one million acupuncture treatments are provided by the NHS each year, and a further two million privately (NHS Centre for Reviews and Dissemination 2001).

Acupuncture has been employed in traditional Chinese medicine for centuries and centers around the belief that the state of health and well being is influenced by a vital energy known as Qi (*'chee'*). This energy must move between organs, via channels called meridians, in the correct strength and quality to maintain health. In this system there are 12 main organs of the body connected by 12 meridians (NHS Direct 2006). The flow of energy along the meridians can be altered by stimulation at certain points, so called acupuncture points. Insertion of needles at different points is believed to be able treat different illnesses. The contemporary belief is that acupuncture might exert its effect on anatomical and physiological points, such as junctions of peripheral nerves, increasing blood flow, or release of endorphins and neurotransmitters.

There are differences in individual practice in terms of points used, length and depth of needle insertions and other concomitant treatments that might be applied (massage, herbal products).

Acupuncture is used to treat a variety of illnesses, but with varying degrees of effectiveness. Reviews have concluded that acupuncture is effective for nausea and vomiting (particularly post-op and chemo induced) and dental pain. Evidence is unclear for chronic pain, and acupuncture is ineffective for weight loss or smoking cessation (British Medical Association Board of Science and Education 2000; Vickers 2001; Vickers, Wilson et al. 2002).

4.1.1 What is the aim and rationale of treatment?

The basis for using acupuncture to aid smoking cessation arose from observations made in a group of Chinese opiate addicts treated with electroacupuncture (electrical stimulation to acupuncture needles) who were said to suffer less severe withdrawal symptoms (Wen and Cheung 1973).

It has been postulated that acupuncture might achieve this via release of endorphins (Han 2004) and neurotransmitters such as dopamine, serotonin and noradrenaline (Yoon, Kwon et al. 2004; Cabyoglu, Ergene et al. 2006) which may also assist with stopping smoking.

4.1.2 What is the content of treatment?

Basic acupuncture techniques for smoking cessation are described in White et al (1999). The two main treatments used are as follows:

(1) Acupuncture needles are inserted in the ear (e.g. lung and hunger auricular points) or on the face whilst the patient relaxes for 10-20 minutes. Points on other parts of the body may have needles inserted at the same time and electrical stimulation can also be applied.

(2) Indwelling needle(s) are inserted into point(s) in the ear and secured in place for a length of time (e.g. 1-3 weeks). The patients can press these needles when there is an urge to smoke. Instead of needles small beads or seeds can be used, usually taped in place, and these can be pushed when the urge to smoke occurs. This is known as acupressure.

Acupuncture needles can be stimulated by hand or electrically in a procedure known as electroacupuncture. This is believed to provide more precise stimulation for the release of neurotransmitters (White, Resch et al. 1999). Electrical stimulation can also be provided via electrodes, usually placed over the mastoid process (just behind the ears) or on the ears themselves. This is known as neuroelectrical therapy or transcranial electrotherapy. Another variation of acupuncture uses low level laser. Although there is no sensation

on the skin, laser acupuncture is said to stimulate traditional acupuncture points in a similar way as other techniques.

Some uncontrolled trials have reported high abstinence rates (Fuller 1982). The majority of systematic reviews to date have failed to demonstrate the effectiveness of the acupuncture in helping people to stop smoking, but there remain avid supporters of the technique (Lewith 1995).

4.2 Methodology

4.2.1 Literature Search

The search returned a total of 368 records (after de-duplication), of which 40 were relevant to acupuncture and smoking cessation (19 reviews, and 21 studies).

4.2.2 Selection of Studies for Inclusion

Of the 19 reviews 10 were excluded because they were not conducted systematically, were of poor quality, or were summaries of reviews. The Cochrane Review of acupuncture for smoking cessation (White, Rampes et al. 2006) is the highest quality, most recent, and most inclusive review and it is summarised in the Evidence Table. The other nine reviews are summarised below. Of the 21 studies identified in our searches, 7 were excluded because they were not randomised controlled trials. Thirteen studies (Clavel and Paoletti 1990; Leung 1991; Clavel-Chapelon, Paoletti et al. 1992; Tian and Chu 1996; Clavel-Chapelon, Paoletti et al. 1997; He, Berg et al. 1997; He, Medbo et al. 2001 Pickworth, Fant et al. 1997; Georgiou, Spencer et al. 1998; Waite and Clough 1998; White, Resch et al. 1998; Yiming, Changxin et al. 2000; Bier, Wilson et al. 2002) identified in our literature search have been already assessed in the Cochrane review and will not be discussed separately. We found one abstract of a randomised controlled trial (Docherty, Gordon et al. 2003) that is not mentioned in the Cochrane review and it is summarised below.

4.3 Summary of Findings

4.3.1 Summary of studies identified

Reviews

Many studies investigating the efficacy of acupuncture for smoking cessation are marred by methodological problems that make interpretation of the results difficult. The literature in this area is somewhat paradoxical in that there are more meta-analyses than there are well conducted trials.

Ter Riet et al (1990) reviewed the quality of studies investigating the efficacy of acupuncture in treating addictions. Of 22 randomised controlled trails, 15 concerned smoking cessation. The authors found that most studies were of poor quality (e.g. lack of validation of smoking status, short-term follow-up only, poor methods of randomization, therapist bias not considered, small sample sizes, and use of an inappropriate control). Furthermore, the studies that produced a negative outcome had higher quality scores.

A meta-analysis to examine the efficacy of smoking cessation interventions by Baillie, Mattick et al. 1994 included studies if they were randomised, included a control group, and reported data on smoking cessation as opposed to smoking reduction. Five studies (total n=855) concerned acupuncture treatment, with a mean follow-up of 8.6 months. The authors concluded that acupuncture was no more effective than placebo acupuncture for helping smokers to quit.

Law and Tang (1995) conducted a systematic review of a range of smoking cessation interventions. They included 8 trials of acupuncture, with a total sample size of 2,759 patients. They concluded that acupuncture is not an effective treatment for smoking cessation.

Ashenden et al (1997) entered data from nine RCTs (with a total of 2707 patients) with follow-up of at least six-months into their meta-analysis. In the 5 studies that measured outcome at 6 months, the odds of abstinence in the acupuncture group relative to control group (which could include placebo acupuncture OR no treatment) was 1.83 (95% CI: 0.97-3.46). For those

studies (n=4) that completed 12-month follow-up the superiority of acupuncture was borderline (OR=1.47; 95% CI: 1.10-1.98). Pooling the results from both 6 and 12 months outcome studies resulted in odds ratio of 1.53 (95% CI: 1.17-2.00) suggesting that acupuncture may be more helpful than placebo in helping smokers to quit. However, when the analysis is run on studies (n=2) that compared acupuncture with placebo acupuncture there was no benefit of active treatment on 6-month abstinence rates (OR=0.77; 95% CI: 0.18-3.20). The authors point out that caution is needed when interpreting the results because of the greater proportion of smaller studies reporting positive results.

White et al (1997) identified 16 controlled trials of acupuncture for smoking cessation which they subjected to further scrutiny to identify those with the best methodology. Seven were chosen and six of these showed no superiority of acupuncture over sham acupuncture for helping smokers to stop. The conclusion was that acupuncture is no different to placebo in aiding smoking cessation (White, Resch et al. 1997).

A meta-analysis of acupuncture techniques for smoking cessation from 1999 also concluded that acupuncture was no better than sham acupuncture (White, Resch et al. 1999). Studies with a control group receiving sham acupuncture in which subjects were blind were included in the primary analysis. Continuous abstinence was used in preference to point prevalence. Six-month follow-up was not a condition for inclusion as only 4 studies had this length of follow-up. Dropouts or those lost to follow-up were classified as smokers. No studies reviewed used biochemical validation of smoking status. A total of 14 RCTs met the inclusion criteria, 10 of which had a control group that received a form of sham acupuncture. There was no advantage of acupuncture over sham acupuncture at the first assessment (OR=1.20; 95% CI: 0.98-1.48) or at six months (OR=1.29; 95% CI: 0.82-2.01) after the intervention was delivered.

The US clinical practice guidelines for treating tobacco use and dependence (USDHHS 2000) carried out a series of meta-analyses of various interventions for smoking cessation. Intention-to-treat analysis of data of individual studies

was preferred, however data based on the number of completers was also acceptable. The guidelines used point prevalence abstinence data in preference to continuous abstinence. Five studies that investigated the efficacy of acupuncture compared to 'control acupuncture' were included. There was no difference in the estimated abstinence rates between the two treatments (8.9% vs. 8.3% for acupuncture and control respectively).

Garrison et al (2003) conducted a systematic review of smoking cessation interventions for adolesecents. Within this the authors identified a single study (Yiming et al 2000) from Singapore that randomised 330 adolescent smokers to receive laser acupuncture of placebo control. There was no difference in short-term abstinence rates between the intervention and control groups (17.5% and 17.6% respectively). This study is included in the Cochrane review summarised below.

The Cochrane review of acupuncture and related interventions for smoking cessation (White, Rampes et al. 2006) is the most recent and comprehensive of the systematic reviews, and incorporates all the relevant studies covered in the earlier meta-analyses. It is summarised in the Evidence Table. The review investigated the effects on smoking cessation of the different acupuncture related methods, specifically acupuncture, acupressure, laser therapy, and electrostimulation in comparison to (1) no intervention or waiting list controls; (2) an appropriate placebo; and (3) other smoking cessation treatments with established efficacy. Furthermore the authors went on to investigate whether acupuncture and related therapies have a specific effect when they are used in combination with other treatments and finally to establish if any one of the different acupuncture treatments is better than another. To enter the Cochrane meta-analysis studies had to be randomised controlled trials examining the efficacy of any of the acupuncture methods listed above with one of the comparison groups. All studies had to report complete abstinence from smoking, but no minimum follow-up period was required. The authors categorise the results as 'early' (before 6 weeks) or 'late' (6-12 months) outcomes. Lack of biochemical verification of smoking status did not exclude studies. Twenty-four studies met the inclusion criteria, seven studies provided

one-year abstinence data, and seven provided biochemically verified self-reported smoking status.

Regarding the effectiveness of acupuncture compared to a waiting list or no intervention control, two studies reporting short term outcome (one positive and one negative) showed significant heterogeneity and so were not combined to produce an overall result. Results from three studies (N=393) reporting long-term outcome fail to show a significant advantage of acupuncture (OR=1.91; 95% CI: 0.98-3.70). Combining the results of 12 studies (n=1594) that compared acupuncture to sham treatment produce a positive result for short-term abstinence (OR=1.36, 95% CI: 1.07 – 1.72), but again with significant heterogeneity primarily from the results of one study (n= 117) with a strongly positive result (OR=7). However, when a random-effects model was used this combined result was no-longer significant (OR=1.50; 95% CI: 0.98 to 2.30). The effect also disappears if the outlying study responsible for heterogeneity is removed. Six studies (N=1050) reported on long-term outcome and showed no difference between acupuncture and sham acupuncture (OR=0.99; 95% CI: 0.68-1.44).

There were only a small number of studies that compared acupuncture to other smoking cessation treatments. No differences were demonstrated between acupuncture and a one-week supply (105 pieces) of 2mg nicotine gum (Cavel 1985) and behavioural approaches (three studies). One study showed no difference in adding acupuncture or sham treatment to smoking cessation counselling. There is no evidence that any acupuncture technique is better than another.

Additional studies of the effects of acupuncture on smoking cessation

Docherty et al (2003) in a study not included in the Cochrane review and available only in a brief description compared a laser and placebo laser acupuncture intervention in a sample 355 smokers from a deprived area of Scotland. Participants received a double blind laser or placebo laser acupuncture treatment in addition to smoking cessation counseling. The carbon monoxide validated abstinence rates (not defined) at 6 and 12 months

were not significantly different between the groups. The study is included in the Evidence Table.

Studies of effects of acupuncture on tobacco withdrawal symptoms

We identified one study of the effect of acupuncture, compared to sham acupuncture, on nicotine withdrawal symptoms in 76 participants who wanted to stop smoking (White, Resch et al. 1998). Change in withdrawal scores over 14 days in participants who remained continuously abstinent was not significantly different between the treatment conditions. There was no difference in short-term abstinence either.

4.3.2 Evidence of efficacy

4.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

Acupuncture does not appear to have an effect on the long-term success of quit attempts

4.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

All examined types of acupuncture (auricular vs. indwelling needle vs. facial points) lack efficacy, with no difference between them (White et al 1999).

4.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

Regarding special populations of smokers, two studies have failed to demonstrate the efficacy of acupuncture in helping young smokers stop (Kang 2005; Yiming 2000). Yiming (2000) randomised 330 smokers of at least 5 cigarettes per day and aged between 12 and 18 years to receive laser or sham acupuncture. The analysis was not on an intention-to-treat basis and did not show any significant difference in 3 month continuous abstinence rates (16% for both active and placebo treatments). In a recent non-randomised

trial, 238 young smokers (15-19 years) received either auricular acupuncture (n=159) or placebo acupuncture (n=79). At the end of 4 weeks of treatment there was no difference in abstinence rates between the groups (0.6% and 0% in active vs. placebo treatment).

4.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

Acupuncture appears to lack efficacy in smoking cessation.

4.3.3 Effect size

In the absence of evidence for efficacy no effect size can be estimated.

4.3.4 Acceptability

4.3.4.1 What are the views of those receiving and delivering the intervention?

There are no data to answer this question. However it has been reported that 15% of the UK population would consider a complementary treatment for smoking cessation (from White et al 1999).

4.3.4.2 Is there evidence of unintended or harmful effects?

Acupuncture, when practiced competently, is associated with few adverse events (Birch, Hesselink et al. 2004). However reports of serious adverse events, such as pneumothorax, cardiac tamponade hepatitis B, and spinal lesions have been documented (Halvorsen, Anda et al. 1995; Vickers and Zollman 1999). Slightly less serious events include broken or forgotten needles.

Pain from the skin punctures is the most commonly reported side effect (reported in up to 45% of patients). Other common side effects include bleeding, bruising, fainting, fatigue, and light-headedness (White, Hayhoe et al. 2001).

4.3.4.3 Are there barriers to replication of effective interventions?

Acupuncture has not been proven effective in smoking cessation

4.3.4.4 Is this applicable to the UK?

Three out of the 24 studies included in the Cochrane Review have been undertaken in the UK (Gillams, Lewith et al. 1984; Georgiou, Spencer et al. 1998; Waite and Clough 1998), and like the overall result none found an effect of acupuncture over placebo.

4.3.5 Cost of treatment

The cost of acupuncture varies. Table 4.1 shows the costs obtained from four different UK websites. The average number of treatment sessions calculated from data available in the Cochrane Review was 5.3. The approximate average cost of a course of treatment found is £220.

Table 4.1: Cost of acupuncture

Website	**Costs quoted**
Baby Centre (UK)[1]	£20-£40 per half-hour acupuncture session
The Wholistic Research Company[2]	Initial consultation fees: £30.00 to £80.00 Subsequent treatment fees: £20.00 to £50.00.
Metta.org.uk[3]	£30 to £50 per hour.
Cancer Research UK[4]	Initial consultation: £50 to £80 for your first Subsequent fees: £25 to £70

Web addresses
1. www.babycentre.co.uk/pregnancy/antenatalhealth/quittingsmoking/compareyouroptions/?_requestid=819869
2. www.wholisticresearch.com/info/artshow.php3?artid=82
3. http://www.metta.org.uk/therap/acupuncture.htm
4. http://www.cancerhelp.org.uk/help/default.asp?page=11691#cost

4.3.6 Evidence statement

A body of level 1+ evidence from meta-analyses of randomised controlled trials suggests that acupuncture, acupressure, laser therapy and electrostimulation do not improve long-term abstinence rates over that of a placebo effect.

4.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
White 2006	Meta-analysis	1	+	Smokers wanting help in stopping N=4749	(A) What is the effectiveness of acupuncture, acupressure, laser therapy, and electrostimulation in aiding smoking cessation in comparison to (1) no intervention or waiting list controls; (2) an appropriate placebo; and (3) other smoking cessation treatments with established efficacy? (B) Do these treatments have any specific effect when they are used in combination with other treatments? (C) Is any one of the different acupuncture treatments better than another? Meta-analysis inclusion criteria: Randomised controlled trials Have a suitable comparison groups. Report complete abstinence from smoking, but no minimum follow-up period was required. Lack of biochemical verification of smoking status did not exclude studies.	Early: Short term (0-6 weeks after the quit date) Late: Long-term (6-12 months after the quit date)	No evidence for effectives of any intervention in aiding long-term smoking cessation.	Three studies in UK smokers.	Poor methodology in some included studies. For this reason this meta-analysis scores '+' for quality.
Docherty 2003	RCT Double blind (not included in Cochrane meta-analysis)	1	+	355 smokers from a deprived area of Scotland	What is the effectiveness of laser acupuncture compared to placebo acupuncture on long-term smoking cessation rates Randomly assigned to active (n=145) or placebo (n=210) laser acupuncture. All provided with counseling and had access to telephone helpline. Participants and therapist blind to allocation.	6 and 12 months	CO validated abstinence rates for active vs. placebo 6 month: 12.4% (n=18) vs. 11.9% (n=25) 12 month: 10.3% (n=15) vs. 10% (n=21)	Scottish study	Participants' characteristics unknown. Unknown if continuous of point prevalence abstinence used. Number of sessions and duration of treatment unknown

4.5 Meta-analysis

With the exception of Docherty et al (2003) we found no new data to add to the most recent Cochrane review of acupuncture for smoking cessation (White, Rampes et al. 2006) and so the following results and forest plots are derived directly from this review.

The short- and long-term abstinence rates for acupuncture compared to a waiting list control, or no intervention, are shown in figures 4.1 and 4.22. The meta-analysis of short-term studies shows a positive effect of acupuncture compared to no treatmemt (OR=6.10, 95% CI: 2.49-14.97), but there is marked heterogeneity (I^2=88%) so this needs to be interpreted with caution. When a random effects model is used this results disappears (OR=6.78, 95% CI: 0.35-133.29). There is no long-term effect of acupuncture compared with no treatment (OR=1.91, 95% CI: 0.98-3.70).

Acupuncture had a marginal effect compared to placebo in short term (OR=1.36, 95%CI: 1.07-1.72; see Figure 4.33), but the studies had a significant heterogeneity (I^2=57%) and the effect disappears when a random effects model is used (OR=1.50, 95%CI: 0.98-2.30). The effect was not detected in a group of non-heterogenious long-term studies (OR=0.99, 95% CI: 0.98-1.44; see Figure 4.4).

Regarding laser acupuncture the two studies, one reporting short-term (figure 4.5) and the reporting long-term (figure 4.6) outcomes showing no advantage over placebo laser acupuncture.

Figure 4.1: Effect of acupuncture compared to waiting list or no intervention on short-term smoking abstinence.

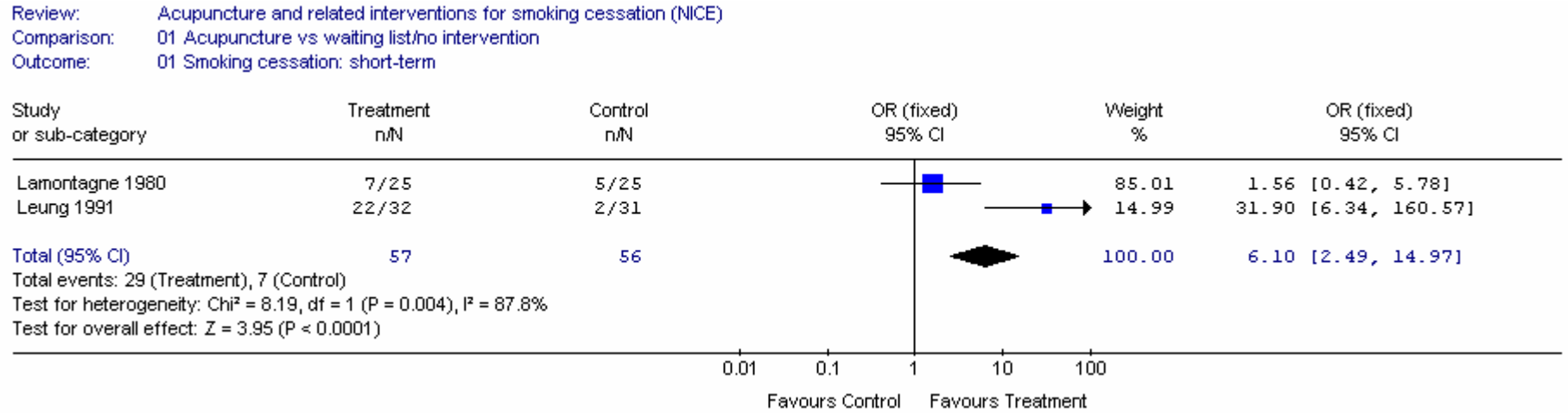


Figure 4.2: Effect of acupuncture compared to waiting list or no intervention on long-term smoking abstinence.

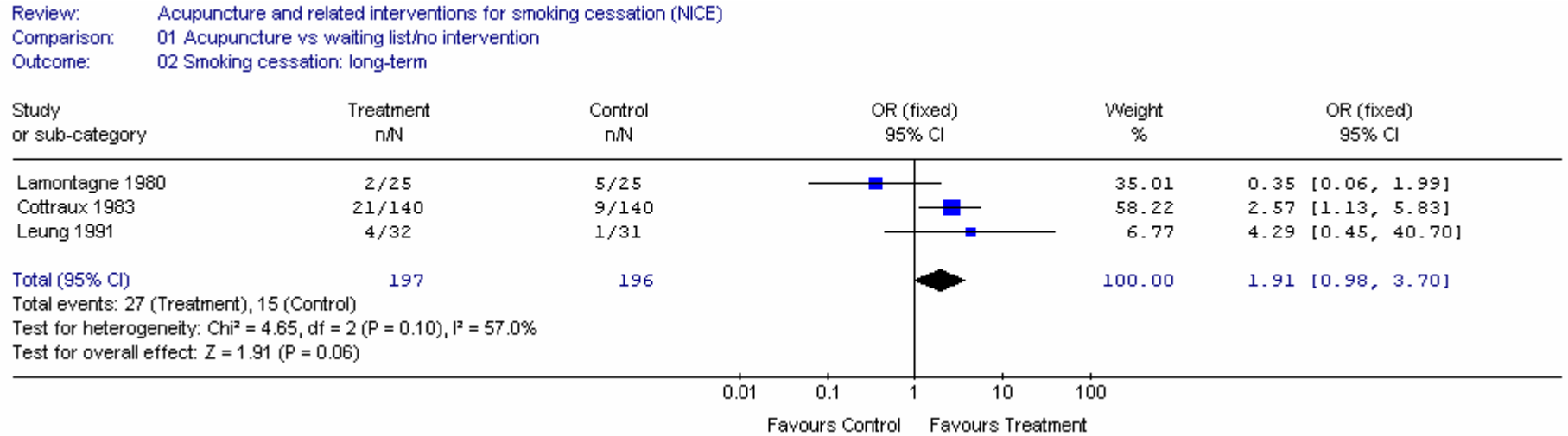
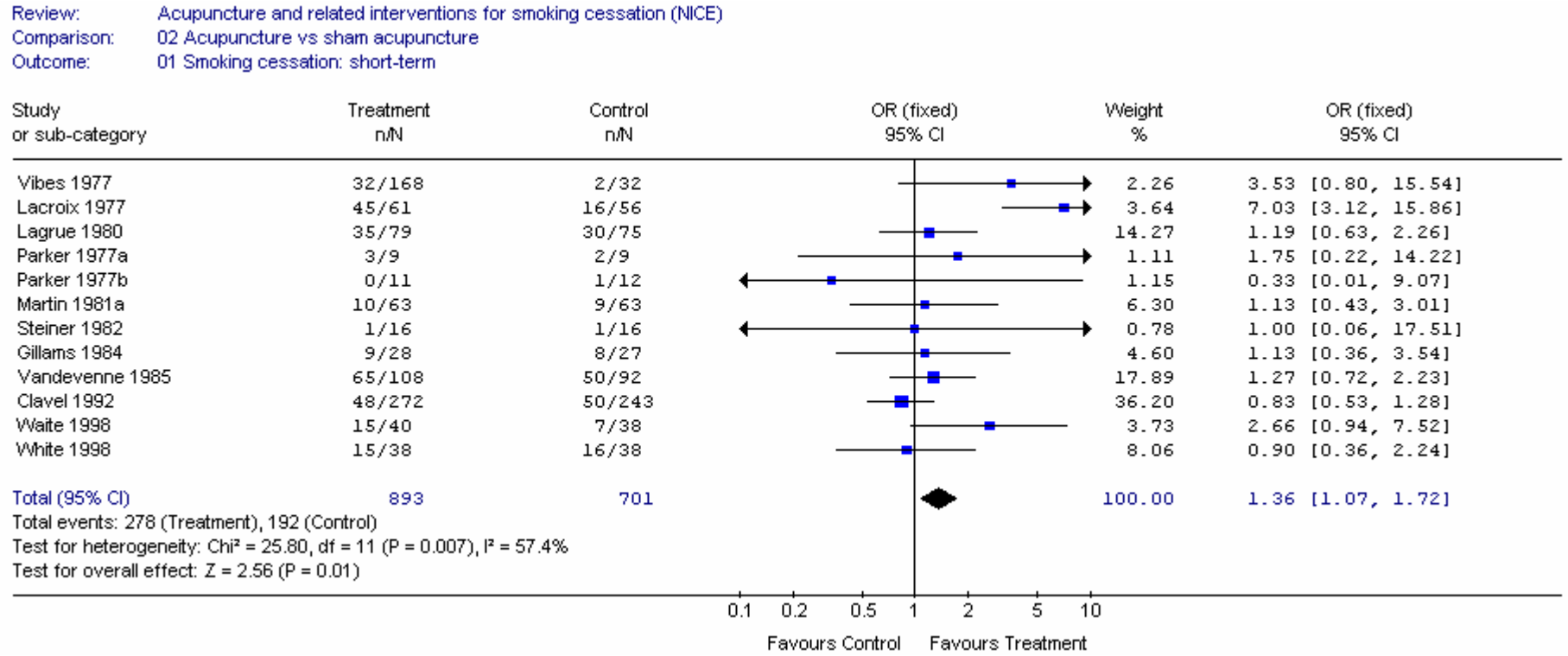


Figure 4.3: Effect of acupuncture compared to placebo acupuncture on short-term smoking abstinence.



Final report 12 Sept 07 with track changes

Figure 4.4: Effect of acupuncture compared to placebo acupuncture on long-term smoking abstinence.

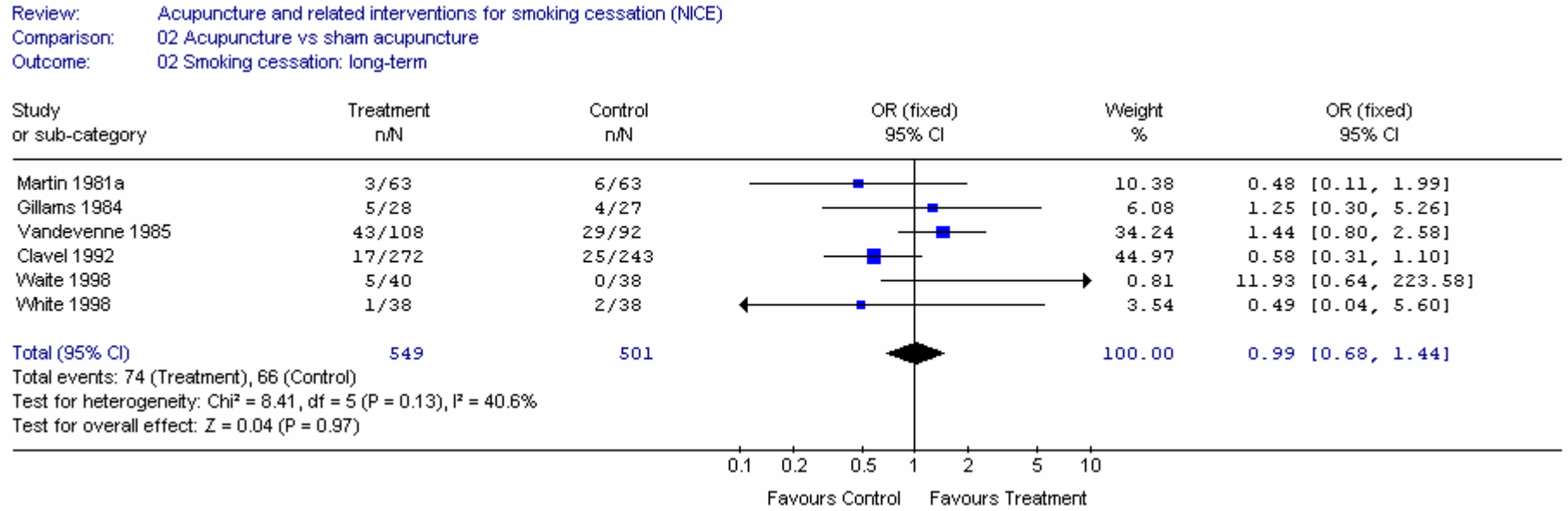


Figure 4.5: Effect of laser acupuncture compared to placebo laser acupuncture on short-term smoking abstinence.

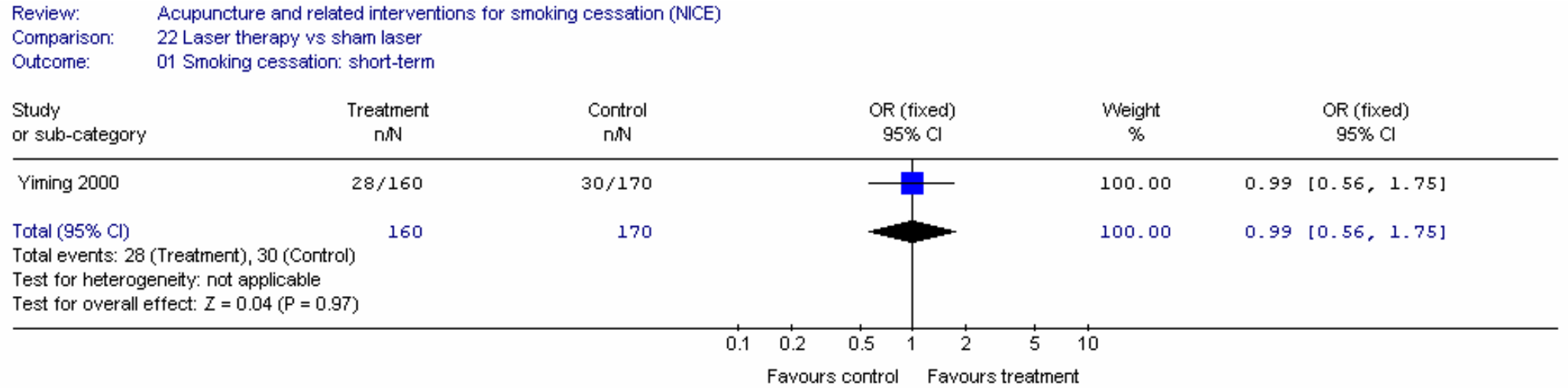
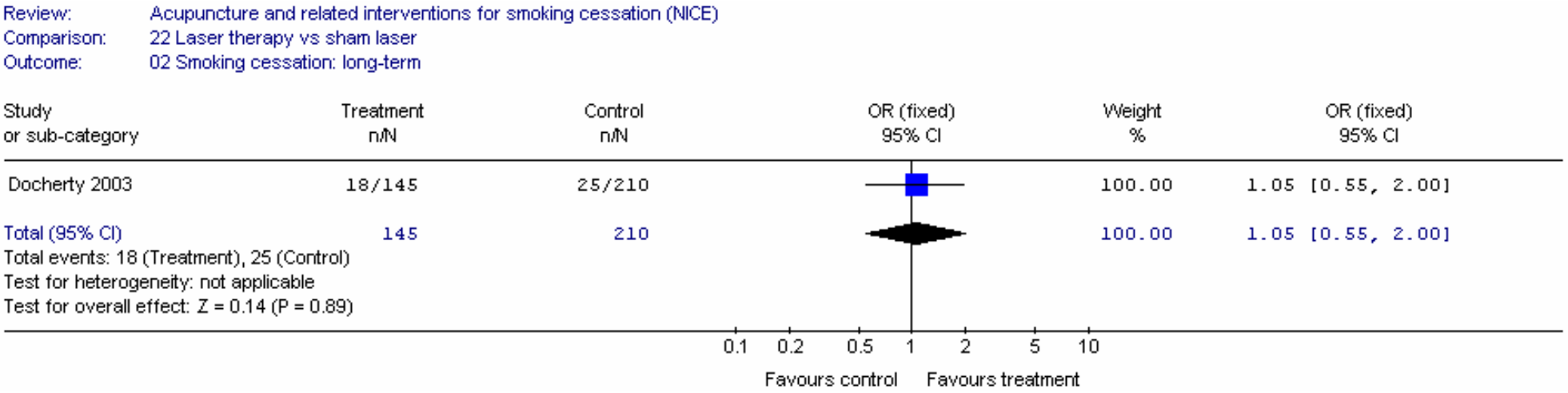


Figure 4.6: Effect of laser acupuncture compared to placebo laser acupuncture on long-term smoking abstinence.



4.6 References

4.6.1 Included reviews and other studies

Ashenden, R., C. A. Silagy, et al. (1997). "A meta-analysis of the effectiveness of acupuncture in smoking cessation." Drug Alcohol Rev **16**(1): 33-40.

Baillie, A. J., R. P. Mattick, et al. (1994). "Meta-analytic review of the efficacy of smoking cessation interventions." Drug and Alcohol Review **13**(2): 157-170.

Docherty, G., D. Gordon, et al. (2003). "Laser and NRT smoking cessation programmes in areas of high social deprivation [Abstract]." Thorax **58**(Suppl 3): iii43.

Garrison, M. M., D. A. Christakis, et al. (2003). "Smoking cessation interventions for adolescents: a systematic review." Am J Prev Med **25**(4): 363-7

Law, M. and J. L. Tang (1995). "An analysis of the effectiveness of interventions intended to help people stop smoking." Archives of Internal Medicine **155**(18): 1933-41.

Ter Riet, G., J. Kleijnen, et al. (1990). "A meta-analysis of studies into the effect of acupuncture on addiction." British Journal of General Practice **40**(338): 379-82.

USDHHS (2000). Treating Tobacco Use and Dependence. Rockville, MD, United States Department of Health and Human Services, Agency for Healthcare Research Quality.

White, A. R., H. Rampes, et al. (2006). "Acupuncture and related interventions for smoking cessation." Cochrane Database of Systematic Reviews (1): CD000009.

White, A. R., K. L. Resch, et al. (1997). "Smoking cessation with acupuncture? A 'best evidence synthesis'." Forsch Komplimentarmed **4**(2): 102-5.

White, A. R., K. L. Resch, et al. (1999). "A meta-analysis of acupuncture techniques for smoking cessation." Tobacco control **8**(4): 393-7.

4.6.2 Retrieved references covered within included reviews

Bier, I. D., J. Wilson, et al. (2002). "Auricular acupuncture, education, and smoking cessation: a randomized, sham-controlled trial." American Journal of Public Health **92**(10): 1642-7.

Clavel, F. and C. Paoletti (1990). "[A study of various smoking cessation programs based on close to 1000 volunteers recruited from the general population: 1-month results]." Revue d'epidemiologie et de sante publique **38**(2): 133-8.

Clavel-Chapelon, F., C. Paoletti, et al. (1992). "A randomised 2 x 2 factorial design to evaluate different smoking cessation methods." Revue d Epidemiologie et de Sante Publique **40**(3): 187-90.

Clavel-Chapelon, F., C. Paoletti, et al. (1997). "Smoking cessation rates 4 years after treatment by nicotine gum and acupuncture." Preventive Medicine **26**(1): 25-8.

Georgiou, A. J., C. P. Spencer, et al. (1998). "Electrical stimulation therapy in the treatment of cigarette smoking." Journal of Substance Abuse **10**(3): 265-74.

He, D., J. E. Berg, et al. (1997). "Effects of acupuncture on smoking cessation or reduction for motivated smokers." Preventive Medicine **26**(2): 208-14.

He, D., J. I. Medbo, et al. (2001). "Effect of acupuncture on smoking cessation or reduction: an 8-month and 5-year follow-up study." Preventive Medicine **33**(5): 364-72.

Leung, J.-p. (1991). "Smoking cessation by auricular acupuncture and behavioral therapy." Psychologia: An International Journal of Psychology in the Orient **34**(3): 177-187.

Pickworth, W. B., R. V. Fant, et al. (1997). "Evaluation of cranial electrostimulation therapy on short-term smoking cessation." Biological Psychiatry **42**(2): 116-121.

Tian, Z. and Y. Chu (1996). "Treating smoking addiction with the ear point seed pressing method." Journal of Chinese Medicine **52**: 5-6.

Waite, N. R. and J. B. Clough (1998). "A single-blind, placebo-controlled trial of a simple acupuncture treatment in the cessation of smoking." British Journal of General Practice **48**(433): 1487-90.

White, A. R., K. L. Resch, et al. (1998). "Randomized trial of acupuncture for nicotine withdrawal symptoms." Archives of Internal Medicine **158**(20): 2251-5.

Yiming, C., Z. Changxin, et al. (2000). "Laser acupuncture for adolescent smokers--a randomized double-blind controlled trial." The American journal of Chinese medicine **28**(3-4): 443-9.

4.6.3 Additional references

Birch, S., J. K. Hesselink, et al. (2004). "Clinical research on acupuncture: Part 1. What have reviews of the efficacy and safety of acupuncture told us so far?" Journal of Alternative & Complementary Medicine **10**(3): 468-480.

British Medical Association Board of Science and Education (2000). Acupuncture: Efficacy, Safety and Practice. London, Harwood Academic Publishers.

Cabyoglu, M. T., N. Ergene, et al. (2006). "The mechanism of acupuncture and clinical applications." Int J Neurosci **116**(2): 115-25.

Fuller, J. A. (1982). "Smoking withdrawal and acupuncture." Med J Aust **1**(1): 28-9.

Gillams, J., G. T. Lewith, et al. (1984). "Acupuncture and group therapy in stopping smoking." Practitioner **228**(1389): 341-4.

Halvorsen, T. B., S. S. Anda, et al. (1995). "Fatal cardiac tamponade after acupuncture through congenital sternal foramen." Lancet **345**(8958): 1175.

Han, J. S. (2004). "Acupuncture and endorphins." Neurosci Lett **361**(1-3): 258-61.

Lewith, G. T. (1995). "The treatment of tobacco addiction." Complementary Therapies in Medicine **3**(3): 142-5.

NHS Centre for Reviews and Dissemination (2001). "Acupuncture." Effective Healthcare **7**(2): 1-12.

NHS Direct (2006). NHS Direct Online Health Encyclopaedia: Acupuncture. Avilable online: http://www.nhsdirect.nhs.uk/articles/article.aspx?printPage=1&articleId=6.

Vickers, A. (2001). "Acupuncture." Effective Healthcare **7**(2): 1-12.

Vickers, A., P. Wilson, et al. (2002). "Effectiveness bulletin:Acupuncture." Qual Saf Health Care **11**: 92-97.

Vickers, A. and C. Zollman (1999). "ABC of complementary medicine. Acupuncture." BMJ **319**: 973-6.

Wen, H. L. and S. Y. C. Cheung (1973). "Treatment of drug addiction by acupuncture and electrical stimulation." Asian Medical Journal **9**: 138-41.

White, A., S. Hayhoe, et al. (2001). "Adverse events following acupuncture: prospective survey of 32 000 consultations with doctors and physiotherapists." Bmj **323**(7311): 485-6.

Yoon, S. S., Y. K. Kwon, et al. (2004). "Acupuncture-mediated inhibition of ethanol-induced dopamine release in the rat nucleus accumbens through the GABAB receptor." Neurosci Lett **369**(3): 234-8.

5 ALLEN CARR'S EASYWAY PROGRAMME

5.1 Background

Allen Carr's book The Easy Way To Stop Smoking (first published in 1985) is one of the best known approaches to helping smokers quit. A web-based search (www.google.com) for "Carr and smoking" reveals over two million hits.

The Allen Carr' Easyway is a commercial organisation providing face-to-face smoking cessation treatment. According to its website it treated more than 35,000 smokers world-wide in 2005, with a quoted success rate of over 90% (Allen Carr's Easyway Worldwide 2006a).

5.1.1 What is the aim of the treatment?

The method claims to 'remove the smoker's conflict of will; there are no bad withdrawal pangs; it is instantaneous and easy; it is equally effective for long-term heavy smokers and light smokers; you need not gain weight; you will not miss smoking' (Allen Carr's Easyway Worldwide 2006b). Smokers are typically seen once, either in groups of up to 25 people or individually. The sessions last for 4-5 hours, with shorter 'booster' sessions available if required by patients. The programme comes with a 'money back' guarantee, in that if the client attends the first session and two subsequent booster sessions within three months and is still smoking, the fee for treatment (approximately £220 in the UK) is refunded in full. Cancellation, postponement, arriving more than 15 minutes late, or failure to attend any of these sessions means that the fee is not refunded (Dicey 2006).

5.1.2 What is the content of the treatment?

Underpinning the treatment is the hypothesis that smokers continue to smoke because they are afraid to quit, fearing the loss of something they enjoy. The treatment, delivered through a structured lecture and discussion, aims to remove the belief that smoking provides pleasure, help smokers to attribute any perceived benefits of smoking to withdrawal relief, and increase the confidence of the smoker that they can stop smoking without suffering any great loss. In the parlance of contemporary clinical psychology, it can be classified as a form of cognitive therapy. Participants are warned against the use of nicotine replacement treatment. Easyway claims to also use elements of hypnotherapy, but the details of what this involves are not clear (Dicey 2006).

5.2 Methodology

5.2.1 Literature Search

Due to limited research data available in this area the database search limits were extended to include all data currently available. In addition information was obtained from the Easyway website (www.allencarr.com) and Easyway director and experts in the field were also contacted for any knowledge of work undertaken in evaluating the method.

The searches returned a total of nine records, with five relevant for this review.

5.2.2 Selection of Studies for Inclusion

The one review (Willemsen, Wagena et al. 2003) and four descriptive studies (Foulds 1996 a and b; Csillag, Feuerstein et al. 2005/Moshammer and Neuberger 2007; Hutter, Moshammer et al. 2006) identified in the search did not include any randomised evaluation of the programme and so meta-

analysis could not be undertaken. However, in absence of any other data, we summarise these sources below.

5.3 Summary of Findings

5.3.1 Summary of studies identified

Willemsen, Wagena et al. (2003) reviewed the efficacy of smoking cessation methods available in the Netherlands. It found no studies on the Allen Carr Method that could be included and so could not come to any conclusion about the efficacy of this treatment method.

Four cohorts treated by Allen Carr method were followed up.

Foulds (1996) covered two small cohort studies in one report. To differentiate between them, we refer to them as Foulds 1996a and Foulds 1996b.

Foulds (1996a) followed up 19 smokers who took part in a group-based Allen Carr smoking cessation clinic in South London. Participants were contacted at one week, four weeks, and three months after their quit date. Those who reported abstinence at four weeks had the level of carbon monoxide (CO) measured in their expired breath to verify their non-smoking status (CO < 10ppm). Sixty-eight percent reported to have stopped smoking in the first week after the session. Of those claiming to be abstinent at 1 month (n=9; 47%), five (26% of the original sample) attended and passed CO validation. Three months after quitting, five participants (26%) reported maintained continuous abstinence, but these self-reports were not validated. To evaluate the claim that smokers do not experience any 'withdrawal pangs' when they stop smoking using the Allen Carr method, Foulds enquired about withdrawal symptoms in the first weeks of the quit attempt and found seven participants (37%) reported an increase in withdrawal symptoms.

Foulds (1996b) also conducted a follow-up of previous clients of the South London Allen Carr clinic. Fifty telephone calls were made to clients whose last name started with the letter ‘F’ and who had London telephone numbers. Ten agreed to answer questions about the treatment. They had been treated on average 21 months earlier. Eight of the ten reported that they had relapsed back to smoking after an average of 6 weeks of abstinence.

Two related Austrian studies (Csillag, Feuerstein et al. 2005/Moshammer and Neuberger 2007; Hutter, Moshammer et al. 2006) reported very high abstinence rates at one to five years after a one-off group seminar held at the workplace.

In the Csilag et al. study (conducted after but published before the Hutter et al. study), 686 employees who attended Easyway seminars at a major Austrian company were followed up 2-5 years later through phone calls by the company's occupational health staff. It is unclear how the smoking status was defined, but it appears that 249 participants reported point prevalence abstinence, i.e. 52% of those providing full information (36% of the baseline sample). Urine samples were collected from a sub-sample for cotinine validation of self-reported smoking status, but despite the reported correlational data suggesting some misreporting, the cotinine results were not taken into account when calculating abstinence rates.

Hutter et al. report the results of a follow-up study of a sample of 357 participants of Allen Carr seminars in an unknown number of Austrian companies three and 12 months after seminars. The follow-up interviews were conducted and data for analysis supplied by a market research company commissioned by Easyway. ‘Computer-aided interviews' were said to have been used but details are not given. It appears that 122 participants (40%) reported not smoking at one year but the definition of abstinence was again unclear, and no validation was attempted.

Moshammer and Neuberger (2007) describe the same study as that reported by Csilag et al., though the authors are different (Csilag, Feurstein, Herbst and Moshammer have been replaced by Moshammer and Neuberger) and no reference to the Csilag paper is made. More details of the validation are provided. An unspecified proportion of participants claiming abstinence agreed to a screening examination. Of 30 consecutive urine samples, 5 (17%) failed cotinine validation.

5.3.2 Evidence of efficacy

5.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

Data from randomised controlled trials are needed to answer the question. The three follow-up studies report a range of outcomes, but this is in part at least explainable by differences in the methodology used. Two small studies reported 26% one-month and between 4% and 20% long-term abstinence rates in UK smokers (Foulds 1996 a,b). The other two larger studies report much bigger effects in Austrian smokers (40-52% long-term abstinence), but they used more lenient study designs (Csillag, Feuerstein et al. 2005/Moshammer and Neuberger 2007; Hutter, Moshammer et al. 2006).

5.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

There is insufficient evidence to answer this question.

5.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

There is insufficient evidence to answer this question.

5.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

There is insufficient evidence to answer this question.

5.3.3 Effect size

In the absence of evidence for long-term efficacy no effect size can be estimated.

5.3.4 Acceptability

5.3.4.1 What are the views of those receiving and delivering the intervention?

Foulds (1996) asked for participant feedback. The majority were satisfied with the treatment and 74% said that they would recommend it to friends.

5.3.4.2 Is there evidence of unintended or harmful effects?

Discouraging clients from using NRT may have adverse consequences. The majority of clients will continue to smoke and are likely to seek further help. The Easyway message may discourage them from using one of the very few evidence-based treatments available.

5.3.4.3 Are there barriers to replication of effective interventions?

The effectiveness of the Allen Carr method remains to be determined.

5.3.4.4 Is this applicable to the UK?

The effectiveness of the Allen Carr method remains to be determined.

5.3.5 Cost of treatment

The current cost to an individual to attend an Allen Carr clinic is approximately £220.

5.3.6 Evidence statement

There are no controlled data available on the efficacy of Allen Carr's Easyway Programme. Two cohort studies suggest that it may have an effect on smoking cessation rates but this evidence is weak and further research is needed to determine their effectiveness.

5.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Foulds 1996	Cohort	2	-	Dependent smokers motivated to quit (n=19) attending an Easyway stop smoking clinic in South London	To evaluate effectiveness of the 'Easyway' smoking cessation clinic.	1 & 3 months	26% (5) 1 month continuous abstinence (CO validated) 26% (5) 3 month continuous abstinence Intention to treat analysis	Yes – South London study	Small study No validation at 3 months
Foulds 1996	Cohort	2	-	Dependent smokers motivated to quit selected randomly from Easyway clinic records (n=50)	To evaluate effectiveness of the 'Easyway' smoking cessation clinic.	21 months on average	10 agreed to answer questions, 2 (20% or 4%, depending on base) reported not smoking	Yes – South London study	
Csillag 2005, Mosham mer 2007	Cohort	2	-	Dependent smokers motivated to quit. Sample (n=686/515) from cohort of n=1311 who attended an 'Easyway' group based clinic as part of a workplace smoking cessation initiative	To evaluate effectiveness of the 'Easyway' smoking cessation clinic in a workplace setting	2-4.5 years	36%/51% (249/262) self-reported point-prevalence	Probably, and workplace	Non-random sample, unclear abstinence criteria, validation results not used
Hutter 2006	Cohort	2	-	Dependent smokers motivated to quit (n=308) who attended an 'Easyway' group based clinic over a 4 month period in 2002	To evaluate effectiveness of the 'Easyway' smoking cessation clinic in a workplace setting	1 year	40% (122) self-reported point-prevalence Intention to treat analysis	Probably, and workplace	No details of follow-up method and definition of outcome, no

									validation

5.5 Meta-analysis

Not applicable

5.6 References

5.6.1 Included reviews and other studies

Csillag, H., A. Feuerstein, et al. (2005). "The long term success of occupational non-smoking seminars." Sichere Arbeit: 28-34.

Foulds, J. (1996a,b). Brief evaluation of the "Easy Way To Stop Smoking" Clinic, Raynes Park. London, St George's Hospital Medical School**:** 1-7.

Hutter, H. P., H. Moshammer, et al. (2006). "Smoking cessation at the workplace: 1 year success of short seminars." International Archives of Occupational & Environmental Health **79**(1): 42-48.

Moshammer, H., Neuberger, M. (2007). "Long term success of short smoking cessation seminars supported by occupational health care." Addictive Behaviors **32** (7): 1486-93.

Willemsen, M. C., E. J. Wagena, et al. (2003). "[The efficacy of smoking cessation methods available in the Netherlands: a systematic review based on Cochrane data]." Nederlands Tijdschrift voor Geneeskunde **147**(19): 922-7.

5.6.2 Additional references

Allen Carr's Easyway Worldwide (2006a). Stop smoking clinics, http://allencarr.com/central/article/41/stop-smoking-clinics. 2006.

Allen Carr's Easyway Worldwide (2006b). The Allen Carr Method, www.allencarr.com/central/article/36/the-allen-carr-method. 2006.

Dicey, J. (2006). Allen Carr Method. H. McRobbie. Auckland: Personal communication with John Dicey, Easyway Director.

6 HYPNOSIS

6.1 Background

Hypnosis is one of the most widely advertised and best known alternative treatments for smokers. In a telephone survey of a random sample of 250 participants (smokers and non-smokers) hypnotherapy was ranked as the third most effective treatment for stopping smoking, following patches and going ‘cold turkey’ (de Zwart and Sellman 2002).

6.1.1 What is the aim and rationale of treatment?

Entering a hypnotic state is said to place the smoker in a heightened level of attention during which suggestions regarding the risks of smoking, the benefits of quitting, and the determination and commitment to stop can be imparted. These are thought to weaken the desire to smoke and increase the motivation to quit and stay stopped (Flammer and Bongartz 2003).

6.1.2 What is the content of treatment?

The most commonly used technique is Spiegel's single treatment session (Spiegel 1970). It combines post-hypnotic suggestion with self-hypnosis. Smokers are taught to repeat to themselves the suggestions that they have a responsibility to their body, they need their body to live, smoking is poisonous to their body, they owe their body protection and they owe it to their body to stop smoking (Abbot, Stead et al. 2006). Other versions of hypnosis treatment are more intensive. Elkins and Rajab (2004) describe a three-session treatment programme that involves an initial assessment session (assessment of mental status and smoking history, discussion about smoking, reasons for quitting, setting a quit day), and two hypnotherapy sessions that incorporate reinforcement of commitment to stop smoking, hypnotic suggestion of a decreased level of craving and feeling relaxed, post-hypnotic suggestions of accomplishment, being in control and improvement in smell and taste, and teaching self hypnosis.

6.2 Methodology

6.2.1 Literature Search

The searches returned a total of 444 records (after de-duplication), of which 30 were relevant to this review (11 reviews, and 19 studies).

6.2.2 Selection of Studies for Inclusion

Of the 11 reviews 6 were not conducted systematically and were excluded. The Cochrane Review on hypnotherapy for smoking cessation (Abbot, Stead et al. 2006) is the highest quality, most recent and most inclusive of the reviews.

Of the 19 studies, ten were excluded because they were not randomised controlled trials or were of poor quality. Seven studies (Spanos, Sims et al. 1992; Spiegel, Frischholz et al. 1993; Johnson and Karkut 1994; Valbo and Eide 1996; Ahijevych, Yerardi et al. 2000; Richard 2002; Casmar 2003) were assessed in the Cochrane review and three were excluded on the basis of short-term follow-up (Spanos, Sims et al. 1992; Valbo and Eide 1996; Casmar 2003). These are discussed below. We found abstracts of two new randomised controlled trials that have not yet been considered by the Cochrane review, and they are summarised below (Carmody, Duncan et al. 2006; Tindel, Rigotti et al. 2006).

6.3 Summary of Findings

6.3.1 Summary of studies identified

The methodological issues that plague the other behavioural research also affect hypnotherapy. The US clinical practice guidelines for treating tobacco use and dependence (USDHHS 2000) noted that few studies assessing the efficacy of hypnosis for smoking cessation met their inclusion criteria. In addition they found no clear method of hypnosis to examine.

Most of the literature in this area uses methodology considered poor by today's standard. For example definitions of abstinence are not provided, self-reports are not biochemically validated, studies lack adequate control groups, sample sizes are small, follow-ups are not blind, etc. In addition, it is difficult to blind the subjects and usually no attempt is made to minimise bias due to demand characteristics and expectations.

Reviews

A meta-analysis of smoking cessation methods (Viswesvaran and Schmidt 1992) identified 48 studies using hypnosis with a follow-up period of at least three months. The mean quit rate reported for hypnotherapy was 36% (with an 80% credibility interval of 12% to 60%). The ‘control group’ quit rate was 6% (80% credibility interval: -2% to 16%). The methodology used in this review is poor (basically a comparison of success rates ignoring length of follow-up, wildly different definitions of success rates, lack of randomisation, or any other methodological consideration).

Another meta-analysis examining the efficacy of a wide range of smoking cessation interventions (Baillie, Mattick et al. 1994) included studies if they were randomised, and found six studies concerning hypnosis, with a mean follow-up of 7 months and varying methods of treatment. The calculated effect sizes were homogeneous despite the seemingly very different interventions. The mean difference in abstinence rates between hypnosis and comparison groups was 9% (OR=1.68; 95% CI: 1.03-2.76). No selection criteria were used for comparison groups and they included waiting list control.

Law and Tang (1995) identified 10 studies of hypnosis that qualified for inclusion in their meta-analysis of randomised controlled trials that reported at least 6-month follow-up. This review used intention-to-treat analysis. None of the studies provided biochemical verification of abstinence. The difference in effectiveness between the intervention and comparison groups was 23% ($p<0.001$).

Seven studies (mix of randomised and non-randomised) of hypnosis for smoking cessation were included in a review by Flammer and Bongartz

(2003). All but one (Lambe 1986) were classified as classical methods of hypnosis. Inclusion criteria: (1) clinical study; (2) treat condition applies only hypnosis intervention; (3) comparison group (waiting list controls were not allowed to have any psychotherapeutic content); (4) randomised. Short length of follow-up did not exclude studies. The total sample size was 480 smokers who completed the treatment (mean duration of treatment was 2 weeks). Those who underwent hypnosis were significantly more likely to achieve abstinence. The mean weight effect size was 28% (d=0.59; p<0.001).

The Cochrane review of hypnotherapy for smoking cessation (Abbot, Stead et al. 2006) is the most recent and comprehensive of the systematic reviews, and incorporates all relevant studies covered in the earlier meta-analyses. Studies were included if they were randomised controlled trials and follow up was at least six months after the quit day. Lack of biochemical verification did not exclude studies.

Nine studies, all published before 1990, qualified for inclusion. The methods of hypnosis varied in intensity (from a single session to a nine week programme) and duration (from 30 minutes to seven hours in total). The included studies utilised five different comparison groups: (a) waiting list or no treatment; (b) attention placebo or advice; (c) psychological treatments; (d) rapid or focused smoking; and (e) group therapy with or without hypnosis. There was significant heterogeneity in among the studies in comparisons a, b, and e, with some studies reporting no quitting in the comparison groups. Odds ratios were not calculated for these comparisons. We have calculated them and hypnosis has shown superiority to no treatment (OR=2.39, 95% CI: 1.23 to 4.65) but not to attention/placebo controls. With significant heterogeneity, these results need to be considered with caution. The other two comparison groups (psychological treatments and rapid/focused smoking) had only two studies each. Hypnosis was not shown to differ from other psychological treatments (OR= 0.92, 95% CI: 0.42 to 2.02) or aversive smoking (OR=1.00, 95% CI 0.32 to 3.11), but sample sizes were small.

Randomised controlled trials

We were unable to obtain the full paper for Spanos, Sims et al. (1992). The abstract describes a study in which 191 adult smokers were allocated to hypnotic or non-hypnotic treatments for smoking cessation and followed-up for between 12 and 24 weeks. The abstract does not allow data extraction, but the authors report low abstinence rates and no significant differences between groups.

In a study assessing the effectiveness of hypnosis for smoking cessation in pregnancy (Valbo and Eide 1996) 158 women who were smoking ar 18 weeks gestation were randomly allocated to two 45 minute sessions of hypnosis (2 weeks apart) or routine care. The continuous abstinence rates at delivery (approximately 4 months later), using intention-to-treat analysis, were 13% in both groups.

Casmar (2003) randomised 75 smokers who were standardised for level of hypnotisability to one of three groups: (1) Spiegel's standard smoking cessation hypnosis procedure; (2) Spiegel's procedure plus extra suggestion to anaesthetise urges to smoke; and (3) placebo control (subliminal messages). All group sessions lasted 90 minutes. The one and three month abstinence rates (undefined) were 16%, 12%, 20% and 16%, 8%, 8% for the three groups respectively. The differences observed were not statistically significant.

The following two recent studies were not included in the Cochrane analysis. Carmody et al (2006) investigated the effect of self-hypnosis in a sample of 286 smokers. The self-hypnosis group (n=145) received two 45 minute sessions of self-hypnosis training plus a supply of transdermal nicotine patches. The comparison group (n=141) received two 45 minute sessions of standard behavioural counselling with additional phone counselling at 1,2 and 8 weeks, plus nicotine patches. At 6 and 12 month follow-up point-prevalence validated (salivary cotinine) abstinence rates for the self-hypnosis and counselling groups were 26% (n=36) vs. 19% (n=24) and 20% (n=27) vs. 15% (n=19). The differences between groups were not significant (Carmody,

Duncan et al. 2006). The study has been included in the meta-analysis in Figure 3.

In a pilot study examining the efficacy of guided imagery for smoking cessation (Tindel, Rigotti et al. 2006), 34 smokers were randomised to a 6-session group-based guided imagery programme or a waiting list control group (who were offered the guided imagery training at the end of 12 weeks). All participants received brief advice to quit by a physician. Seven-day point prevalence abstinence rates at 12 weeks were 30% and 12% respectively (NS). At one year the rates were 24% (n=4) and 6% (n=1), but the long-term results are difficult to interpret as the control group received treatment at week 12. This study is not included in the meta-analysis because of the short follow-up.

6.3.2 Evidence of efficacy

The evidence of efficacy for hypnotherapy to aid smoking cessation was identified from the systematic review conducted by Abbot et al (2006) whose findings have been updated with recent data from Carmody et al (2006).

6.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

Hypnosis does not differ from attention control, and does not seem to improve efficacy of other methods if added to them. It may match some behavioural treatments and it may be superior to no treatment. The last statement needs to be treated with caution as the relevant studies showed significant heterogeneity.

6.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

The intervention appears to lack specific efficacy

6.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

It has been argued that hypnosis may only work for smokers with high hypnotic susceptibility. However, Holroyd (1991) found no relationship between hypnotisability and short- or long-term smoking cessation outcomes.

One study found no effect of hypnosis compared to usual care in a sample of pregnant smokers wanted to quit (Valbo and Eide 1996).

6.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

The intervention appears to lack specific efficacy

6.3.3 Effect size

In the absence of evidence for efficacy no effect size can be estimated.

6.3.4 Acceptability

6.3.4.1 What are the views of those receiving and delivering the intervention?

Sorensen (1995) evaluated the outcome of a hypnotherapy based smoking cessation programme in the workplace following the implementation of a smoking ban and found that satisfaction with treatment was high.

6.3.4.2 Is there evidence of unintended or harmful effects?

It is said that hypnosis may worsen symptoms in those suffering from mental health illnesses such as schizophrenia and bipolar disorder. Hypnosis may also result in emergence of unpleasant memories in those suffering post-traumatic stress disorder (Intelihealth.com 2006). Caution has also been advised in those with major depression and borderline personality. (Bonshtein et al 2005).

6.3.4.3 Are there barriers to replication of effective interventions?

The intervention seems to lacks specific efficacy.

6.3.4.4 Is this applicable to the UK?

One of the largest studies included in the Cochrane Review was undertaken in the UK (Fee 1977). Its results were also negative.

6.3.5 Cost of treatment

The cost of hypnotherapy varies. For example, one website (Baby Centre UK) providing advice to pregnant women who smoke quotes between £30 and £150 and upwards per session.

6.3.6 Evidence statement

A body of level 1+ evidence from a meta-analysis of randomised controlled trials suggests that hypnotherapy does not improve 6-month continuous abstinence rates over that of attention control or when added to other interventions. A body of level 1- evidence suggests that hypnotherapy may be more effective than no treatment.

6.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Abbot 2006	Meta-analysis	1	+	Participants could be any smoker from any background and from any setting who were motivated to quit. N=915	Aim: to examine the efficacy of hypnotherapy compared to no treatment and other therapeutic interventions Meta-analysis: included only randomised controlled trials with suitable control groups, and at least 6-months follow-up. Five different comparison groups: (a) waiting list or no treatment; (b) attention placebo or advice; (c) psychological treatments; d) rapid or focused smoking; e) group therapy with or without hypnosis.	6 months	Hypnosis was not shown to be more effective than other psychological treatments (OR= 0.92, 95% CI: 0.42 to 2.02) or than aversive smoking (OR=1.00, 95% CI 0.32 to 3.11). Odds ratios not calculated for the other comparisons because of significant heterogeneity.	One study was UK based (Fee 1977)	Poor methodology in some studies.
Carmody 2006	RCT	1	+	266 smokers motivated to quit	What is the efficacy of self-hypnosis + nicotine patch compared to a standard behavioural counselling programme + nicotine patch Randomised controlled trial Intervention group (n=145) had 2 x 45 minute session of self-hypnosis + patches Comparison group (n=141) had	6 and 12 months Self-reports point-prevalence verified with salivary cotinine	Abstinence rates for intervention vs. comparison groups were: 6 month: 26% (n=36) vs. 19% (n=24) 12 month: 20% (n=27) vs. 15% (n=19).		Abstract data only

					2 x 45 minute session of behavioural counselling + phone counselling at 1,2, and 8 weeks		Differences were not significant.		
Tindel 2006	RCT	1	-	34 smokers motivated to quit	Is guided imagery plus brief advice more effective than brief advice alone for smoking cessation? Intervention (n=17): 6-session group-based guided imagery programme Comparison (n=17): waiting list control group (who were offered the guided imagery training at the end of 12 weeks). All participants received brief advice to quit by a physician	6 weeks 12 weeks Seven-day point prevalence abstinence	36% (n=6) vs, 18% (n=3) 30% (n=5) vs. 12% (n=2) in the intervention and control groups respectively. Difference was not significant.		Abstract data only Small sample size
Casmar 2002	RCT	1	-	75 adult smokers of at least 10 cigarettes per day. Standardised for level of hypnotisability	Does the addition of suggestion to anaethetise craving to a standard hypnosis procedure for smoking cessation reduce the recidivism rate compared to the standard procedure and control? Participants randomised to three groups (n=25 in each): (1) Speigels standard smoking cessation hypnosis procedure (2) above plus suggestion to anaethetise craving (3) placebo control All sessions lasted 90 minutes	1 month 3 month	Group 1: 16% (n=4) Group 2: 12% (n=3) Group 3: 20% (n=5) Group 1: 16% (n=4) Group 2: 8% (n=2) Group 3: 8% (n=2) No significant differences between groups. Abtsinece rates validated with salivary cotinine at 3 months. Outcome measure not		Small sample size

							defined.		
Valbo 1996	RCT	1	+	Pregnant women still smoking at 18 weeks gestation	Is hypnosis more effective than usual care in achieving smoking cessation? Intevention (n=80): received 2x45 minute hypnosis sessions 2 weeks apart. Control: (n=78) usual care (not described)	Date of delivery (approx. 4 months)	Continuous abstinence rates were 8% (n=10) in both groups (intention-to-treat).		

6.5 Meta-analysis

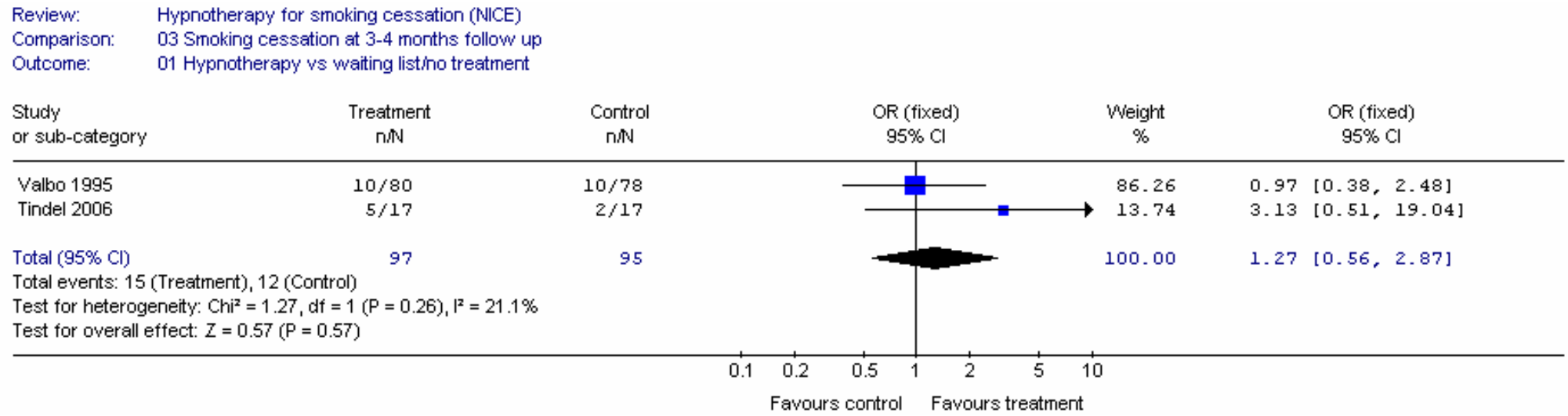
Individual meta-analyses were undertaken for each comparison and are shown below. All are taken from Abbot et al (2006). Odds ratios were calculated for all comparisons, regardless of evidence of heterogeneity. The meta-analysis of three studies shows hypnosis more effective than no treatment. However, there is a substantial heterogeneity between these studies (I^2=74%). When a random effects model is applied the beneifit of hypnosis over no treatment disappears (OR=4.52, 95% CI: 0.63-32.32). Figure 6.3 shows the results of the Cochrane analysis with the additional data from Carmody et al (2006). The addition of these data does not change the original findings.

Odds ratios for the efficacy of hypnosis versus comparison groups in aiding long-term (6 month) smoking cessation

Comparison group	Number of studies	Number of participants	Odds ratio (95% confidence interval)
No treatment or waiting list	3	252	2.39 (1.23, 4.65)
Attention control or advice	4	183	1.70 (0.84, 3.44)
Psychological treatments	3	497	1.22 (0.74, 2.00)
Rapid or focused smoking	2	54	1.00 (0.32, 3.11)
Hypnotherapy + other treatment vs. other treatment alone.	3	109	2.08 (0.93, 4.65)

Figure 6.1: Smoking cessation for hypnotherapy versus no treatment or waiting list control

(a) Medium-term (3-4 months)



(b) Long-term (6+ months)

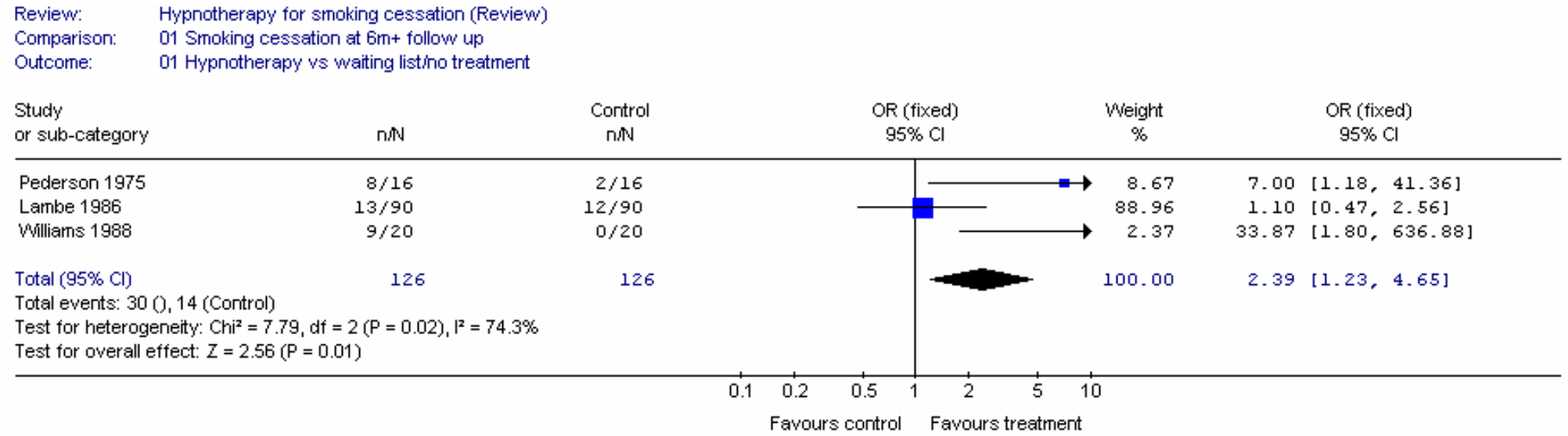


Figure 6.2: Long-term smoking cessation for hypnotherapy versus attention/advice

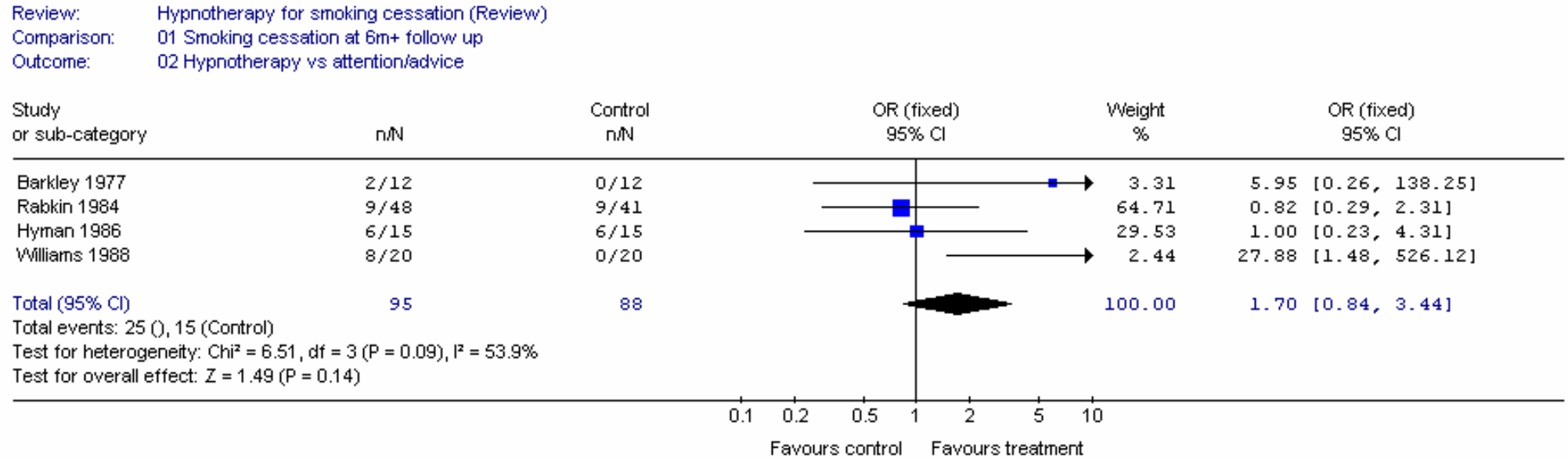


Figure 6.3: Long-term smoking cessation for hypnotherapy versus psychological treatments

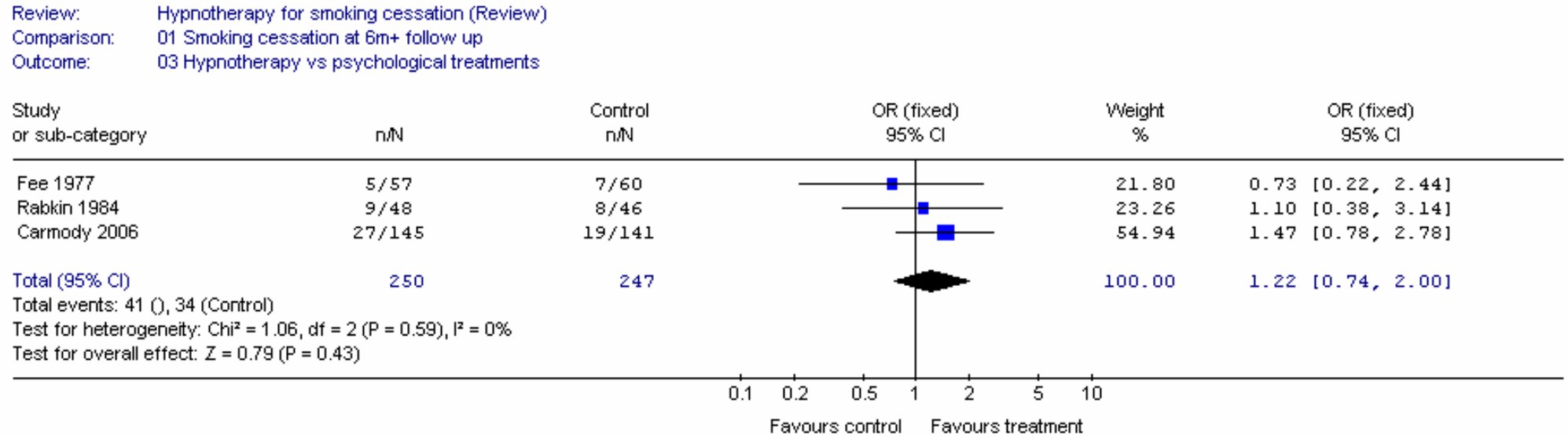


Figure 6.4: Long-term smoking cessation for hypnotherapy versus rapid/focussed smoking

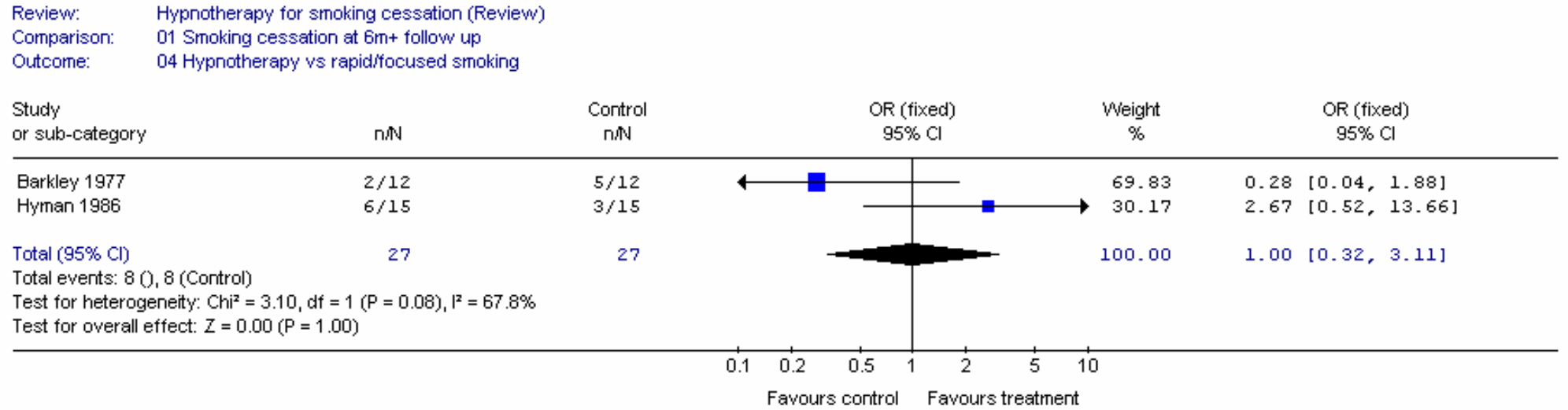
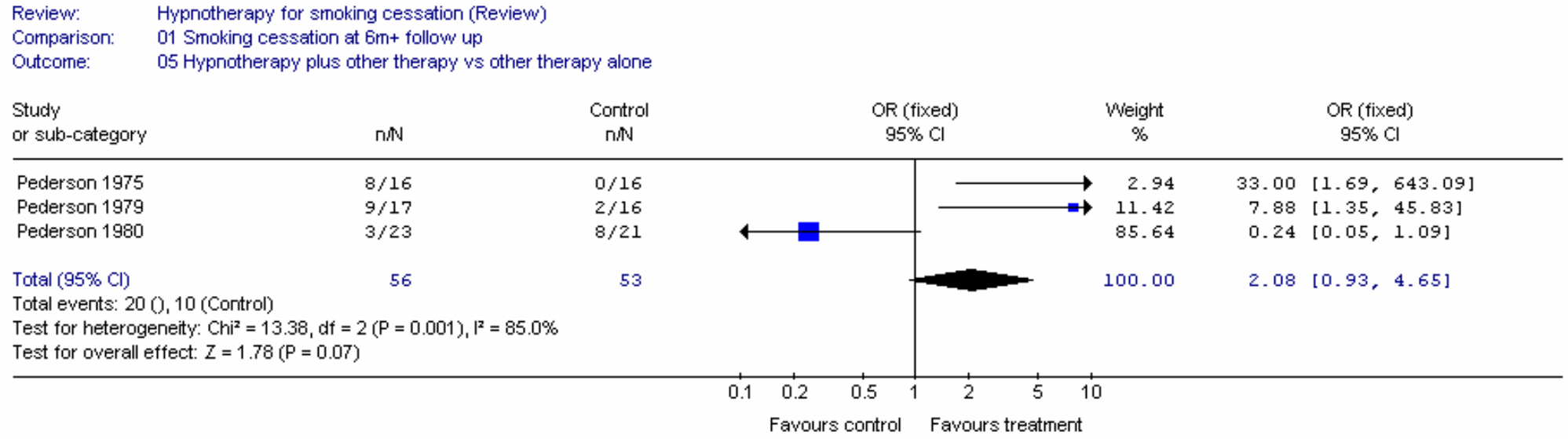


Figure 6.5: Long-term smoking cessation for hypnotherapy in addition to other therapy versus other therapy alone



6.6 References

6.6.1 Included reviews and other studies

Abbot, N. C., L. F. Stead, et al. (2006). "Hypnotherapy for smoking cessation [Systematic Review]." Cochrane Database of Systematic Reviews (1): 1-15.

Baillie, A. J., R. P. Mattick, et al. (1994). "Meta-analytic review of the efficacy of smoking cessation interventions." Drug and Alcohol Review **13**(2): 157-170.

Carmody, T., C. Duncan, et al. (2006). Self-hypnosis for smoking cessation: A randomised controlled trial. Society for Research on Nicotine & Tobacco, 12th Annual Meeting, Orlando, Florida.

Flammer, E. and W. Bongartz (2003). "On the efficacy of hypnosis: A meta-analytic study." Contemporary Hypnosis **20**(4): 179-197.

Law, M. and J. L. Tang (1995). "An analysis of the effectiveness of interventions intended to help people stop smoking." Archives of Internal Medicine **155**(18): 1933-41.

Tindel, H., N. Rigotti, et al. (2006). Guided imagery for smoking cessation: A pilot randomised trial. Society for Research on Nicotine & Tobacco, 12th Annual Meeting, Orlando, Florida.

Viswesvaran, C. and F. L. Schmidt (1992). "A meta-analytic comparison of the effectiveness of smoking cessation methods." Journal of Applied Psychology **77**(4): 554-61.

6.6.2 Retrieved references covered within included reviews

Ahijevych, K., R. Yerardi, et al. (2000). "Descriptive outcomes of the American Lung Association of Ohio hypnotherapy smoking cessation program." International Journal of Clinical & Experimental Hypnosis **48**(4): 374-87.

Casmar, P. V. (2003). "Hypnosis and smoking cessation: Anesthetization of craving." Dissertation Abstracts International: Section B: The Sciences and Engineering **63**(11-B): 5507.

Johnson, D. L. and R. T. Karkut (1994). "Performance by gender in a stop-smoking program combining hypnosis and aversion." Psychological Reports **75**(2): 851-7.

Richard, K. T. (2002). Tobacco cessation using hypnosis as part of a multimodal treatment approach: Program development and demonstration, Richard, Katie Tesla: Alliant International U., US.

Spanos, N. P., A. Sims, et al. (1992). "A comparison of hypnotic and nonhypnotic treatments for smoking." Imagination, Cognition and Personality **12**(1): 23-43.

Spiegel, D., E. J. Frischholz, et al. (1993). "Predictors of smoking abstinence following a single-session restructuring intervention with self-hypnosis." American Journal of Psychiatry **150**(7): 1090-7.

Valbo, A. and T. Eide (1996). "Smoking cessation in pregnancy: the effect of hypnosis in a randomized study." Addictive Behaviors **21**(1): 29-35.

6.6.3 Additional references

de Zwart, K. M. and J. D. Sellman (2002). "Public knowledge and attitudes regarding smoking and smoking cessation treatments." New Zealand Medical Journal **115**(1153): 219-22.

Intelihealth.com (2006). Complementary and Alternative Medicine: Hypnotherapy, Hypnosis, Available online at: www.intelihealth.com.

Sorensen, G., B. Beder, et al. (1995). "Reducing smoking at the workplace: implementing a smoking ban and hypnotherapy." Journal of Occupational & Environmental Medicine **37**(4): 453-60.

7 NICOBLOC

7.1 Background

NicoBloc (also known as Accu Drop, and Take-out; these are all equivalent products with the same formula) is marketed in the UK and 11 other countries as a smoking cessation aid (NicoBloc 2006a; NicoBloc 2006b). It is a viscous fluid containing a sugar compound that is applied to the cigarette filter. As this fluid dries it forms an occlusive barrier to nicotine and tar, as well as other components of cigarette smoke, thus reducing the delivery of these substances to the smoker. At its 'full dose' it is said to trap up to 99% of tar and nicotine (one drop traps 33%, two drops traps 66%, and three drops 99%) without affecting the taste or satisfaction of the cigarette.

Promotional material reports that NicoBloc (3 drops) reduced the yields of nicotine and tar in smoke from Winston and Marlboro cigarettes, measured using standard smoking machine, by 87-99% compared to untreated cigarettes. Pickworth et al 1998 report a lower level of reduction (20% for tar and 30% for nicotine) as measured by a smoking machine. These conflicting data were highlighted in a letter to the British Medical Journal online (King 2004).

7.1.1 What are the aim, content, and rationale of the treatment?

The proposed mechanism of action of this product is that of gradual reduction of cigarette consumption and nicotine intake. NicoBloc aims to stop the compensatory smoking that usually occurs with reduction in cigarette consumption. The manufacturer suggests that smokers reduce their cigarette consumption over a six-week period, as they increase the number of drops of NicoBloc solution applied to the filter. An example of the reduction plan for a 20/day smoker is shown in Table 7.1. The user makes a deep indentation in the filter of each cigarette and dispenses into this the correct number of drops

of solution. After the application smokers are instructed to light the cigarette and inhale, taking a strong draw initially and then smoking normally.

Table 7.1: reduction plan for a 20/day smoker						
Week	**1**	**2**	**3**	**4**	**5**	**6**
Cigarette consumption	16	12	8	4	2	0
No. of drops of NicoBloc	1	1	2	2	3	3
Each 15ml bottle of NicoBloc is said to last 2 weeks.						

The website quotes an average 60% success rate based on experience of workplace stop smoking programmes (NicoBloc 2006).

7.2 Methodology

7.2.1 Literature Search

Due to limited research data available in this area the database search limits originally set were extended to include all data currently available. In addition information was obtained from the NicoBloc website (www.nicobloc.com). The searches returned a total of 380 records (after de-duplication), of which four were relevant to this review. The large number of records returned in the search strategy was primarily due to using ‘take-out’ as a search term.

7.2.2 Selection of Studies for Inclusion

Only one randomised controlled trial met the inclusion criteria, however the three other studies (two cohort reports and one non-cessation) study are summarised below.

7.3 Summary of Findings

7.3.1 Summary of studies identified

Controlled smoking cessation trials

To examine the merit of the NicoBloc solution (the preparation used in this study was called Accu Drop) Gariti et al (2004) conducted a randomised double blind placebo controlled trial. Sixty participants were randomly allocated to used Accu Drop (n=30) or placebo (n=30) in combination with a 6-week cigarette tapering programme (cigarette consumption reduced by a third every two weeks, similar to that outlined in table 1) and six weekly counselling sessions. Smoking cessation rates were assessed at 1 week, 1 month and 6 months. Self-reported 7-day point prevalence abstinence was validated with CO in expired breath (< 10 ppm) and urinary cotinine (<50 ng/L). Data on nicotine withdrawal symptoms were also collected (although no baseline data was obtained). There was a large drop-out rate, with 45% of participants not completing the course of treatment. Abstinence rates (based on intention-to-treat, dropouts counted as smokers) at 1 week, 1 month and 6 months did not differ between groups (10%, 13%, 10% for the Accu Drop group and 3%, 10%, 13% for the control group). Ratings of withdrawal symptoms also did not differ between the groups. The trial was of good methodological quality, but because of the small sample size it is rated as 1-.

Cohort studies

Data presented in company documentation report on a cohort of 680 smokers who enrolled on the Rosen Stop Smoking course between 1998 and 2000. In addition to using the NicoBloc smokers attended a weekly group session over the course of treatment where they would watch a health promotion video (a different one each week) and also be seen individually by the facilitator and have CO levels monitored. A total of 285 (42%) smokers who enrolled in the treatment course were said to be abstinent at the end of the course. There is no indication of the length of follow-up or definition of abstinence (NicoBloc 2003).

Leahy (2003) reports on the results of the Rosen Gradual Reduction Method used in workplace programmes over a 10 year period. The programme consisted of 4-6 weekly treatments sessions as described above. No sample size is provided in the abstract, but smoking cessation was achieved in 58% of participants who completed the programme. It is not stated how many non-completers were excluded or how was abstinence defined (Leahy 2003).

Non-cessation studies

Pickworth et al (1998) conducted a randomised double blind study to investigate the effects of smoking through a filter that was partially occluded by Take Out®. Participants (n=19) were randomly allocated to smoke each one of four cigarettes that had been treated with 0, 1, 2, and 3 drops of the solution. Results demonstrated a dose dependent effect of the solution on plasma nicotine and CO boost. Of the subjective ratings, the 2 and 3-drop treated cigarettes were significantly harder to draw on than the control cigarette.

7.3.2 Evidence of efficacy

7.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

One small, but well-designed, randomised double blind placebo controlled trial showed no benefit of NicoBloc over placebo.

7.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

The intervention appears to lack efficacy.

7.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

The intervention appears to lack efficacy.

7.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

The intervention appears to lack efficacy.

7.3.3 Effect size

In the absence of evidence for efficacy no effect size can be estimated.

7.3.4 Acceptability

7.3.4.1 What are the views of those receiving and delivering the intervention?

There are no data to answer this question

7.3.4.2 Is there evidence of unintended or harmful effects?

There is no evidence of adverse effects of NicoBloc in any of the studies summarised above.

7.3.4.3 Are there barriers to replication of effective interventions?

NicoBloc has not been proven to be effective in smoking cessation.

7.3.4.4 Is this applicable to the UK?

The results of the studies reviewed are likely to be generalisable to the UK population.

7.3.5 Cost of treatment

One UK website (www.stopsmokingnow.co.uk/Shop.html) quotes the cost of one 15ml bottle of NicoBloc to be £22.59. Each bottle is said to last 2 weeks; therefore the cost of a full course of treatment is £67.77.

7.3.6 Evidence statement

One trial (level 1-) indicates that NicoBloc has no effect on long-term smoking cessation rates.

7.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Gariti 2004	RCT	1	-	N=60 highly dependent smokers (62% female) Accu Drop (n=30) vs. placebo (n=30)	Is nicotine blocking substance (Accu Drop) more effective than placebo when added to a cigarette tapering programme and counselling? Randomised double blind placebo controlled trial. Accu Drops or placebo added to cigarette tapering and weekly counselling over 6-weeks.	1 week 1 month 6 months Outcome: 7-day validated point prevalence	Accu Drop vs. placebo 10% vs. 3% 13% vs. 10% 10% vs. 13% Intention to treat analysis No significant differences	Likely to be applicable to UK setting	High drop out (45%)

7.5 Meta-analysis

Abstinence data from Gariti (2004) were entered into RevMan Software. This shows no effect of NicoBloc on smoking cessation at one month (OR=1.38. 95% CI: 0.28-6.80) or at six months (OR=1.38, 95% CI: 0.28 to 6.80).

Figure 7.1: One month point prevalence abstinence rates in NicoBloc versus placebo.

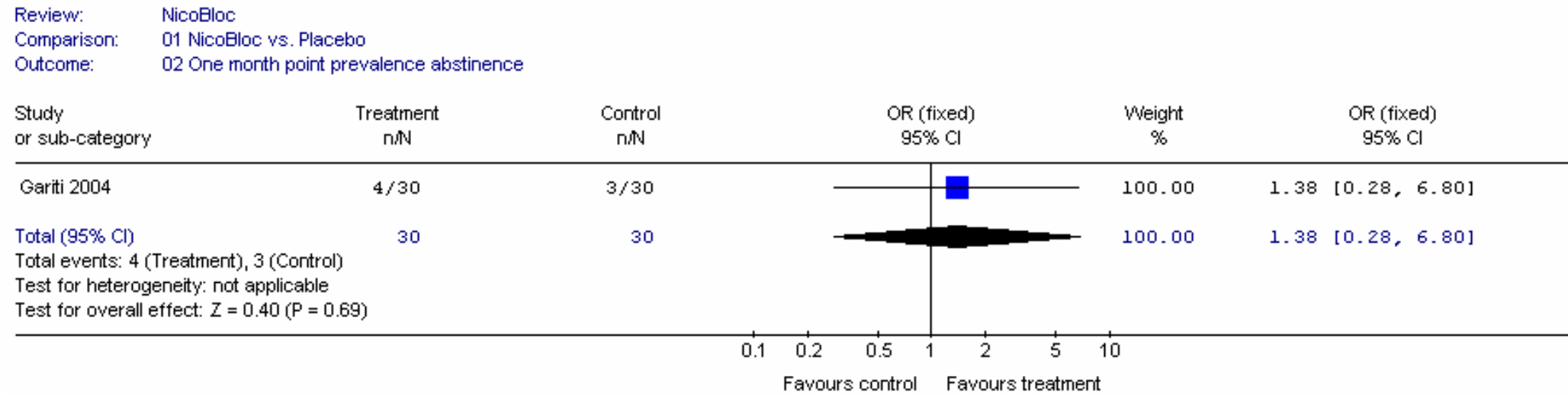
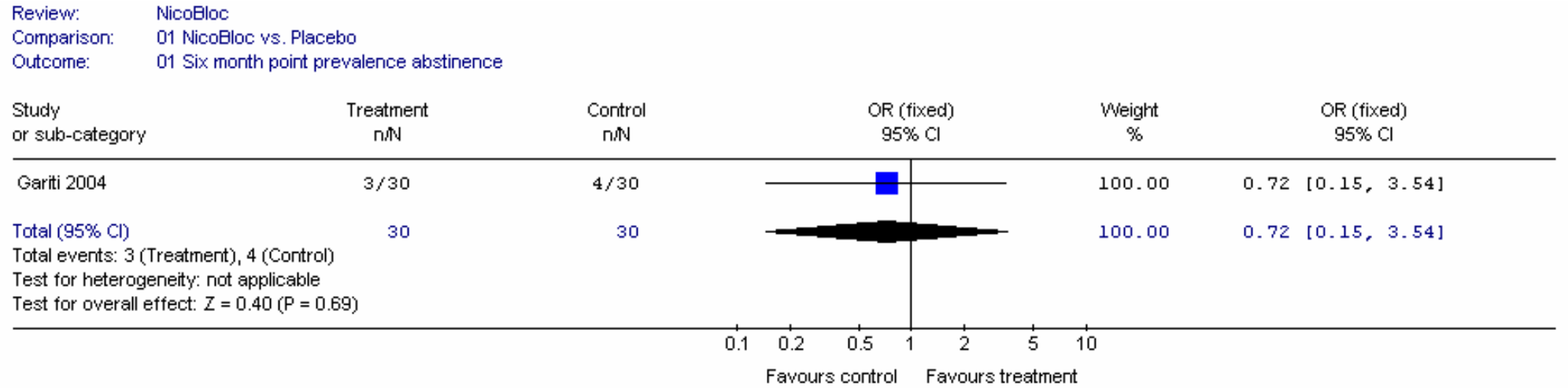


Figure 7.2: Six month point prevalence abstinence rates in NicoBloc versus placebo.



7.6 References

7.6.1 Included reviews and other studies

Gariti, P., A. I. Alterman, et al. (2004). "Adding a nicotine blocking agent to cigarette tapering." J Subst Abuse Treat **27**(1): 17-25.

Leahy, M. (2003). Stop smoking gradually with NicoBloc. The 2003 National Conference on Tobacco or Health, Boston, USA.

NicoBloc (2003). Summary of data available. Available online: http://www.stopsmokingnow.co.uk/nicobloc/research.pdf (Accessed: 09/05/06).

7.6.2 Additional references

King, B. (2004). Smoking cessation devices: does lack of regulation encourage misleading claims about evidence of effectiveness?, BMJ: Rapid Responses. Available online: http://bmj.bmjjournals.com/cgi/eletters/328/7436/397. **2006**.

NicoBloc (2006a). NicoBloc Home Page. www.nicobloc.com (Access date: 05/05/06).

NicoBloc (2006b). Pregnancy and smoking website – research & pregnancy. www.pregnancyandsmoking.co.uk/NicoBloc-Studies%20Carried%20Out.htm (Access date: 05/05/06).

8 NICOBREVIN

8.1 Background

Nicobrevin is a product marketed for smoking cessation in the UK and 11 other countries (Nicobrevin 2006). It was first developed in Germany and has been available in the UK now for over 30 years.

8.1.1 What are the aim, content, and rationale of the treatment?

Nicobrevin is composed of four main ingredients each with an action claimed (without any supporting evidence) to facilitate smoking cessation: (1) menthyl valerate, to help via its sedative and anxiolytic effects, (2) quinine, to relieve withdrawal, (3) camphor and (4) eucalyptus oil, to relieve 'airway symptoms' (Nicobrevin 2006).

The Nicobrevin website quotes a 62.5% success rate. This figure is based on the outcome of a study by Dankwa, Perry et al. (1988) described below. The course of treatment is 28 days and the dosing schedule is outlined in Table 8.1.

Table 8.1: dosage schedule (Nicobrevin 2006)

Week	Day	Dosage
1	1	2 capsules before going to bed. This is the last day of smoking.
	2-7	1 capsule in the morning 2 capsules at night
2	8-14	1 capsule twice daily
3-4	15-28	1 capsule in the evening

8.2 Methodology

8.2.1 Literature Search

Due to limited research data available in this area the database search limits originally set were extended to include all data currently available. In addition information was obtained from the Nicobrevin website (www.nicobrevin.com)

8.2.2 Selection of Studies for Inclusion

A total of 11 records were identified (including duplicate records). Three (1 review and 2 studies) were relevant to this review. The review was a Cochrane Collaboration systematic review of Nicobrevin for smoking cessation (Stead and Lancaster 2006). The two studies (Schmidt 1974; Dankwa, Perry et al. 1988) were both randomised controlled trials reporting on short-term follow-up and therefore were not entered into the Cochrane meta-analysis. We summarise them below.

8.3 Summary of Findings

8.3.1 Summary of studies identified

Reviews

The recently published Cochrane review identified two studies (Schmidt 1974; Dankwa, Perry et al. 1988). As neither provided six-month or longer follow-up they were not entered into the meta-analysis.

Controlled trials

Schmidt (1974) compared 16 different medications with a placebo in what was at the time an epic trial involving 2,475 smokers. The study involved no face to face contact, and relied on posted questionnaires. It is unclear how drugs were assigned. Two-hundred participants were allocated to Nicobrevin and 270 to non-matched placebo. Using intention-to-treat analysis (which is strict under the circumstances of this study), the end-of-treatment (4 weeks) self-

reported abstinence rates were 37% and 31% in Nicobrevin and placebo groups (NS). At 3-month the figures were 32% and 21% (Chi-square=7.13, p<0.01). An increase in efficacy after the active medication has been discontinued is unprecedented in this type of studies and raises questions about a number of study details not provided in the publication.

In a randomised double-blind placebo controlled study 92 smokers were assigned to a 28-day course of Nicobrevin (n=44) or matched placebo (n=48) (Dankwa, Perry et al. 1988). Self-reported smoking cessation in the 3rd week of treatment (7-day point-prevalence) and self-reported smoking cessation on the last (28th) day (rather than 7-days) of treatment were assessed. The abstinence rates on the last day of treatment were 59% and 27% for the active and placebo groups respectively. Those on active treatment had a greater reduction in COHb compared to baseline (mean reduction 3.37% vs. 1.84%, p<0.01). Taking into account that smokers knew they had a 50% chance of getting a placebo, had apparently received no specific instruction to stop smoking, and received no further contact over 28 days, the reported 59% cessation rate seems very high. The paper presents data in an unorthodox way with several definitions and figures not tallying. There are other methodological problems. Carboxyhaemoglobin (COHb) data were available but were not used to validate self-reported abstinence, the meaning of 24-hour abstinence as outcome is unclear, the two groups differed significantly in age, but this was not controlled for in the analysis, etc.

8.3.2 Evidence of efficacy

8.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

No data are available on the effects of Nicobrevin on long-term smoking cessation. Two trials suggest that Nicobrevin may have an effect on short-term outcome but both studies pose methodological problems.

8.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

There is insufficient evidence to answer this question.

8.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

There is insufficient evidence to answer this question.

8.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

There is insufficient evidence to answer this question.

8.3.3 Effect size

The effect size for the effect of Nicobrevin vs. placebo on end of treatment (4 weeks) abstinence is d=0.22 (4-week abstinence rates were 41% vs. 31% for Nicobrevin vs. placebo respectively. Chi-square=6.66, p<0.01). At three months (based on one study) d=0.25 (3-month abstinence rates were 32% vs. 21% Nicobrevin vs. placebo respectively. Chi-square=7.13, p<0.01).

No effect size can be estimated for long-term outcome.

8.3.4 Acceptability

8.3.4.1 What are the views of those receiving and delivering the intervention?

There is no evidence to answer this question.

8.3.4.2 Is there evidence of unintended or harmful effects?

The manufacturer of Nicobrevin does not list any side effects or contraindications although they recommend that it is not used in pregnant or breastfeeding women.

Dankwa et al (1988) reported mild gastrointestinal side effects (nausea, stomach upset, and change in appetite) in four and three participants using Nicobrevin and placebo respectively.

8.3.4.3 Are there barriers to replication of effective interventions?

The effectiveness of Nicobrevin remains to be determined.

8.3.4.4 Is this applicable to the UK?

The effectiveness of Nicobrevin remains to be determined.

8.3.5 Cost of treatment

Nicobrevin is available online and in community pharmacies. The cost of a full course of treatment varies among suppliers (e.g. £25 (Expresschemist 2006); €107/£73 (Nicobrevin 2006))

8.3.6 Evidence statement

There is level 1- evidence that Nicobrevin may have a short-term effect, but no data are available on its long-term efficacy.

8.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Schmidt 1974	Controlled trial	2	-	N=2470 smokers Mean cigarette consumption of 25 cigs/day Recruited via ads on TV and papers Nicobrevin N=200 Placebo N=270	Efficacy of 16 smoking cessation medicines compared to placebo No individual contact, all done by post. Placebo not matched to individual medicines 3 month follow-up by postal questionnaire (N=1824, 74% response rate)	4 weeks 3 months	Nicobrevin: 37% (n=74) Placebo: 31% (n=84) (Not significant) Nicobrevin: 32% (n=64) Placebo: 21% (n=57) (p<0.01)	German study	Not clear how drug was assigned. Self-report and no validation of outcome. One placebo not matched to 16 other interventions
Dankwa 1988	RCT	1	-	N=92 middle aged smokers, 35% female, 55% reported >20 cigs/day Recruit from a hospital. Unclear if inpatients outpatients Nicobrevin N= 44 Placebo N=48	Examined the efficacy of a 28 –day course of Nicobrevin or matched placebo on short-term cessation. Randomised double-blind placebo controlled trail	4 weeks	3-week self-reported point prevalence abstinence: Nicobrevin: 52% (n=23) Placebo: 17% (n=8) (p<0.001) Self-reported abstinence on day-28: Nicobrevin: 59% (n=26) Placebo: 27% (n=13) (p<0.01)	Swiss study	Active treatment group were older. Participants did not have to quit. No validation of outcome.

8.5 Meta-analysis

Abstinence data from Schmidt (1974) and Dankwa (1988) were entered into RevMan Software. This shows a significant effect of Nicobrevin on smoking cessation at 4-weeks (OR=1.56, 95% CI: 1.10-2.22, see figure 8.1). However, significant heterogeneity (I^2=80%) is present. When a random effects model is used the effect of Nicobrevin disappears (OR=2.02, 95% CI: 0.72-6.06). The effect on medium-term (3-month) cessation is shown in figure 8.2.

Figure 8.1: Short-term (4-Week) point prevalence abstinence rates in Nicobrevin versus placebo

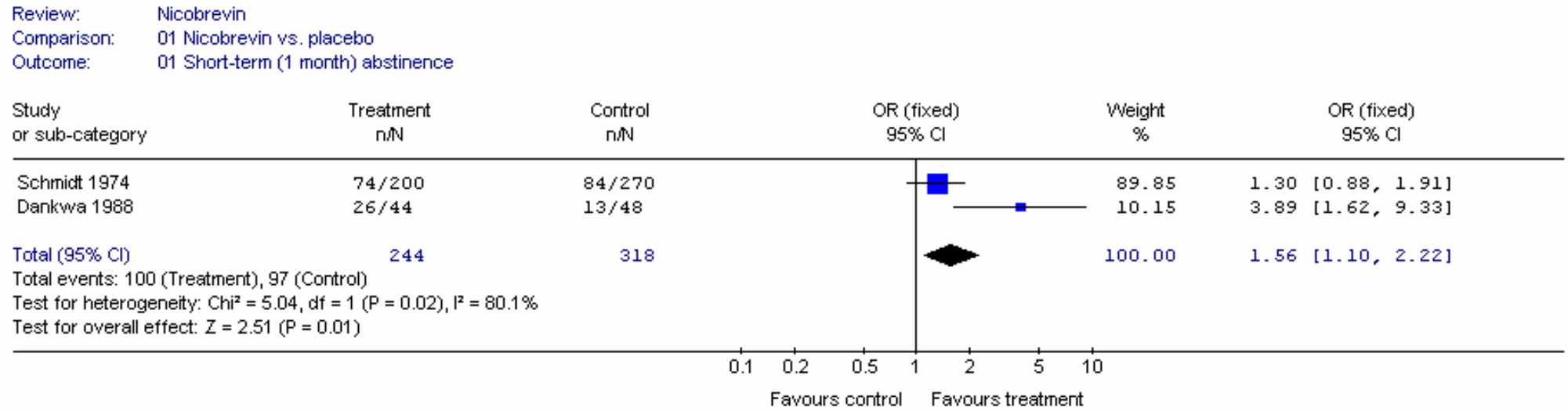
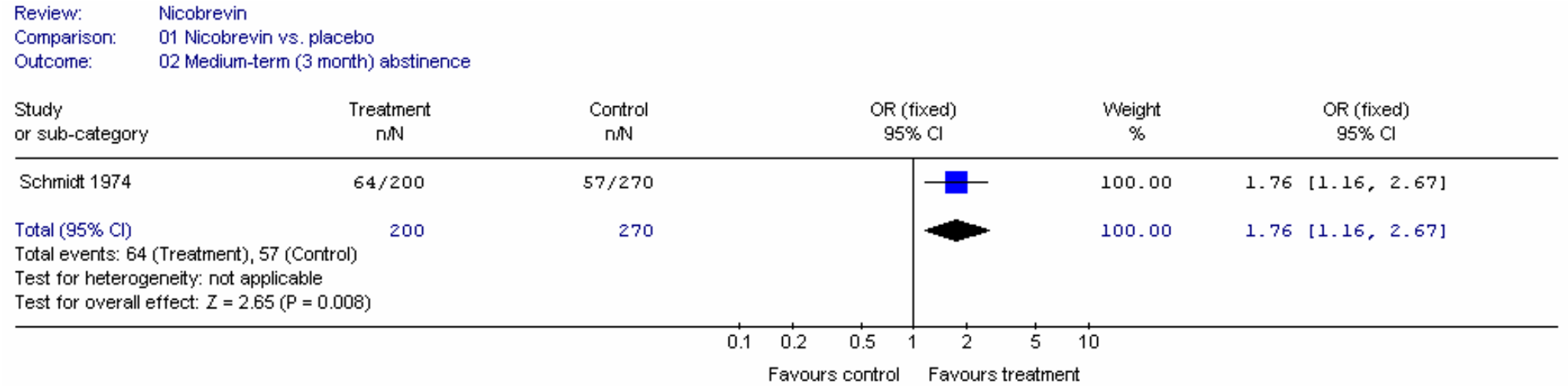


Figure 8.2: Medium-term (3-month) point prevalence abstinence rates in Nicobrevin versus placebo



8.6 References

8.6.1 Included reviews and other studies

Dankwa, E., L. Perry, et al. (1988). "A double-blind, placebo-controlled study to determine the efficacy of Nicobrevin anti-smoking capsules." Br J Clin Pract **42**(9): 359-63.

Schmidt, F. (1974). "Drug support during breaking of smoking habit - report about experiment with over 5000 smokers (double blind experiment)." Munchener Medizinsicher Wochenschrift **116**(11): 557-564.

Stead, L. and T. Lancaster (2006). "Nicobrevin for smoking cessation." Cochrane Database Syst Rev(2): CD005990.

8.6.2 Additional references

Expresschemist (2006). Expresschemist home page. www.expresschemist.co.uk/category_2180_nicobrevin.html (access date: 05/05/06).

Nicobrevin (2006). Nicobrevin Website. www.nicobrevin.com (accessed 05/05/06).

9 RAPID SMOKING

9.1 Background

Aversive treatments for smoking cessation reached their height of popularity in the 1970's and into the early 1980's. With the advent of nicotine replacement and other pharmacological treatments for smokers, the interest in aversive techniques declined and they are now rarely used. Nevertheless, there is a large body of literature on rapid smoking in particular, and the US guidelines consider the method effective (USDHHS 2000). A recent Cochrane review, although more guarded, also found signs of efficacy (Hajek and Stead 2006). There is now some renewed interest in this approach and in its potential to provide a behavioural complement to modern pharmacological treatments.

9.1.1 What is the aim and rationale of treatment?

The aim of aversive treatments for smoking cessation is to link smoking with an unpleasant stimulus to reduce its desirability.

9.1.2 What is the content of treatment?

The first version of aversion therapy for smokers involved blowing warm stale smoke in subject's faces while they smoked (Wilde 1964). Among other methods, unpleasant electric stimulation was also tried (Russell 1970). The approach which eventually became the treatment of choice was 'rapid smoking', first proposed in 1968 (Lublin and Joslyn 1968). It has also become the most extensively examined behavioural treatment for smoking cessation. The other aversive treatments will not be described in detail in this review but are summarized in Table 9.1.

Smoking cigarettes rapidly produces swift increases in plasma nicotine levels leading to a degree of 'nicotine overdose' and unpleasant central symptoms such as nausea. In addition there are also irritant sensory effects of the tobacco smoke on the oral mucus membranes, throat and airways. The

standard method of rapid smoking requires the smokers to puff on their own brand of cigarette once every six seconds. The treatment session continues until the patient has smoked a certain number of cigarettes or until they cannot tolerate further smoking. After a five-minute rest period where participants have a chance to recover and reflect on the experience, the procedure is repeated (Lichtenstein and Rodrigues 1977). This pattern continues until the patient cannot tolerate any further treatment. Timing of treatment could vary from consecutive days to weekly intervals. During the intervals between sessions patients are instructed not to smoke and to concentrate on the unpleasant sensations rapid smoking has caused.

Rapid smoking is not a 'stand-alone' treatment as most studies combined it with cognitive behavioral components, and regular support from the therapist coordinating the sessions (Lichtenstein 2002).

Table 9.1: Aversive treatments for smoking cessation

Treatment	**Description**
Electric Shock	Shocks were typically dispensed to the forearm following taking a puff on a cigarette. Sessions were carried out daily and then with increasing intervals between sessions.
Taste aversion	Products (tablets, sprays etc) containing substances that produce an unpleasant taste (e.g. cloves, ginger, menthol, licorice) when sucked or chewed were used whenever the smoker has a desire to smoke. Once the unpleasant taste was produced a cigarette was smoked in the normal way, so that smoking would become associated with the unpleasant stimulus. (Whitman 1972). Silver acetate which creates an unpleasant taste when combined with cigarette smoke have also been examined, but without proven effect (Lancaster and Stead 1997).
Focused Smoking	Smokers smoke at their own pace, but focus on the negative sensations associated with smoking (tiredness, nausea, burning sensation, coughing, breathing discomfort) (Lichtenstein and Danaher 1976).
Covert sensitization or symbolic aversion	Smokers are asked to imagine the aversive effects of smoking (burning sensations, nausea, health damage) and then to imagine the relief on putting out their cigarette (Fee 1977; Lowe, Green et al. 1980). This is sometimes done within hypnotic or auto-hypnotic treatment.
Excessive smoking	This simply involves the smoker increasing their cigarette consumption (Lando 1975; Delahunt and Curran 1976).

Taste satiation and smoke holding	*Taste satiation* involved smokers closing their eyes and focusing on sensations in their throat, lung and mouth while smoke is held in the mouth for an extended period of time, thus becoming unpleasant, and then inhaled into the lungs. The *smoke holding* technique is similar but without smoke inhalation (Kopel, Suckerman et al. 1979; Becona and Garcia 1993).
Rapid puffing	Cigarettes are puffed rapidly but not inhaled. It provides some unpleasant stimulation but not the central malaise (Erickson and Denney 1978).

9.2 Methodology

9.2.1 Literature Search

The database searches returned a total of 470 records (after de-duplication) of which nine were relevant to this review (four reviews, and five trials).

9.2.2 Selection of Studies for Inclusion

Of the four review papers identified, the Cochrane Review on aversive smoking for smoking cessation is the highest quality and most relevant to this rapid review (Hajek and Stead 2006) and it is used in the evidence tables. The other reviews which are less comprehensive are summarised below.

The most recent substantive amendment of the Cochrane review was undertaken in May 2001, and since this date only two other trials were identified (Dallery, Houtsmuller et al. 2003; McRobbie and Hajek 2005). Both of these concern withdrawal symptomatology and not smoking cessation outcome and therefore are not included in the evidence for smoking cessation. However, because these are modern studies (which is rare in this area of research, most studies of aversive smoking were published in 1970's) they are briefly summarised below, together with another trial assessing the effect of rapid smoking on withdrawal identified in our search (Houtsmuller and Stitzer 1999).

Most of the relevant literature is from early days of smoking cessation research, with methodology considered poor by today's standard. For example, self-reported reduction in cigarette consumption is often used as an outcome and are rarely biochemically validated; when abstinence is measured it is not clearly defined; studies often lack a good control group; sample sizes are very small; follow-ups are not blind to subject allocation, etc. A therapist effect is sometimes noted, and as in all behavioural treatments, it is difficult to blind subjects and investigators (Hajek and Stead 2006).

9.3 Summary of Findings

9.3.1 Summary of studies identified

Reviews

A meta-analysis of a range of smoking cessation methods which was noted earlier for its poor methodology (Viswesvaran and Schmidt 1992) identified 103 studies (involving 2557 smokers) of aversive smoking techniques and 178 studies (N=3926) investigating other aversive techniques such as electric shocks and taste aversion methods. Only 6 studies of aversive smoking had control groups. The mean quit rate (mixing different durations of follow-up and different definitions of abstinence) reported for aversive techniques (a combination of aversive smoking and other aversive methods) was 29% (with an 80% credibility interval of 11%-47%). The ‘control group’ quit rate was 6% (80% credibility interval: -2% - 16%).

Law and Tang (1995) conducted a systematic review of a range of smoking cessation interventions. They entered data from randomised controlled trials that reported at least 6-month follow-up and intention-to-treat analysis was used. 14 trials of rapid smoking or satiated smoking were included. Two of the studies (Raw and Russell 1980; Lando and McGovern 1985) included in this review were excluded from the later Cochrane review. The difference in effectiveness between the intervention and control groups was 14%, and statistically significant ($p<0.001$).

The US clinical practice guidelines for treating tobacco use and dependence (USDHHS 2000) carried out a series of meta-analyses of various interventions for smoking cessation. Randomised controlled trials with at least 5 months follow-up after the quit date were included. Intention-to-treat analysis was preferred, but data based on the number of completers were also acceptable. Point prevalence abstinence data were used in preference to continuous abstinence. Twelve studies that investigated the effect of aversive smoking procedures were included, with a total of 19 treatment arms. Separate analyses were undertaken for rapid smoking and other aversive smoking procedures. The estimated odds ratio for rapid smoking was 2.0 (95% confidence interval 1.1-3.5). The effect was borderline for other aversive smoking treatments; OR=1.7 (95% CI: 1.04-2.8). Estimated abstinence rates for rapid smoking, other aversive smoking treatments and controls were 19.9%, 17.7%, and 11.2% respectively. It should be noted that the largest (N=123) and probably the best of the rapid smoking studies (Hall, Rugg et al. 1984) which had a negative results was not included in this meta-analysis.

The most complete and stringent systematic review of aversive smoking for smoking cessation is the Cochrane review (Hajek and Stead 2006). To enter the meta-analysis studies had to be randomised controlled trials examining the efficacy of any non-pharmacological aversion treatment. Additionally for studies to be included, the control and active treatment groups had to have equal therapist contact and any other treatments used. Abstinence rates of at least six months after the beginning of treatment were required. Where several outcome measures were used, the most stringent one was included. Literature searches were made from the Cochrane Tobacco Group's specialist register, as well as the PsychINFO database. In addition hand searches of relevant behavioural science journals were undertaken.

The search strategy identified 66 studies of aversive treatments for smoking cessation. These examined a range of interventions that included rapid smoking, rapid puffing, excessive smoking, focused smoking, smoke holding, covert sensitisation, and electric shock treatment. Twenty-five studies met the criteria for inclusion. Only one study verified self-reported smoking status

(Hall, Rugg et al. 1984). Of these studies 12 (N=536 smokers) examined the efficacy of the rapid smoking procedure and nine (N=475 smokers) concerned other aversive procedures. A total of ten studies (N=326 smokers) provided data that enabled the comparison of varying intensity of aversive methods.

Abstinence data (on an intention to treat basis) was pooled and odds ratios calculated for 6-month outcome for (1) rapid smoking vs. 'attention placebo control', (2) other aversive methods vs. 'attention placebo control', and (3) intensity of aversion therapy (more vs. less aversive). The 6-month abstinence rates for rapid smoking compared to a control were 36% versus 22%, OR=1.98, CI: 1.36 - 2.90. The other aversive methods showed no significant effect (OR=1.15; 95% CI: 0.73-1.82). The intensity of aversive stimulation was marginally related to outcome (OR=1.66, CI: 1.00-2.78).

Studies of effects of rapid smoking on tobacco withdrawal symptoms

We identified three modern studies, outlined briefly in chronological order, which investigated the effect of rapid smoking on withdrawal but not on stopping smoking.

In the first study (Houtsmuller and Stitzer 1999), 14 smokers participated in each of three experimental sessions; (1) rapid smoking (smoking up to 9 cigarettes taking a puff every 6 seconds), (2) Self-paced smoking and (3) no smoking. Rapid smoking, compared to other conditions, suppressed craving, and although it did not affect significantly the latency to the first allowed cigarette, the cigarette was rated as less pleasurable.

The second study had 15 smokers undergo four smoking procedures, rapid and normal paced smoking with nicotinised and denicotinised cigarettes. Craving was suppressed by all smoking procedures, but only the rapid smoking of nicotinised cigarettes significantly increased latency to the first post-experiment cigarette (Dallery, Houtsmuller et al. 2003).

McRobbie and Hajek (2005) examined the effect of rapid smoking on urges to smoke in the first week of abstinence. One hundred smokers were randomised to a single session of rapid smoking, or to watching a motivational

film on smoking cessation immediately prior to quitting and starting a standard course of treatment combining group support and smoking cessation medication. Rapid smoking intervention reduced urges to smoke during the first 24-hours and the first week of abstinence compared to the control procedure (McRobbie and Hajek 2005).

9.3.2 Evidence of efficacy

The conclusions below are drawn primarily from the Cochrane review.

9.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

The existing studies show a significant effect of rapid smoking. However a cautionary note was added to the findings from the Cochrane review, as a funnel plot of included studies was asymmetric due to the relative absence of studies with negative results. Also, most trials used methodologies which were 'state of the art' at the time but which would not be up to current standards. The review concluded that rapid smoking cannot be considered a proven method, but there are sufficient indications of promise to warrant further evaluation. There are other strands of evidence suggesting that the method may have an active ingredient. These include the evidence for a dose response effect and the finding from recent studies that rapid smoking has an effect on craving.

9.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

In terms of whether the method is more effective on its own or within a comprehensive treatment, it would be nowadays combined with smoking cessation medications and behavioural support.

9.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

There is insufficient evidence to answer this question.

9.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

There is some evidence that increased intensity of aversive stimulation improves outcome.

9.3.3 Effect size

The effect size for the effect of rapid smoking on 6-month abstinence is d=0.32. (6 month abstinence rates were 36% vs. 22% for rapid smoking vs. control respectively. Chi-square=13.06, p<0.001).

9.3.4 Acceptability

9.3.4.1 What are the views of those receiving and delivering the intervention?

In a study comparing the efficacy of rapid smoking, rapid puffing, and behavioural counselling, participants were asked to rate (on a 5-point scale) perceived effectiveness (1=not at all effective to 5=extremely effective) at the end of treatment (Erickson, Tiffany et al. 1983). Those in the rapid smoking and puffing groups had higher mean ratings (4.8 and 4.6) than the behavioural counselling group (3.9) although the differences between groups were not significant.

9.3.4.2 Is there evidence of unintended or harmful effects?

Two main concerns regarding the use of this procedure are the risk of nicotine poisoning and cardiovascular events. The likelihood of nicotine poisoning is extremely unlikely (Russell, Raw et al. 1978). However, given that smoking in this fashion increases heart rate, systolic blood pressure and

carboxyhaemoglobin the possibility of an adverse cardiac event is of greater concern.

Detailed laboratory studies in healthy participants (participants with a history of cardiovascular disease were still screened out) have demonstrated the safety of this procedure (Sachs, Hall et al. 1978; Poole, Sanson-Fisher et al. 1980). Hall and colleagues (1984) assessed 18 individuals with documented cardiopulmonary disease before and after a period of normal and rapid smoking (Hall, Sachs et al. 1984). Despite an increase in serum nicotine concentrations there were no adverse events associated with the rapid smoking procedure. In fact arrhythmias were less frequent during rapid smoking than in periods of normal smoking and physical exertion. The conclusions drawn were that smokers with mild to moderate cardiovascular disease could safely undergo rapid smoking. However it must be acknowledged that it is unlikely that an impact of rapid smoking on cardiac events would be picked up by the relatively small numbers studied in these safety evaluations. To rule out or quantify an effect of rapid smoking on cardiac events would require pooling of data from a very large number of trial participants. There are some 'real life' data from the 1970's however estimating that over thirty thousand smokers had used the procedure and there were no reports of serious adverse events (Lichtenstein and Glasgow 1977). No reports of significant adverse events related to the use of this procedure have emerged up to now.

9.3.4.3 Are there barriers to replication of effective interventions?

Rapid smoking is unlikely to be used as the main treatment within the NHS stop smoking services. It may possibly improve the existing outcomes if incorporated as a single rapid smoking session on the quit day (McRobbie and Hajek, 2005), but further studies are needed to ascertain its efficacy in this format, and it is likely to be impracticable in most settings.

9.3.4.4 Is this applicable to the UK?

Most of the data included in the Cochrane reviews are from American studies. However, participants were mostly dependent smokers who wanted help in stopping smoking and therefore the results are generally applicable to the population of UK smokers.

9.3.5 Cost of treatment

The method only incurs time costs.

9.3.6 Evidence statement

A body of level 1+ evidence suggests that rapid smoking improves long-term abstinence rates. The method could be implemented within the UK specialist services at almost no additional cost, but it is likely to be impracticable in most settings.

9.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Hajek 2006	Meta analysis	1	+	Smokers wanting help in stopping Average age: 34 Average cigarette consumption: 28 N=536 for effect of rapid smoking on long-term abstinence analysis N=475 for effect of other aversive smoking methods on long-term abstinence analysis N=326 for dose response effect of rapid smoking on long-term abstinence analysis	Is rapid smoking more effective than an 'attention placebo control? Are other aversion methods more effective than an 'attention placebo control? Is there are dose response effect of rapid smoking? Meta-analysis Inclusion criteria: Randomised controlled trials Suitable control group At least 6-months follow-up	At least 6 months	Rapid smoking vs. control: OR=1.98 (95% CI: 1.36-2.90) Abstinence rates: 36% vs. 22% (effect size=14%) Other aversive methods vs. control: OR=1.15 (95% CI: 0.73-1.82) More aversive vs. less aversive methods: OR=1.66 (95% CI: 1.00-2.78)	Slightly younger participants and higher cigarette consumption than typically seen in NHS stop smoking services.	Poor methodology in most studies. Publication bias.

9.5 Meta-analysis

Individual meta-analyses were undertaken for each comparison and are shown below. All are taken from Hajek & Stead (2006). Rapid smoking doubles the 6-month abstinence rates relative to control procedures matched for treatment contact (OR=1.98, 95% CI: 1.36 to 2.90, see figure 9.1). The dose response effect is borderline (see figure 9.2).

Figure 9.1: Six month abstinence rates for aversive (rapid) smoking versus attention placebo control.

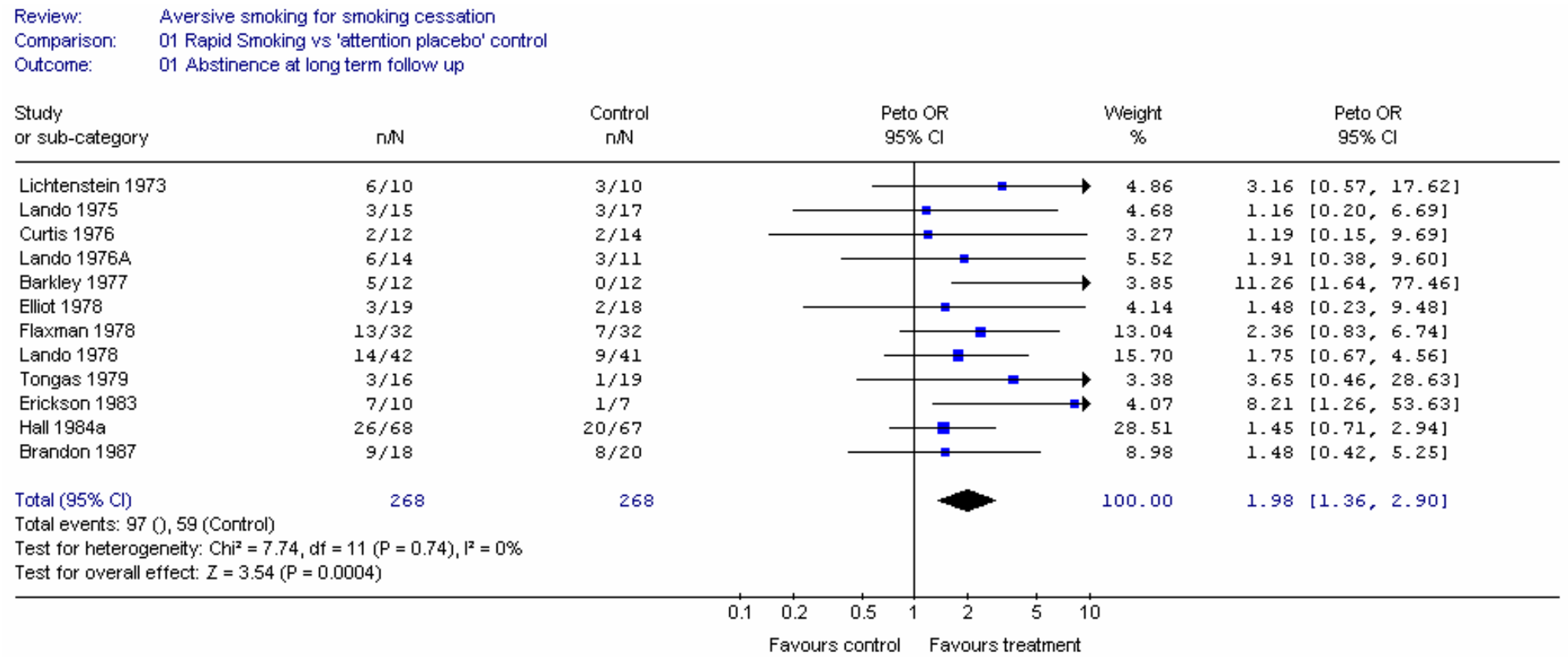
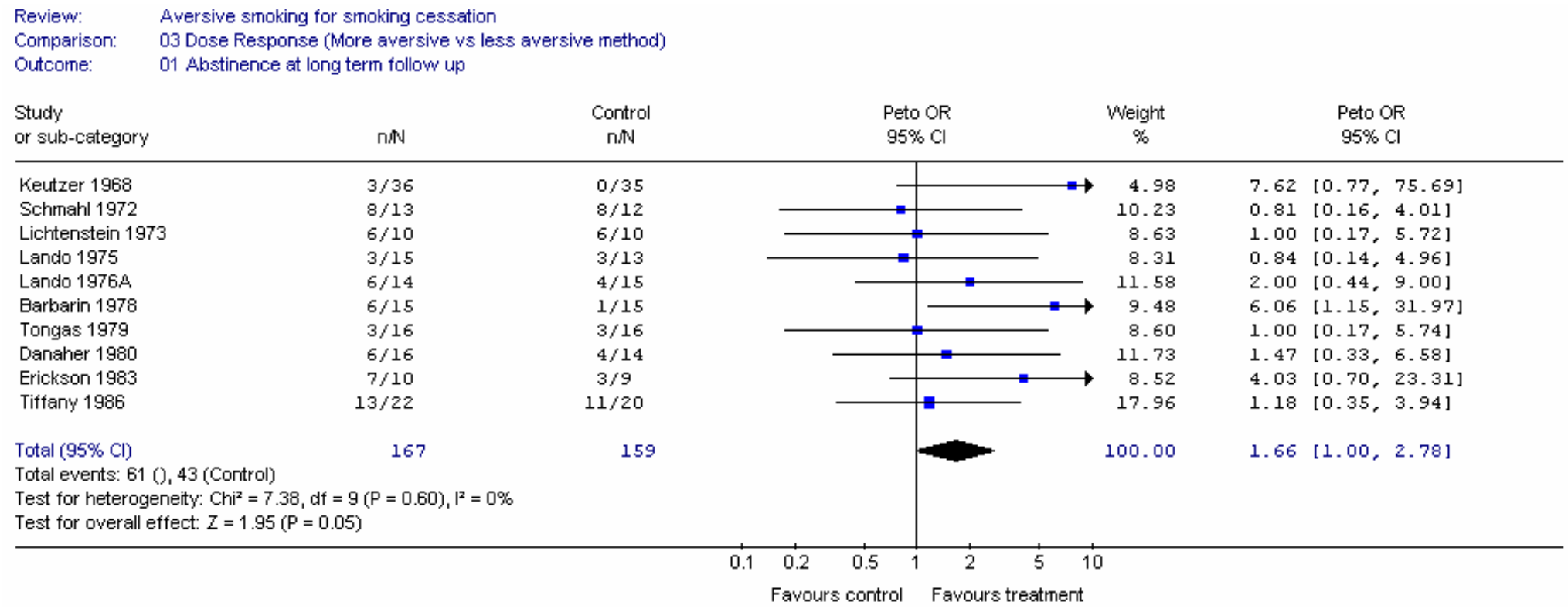


Figure 9.2: Six month abstinence rates for a dose response effect (more aversive vs. less aversive) of rapid smoking.



9.6 References

9.6.1 Included reviews and other studies

Hajek, P. and L. F. Stead (2006). "Aversive smoking for smoking cessation [Systematic Review]." Cochrane Database of Systematic Reviews **1**:1.

Law, M. and J. L. Tang (1995). "An analysis of the effectiveness of interventions intended to help people stop smoking." Archives of Internal Medicine **155**(18): 1933-41.

USDHHS (2000). Treating Tobacco Use and Dependence. Rockville, MD, United States Department of Health and Human Services, Agency for Healthcare Research Quality.

Viswesvaran, C. and F. L. Schmidt (1992). "A meta-analytic comparison of the effectiveness of smoking cessation methods." Journal of Applied Psychology **77**(4): 554-61.

9.6.2 Retrieved references covered within included reviews

Becona, E. and M. P. Garcia (1993). "Nicotine fading and smokeholding methods to smoking cessation." Psychol Rep **73**(3 Pt 1): 779-86.

Zelman, D. C., T. H. Brandon, et al. (1992). "Measures of affect and nicotine dependence predict differential response to smoking cessation treatments." J Consult Clin Psychol **60**(6): 943-52.

9.6.3 Additional references

Delahunt, J. and J. P. Curran (1976). "Effectiveness of negative practice and self-control techniques in the reduction of smoking behavior." J Consult Clin Psychol **44**(6): 1002-7.

Erickson, C. H. and D. R. Denney (1978). "A multiple-component treatment approach to smoking reduction." J Consult Clin Psychol **46**: 1330-9.

Erickson, L. M., S. T. Tiffany, et al. (1983). "Aversive smoking therapies: a conditioning analysis of therapeutic effectiveness." Behav Res Ther **21**(6): 595-611.

Fee, W. M. (1977). "Searching for the simple answer to cure the smoking habit." Health and Social Service Journal **87**: 292-3.

Hall, R. G., D. P. Sachs, et al. (1984). "Two-year efficacy and safety of rapid smoking therapy in patients with cardiac and pulmonary disease." J Consult Clin Psychol **52**(4): 574-81.

Hall, S. M., D. Rugg, et al. (1984). "Preventing relapse to cigarette smoking by behavioral skill training." J Consult Clin Psychol **52**(3): 372-82.

Kopel, S. A., K. R. Suckerman, et al. (1979). "Smoking holding: An evaluation of physiological effects and treatment efficacy of a new no hazardous aversive smoking procedure. 13th Annual Meeting of the Association for Advancement of Behavior Therapy, San Francisco."

Lancaster, T. and L. F. Stead (1997). "Silver acetate for smoking cessation." Cochrane Database Syst Rev(3): CD000191.

Lando, H. A. (1975). "A comparison of excessive and rapid smoking in the modification of chronic smoking behavior." J Consult Clin Psychol **43**(3): 350-5.

Lando, H. A. and P. G. McGovern (1985). "Nicotine fading as a nonaversive alternative in a broad-spectrum treatment for eliminating smoking." Addict Behav **10**: 153-61.

Lichtenstein, E. (2002). "From rapid smoking to the Internet: five decades of cessation research." Nicotine Tob Res **4**(2): 139-45.

Lichtenstein, E. and B. G. Danaher (1976). Modification of smoking behavior: A critical analysis of theory, research and practice. Progress in behavior modification. P. M. Miller. New York, Academic Press. **3:** 79-132.

Lichtenstein, E. and R. E. Glasgow (1977). "Rapid smoking: side effects and safeguards." J Consult Clin Psychol **45**(5): 815-21.

Lichtenstein, E. and M. R. Rodrigues (1977). "Long-term effects of rapid smoking treatment for dependent cigarette smokers." Addict Behav **2**(2-3): 109-12.

Lowe, M. R., L. Green, et al. (1980). "Self-initiated, cue extinction, and covert sensitization procedures in smoking cessation." J Behav Med **3**(4): 357-72.

Lublin, I. and L. Joslyn (1968). Aversive conditioning of cigarette addiction. Paper presented at the meeting of the Western Pyschological Association. Los Angeles, US.

Poole, A. D., R. W. Sanson-Fisher, et al. (1980). "The rapid-smoking technique: some physiological effects." Behav Res Ther **18**(6): 581-6.

Raw, M. and M. A. Russell (1980). "Rapid smoking, cue exposure and support in the modification of smoking." Behaviour research and therapy **18**(5): 363-72.

Russell, M. A. (1970). "Effect of electric aversion on cigarette smoking." Br Med J **1**(688): 82-6.

Russell, M. A., M. Raw, et al. (1978). "Blood nicotine and carboxyhemoglobin levels after rapid-smoking aversion therapy." J Consult Clin Psychol **46**(6): 1423-31.

Sachs, D. P., R. G. Hall, et al. (1978). "Effects of rapid smoking. Physiologic evaluation of a smoking-cessation therapy." Ann Intern Med **88**(5): 639-41.

Whitman, T. L. (1972). "Aversive control of smoking behavior in a group context." Behav Res Ther **10**(2): 97-104.

Wilde, G. (1964). "Behaviour therapy for addicted cigarette smokers." Behav Res Ther **2**: 107-110.

10 CYTISINE

10.1 Background

10.1.1 What are the aim, content, and rationale of the treatment?

Cytisine is an alkaloid from a plant Cytisus laburnum (Golden Rain). All parts of the plant contain cytisine, with the highest concentration found in the seeds (Sopharma 2000). The reason it is being considered for smoking cessation is that it is a nicotine analogue, acting as a partial nicotinic acetylcholine receptor agonist. It has a high affinity for the alpha-4 beta-2 receptor subtype, which is thought to be the main receptor that mediates the central effects of nicotine.

Cytisine was introduced in several Eastern European countries as a smoking cessation medication in the late 1960's and it remains in use e.g. in Bulgaria and Poland.

The dosing regimen and contraindications and cautions are shown in Table 10.1.

Cytisine is currently marketed as Tabex® by Sopharma, a Bulgarian pharmaceutical company (see http://tabex.sopharma.bg/en/tabex.html). The company claims that the efficacy of cytisine in aiding smoking cessation has been examined in eight clinical trials involving over 1000 smokers using cytisine and comparing these to smokers using placebo (n=400) or other smoking cessation medications (n=1500). The site states that *"The clinical results show a high percentage of giving up smoking with Tabex®, which is higher and statistically trustworthy as compared with placebo and the other preparations."*

There are indeed several trials of Tabex®, published in Eastern Europe, but largely unnoticed in Western countries. Pfizer is now close to launching a partial nicotinic receptor agonist varnicline, inspired by and similar to cytisine, shown to be an effective smoking cessation medication (Gonzales, Rennard

et al. 2006). Given that in theory cytisine might have similar efficacy and that it is very inexpensive (in Bulgaria it costs approximately £1.50 for a full course of treatment), its evaluation has assumed a high priority.

Table 10.1: Tabex® Contraindications and cautions for use, and dosage schedule (Sopharma 2000)
Tabex® as film tablets of 1.5 mg, 100 tablets per package
Contraindications Advanced atherosclerosis, some forms of schizophrenia, pheochromocytoma, malignant hypertension, severe cardiovascular disease, and pregnancy
Cautions Use of Tabex® in smokers with ischemic heart disease, heart failure, cerebrovascular lesions, obliterating arterial diseases, hyperthyroidism, diabetes, renal or hepatic failure, and peptic ulcer disease should be done after a risk benefit assessment by the smokers' physician.
Dosage Days 1-3: 1 tablet every 2 hours (up to six tablets per day) This is supposed to correspond with a reduction in the number of cigarettes smoked. Days 4-12: 1 tablet every 2.5 hours (up to 5 per day) *The quit day should occur on Day 5* Days 13-16: 1 tablet every 3 hours (up to 4 per day) Days 17-20: 1 tablet every 4 hours (3 per day) Days 21-25: 1 tablet every 6 hours (2 per day)

10.2 Methodology

10.2.1 Literature Search

Due to the nature of research data, mostly in foreign language and undertaken pre-1990s, the search limits originally set were extended to include all data currently available. In addition, information was obtained from the Tabex website (http://tabex.sopharma.bg/en/tabex.html and www.bpg.bg/tabex).

Of 37 records identified (after de-duplication), 16 were relevant to this review (3 reviews, and 13 studies).

10.2.2 Selection of Studies for Inclusion

Most of the literature identified was published before 1986 and in German or one of the East European languages. Of the three reviews identified in the literature search two were excluded because they provided only a brief mention of cytosine with no data. Of the 13 studies identified, 4 were controlled trials. Another controlled trial was identified in the manufacturer's literature.

10.3 Summary of Findings

10.3.1 Summary of studies identified

Reviews

Etter (2006) reported an odds ratio of 1.93 (95% CI: 1.21-3.06) for 3-8 weeks of abstinence in the three German placebo-controlled trials of cytisine. For the two placebo controlled double-blind studies the odds of being abstinent for 3-6 months in the cytisine group was 1.83 (95% CI: 1.12-2.99). The meta-analysis was reported in a brief form at a recent conference (Etter 2006). However, because the paper has only just been submitted for publication, further details were not available for this rapid review (Personal communication with JF Etter, April 2006), and thus it is not included in the evidence table.

Controlled trials

Paun and Franze (1968) compared cytisine and placebo in a poorly reported placebo controlled trial. Subjects were not randomised and it is not clear if the two groups received the same behavioural support and treatment contact. Cytisine appeared significantly more effective than placebo at 8 weeks and in a subgroup for which data were available for '2-4 months' (Paun and Franze 1968).

Scharfenberg et al (1971) reported the long-term results of a relatively well designed and well reported trial, well ahead of other literature at that time. In a

double-blind randomised trial on a large sample (N=1,214) with follow-ups at 1, 6 and 24 months, cytisine was superior to placebo at all time points (Scharfenberg, Benndorf et al. 1971). The key publication was preceded by papers covering preliminary results (Benndorf, Kempe et al. 1968).

Schmidt (1974) compared 16 different medications with a placebo in what was at the time an epic trial involving 2,475 smokers. The study involved no face to face contact, and relied on posted medications and questionnaires. The placebo was not matched to Tabex. Tabex surpassed placebo at both end-of-treatment and 3-months postal follow up in subjects who reported their outcomes, but within the intention-to-treat sample assuming non-responders to smoke (a strict assumption for a no-contact trial), the effects diminished.

Ostrovskaya (1994) in a small Russian study allocated 62 smokers to anabasine, cytisine, or their equal mixture. It is not clear if the subjects were randomised. At 15 days, the author claims that cytisine and cytisine/anabasine combination were more effective than anabasine alone (Ostrovskaya 1994). However data extraction is not possible and so the study is not included in the meta-analysis.

A review of evidence produced by Tabex manufacturers (Dobreva and Danchev 2005) mentions an unpublished Bulgarian trial by Monova in 2004 showing superiority of Tabex over placebo. The 4-week abstinence rates were 37% on Tabex and 3% on placebo. Given the insufficient details of this study, the unusually large effect reported and the fact that this information was only available in the company material, we decided not to include the trial in the meta-analysis.

Cohort studies

We found five East European papers from 1967 - 1972 reporting smoking cessation outcomes for cohorts using Cytisine (Bacvarov 1967; Paun and Franze 1968; Benndorf, Scharfenberg et al. 1969; Maliszewski and Straczynski 1972; Stoyanov and Yanachkova 1972). With relatively small samples, unclear measures of outcome, and absence of controls, the data

provide little relevant information. A recent cohort study however deserves to be mentioned.

Zatonski et al (in press) followed up 436 consecutive smokers attending a smoking cessation clinic in Warsaw, Poland. The participants received Tabex and a single session of brief behavioural support and were followed up at 12 weeks. Those reporting abstinence were contacted again at 12 months. Overall, 14% of the sample was continuously abstinent for one year, validated by CO reading (Zatonski, Cedzynska et al. In Press). This strictly established outcome of a course of Tabex with minimal behavioural support suggests an active treatment ingredient.

10.3.2 Evidence of efficacy

10.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

There is evidence from one unpublished meta-analysis that cytisine increases abstinence rates, but details of that review were not available to us. We conducted our own meta-analysis. The results show that cytisine is an effective smoking cessation treatment in both short (OR=2.35, 95% CI: 1.98-2.78) and long-term (1.86, 95% CI:1.49-2.31), but studies from the 1960's lack biochemical validation and pose other methodological problems. There was also a significant heterogeneity for some results. The meta-analysis was conservative, using intention-to-treat for the no-contact trial (Schmidt 1976), and excluding a more recent study reporting high cytisine efficacy because of insufficient details of study methodology (Dobreva and Danchev).

In addition to the results of the meta-analysis there are other independent strands of evidence supporting the conclusion that this is an effective medication. A recent rigorous cohort follow-up study (Zatonski et al., in press) demonstrated long-term validated continuous abstinence rates suggesting an active treatment ingredient; and a closely related partial nicotinic receptor agonist, varenicline, has recently been shown highly effective in smoking cessation (Gonzales, Rennard et al. 2006). Further trials conforming to

modern regulatory standards are needed as due to its low cost, this is potentially a highly cost-effective treatment.

10.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

There is insufficient evidence to answer this question.

10.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

There is insufficient evidence to answer this question.

10.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

There is insufficient evidence to answer this question.

10.3.3 Effect size

The effect size for the effect of cytisine on 4-8 week abstinence is d=0.45 (abstinence rates were 57% vs. 37% for cytisine vs. placebo respectively. Chi-square=98.33, p<0.001).

The effect size for the effect of cytisine on 2-6 month abstinence is d=0.19 (abstinence rates were 29% vs. 21% for cytisine vs. placebo respectively. Chi-square=18.75, p<0.001).

10.3.4 Acceptability

10.3.4.1 What are the views of those receiving and delivering the intervention?

There appear to be few side effects, the most prominent being nausea and gastroenterological disturbance affecting up to 10% of users. Altogether the discontinuation rate due to side effects in the recent cohort study was 16%. This is comparable to other current mediations such as bupropion and oral NRT products.

10.3.4.2 Is there evidence of unintended or harmful effects?

Cytisine is toxic in animals when ingested in large amounts. Phase I and II studies showed an increase in liver transaminases in animals given a dose of 1.35 mg/kg for a period of 90 days. However, there is a Bulgarian case report of a psychiatric patient who survived two suicide attempts which involved digesting very large amounts of cytisine tablets (Dobreva and Danchev).

When used in its therapeutic dose (1.5 – 9mg per day) cytisine is well tolerated and there are few adverse effects. The manufactures specify several contraindications and cautions listed in Table 1 above, but the medication, used for some 40 years in several countries, seems safe for the vast majority of smokers.

10.3.4.3 Are there barriers to replication of effective interventions?

Licencing requirements mean that a study conforming to current standards may be required for the treatment to be licenced in the UK.

10.3.4.4 Is this applicable to the UK?

The results of the studies reviewed concern dependent smokers seeking help and are thus likely to be generalisable to the clientele of UK specialist smoking cessation service.

10.3.5 Cost of treatment

The cost of a full course of Tabex treatment (100 tablets) in Bulgaria is approximately £1.50, and in Poland £6.00. Tabex® is available for purchase online (www.tabex.net) for approximately £20.00. Even at this price, cytisine is significantly cheaper than a course of other smoking cessation medications currently available.

10.3.6 Evidence statement

Level 1+ evidence from one randomised controlled trial suggests that cytisine improves six month abstinence rates. Evidence from studies with shorter follow-ups and recent highly positive results of a similar medication corroborate the verdict.

10.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Paun 1968	Controlled Trial	2	-	N=605 smokers German study Cytisine: N=366 Placebo: N=239	Aim: To assess the efficacy of cytisine compared to a placebo in aiding smoking cessation Non-randomised placebo control trial.	8 weeks	Cytisine: 55% (n=202) Placebo: 33% (n=80) (p<0.001) These data were entered into the 4-8 week meta-analysis. For the Potsdam group the 2-4 month abstinence rates were: Cytisine: 42% (n=15/36) Placebo: 34% (n=81/239) (NS) These data were entered into the 2-6month meta-analysis.		No definition of abstinence No validation All placebo group at one study site (Potsdam)
Scharfenberg 1971	RCT double blind	1	+	Recruited 1452 smokers. Exclusion criteria: hypertension, arteriosclerosis (n=216 excluded) N=1214 randomised (607 each to	Aim: To assess the efficacy of cytisine compared to a placebo in aiding smoking cessation Randomised double blind placebo controlled trial. Medication plus 'intensive	4 weeks 6 months 2 years	Cytisine: 65% (n=395) Placebo: 41% (n=246) (p<0.001) Cytisine: 30 % (n=185) Placebo: 16% (n=97) (p<0.001) Cytisine: 21% (n=127) Placebo: 13% (n=79) (p<0.001)		2-year follow-up by mail, with a 66% response rate. This is the same study as Benndorf et al (1968). Side effects similar in both

				cytisine and placebo)	psychological treatment'				groups.
Schmidt 1974	Controlled trial	2	-	N=2470 smokers Mean cigarette consumption of 25 cigs/day Recruited via ads on TV and papers Cytisine N=250 Placebo N=270	Examined the efficacy of 16 smoking cessation medicines against a placebo No individual contact, all done by post. Medicines packed with instructions for use but without labels identifying the medicine. 3 month follow-up by postal questionnaire (N=1824, 74% response)	4 weeks (end of treatment) 3 months	Cytisine: 41% (n=103) Placebo: 31% (n=84) ($p<0.05$) Cytisine: 25% (n=63) Placebo: 21% (n=57) (NS)		Not clear how drug was assigned. Self-report and no validation of outcome. One placebo not matched to 16 other interventions Report few side effects.

10.5 Meta-analysis

Data from the three included studies were entered into meta-analyses for short-term (4-8 week) and medium-to long-term (2-6 month) abstinence. Overall, cytisine is more effective than placebo in promoting abstinence at 4-8 weeks (OR=2.35, 95% CI: 1.98-2.78; see figure 10.1) and 2-6 months (OR=1.86, 95% CI: 1.49-2.31) after quitting. There is substantial heterogeneity between the results of the studies in both meta-analyses. Although it does not solve the problem of heterogeneity a random effects model showed a similar result to those produced by a fixed effects model: short-term OR=2.23 (95% CI: 1.60-3.09); and long-term OR=1.66 (1.06-2.61). Removing Schmidt's study removes significant heterogeneity while the results remain positive. (OR=2.16, 95% CI: 1.67-2.80).

Figure 10.1: Smoking cessation at 4-8 weeks for smokers using cytisine compared to placebo

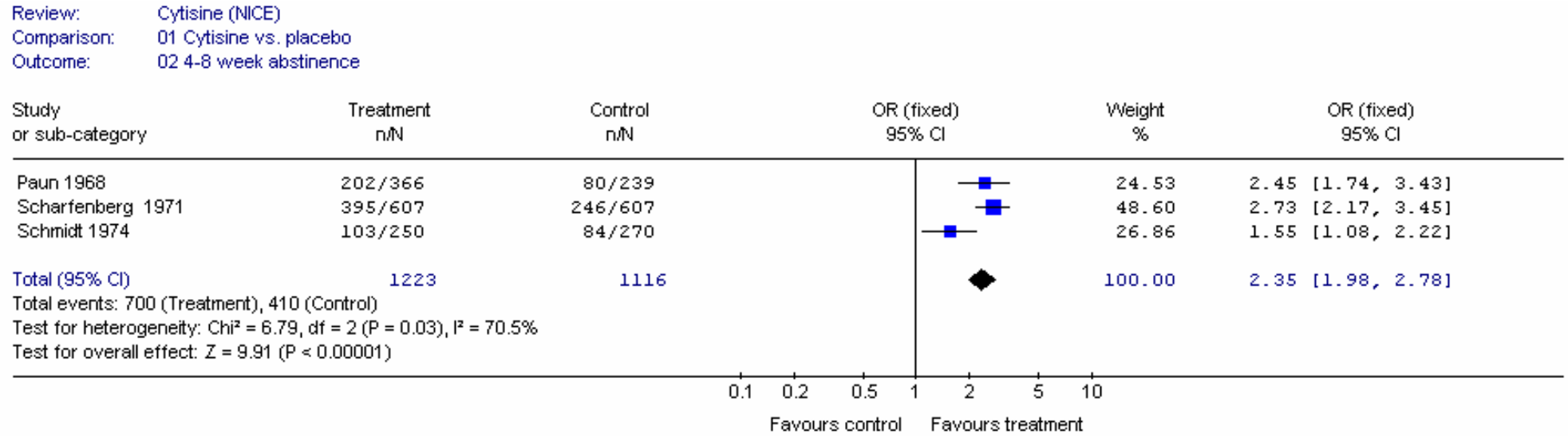
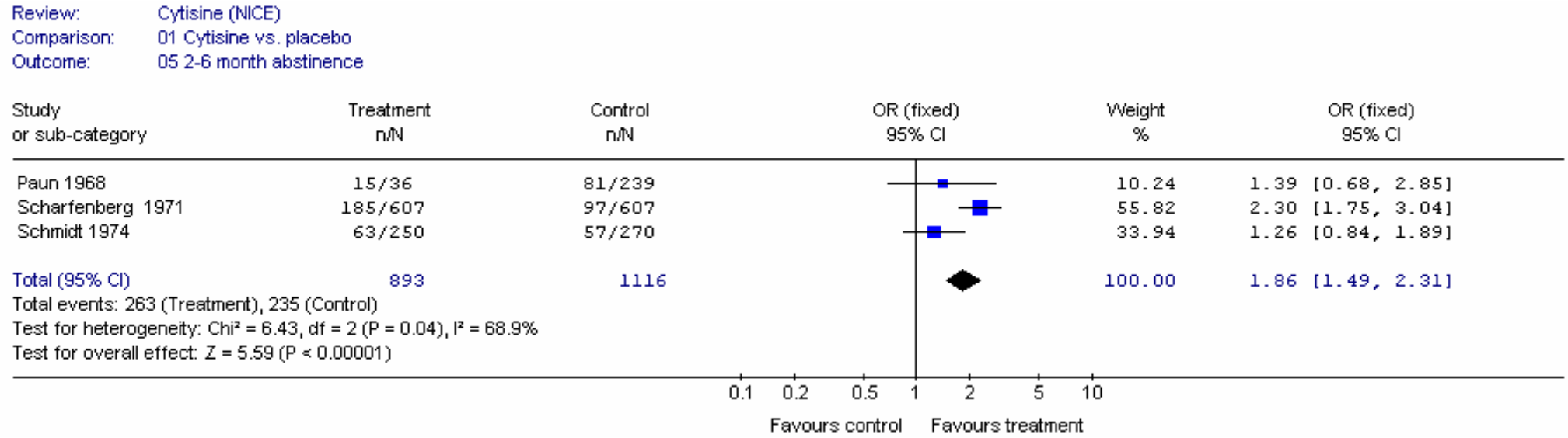


Figure 10.2: Smoking cessation at 2 to 6 months for smokers using cytisine compared to placebo



10.6 References

10.6.1 Included reviews and other studies

Benndorf, S., G. Kempe, et al. (1968). "[Results of the smoking-habit breaking using cytisin (Tabex). I]." Deutsche Gesundheitswesen **23**(44): 2092-6.

Paun, D. and J. Franze (1968). "[Breaking the smoking habit using cytisin containing "Tabex" tablets]." Deutsche Gesundheitswesen **23**(44): 2088-91.

Scharfenberg, G., S. Benndorf, et al. (1971). "[Cytisine (Tabex) as a pharmaceutical aid in stopping smoking]." Deutsche Gesundheitswesen **26**(10): 463-5.

Schmidt, F. (1974). "Drug support during breaking of smoking habit - report about experiment with over 5000 smokers (double blind experiment)." Munchener Medizinsicher Wochenschrift 116(11): 557-564.

10.6.2 Additional references

Gonzales, D. H., S. I. Rennard, et al. (2006). A pooled-analysis of varenicline, an alpha 4 beta 2 nicotinic receptor partial agonist vs. bupropion for smoking cessation (PA9-2). Society for Research on Nicotine and Tobacco, 12th Annual Meeting, Orlando, Florida.

Sopharma (2000). Tabex. For clean lungs, for a healthy heart. Available at: http://www.bpg.bg/tabex/support/EB028041814tabex_brochure.pdf.

11 GLUCOSE

11.1 Background

11.1.1 What are the aim, content, and rationale of the treatment?

Glucose is known to reduce appetite (Ganong 2001) and it is because of this effect that its role in helping smokers to quit has been investigated. The relationship between smoking and appetite is complex. Caloric restriction increases cigarette consumption (Cheskin, Hess et al. 2005), and restricting food intake while trying to stop smoking is associated with an increased risk of relapse (Hall, Tunstall et al. 1992; Borrelli, Spring et al. 2001). Smoking acutely reduces hunger (Perkins, Epstein et al. 1991; Jo, Talmage et al. 2002; Li, Kane et al. 2003), and in some studies has been found to decrease the desire for and consumption of sweet tasting foods (Grunberg 1982). This is unlikely to be due to nicotine alone as de-nicotinised cigarettes, in the short term at least, appear to be as effective as standard cigarettes in reducing hunger and 'desire for sweets' (Buchhalter, Acosta et al. 2005).

Using glucose to help smokers stop was first proposed by West in 1990 (West, Hajek et al. 1990). It was initially hypothesised that due to the hunger-suppressing effects of smoking and other physiological mechanisms (e.g. effects of smoking on glucoregulation), hunger may become a cue for smoking. Glucose might alleviate the urge to smoke by satisfying the need for carbohydrates and satiating appetite.

West (2001) suggested other mechanisms by which glucose may exert an effect on withdrawal relief via a complex pathway involving serotonin, tryptophan and insulin. Drugs that increase serotonin release reduce appetite. Nicotine stimulates serotonin release in parts of the brain (Ribeiro, Bettiker et al. 1993) whereas smoking cessation leads to a reduction in serotonin levels. Production of serotonin depends upon tryptophan, and the entry of tryptophan into the brain is indirectly influenced by insulin (Berlin, Vorspan et al. 2005). Glucose increases plasma insulin levels which lead to a reduction in blood

levels of large amino acids that compete with tryptophan for uptake into the brain. Therefore a relative decrease in these amino acids would result in a greater uptake of tryptophan into the brain, leading to an increase in serotonin.

Throughout the review the terms ‘glucose’ and ‘dextrose’ are used interchangeably. They are the same substance.

11.2 Methodology

11.2.1 Literature Search

The searches returned a total of 572 records (after de-duplication), with two unpublished papers also obtained. Fourteen papers (four review papers and ten studies) were relevant to this review.

11.2.2 Selection of Studies for Inclusion

The four review papers identified by our search did not undertake any data analysis and so do not contribute to the results of this review. Their conclusions are briefly summarised below.

Two randomised studies by West and colleagues examined the effects of glucose on abstinence (West and Willis 1998; West, May et al. Unpublished [a]). The first considered short-term (four weeks) outcome and the latter measured abstinence at six months. These studies are summarised in the evidence tables.

Nine studies investigated the effects of glucose on tobacco withdrawal symptoms. They do not contribute to the evidence for smoking cessation outcomes. However, given the paucity of data in this area and the fact that these studies are relevant for considerations of whether there is an active ingredient to the treatment, we have also summarised these below.

11.3 Summary of Findings

11.3.1 Summary of studies identified

Reviews

Dextrose for smoking cessation is mentioned in 'Practice Guidelines for the Treatment of Patients with Nicotine Dependence (Hughes, Fiester et al. 1996). At that time there were no controlled trials of long-term abstinence and so dextrose could not be recommended as a treatment for smoking cessation. Covey et al (2000) cited the results from West et al (1990, 1998) but made no recommendations. West (2001) concluded that early results for glucose were promising but not conclusive and emphasised the need for a randomised controlled trial with a long-term outcome. Finally, Foulds et al (2004) concluded that since glucose is safe and inexpensive it might be a useful adjunct to other smoking cessation medications. With more data now available since the publication of these reviews, we summarise below all current evidence.

Outcome studies

West and Willis (1998) examined the efficacy of 3g dextrose tablets in aiding short-term (four-week) abstinence in a randomised double blind placebo controlled trial. 308 smokers were randomised to one of four arms: (1) Up to 15 dextrose tablets per day plus 15 mg/16 hr nicotine patch; (2) placebo tablets plus 15 mg/16 hr nicotine patch; (3) dextrose tablets plus placebo patch; and (4) placebo tablets plus placebo patch. All participants received six one-hour support sessions over five weeks. The primary outcome measure was four week continuous abstinence, biochemically validated by carbon monoxide (CO) in expired breath (CO<10ppm). A significantly greater proportion of participants using dextrose tablets were abstinent compared to the placebo group (46% vs. 33%, $p<0.01$). No difference in weight gain was observed between the groups.

In the second trial, a double blind placebo controlled randomised study of 3g dextrose tablets (West, May et al. Unpublished [a]), 452 smokers received

glucose tablets and 476 received a placebo. Participants were encouraged to use at least 12 tablets per day. Approximately half-way through the recruitment period NRT and bupropion became reimbursable by the NHS and for the rest of the study participants were free to also use NRT or bupropion. The six-month continuous abstinence rates for the glucose and placebo treatment arms were not significantly different (15% and 13% respectively). In the sub-sample who used NRT or bupropion (n=474), 6-months abstinence rates favoured glucose (18% for glucose users versus 13% for placebo, $p<0.05$). The positive finding is based on post-hoc analyses and will require confirmation from future studies.

Studies of effects of glucose on tobacco withdrawal symptoms

We identified nine studies, outlined briefly in chronological order, which investigated the effect of glucose on withdrawal but not on stopping smoking.

1. Twenty participants who had achieved one week of abstinence were randomised to receive dextrose or placebo tablets to use ad lib (up to 20 tablets per day) over the following week (West, Hajek et al. 1990). All participants used 2mg nicotine gum ad lib in addition to the study tablets. Those who maintained abstinence over that week (n=8 in each group) were included in the analysis. Pre- and post-tablet ratings of urges to smoke were compared between the glucose and placebo groups. A significantly larger reduction in urges to smoke (reduced craving for a cigarette, time spent with urges, strength of urges, and difficulty not smoking) was reported in the glucose group compared to placebo users.

2. In a study not directly testing the glucose hypothesis, Helmers and Young (1998) randomly assigned 67 female smokers to one of two groups: normal smoking, or a twelve hour period of abstinence. Within these groups participants were then randomised to receive either a sucrose or placebo (aspartame) drink. Withdrawal ratings (craving, irritability, anxiety, difficulty concentrating, restlessness, headache, drowsiness, GI disturbances, fatigue, impatience, hunger, sweating, and dizziness) were collected at baseline and at 40 minutes after drink consumption. Compared to placebo those who

received sucrose had significantly lower ($p<0.05$) post-drink ratings of anxiety and drowsiness (Helmers and Young 1998) but not for other withdrawal symptoms.

3. Jarvik et al (1998) randomised 27 participants to glucose or placebo (sorbitol) tablets. Participants were also provided with 2mg nicotine gum and instructed to use 1-2 pieces hourly up to 20 pieces per day. Glucose had no effect on urges to smoke over two weeks of monitoring, but as only five participants abstained from smoking, 25% stopped using the study tablets a day after starting, and the analysis included smoking participants as well the five abstainers, this is difficult to interpret. The paper also reports another study that compared effects of glucose and aspartame drink on craving in a sample of 28 smokers abstaining for 3 hours, in which no effect of glucose on was found (Jarvik, Olmstead et al. 1998).

4. In their first outcome study described below, West and Willis (1998) recorded ratings of craving in the first week of abstinence. There was no significant difference between the dextrose and placebo groups.

5. In a study investigating effects of glucose on nicotine withdrawal following a period of overnight (12 hours) abstinence West et al (1999) asked 38 smokers to rate their urges to smoke in the morning before being randomly allocated to chew either four 3g glucose tablets or four sweet tasting placebo tablets. Participants then rated their urges to smoke every five minutes for 20 minutes. Glucose was significantly more effective than placebo in alleviating desire to smoke (West, Courts et al. 1999).

6. Harakas and Foulds (2002) randomised 41 students who smoked to receive a single dose of glucose (4x3g tablets) or sorbitol (placebo) following 12 hours of abstinence. Ratings of withdrawal symptoms and urges to smoke were obtained at baseline and at 5-minute intervals for 20 minutes after taking the tablets. A task to assess sustained attention was also undertaken. There were no significant effects of glucose on any of the ratings or tasks (Harakas and Foulds 2002).

7. A single dose of glucose (12g) or placebo was given by randomised allocation to 75 recent quitters attending a smokers' clinic who had achieved one week of smoking abstinence (McRobbie and Hajek 2004). Thirty-three were using bupropion and 44 were using NRT. Participants rated their withdrawal symptoms (desire to smoke, irritability, depression, hunger, restlessness and difficulty concentrating) at baseline and every 5 minutes over the next 20 minutes after chewing the tablets. Glucose had no overall effect, but it produced a significant reduction in irritability and hunger in participants using bupropion.

8. In a within subjects design 12 smokers who had abstained for 12 hours drank solution of two doses of glucose (75g and 32.5g) or placebo (aspartame 0.6g) and rated urges to smoke and withdrawal symptoms over a further 5 hour period of abstinence. Both doses of glucose had a significant effect (Berlin, Vorspan et al. 2005).

9. West et al (Unpublished b) conducted a double blind randomised controlled trial to investigate the dose response effect of single dose of glucose on desire to smoke. Participants (n=42) attended a single session after overnight abstinence, completed baseline ratings of desire to smoke, and were randomly allocated to take high dose glucose (12g), low dose glucose (6g) or placebo tablets. They then rated their urges to smoke at five minute intervals over 20 minutes. Both doses of glucose significantly reduced ratings of strength desire to smoke compared to baseline, whereas the placebo group showed no significant change. Ratings of agreement with the statement ‘I have a desire for a cigarette right now’ were significantly lower in the high dose, but not the low dose, group compared to placebo (West, Maini et al. Unpublished [b]).

11.3.2 Evidence of efficacy

11.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

There is evidence from one good quality randomised controlled trial that glucose on its own does not improve 6-month continuous abstinence rates. This trial suggests that glucose may improve efficacy of other smoking cessation medications (bupropion or NRT) (West, May et al. Unpublished [a]).

There is evidence that glucose improves short-term abstinence, and the effect seems stronger when used concomitantly with NRT or bupropion (West and Willis 1998; West, May et al. Unpublished [a]).

11.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

Glucose seems to improve abstinence only when used in combination with NRT or bupropion. On the available evidence, it is unlikely to be an effective smoking cessation agent when used on its own.

11.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

The two outcome studies were not designed with sufficient statistical power for subgroup analysis. In the withdrawal studies, effects of glucose on urges to smoke were seen in heavy smokers after a period of abstinence, but not on younger lighter smokers and those abstaining for only a short period of time and/or experiencing little withdrawal discomfort.

11.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

There is insufficient evidence to answer this question.

11.3.3 Effect size

In the absence of evidence for efficacy no effect size can be estimated for the effect of glucose on long-term abstinence.

The effect size for short term abstinence (4-week validated abstinence rates were 40% vs. 33% for glucose vs. placebo respectively. Chi-square=5.75, $p<0.05$) is d=0.14.

11.3.4 Acceptability

11.3.4.1 What are the views of those receiving and delivering the intervention?

Overall glucose tablets are well tolerated and acceptable. Participants in West & Willis (1998) rated tablet palatability on a ten point scale (1=not very pleasant to10=extremely pleasant) with no difference found between glucose and placebo, and an average score of approximately five. McRobbie & Hajek (2004) obtained ratings of sickness from participants in their study. Overall mean sickness ratings were low (less than two on a seven point scale) with no difference between the glucose and placebo groups.

11.3.4.2 Is there evidence of unintended or harmful effects?

Glucose is generally safe, but cannot be used in those with diabetes. A simple urine dipstick test for glucose should therefore be undertaken before giving smokers large quantities of glucose (West 2001). It is not clear what risks the short term use of glucose presents for dental health.

Smokers may be concerned about additional weight gain when using glucose, but West and Willis (1998) showed no significant difference in post-cessation weight gain between participants on glucose and placebo.

11.3.4.3 Are there barriers to replication of effective interventions?

Further studies are needed to replicate the positive post-hoc findings. Given the non-hazardous nature and low cost of glucose such studies should be feasible, perhaps as project within the current NHS Stop Smoking Service.

11.3.4.4 Is this applicable to the UK?

The only outcome trials of glucose and smoking cessation were undertaken in the UK.

11.3.5 Cost of treatment

Glucose tablets are inexpensive. Commercially manufactured tablets such as 'Dextro Energy' which contain 80% dextrose (this is slightly lower than those used in the West studies which contain 96% dextrose) are available for approximately fifty pence per 10 tablets (Allcures.com).

11.3.6 Evidence statement

A body of level 1+ evidence suggests that glucose on its own does not increase long-term abstinence rates. A body of level 1- evidence suggests that glucose may increase efficacy of other smoking cessation medications

11.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
West 1998	RCT	1	+	N=308 smokers seeking treatment	To assess the effectiveness of glucose, compared to placebo, on short term abstinence and carving relief Randomised double-blind placebo-controlled trial 4 groups: 1) glucose (3g) + active patch (15mg/16hr) 2) glucose + placebo patch 3) placebo (sorbitol) + active patch 4) placebo + placebo patch 6-session group based behavioural support	4 weeks Intention to treat analysis	4-week CO validated continuous abstinence rates for each group were % (n): 1) 49% (38) 2) 44% (35) 3) 36% (29) 4) 30% (21) Glucose vs. placebo: 46% vs. 33%; (p<0.01) (Effect size: 13%) Active vs. placebo patch: 43% vs. 37% (NS) No effect of glucose on craving	Applicable to UK population, and all smokers, except those with diabetes	
West 2006	RCT	1	+	N=928 smokers seeking treatment	To assess the effectiveness of glucose, compared to placebo, on 6-month	Primary end point: 6 month continuous	4-week CO validated continuous abstinence: Glucose 37% (169) Placebo: 33% (158)	Applicable to UK population, and all smokers, except those	Additional medication was provided half way through recruitment

					abstinence Randomised double-blind placebo-controlled trial 1) Glucose (3g tablets) (N=452) 2) Placebo (sorbitol) (N=476) 452 participants received no additional medication; 255 received NRT; 188 received bupropion; 31 received both	abstinence Secondary end points: Continuous abstinence at week 1, 2 3, and 4. Intention to treat analysis	6-month CO validated continuous abstinence: Glucose 15% (66) Placebo: 13% (64) In the group that received additional medication the glucose vs. placebo rates were 18% vs. 13% ($p<0.05$). In the group that received no additional medication the glucose vs. placebo rates were 11% vs. 14% (NS).	with diabetes.	because NRT and bupropion became reimbursable on NHS prescription.

11.5 Meta-analysis

Six month abstinence data from West (unpublished) were entered into RevMan Software. This shows no effect of glucose on smoking cessation (OR 1.10, 95% CI 0.76 – 1.59; see figure 11.1). When considering short term outcome (4-week) as used in the NHS Stop Smoking Service, glucose is shown to be more effective than placebo in helping smokers to stop (OR 1.32, 95%CI 1.05 – 1.67; see figure 11.2).

Figure 11.1: Effect of glucose on six month abstinence rates

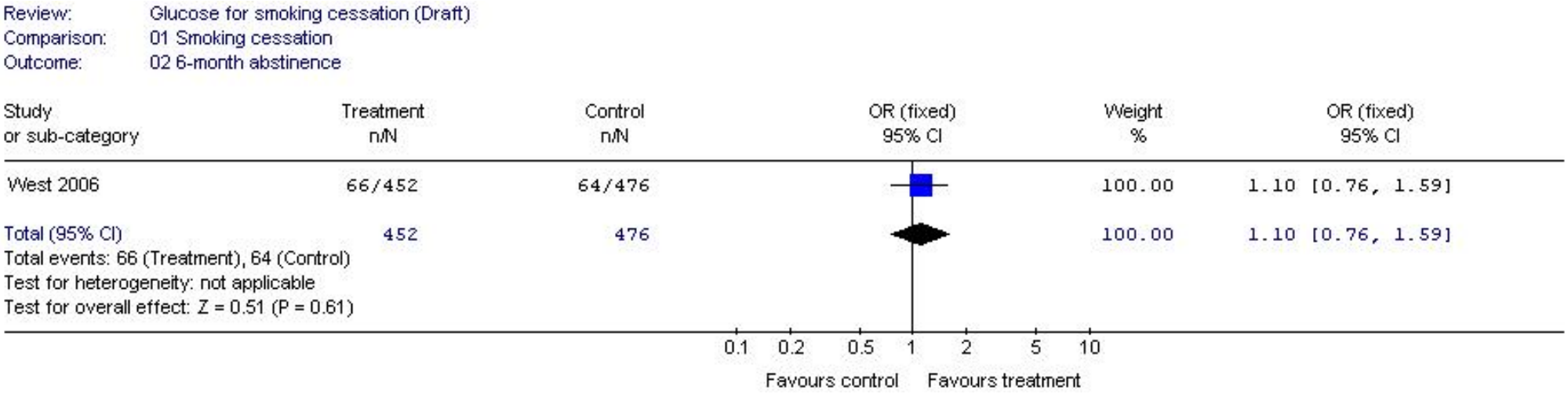
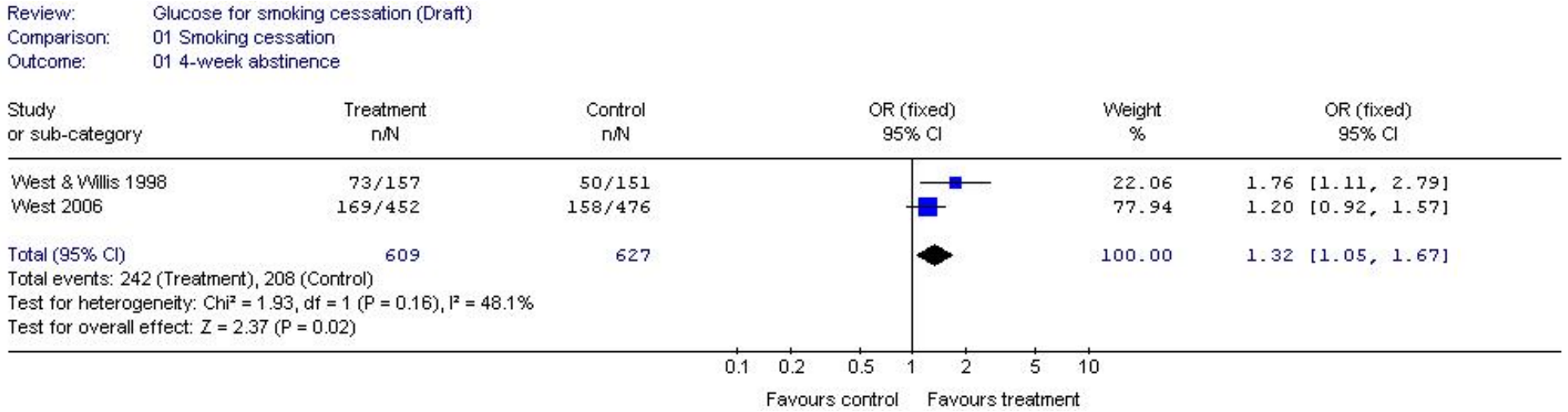


Figure 11.2: Effect of glucose on short-term (4-week) abstinence rates



11.6 References

11.6.1 Included reviews and other studies

West, R., S. May, et al. (Unpublished [a]). "A randomised trial of gluocse tablets to aid smoking cessation."

West, R. and N. Willis (1998). "Double-blind placebo controlled trial of dextrose tablets and nicotine patch in smoking cessation." Psychopharmacology **136**(2): 201-4.

11.6.2 Additional references

Allcures.com Costs of dextrose tablets. www.allcures.com/shared/product.asp?id=61481&txt=DEXTRO+ENERGY (Accessed 09/05/06).

Borrelli, B., B. Spring, et al. (2001). "Influences of gender and weight gain on short-term relapse to smoking in a cessation trial." J Consult Clin Psychol **69**(3): 511-5.

Buchhalter, A. R., M. C. Acosta, et al. (2005). "Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes." Addiction **100**(4): 550-9.

Cheskin, L. J., J. M. Hess, et al. (2005). "Calorie restriction increases cigarette use in adult smokers." Psychopharmacology **179**(2): 430-6.

Ganong, W. F. (2001). Review of medical physiology. London, McGraw-Hill.

Grunberg, N. E. (1982). "The effects of nicotine and cigarette smoking on food consumption and taste preferences." Addict Behav **7**(4): 317-31.

Hall, S. M., C. D. Tunstall, et al. (1992). "Weight gain prevention and smoking cessation: cautionary findings." Am J Public Health **82**(6): 799-803.

Perkins, K. A., L. H. Epstein, et al. (1991). "Acute effects of nicotine on hunger and caloric intake in smokers and nonsmokers." Psychopharmacology (Berl) **103**(1): 103-9.

Ribeiro, E. B., R. L. Bettiker, et al. (1993). "Effects of systemic nicotine on serotonin release in rat brain." Brain Res **621**(2): 311-8.

12 ST JOHNS WORT

12.1 Background

St John' Wort (*Hypericum perforatum L.*; SJW) extracts are known to have antidepressant properties and have been used for many years to treat mild to moderate depression, anxiety and sleep disorders (Anonymous 2004). The antidepressant effects of SJW have been reported to be at least as good as paroxetine (a selective serotonin reuptake inhibitor), but with the advantage of being better tolerated (Szegedi, Kohnen et al. 2005). However, a recent Cochrane systematic review suggests that the evidence for its effectiveness as an antidepressant may not be as robust as initially suggested (Linde, Mulrow et al. 2005).

12.1.1 What are the aim, content, and rationale of the treatment?

The effect of an antidepressant bupropion on smoking cessation was discovered by chance, but the link between smoking and depression has been long recognized. There is a higher prevalence of smoking among people who have a history, or current diagnosis, of depression (Glassman, Helzer et al. 1990), smokers who are depressed find it more difficult to quit, some smokers become depressed when they stop smoking, and post-cessation depression is related to relapse (West, Hajek et al. 1989; Killen, Fortmann et al. 1992). Antidepressants such as bupropion and nortriptyline have proven efficacy in aiding smoking cessation (Hughes, Stead et al. 2004), but not all antidepressants aid smoking cessation (Hughes, Stead et al. 2004). Those that have been shown to be effective are assumed to work via dopamine, noradrenaline and serotonin effects. SJW also acts on these systems (Barnes, Anderson et al. 2001; Calapai, Crupi et al. 2001) and so it may plausibly also aid smoking cessation. To date SJW has been shown to attenuate nicotine withdrawal symptoms in an animal study (Catania, Firenzuoli et al. 2003), and in a single study in humans (Becker, Bock et al. 2003).

Although so-called natural products are often no safer than pharmaceutical products they have greater appeal, are often cheaper and, because they are not subject to the same rigorous regulation, are more widely available.

12.2 Methodology

12.2.1 Literature Search

Due to the lack of research data the search limits originally set were extended to include all data currently available.

The searches returned a total of 17 records (after de-duplication). A search of www.controlled-trialls.com identified a UK based study investigating the effectiveness of SJW on short-term abstinence rates compared to placebo. However, this study has not yet commenced (Franklin 2006).

12.2.2 Selection of Studies for Inclusion

One review and two outcome studies were relevant for this review. No reviews or studies met the criteria for inclusion. However, due to paucity of data the studies identified are summarised below.

12.3 Summary of Findings

12.3.1 Summary of studies identified

Reviews

In a review of natural and complementary therapies for substance use disorders (Dean 2005) SJW was identified as a potential treatment for nicotine withdrawal. Results regarding the effect of SJW on withdrawal symptoms in animals (Catania, Firenzuoli et al. 2003) and in humans (Becker, Bock et al. 2003) were summarised. This latter study is summarised below. No cessation

data were identified and so no conclusions drawn regarding the effects of SJW on stopping smoking.

Outcome studies

Becker et al (2003) conducted a randomised controlled trial of combined use of a nicotine patch and SJW oral spray versus nicotine patch and placebo oral spray in 45 smokers to examine the effect of SJW on tobacco withdrawal symptoms. Both groups received brief smoking cessation counselling. Following their quit day participants rated their level of withdrawal discomfort daily for two weeks. Levels of craving, anxiety, restlessness, and sleepiness were significantly lower among the SJW group. However, no difference in 4-week quit rates was detected (33% in each group).

Barnes, Barber et al. (2006) examined the efficacy of two regimens of SJW (300mg once or twice daily) in a randomised trial involving 28 smokers. Participants commenced the medication one week before their target quit day after which they continued to use the medication for 3 months. Participants received behavioural support from a trained pharmacist at enrolment and follow-up visits at 4 weeks, and 3, 6 and 12 months after the quit day. The primary outcome measures were point prevalence and continuous abstinence rates at each follow-up time point, validated by CO reading. Participants lost to follow-up were considered to be smoking. At 3 months 18% (n=5) were verified as continuous abstainers. However, by months 6 and 12 all had relapsed. The authors suggest the study does not rule out a possibility that SJW may have an effect with a longer ‘run in time’ before the quit day and/or a higher dose (e.g. 900mg per day). Although the study was not testing SJW against placebo, the finding of 0% abstinence rate suggests of lack of efficacy.

12.3.2 Evidence of efficacy

12.3.2.1 Does the treatment have any effect on at least 6 months continuous abstinence?

Two small studies suggest that SJW, at doses up to 600mg per day, has no effect on smoking cessation.

12.3.2.2 How does the structure and content of the treatment/intervention influence effectiveness?

The medication does not appear effective in smoking cessation

12.3.2.3 Does effectiveness vary by sex, age, ethnicity, cultural practices or social or professional group of those receiving or delivering the treatment/intervention?

The medication does not appear effective in smoking cessation

12.3.2.4 Does effectiveness vary with site/setting or intensity/duration of the intervention?

The medication does not appear effective in smoking cessation

12.3.3 Effect size

In the absence of evidence for efficacy no effect size can be estimated.

12.3.4 Acceptability

12.3.4.1 What are the views of those receiving and delivering the intervention?

There is insufficient evidence to answer this question.

12.3.4.2 Is there evidence of unintended or harmful effects?

The most common adverse events reported in users of SJW are gastrointestinal disturbances, restlessness, fatigue and allergic skin reactions

(Anonymous 2004). These symptoms are experienced by only a small percentage of those who use the drug. There are also drug interactions that need to be considered. For example SJW can result in decreased plasma concentrations of amitriptyline, warfarin, atorvastatin and theophyline (Madabushi, Frank et al. 2006) via an enzyme inducing effect.

12.3.4.3 Are there barriers to replication of effective interventions?

The medication does not appear effective in smoking cessation

12.3.4.4 Is this applicable to the UK?

The medication does not appear effective in smoking cessation

12.3.5 Cost of treatment

The cost of SJW varies among suppliers. The approximate cost of 12 weeks of treatment with a good quality SJW extract (as used in Barnes et al 2006) costs approximately GBP 60 [personal communication].

12.3.6 Evidence statement

There are no placebo controlled trials available on long-term effects of SJW, but two grade 1- studies suggest indirectly that it lacks efficacy when added to nicotine patches or used on its own.

12.4 Evidence table

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Becker 2003	RCT	1	-	N=45 smokers motivated to quit	Effect of SJW on withdrawal symptoms Randomised to nicotine patch + SJW oral spray OR placebo oral spray	1 month Symptoms assessed over 2 weeks	Craving, anxiety, restlessness, & sleepiness lower in SJW users No difference in 1 month abstinence rates (33%) (N's not available).		These data were collected from an abstract only. An attempt to contact the authors was made, but there was no response. Not clear if withdrawal was reported for total sample or just abstainers
Barnes 2006	Randomised trial	No grade assigned	No grade assigned	N=28 smokers motivated to quit. Randomised to 300mg (n=13) or 600mg (n=15) SJW/day	Compare effects of 2 doses of SJW on smoking cessation	3 & 12 months	3 months: Overall 18% (n=4; 31% 300mg; n=1; 7% 600mg – non significant difference) 12 months: 0% Abstinence rates were continuous and CO validated.	Yes (UK study)	Small sample No control group

12.5 Meta-analysis

Not applicable

12.6 References

12.6.1 Included reviews and other studies

Barnes, J., N. Barber, et al. (2006). "A Pilot Randomised, Open, Uncontrolled, Clinical Study of Two Dosages of St John's Wort (Hypericum perforatum) Herb Extract (LI-160) as an Aid to Motivational/Behavioural Support in Smoking Cessation." Planta Med **72**(4): 378-82.

Becker, B., B. Bock, et al. (2003). "St. John's Wort oral spray reduces withdrawal symptoms during quitting smoking (POS4-82)." Society for Research on Nicotine and Tobacco 9th Annual Meeting February.

12.6.2 Additional references

Anonymous (2004). "Monograph. Hypericum perforatum." Altern Med Rev **9**(3): 318-25.

Barnes, J., L. A. Anderson, et al. (2001). "St John's wort (Hypericum perforatum L.): a review of its chemistry, pharmacology and clinical properties." J Pharm Pharmacol **53**(5): 583-600.

Calapai, G., A. Crupi, et al. (2001). "Serotonin, norepinephrine and dopamine involvement in the antidepressant action of hypericum perforatum." Pharmacopsychiatry **34**(2): 45-9.

Catania, M. A., F. Firenzuoli, et al. (2003). "Hypericum perforatum attenuates nicotine withdrawal signs in mice." Psychopharmacology **169**(2): 186-9.

Glassman, A. H., J. E. Helzer, et al. (1990). "Smoking, smoking cessation, and major depression." Jama **264**(12): 1546-9.

Hughes, J. R., L. F. Stead, et al. (2004). "Antidepressants for smoking cessation." Cochrane Database Syst Rev(4): CD000031.pub2.

Killen, J. D., S. P. Fortmann, et al. (1992). "Who will relapse? Symptoms of nicotine dependence predict long-term relapse after smoking cessation." J Consult Clin Psychol **60**(5): 797-801.

Linde, K., C. D. Mulrow, et al. (2005). "St John's wort for depression." Cochrane Database Syst Rev(2): CD000448.

Madabushi, R., B. Frank, et al. (2006). "Hyperforin in St. John's wort drug interactions." Eur J Clin Pharmacol **62**(3): 225-33.

Szegedi, A., R. Kohnen, et al. (2005). "Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine." Bmj **330**(7490): 503.

West, R. J., P. Hajek, et al. (1989). "Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking." Psychol Med **19**(4): 981-5.

Appendix A: Search strategies

Ovid MEDLINE(R) 1966 to May Week 2 2006

#	Search History	Results
1	smoking cessation.mp.	11844
2	smoking cessation/	9277
3	"tobacco use cessation"/	260
4	stopping smoking.mp.	471
5	Smoking/pc [Prevention & Control]	9674
6	1 or 2 or 3 or 4 or 5	19286
7	exp Tobacco/	16133
8	tobacco.mp.	46595
9	Nicotine/	14304
10	nicotine.mp.	19834
11	cigarette$.mp.	29986
12	smoking.mp.	114980
13	7 or 8 or 9 or 10 or 11 or 12	151613
14	withdraw$.mp.	64875
15	quit$.mp.	56053
16	stop$.mp.	57324
17	14 or 15 or 16	174774
18	13 and 17	9466
19	6 or 18	23188
20	Acupuncture Therapy/ or Acupuncture Points/ or Acupuncture/ or Acupuncture, Ear/ or acupuncture.mp.	9993
21	acupressure.mp. or Medicine, Chinese Traditional/ or Acupressure/	5990
22	transcranial.mp.	9758
23	transcutaneous.mp.	9120
24	Electric Stimulation/ or Electric Stimulation Therapy/ or electrostimulation.mp.	99513
25	electric stimulation.mp.	99563
26	electroacupuncture.mp. or Electroacupuncture/	1604
27	neuroelectrotherapy.mp.	0
28	laser therapy.mp.	3828
29	or/20-28	133755
30	allen carr$.mp.	1
31	easy way.mp.	504
32	30 or 31	505
33	hypnosis.mp. or Hypnosis/	7234

34	hypnotherapy.mp.	546
35	33 or 34	7305
36	nicobloc.mp.	0
37	accu drop.mp.	1
38	take-out.mp.	76
39	or/36-38	77
40	nicobrevin.mp.	3
41	Aversive Therapy/ or aversive.mp.	5446
42	avers$.mp.	9288
43	rapid.mp.	276804
44	or/41-43	285869
45	tabex.mp.	6
46	golden rain.mp.	3
47	cytisus laburnum.mp. or Laburnum/	7
48	cytisine.mp.	504
49	or/45-48	519
50	glucose.mp. or Glucose/	271067
51	sweet$.mp.	9642
52	dextrose.mp.	5350
53	Carbohydrates/ or carbohydrate.mp.	95059
54	sugar.mp.	40875
55	Sucrose/ or sucrose.mp.	43344
56	Fructose/ or fructose.mp.	23789
57	or/50-56	422136
58	exp Hypericum Perforatum/ or st john$ wort.mp.	1222
59	hypericum.mp.	1166
60	58 or 59	1355
61	19 and 29	139
62	limit 61 to (english language and yr="1990 - 2005")	72
63	19 and 32	3
64	19 and 35	133
65	limit 64 to (english language and yr="1990 - 2005")	46
66	19 and 44	431
67	limit 66 to (english language and yr="1990 - 2005")	251
68	19 and 49	18
69	19 and 57	319
70	limit 69 to (english language and yr="1990 - 2005")	229
71	19 and 60	1
72	19 and 39	2

AMED (Allied and Complementary Medicine) 1985 to May 2006

#	Search History	Results
1	Acupuncture Therapy/ or Acupuncture Points/ or Acupuncture/ or Acupuncture, Ear/ or acupuncture.mp.	6598
2	acupressure.mp. or Medicine, Chinese Traditional/ or Acupressure/	274
3	transcutaneous.mp.	686
4	transcranial.mp.	118
5	Electric Stimulation/ or Electric Stimulation Therapy/ or electrostimulation.mp.	892
6	electric stimulation.mp.	1383
7	electroacupuncture.mp. or Electroacupuncture/	668
8	neuro?electric therapy.mp.	0
9	laser therapy.mp.	147
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	8979
11	allen carr$.mp.	0
12	easy way.mp.	18
13	11 or 12	18
14	hypnosis/ or hypnosis.mp.	3147
15	hypnotherapy.mp.	342
16	14 or 15	3166
17	nicobloc.mp.	0
18	accu drop.mp.	0
19	take-out.mp.	1427
20	or/17-19	1427
21	nicobrevin.mp.	0
22	avers$.mp.	88
23	rapid.mp.	1078
24	22 or 23	1166
25	tabex.mp.	0
26	golden rain.mp.	0
27	cytisus laburnum.mp.	0
28	laburnum.mp.	1
29	cytisine.mp.	2
30	25 or 26 or 27 or 28 or 29	3
31	sweet$.mp.	104
32	dextrose.mp.	20
33	Fructose/ or fructose.mp.	35
34	sugar.mp.	227
35	Carbohydrates/ or carbohydrate.mp.	514
36	Sucrose/ or sucrose.mp.	76
37	Glucose/ or glucose.mp.	871

38	31 or 32 or 33 or 34 or 35 or 36 or 37	1573
39	st john$ wort.mp.	139
40	exp Hypericum Perforatum/ or st john$ wort.mp.	223
41	hypericum.mp.	286
42	39 or 40 or 41	315
43	smoking/ or smoking cessation/	287
44	stopping smoking.mp.	3
45	"tobacco use cessation".mp.	0
46	tobacco smoking.mp.	10
47	smokeless tobacco.mp.	1
48	tobacco.mp.	109
49	nicotine.mp.	67
50	cigarette$.mp.	119
51	smoking.mp.	672
52	withdraw$.mp.	605
53	quit$.mp.	51
54	stop$.mp.	509
55	43 or 44 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54	1841
56	10 and 55	125
57	limit 56 to (english language and yr="1990 - 2005")	100
58	13 and 55	0
59	16 and 55	70
60	limit 59 to (english language and yr="1990 - 2005")	40
61	24 and 55	36
62	limit 61 to (english language and yr="1990 - 2005")	35
63	30 and 55	0
64	38 and 55	24
65	limit 64 to (english language and yr="1990 - 2005")	18
66	42 and 55	2
67	20 and 55	28

CINAHL - Cumulative Index to Nursing , Allied Health Literature 1982 to May Week 2 2006

#	Search History	Results
1	Acupuncture Therapy/ or Acupuncture Points/ or Acupuncture/ or Acupuncture, Ear/ or acupuncture.mp.	3344
2	acupressure.mp. or Medicine, Chinese Traditional/ or Acupressure/	1286
3	transcranial.mp.	362
4	transcutaneous.mp.	1269

5	Electric Stimulation/ or Electric Stimulation Therapy/ or electrostimulation.mp.	2370
6	electric stimulation.mp.	2710
7	electroacupuncture.mp. or Electroacupuncture/	177
8	neuroelectrotherapy.mp.	0
9	laser therapy.mp.	281
10	or/1-9	8196
11	allen carr$.mp.	0
12	easy way.mp.	83
13	11 or 12	83
14	hypnosis.mp. or Hypnosis/	755
15	hypnotherapy.mp.	95
16	14 or 15	779
17	nicobloc.mp.	0
18	accu drop.mp.	0
19	take-out.mp.	20
20	or/17-19	20
21	nicobrevin.mp.	0
22	Aversive Therapy/ or aversive.mp.	127
23	avers$.mp.	274
24	rapid.mp.	6842
25	or/22-24	7113
26	tabex.mp.	0
27	golden rain.mp.	0
28	cytisus laburnum.mp. or Laburnum/	0
29	cytisine.mp.	0
30	or/26-29	0
31	glucose.mp. or Glucose/	7634
32	sweet$.mp.	944
33	dextrose.mp.	187
34	Carbohydrates/ or carbohydrate.mp.	1772
35	sugar.mp.	946
36	Sucrose/ or sucrose.mp.	679
37	Fructose/ or fructose.mp.	169
38	or/31-37	10664
39	exp Hypericum Perforatum/ or st john$ wort.mp.	466
40	hypericum.mp.	82
41	39 or 40	475
42	smoking cessation.mp.	4354
43	smoking cessation/	3343
44	exp Smoking Cessation Programs/ or "tobacco use	733

	cessation".mp.	
45	stopping smoking.mp.	70
46	Smoking/pc [Prevention & Control]	1891
47	or/42-46	5727
48	exp Tobacco/	1273
49	tobacco.mp.	4265
50	nicotine/	633
51	nicotine.mp.	1532
52	cigarette$.mp.	2798
53	smoking.mp.	15379
54	or/48-53	16871
55	withdraw$.mp.	3547
56	quit$.mp.	3486
57	stop$.mp.	4431
58	or/55-57	11059
59	54 and 58	1993
60	47 or 59	6110
61	10 and 60	49
62	limit 61 to (english and yr="1990 - 2005")	46
63	13 and 60	0
64	16 and 60	22
65	limit 64 to (english and yr="1990 - 2005")	20
66	20 and 60	0
67	25 and 60	23
68	limit 67 to (english and yr="1990 - 2005")	20
69	30 and 60	0
70	38 and 60	47
71	limit 70 to (english and yr="1990 - 2005")	42
72	41 and 60	0

EBM Reviews - Cochrane Central Register of Controlled Trials
2nd Quarter 2006

#	Search History	Results
1	smoking cessation.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	2121
2	"tobacco use cessation".mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	70
3	stopping smoking.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	77
4	smoking/pc	639
5	1 or 2 or 3 or 4	2501
6	tobacco.mp. [mp=title, original title, abstract, mesh	1381

	headings, heading words, keyword]	
7	nicotine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1690
8	cigarette$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	2123
9	smoking.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	7366
10	6 or 7 or 8 or 9	8208
11	withdraw$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	8363
12	quit$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	926
13	stop$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	4303
14	11 or 12 or 13	13018
15	10 and 14	1554
16	5 or 15	2954
17	acupuncture points.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	339
18	acupuncture.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1796
19	acupuncture therapy.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	608
20	ear acupuncture.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	26
21	chinese traditional medicine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	29
22	acupressure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	139
23	transcutaneous.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1313
24	transcranial.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	824
25	electrostimulation.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	340
26	electric stimulation.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1691
27	electric stimulation therapy.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	704
28	electroacupuncture.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	215
29	laser therapy.mp. [mp=title, original title, abstract,	383

	mesh headings, heading words, keyword]	
30	neuroelectric therapy.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1
31	or/17-30	5828
32	allen carr$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	0
33	easy way.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	9
34	32 or 33	9
35	hypnosis.mp.	553
36	hypnotherapy.mp.	62
37	35 or 36	571
38	nicobloc.mp.	0
39	accu drop.mp.	1
40	take-out.mp.	2359
41	or/38-40	2360
42	nicobrevin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1
43	avers$.mp.	411
44	rapid.mp.	9416
45	43 or 44	9807
46	tabex.mp.	2
47	golden rain.mp.	0
48	cytisus laburnum.mp.	0
49	cytisine.mp.	1
50	or/46-49	2
51	glucose.mp.	13478
52	dextrose.mp.	729
53	carbohydrate.mp.	3242
54	sugar.mp.	1027
55	sweet.mp.	208
56	fructose.mp.	514
57	sucrose.mp.	996
58	or/51-57	16854
59	st john$ wort.mp.	99
60	hypericum.mp.	153
61	hypericum/	81
62	or/59-61	172
63	16 and 31	44
64	limit 63 to yr="1990 - 2005"	25
65	16 and 34	1

66	16 and 37	14
67	limit 66 to yr="1990 - 2005"	2
68	16 and 41	34
69	16 and 45	63
70	limit 69 to yr="1990 - 2005"	30
71	16 and 50	1
72	16 and 58	47
73	limit 72 to yr="1990 - 2005"	43
74	16 and 62	1

EBM Reviews - Cochrane Database of Systematic Reviews 1st Quarter 2006

#	Search History	Results
1	smoking cessation.mp. [mp=title, abstract, full text, keywords, caption text]	105
2	"tobacco use cessation".mp. [mp=title, abstract, full text, keywords, caption text]	13
3	stopping smoking.mp. [mp=title, abstract, full text, keywords, caption text]	29
4	[smoking/pc]	0
5	1 or 2 or 3 or 4	115
6	tobacco.mp. [mp=title, abstract, full text, keywords, caption text]	117
7	nicotine.mp. [mp=title, abstract, full text, keywords, caption text]	78
8	cigarette$.mp. [mp=title, abstract, full text, keywords, caption text]	131
9	smoking.mp. [mp=title, abstract, full text, keywords, caption text]	410
10	6 or 7 or 8 or 9	452
11	withdraw$.mp. [mp=title, abstract, full text, keywords, caption text]	2328
12	quit$.mp. [mp=title, abstract, full text, keywords, caption text]	101
13	stop$.mp. [mp=title, abstract, full text, keywords, caption text]	1005
14	11 or 12 or 13	2709
15	10 and 14	349
16	5 or 15	372
17	acupuncture points.mp. [mp=title, abstract, full text, keywords, caption text]	43
18	acupuncture.mp. [mp=title, abstract, full text, keywords, caption text]	174

19	acupuncture therapy.mp. [mp=title, abstract, full text, keywords, caption text]	27
20	ear acupuncture.mp. [mp=title, abstract, full text, keywords, caption text]	9
21	chinese traditional medicine.mp. [mp=title, abstract, full text, keywords, caption text]	19
22	acupressure.mp. [mp=title, abstract, full text, keywords, caption text]	27
23	transcutaneous.mp. [mp=title, abstract, full text, keywords, caption text]	117
24	transcranial.mp. [mp=title, abstract, full text, keywords, caption text]	24
25	electrostimulation.mp. [mp=title, abstract, full text, keywords, caption text]	31
26	electric stimulation.mp. [mp=title, abstract, full text, keywords, caption text]	37
27	electric stimulation therapy.mp. [mp=title, abstract, full text, keywords, caption text]	25
28	electroacupuncture.mp. [mp=title, abstract, full text, keywords, caption text]	27
29	laser therapy.mp. [mp=title, abstract, full text, keywords, caption text]	46
30	neuroelectric therapy.mp. [mp=title, abstract, full text, keywords, caption text]	1
31	or/17-30	348
32	allen carr$.mp. [mp=title, abstract, full text, keywords, caption text]	0
33	easy way.mp. [mp=title, abstract, full text, keywords, caption text]	3
34	32 or 33	3
35	hypnosis.mp.	71
36	hypnotherapy.mp.	29
37	35 or 36	85
38	nicobloc.mp.	0
39	accu drop.mp.	0
40	take-out.mp.	1113
41	or/38-40	1113
42	nicobrevin.mp. [mp=title, abstract, full text, keywords, caption text]	0
43	avers$.mp.	45
44	rapid.mp.	602
45	43 or 44	632
46	tabex.mp.	0

47	golden rain.mp.	0
48	cytisus laburnum.mp.	0
49	cytisine.mp.	0
50	or/46-49	0
51	glucose.mp.	364
52	dextrose.mp.	106
53	carbohydrate.mp.	121
54	sugar.mp.	136
55	sweet.mp.	23
56	fructose.mp.	18
57	sucrose.mp.	34
58	or/51-57	573
59	st john$ wort.mp.	11
60	hypericum.mp.	7
61	[hypericum/]	0
62	or/59-61	13
63	16 and 31	29
64	limit 63 to yr="1990 - 2005"	29
65	16 and 34	0
66	16 and 37	14
67	limit 66 to yr="1990 - 2005"	14
68	16 and 41	153
69	16 and 45	80
70	limit 69 to yr="1990 - 2005"	80
71	16 and 50	0
72	16 and 58	79
73	limit 72 to yr="1990 - 2005"	79
74	16 and 62	1

EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2006

#	Search History	Results
1	smoking cessation.mp. [mp=title, full text, keywords]	79
2	"tobacco use cessation".mp. [mp=title, full text, keywords]	3
3	stopping smoking.mp. [mp=title, full text, keywords]	8
4	[smoking/pc]	0
5	1 or 2 or 3 or 4	83
6	tobacco.mp. [mp=title, full text, keywords]	41
7	nicotine.mp. [mp=title, full text, keywords]	26
8	cigarette$.mp. [mp=title, full text, keywords]	30
9	smoking.mp. [mp=title, full text, keywords]	156

10	6 or 7 or 8 or 9	171
11	withdraw$.mp. [mp=title, full text, keywords]	517
12	quit$.mp. [mp=title, full text, keywords]	24
13	stop$.mp. [mp=title, full text, keywords]	98
14	11 or 12 or 13	610
15	10 and 14	58
16	5 or 15	100
17	acupuncture points.mp. [mp=title, full text, keywords]	10
18	acupuncture.mp. [mp=title, full text, keywords]	91
19	acupuncture therapy.mp. [mp=title, full text, keywords]	39
20	ear acupuncture.mp. [mp=title, full text, keywords]	2
21	chinese traditional medicine.mp. [mp=title, full text, keywords]	1
22	acupressure.mp. [mp=title, full text, keywords]	10
23	transcutaneous.mp. [mp=title, full text, keywords]	52
24	transcranial.mp. [mp=title, full text, keywords]	7
25	electrostimulation.mp. [mp=title, full text, keywords]	7
26	electric stimulation.mp. [mp=title, full text, keywords]	34
27	electric stimulation therapy.mp. [mp=title, full text, keywords]	29
28	electroacupuncture.mp. [mp=title, full text, keywords]	18
29	laser therapy.mp. [mp=title, full text, keywords]	18
30	neuroelectric therapy.mp. [mp=title, full text, keywords]	0
31	or/17-30	171
32	allen carr$.mp. [mp=title, full text, keywords]	0
33	easy way.mp. [mp=title, full text, keywords]	1
34	32 or 33	1
35	hypnosis.mp.	38
36	hypnotherapy.mp.	16
37	35 or 36	46
38	nicobloc.mp.	0
39	accu drop.mp.	0
40	take-out.mp.	142
41	or/38-40	142
42	nicobrevin.mp. [mp=title, full text, keywords]	0
43	avers$.mp.	6
44	rapid.mp.	130
45	43 or 44	135
46	tabex.mp.	0

47	golden rain.mp.	0
48	cytisus laburnum.mp.	0
49	cytisine.mp.	0
50	or/46-49	0
51	glucose.mp.	81
52	dextrose.mp.	13
53	carbohydrate.mp.	11
54	sugar.mp.	17
55	sweet.mp.	0
56	fructose.mp.	3
57	sucrose.mp.	4
58	or/51-57	117
59	st john$ wort.mp.	11
60	hypericum.mp.	10
61	[hypericum/]	0
62	or/59-61	12
63	16 and 31	5
64	limit 63 to yr="1990 - 2005" [Limit not valid; records were retained]	5
65	16 and 34	0
66	16 and 37	2
67	16 and 41	7
68	16 and 45	1
69	16 and 50	0
70	16 and 58	6
71	16 and 62	0

EMBASE 1980 to 2006 Week 19

#	Search History	Results
1	smoking cessation.mp.	13574
2	smoking cessation/	12594
3	"tobacco use cessation"/	12594
4	stopping smoking.mp.	429
5	1 or 2 or 3 or 4	13731
6	exp Tobacco/	9338
7	tobacco.mp.	29884
8	Nicotine/	17171
9	nicotine.mp.	21026
10	cigarette$.mp.	38083
11	smoking.mp.	94347
12	6 or 7 or 8 or 9 or 10 or 11	120499

13	withdraw$.mp.	74573
14	quit$.mp.	4485
15	stop$.mp.	48485
16	13 or 14 or 15	123774
17	12 and 16	8295
18	5 or 17	17007
19	Acupuncture Therapy/ or Acupuncture Points/ or Acupuncture/ or Acupuncture, Ear/ or acupuncture.mp.	9184
20	acupressure.mp. or Medicine, Chinese Traditional/ or Acupressure/	5468
21	transcranial.mp.	9250
22	transcutaneous.mp.	7426
23	Electric Stimulation/ or Electric Stimulation Therapy/ or electrostimulation.mp.	27182
24	electric stimulation.mp.	1089
25	electroacupuncture.mp. or Electroacupuncture/	1236
26	neuroelectrotherapy.mp.	0
27	laser therapy.mp.	4109
28	or/19-27	59861
29	allen carr$.mp.	2
30	easy way.mp.	435
31	29 or 30	437
32	hypnosis.mp. or Hypnosis/	5706
33	hypnotherapy.mp.	485
34	32 or 33	5769
35	nicobloc.mp.	0
36	accu drop.mp.	1
37	take-out.mp.	57901
38	or/35-37	57902
39	nicobrevin.mp.	9
40	Aversive Therapy/ or aversive.mp.	4608
41	avers$.mp.	7983
42	rapid.mp.	235037
43	or/40-42	242834
44	tabex.mp.	4
45	golden rain.mp.	0
46	cytisus laburnum.mp. or Laburnum/	2
47	cytisine.mp.	650
48	or/44-47	652
49	glucose.mp. or Glucose/	202634
50	sweet$.mp.	6628

51	dextrose.mp.	4530
52	Carbohydrates/ or carbohydrate.mp.	61767
53	sugar.mp.	29654
54	Sucrose/ or sucrose.mp.	26706
55	Fructose/ or fructose.mp.	14073
56	or/49-55	299772
57	exp Hypericum Perforatum/ or st john$ wort.mp.	1426
58	hypericum.mp.	2662
59	57 or 58	2793
60	18 and 28	200
61	limit 60 to (english language and yr="1990 - 2005")	133
62	18 and 31	2
63	18 and 34	124
64	limit 63 to (english language and yr="1990 - 2005")	84
65	18 and 43	371
66	limit 65 to (english language and yr="1990 - 2005")	269
67	18 and 48	24
68	18 and 56	501
69	limit 68 to (english language and yr="1990 - 2005")	416
70	18 and 59	13
71	18 and 38	310

PsycINFO 1806 to May Week 1 2006

#	Search History	Results
1	smoking cessation.mp.	4682
2	smoking cessation/	3843
3	"tobacco use cessation"/	0
4	stopping smoking.mp.	110
5	1 or 2 or 3 or 4	4713
6	exp Tobacco/	0
7	tobacco.mp.	5925
8	Nicotine/	3854
9	nicotine.mp.	5876
10	cigarette$.mp.	6961
11	smoking.mp.	15457
12	6 or 7 or 8 or 9 or 10 or 11	22065
13	withdraw$.mp.	20134
14	quit$.mp.	3341
15	stop$.mp.	9023
16	13 or 14 or 15	31614

17	12 and 16	3790
18	5 or 17	6083
19	Acupuncture Therapy/ or Acupuncture Points/ or Acupuncture/ or Acupuncture, Ear/ or acupuncture.mp.	759
20	acupressure.mp. or Medicine, Chinese Traditional/ or Acupressure/	34
21	transcranial.mp.	1450
22	transcutaneous.mp.	281
23	Electric Stimulation/ or Electric Stimulation Therapy/ or electrostimulation.mp.	184
24	electric stimulation.mp.	403
25	electroacupuncture.mp. or Electroacupuncture/	82
26	neuroelectrotherapy.mp.	0
27	laser therapy.mp.	11
28	or/19-27	3049
29	allen carr$.mp.	0
30	easy way.mp.	72
31	29 or 30	72
32	hypnosis.mp. or Hypnosis/	12579
33	hypnotherapy.mp.	3794
34	32 or 33	13694
35	nicobloc.mp.	0
36	accu drop.mp.	1
37	take-out.mp.	30067
38	or/35-37	30068
39	nicobrevin.mp.	0
40	Aversive Therapy/ or aversive.mp.	7563
41	avers$.mp.	14120
42	rapid.mp.	19317
43	or/40-42	33176
44	tabex.mp.	0
45	golden rain.mp.	1
46	cytisus laburnum.mp. or Laburnum/	0
47	cytisine.mp.	44
48	or/44-47	45
49	glucose.mp. or Glucose/	4852
50	sweet$.mp.	2245
51	dextrose.mp.	139
52	Carbohydrates/ or carbohydrate.mp.	1497
53	sugar.mp.	1701
54	Sucrose/ or sucrose.mp.	3343

55	Fructose/ or fructose.mp.	220
56	or/49-55	11931
57	exp Hypericum Perforatum/ or st john$ wort.mp.	237
58	hypericum.mp.	161
59	57 or 58	257
60	18 and 28	31
61	limit 60 to (english language and yr="1990 - 2005")	22
62	18 and 31	1
63	18 and 34	141
64	limit 63 to (english language and yr="1990 - 2005")	67
65	18 and 43	193
66	limit 65 to (english language and yr="1990 - 2005")	113
67	18 and 48	2
68	18 and 56	61
69	limit 68 to (english language and yr="1990 - 2005")	53
70	18 and 59	2
71	18 and 38	116

British Nursing Index

Search strategy
1994-26.04.2006

BNID 1 HYPNO$.TI,AB.
RESULT 55
BNID 2 (ACUPUNCTURE OR ACUPRESSURE OR TRANCRANIAL OR TRANSCUTANEOUS).TI,AB.
RESULT 178
BNID 4 (ELECTRIC ADJ STIMULATION).TI,AB.
RESULT 0
BNID 5 (ELECTROSTIMULATION OR ELECTROACUPUNCTURE).TI,AB.
RESULT 2
BNID 6 (NEUROELECTROTHERAP$ OR LASER ADJ THERAP$).TI,AB.
RESULT 17
BNID 7 (ALLEN ADJ CARR$).TI,AB.
RESULT 0
BNID 8 (EASY ADJ WAY).TI,AB.
RESULT 3
BNID 9 (AVERSION OR AVERSIVE OR RAPID ADJ THERAP$).TI,AB.
RESULT 15
BNID 10 (GLUCOSE OR DEXTROSE OR CARBOHYDRATE OR SUGAR OR SWEET OR FRUCTOSE OR SUCROSE).TI,AB.
RESULT 303
BNID 11 (TABEX OR CYTISINE OR CYTISUS ADJ LABURNUM OR GOLDEN ADJ RAIN).TI,AB.

RESULT 0
BNID 12 (WORT OR HYPERICUM).TI,AB.
RESULT 12
BNID 13 (NICOBLOC OR NICOBREVIN).TI,AB.
RESULT 0
BNID 14 HYPNOSIS.DE.
RESULT 43
BNID 15 (ALTERNATIVE ADJ THERAPIES).DE.
RESULT 1636
BNID 16 LASER.DE.
RESULT 0
BNID 17 LASERS.DE.
RESULT 90
BNID 18 SMOKING.DE.
RESULT 1054
BNID 19 (SMOKING OR TOBACCO OR NICOTINE OR CIGARETTE$).TI,AB.
RESULT 1176
BNID 20 (1 OR 14) AND (18 OR 19)
RESULT 1
BNID 21 2 AND (18 OR 19)
RESULT 1
BNID 22 (2 OR 4 OR 5 OR 6) AND (18 OR 19)
RESULT 2
BNID 23 (7 OR 8) AND (18 OR 19)
RESULT 0
BNID 24 9 AND (18 OR 19)
RESULT 0
BNID 25 10 AND (18 OR 19)
RESULT 1
BNID 26 12 AND (18 OR 19)
RESULT 0
BNID 27 15 AND (18 OR 19)
RESULT 1

ASSIA (Applied and Social Sciences Index and Abstracts)

Date Range: 1990-2006
Search history
((((DE="smoking") or (smoking) or (DE=("tobacco" or "cigarettes" or "cigars" or "snuff")) or (tobacco) or (DE="nicotine") or (nicotine) or (cigarette*)) and (withdraw* or quit* or stop*)) and ((DE="acupuncture") or (DE="acupressure") or (DE="laser therapy") or (DE="transcutaneous electrical nerve stimulation") or ((acupuncture or acupressure or transcranial) or (transcutaneous or (electric stimulation) or (transcutaneous electric nerve stimulation)) or (electrostimulation or electroacupuncture or neuroelectrotherapy)) or (laser therapy)) or ((Allen Carr*) or (easy way)) or ((DE="hypnotherapy") or (DE="hypnosis") or (hypnotherapy or hypnosis)) or ((DE="aversion therapy") or (avers* or rapid)) or ((tabex or cytisine or (cytisus laburnum)) or (golden rain)) or ((DE="glucose") or (DE="carbohydrates") or (DE="sugar") or

(DE="sucrose") or ((glucose or dextrose or carbohydrate*) or (sugar or sweet or fructose) or sucrose)) or ((DE="st john s wort") or ((st john's wort) or (st johns wort) or hypericum)))

Sociological abstracts

(smoking cessation or tobacco use cessation or stopping smoking or tobacco or nicotine or cigarette* or withdraw* or quit* or stop*)
AND
(acupuncture or acupressure or transcranial or transcutaneous or electric stimulation or electrostimulation or electroacupuncture or neuroelectrotherapy or laser therapy)
OR
(allen carr* or easyway)
OR
(hypnosis or hypnotherapy)
OR
(nicobloc or take-out or accu drop)
OR
(nicobrevin)
OR
(avers* or rapid)
OR
(tabex or cytisine or golden rain or cytisus laburnum or laburnum)
OR
(glucose or sweet* or dextrose or carbohydrate* or sugar or sucrose or fructose)
OR
(st john* wort or hypericum)

Controlled Clinical Trials

(smoking cessation or tobacco use cessation or stopping smoking or tobacco or nicotine or cigarette* or withdraw* or quit* or stop*)
AND
(acupuncture or acupressure or transcranial or transcutaneous or electric stimulation or electrostimulation or electroacupuncture or neuroelectrotherapy or laser therapy)
OR
(allen carr* or easyway)
OR
(hypnosis or hypnotherapy)
OR
(nicobloc or take-out or accu drop)
OR
(nicobrevin)
OR
(avers* or rapid)
OR
(tabex or cytisine or golden rain or cytisus laburnum or laburnum)

OR
(glucose or sweet* or dextrose or carbohydrate* or sugar or sucrose or fructose)
OR
(st john* wort or hypericum)

Appendix B: Data extraction form

NON NHS SMOKING CESSATION TREATMENTS DATA EXTRACTION

Reviwer ID		Date		Include	Exclude

Study Details

First Author					
Title					
Journal					
Year		Volume		Issue		Pages	
Other source					
Published	Yes	No			
Country of origin		Language	English/Other		

Quality assessment

Randomisation	Yes	No	Notes	
Allocation concealment	Adequate	Unlcear	Inadequate	Not used
Participants blinded	Yes	No		
Investigators blinded	Yes	No		
Outcome assessor blinded	Yes	No		
Complete follow-up	Yes	No		
Intention to treat analysis	Yes	No		
Similar baseline characteristics	Yes	No		

Participants

	Treatment	Control	Total	Unknown	Total N
%male					
Mean age					
Age range					
Average cigarette consumption					
Number randomised					
Drop-outs					
Other:					

Components

Intervention

Control

Outcomes Other

Group	1 month		3 months		12 months			
	%	N	%	N	%	N	%	N
Interventn								
Control								

Continuous / Point prevalence / Other:

Lost to follow-up Intervention % N

Control % N

Biochemical validation Yes No Time

Method CO Cotinine saliva blood urine

Quality appraisal

++'	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+'	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
-'	Few or no criteria fulfilled.The conclusions of the study are thought likely or very likely to alter.

NOTES

Appendix C: Excluded reviews and studies

ACUPUNCTURE	
Reviews excluded	***Reason for exclusion***
Birch, S., J. K. Hesselink, et al. (2004). "Clinical research on acupuncture: Part 1. What have reviews of the efficacy and safety of acupuncture told us so far?" Journal of Alternative & Complementary Medicine **10**(3): 468-480.	Not a systematic review of RCTs
Brewington, V., M. Smith, et al. (1994). "Acupuncture as a detoxification treatment: an analysis of controlled research." Journal of Substance Abuse Treatment **11**(4): 289-307.	Not a systematic review of RCTs
Dean, A. J. (2005). "Natural and complementary therapies for substance use disorders." Current Opinion in Psychiatry **18**(3): 271-276.	Not a systematic review of RCTs
Jiang, A. and M. Cui (1994). "Analysis of therapeutic effects of acupuncture on abstinence from smoking." Journal of Traditional Chinese Medicine **14**(1): 56-63.	Not a systematic review of RCTs
Lando, H. A. (1996). "Smoking cessation products and programs." Alaska Medicine **38**(2): 65-8.	Not a systematic review of RCTs
Linde, K., A. Vickers, et al. (2001). "Systematic reviews of complementary therapies - an annotated bibliography. Part 1: acupuncture." BMC Complementary & Alternative Medicine **1**: 3.	Bibliography of systematic reviews
Miller, M. and L. Wood (2003). "Effectiveness of smoking cessation interventions: review of evidence and implications for best practice in Australian health care settings." Australian & New Zealand Journal of Public Health **27**(3): 300-9.	Not a systematic review of RCTs
Vickers, A., P. Wilson, et al. (2002). "Effectiveness bulletin: Acupuncture." Qual Saf Health Care **11**: 92-97.	Not a systematic review of RCTs
Villano, L. M. and A. R. White (2004). "Alternative therapies for tobacco dependence." Medical Clinics of North America **88**(6): 1607-21.	Not a systematic review of RCTs
Viswesvaran, C. and F. L. Schmidt (1992). "A meta-analytic comparison of the effectiveness of smoking cessation methods." Journal of Applied Psychology **77**(4): 554-61.	Poor quality systematic review

Studies excluded	***Reason for exclusion***
Ausfeld-Hafter, B., F. Marti, et al. (2004). "Smoking cessation with ear acupuncture. Descriptive study on patients after a smoking cessation treatment with ear acupuncture." Forsch Komplementarmed Klass Naturheilkd **11**(1): 8-13.	Not a RCT
Ballal, S. G. and Y. N. Khawaji (1992). "Auricular stimulation and acupuncture as an adjuvant to an anti-smoking programme: analysis of the results of a 1-year experience." Tubercle & Lung Disease **73**(6): 396.	Not a RCT
Boutros, N. N. and E. M. Krupitsky (1998). "Cranial electrostimulation therapy." Biological Psychiatry **43**(6): 468.	Not a RCT
Kang, H. C., K. K. Shin, et al. (2005). "The effects of the acupuncture treatment for smoking cessation in high school student smokers." Yonsei Medical Journal **46**(2): 206-12.	Not a RCT
Lei, X. (1996). "Ear point tapping and pressing therapy for giving up smoking in 45 cases." Journal of Traditional Chinese Medicine **16**(1): 33-4. Xiuzhen, L. (1996). "Ear point tapping and pressing therapy for giving up smoking in 45 cases." J Trad Chin Med **15**(1): 33-4.	Not a RCT
Marovino, T. A. (1994). "Laser auriculotherapy as part of the nicotine detoxification process: Evaluation of 1280 subjects and theoretical considerations of a developing model." American Journal of Acupuncture **22**(2): 129-135.	Not a RCT
Owen, P. and L. Duncan (1997). "One-year outcomes of a residential smoking cessation program." Journal of Addictive Diseases **16**(4).	Not a RCT

ALLEN CARR'S EASYWAY	
Papers	***Reason for exclusion***
Becona, E. and F. L. Vazquez (1998). "Self-reported smoking and measurement of expired air carbon monoxide in a clinical treatment." Psychol Rep **83**(1): 316-8.	No relevant information. Not a systematic review or RCT.
McRobbie, H. (2005). "Current insights and new opportunities for smoking cessation." British Journal of Cardiology **12**(1): 37-44.	No relevant information. Not a systematic review or RCT.
Millatmal, T., D. Daughton, et al. (1994).	No relevant information.

"Smoking reduction: an alternative approach for smokers who cannot quit." Monaldi Arch Chest Dis **49**(5): 421-4.	Not a systematic review or RCT.
Nardini, S. (2000). "The smoking cessation clinic." Monaldi Arch Chest Dis **55**(6): 495-501.	No relevant information. Not a systematic review or RCT.

HYPNOSIS	
Reviews excluded	***Reason for exclusion***
Bottorff, J. L. (2001). "Review: advice from doctors, counselling by nurses, behavioural interventions, nicotine replacement therapy, and several pharmacological treatments increase smoking cessation rates... commentary on Lancaster T, Stead L, Siagy C et al for the Cochrane Tobacco Addiction Review Group. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. BMJ 2000 Aug 5;321:355-8." Evidence Based Nursing **4**(1).	Not a systematic review of RCTs
Centers for Disease, C. (1992). "Public health focus: effectiveness of smoking-control strategies--United States." MMWR - Morbidity & Mortality Weekly Report **41**(35): 645-7.	Not a systematic review of RCTs
Green, J. P. and S. J. Lynn (2000). "Hypnosis and suggestion-based approaches to smoking cessation: an examination of the evidence." International Journal of Clinical & Experimental Hypnosis **48**(2): 195-224.	Paper not obtainable in time
Luckmann, R. (2001). "Review: advice from doctors and nurses, behavioural interventions, nicotine replacement treatment, and several pharmacological treatments increase smoking cessation rates." Evidence Based Mental Health **4**(1).	Not a systematic review of RCTs
Lynn, S. J., I. Kirsch, et al. (2000). "Hypnosis as an empirically supported clinical intervention: the state of the evidence and a look to the future." International Journal of Clinical & Experimental Hypnosis **48**(2): 239-59.	Not a systematic review of RCTs
Villano, L. M. and A. R. White (2004). "Alternative therapies for tobacco dependence." Medical Clinics of North America **88**(6): 1607-21.	Not a systematic review of RCTs
Studies excluded	***Reason for exclusion***
Bayot, A., A. Capafons, et al. (1997). "Emotional self-regulation therapy: A new and efficacious	Not a RCT

treatment for smoking." American Journal of Clinical Hypnosis **40**(2): 146-156.	
Brown, D. C. (1998). "A group hypnosis smoking cessation program: six month follow-up." Hypnos **25**(2): 98-103.	Not a RCT
Dogris, N. J. (1998). The effect of a prerecorded hypnosis CD and behavioral fading on smoking cessation and locus of control, Dogris, Nicholas James: California School of Professional Psychology - Los Angeles, US.	Poor methodology and difficult to extract outcome data
Elkins, G. R. and M. H. Rajab (2004). "Clinical hypnosis for smoking cessation: preliminary results of a three-session intervention." International Journal of Clinical & Experimental Hypnosis **52**(1): 73-81.	Not a RCT
Johnson, D. L. and R. T. Karkut (1994). "Performance by gender in a stop-smoking program combining hypnosis and aversion." Psychological Reports **75**(2): 851-7.	Not a RCT
Magrath, B. (2001). "Management of tobacco smoking employing psychosomatic techniques: A retrospective study of the results of treating a group of tobacco smokers for smoking cessation." Australian Journal of Clinical Hypnotherapy & Hypnosis **22**(2): 93-106.	Not a RCT
Marriott, J. A. and G. L. Brice (1990). "A single session of hypnosis to stop smoking: A clinical survey." Australian Journal of Clinical Hypnotherapy & Hypnosis **11**(1): 21-28.	Not a RCT
Sorensen, G., B. Beder, et al. (1995). "Reducing smoking at the workplace: implementing a smoking ban and hypnotherapy." Journal of Occupational & Environmental Medicine **37**(4): 453-60.	Not a RCT
Vaughan, G. N. (1995). The treatment utility of the Therapeutic Reactance Scale in relation to single session hypnosis for smoking cessation, Vaughan, Gregory N.: Western Michigan U, US.	Poor methodology and difficult to extract outcome data
Wester, W. C. and J. A. Robinson (1991). "Hypnosis for smoking cessation: a personalized approach with 100 patients." Hypnos **18**(2): 98-106.	Not a RCT

CYTISINE	
Reviews excluded	***Reason for exclusion***
Etter, J.-F. (2006). Cytisine for smoking cessation: a literature review and a meta-analysis (RPOS3-59). Society for Research on Nicotine and Tobacco, 12th Annual Meeting,	Paper unavailable

Orlando, Florida.	
Studies excluded	***Reason for exclusion***
Bacvarov, V. I. (1967). "Medikamentöse Raucherentwöhnung." Munchener Medizinsicher Wochenschrift 109(50): 2663-65.	Uncontrolled cohort follow-up
Benndorf, S., G. Scharfenberg, et al. (1969). "[Smoking withdrawal treatment with Cytisin (Tabex). Results of a semi-annual survey of former smokers after 4 weeks of therapy]." Deutsche Gesundheitswesen 24(17): 774-6.	Uncontrolled cohort follow-up
Dobreva, D. and N. Danchev (2005). Tabex - overview, A natural alternative for giving up smoking and for treatment of nicotine dependence.	Inaccurate and skewed review of older literature
Maliszewski, L. and A. Straczynski (1972). "[Therapeutic use of Tabex]." Wiadomosci Lekarskie 25(24): 2207-10.	Uncontrolled cohort follow-up
Ostrovskaya, T. P. (1994). "Clinical trial of antinicotine drug-containing films." Biomedical Engineering 28(3): 168-171.	Uncontrolled cohort follow-up
Paun, D. and J. Franze (1968). "Tabex - registering and treatment of smokers with chronic bronchitis in the consultation against tobacco-smoking." Medico-biologic information 3(70).	Uncontrolled cohort follow-up
Stoyanov, S. and M. Yanachkova (1972). "On the therapeutic effectiveness and tolerance of Tabex." Savremenna Medicina 23(6): 30-33.	Uncontrolled cohort follow-up
Zatonski, W., M. Cedzynska, et al. (In Press). "An uncontrolled trial of cytisine (Tabex) for smoking cessation." Tobacco Control.	Uncontrolled cohort follow-up

GLUCOSE	
Reviews excluded	***Reason for exclusion***
Covey, L. S., M. A. Sullivan, et al. (2000). "Advances in non-nicotine pharmacotherapy for smoking cessation." Drugs **59**(1): 17-31.	Not a systematic review of RCTs
Foulds, J., M. Burke, et al. (2004). "Advances in pharmacotherapy for tobacco dependence." Expert Opinion on Emerging Drugs **9**(1): 39-53.	Not a systematic review of RCTs
Hughes, J. R., S. Fiester, et al. (1996). "Practice guideline for the treatment of patients with nicotine dependence." American Journal of Psychiatry **153**(10 SUPPL): 1-31.	Not a systematic review of RCTs
West, R. (2001). "Glucose for smoking cessation: does it have a role?" CNS Drugs **15**(4): 261-5.	Not a systematic review of RCTs

Studies excluded	***Reason for exclusion***
Berlin, I., F. Vorspan, et al. (2005). "Effect of glucose on tobacco craving. Is it mediated by tryptophan and serotonin?" Psychopharmacology **178**(1): 27-34.	Not a cessation outcome study
Harakas, P. and J. Foulds (2002). "Acute effects of glucose tablets on craving, withdrawal symptoms, and sustained attention in 12-h abstinent tobacco smokers." sychopharmacology **161**(3): 271-7.	Not a cessation outcome study
Helmers, K. F. and S. N. Young (1998). "The effect of sucrose on acute tobacco withdrawal in women." Psychopharmacology **139**(3): 217-21.	Not a cessation outcome study
Jarvik, M. E., R. E. Olmstead, et al. (1998). "Sweeteners and cigarette craving: Glucose, aspartame, sorbitol." American Journal of Health Behavior Vol 22(2) Mar-Apr 1998, 130-140.	Not a cessation outcome study
McRobbie, H. and P. Hajek (2004). "Effect of glucose on tobacco withdrawal symptoms in recent quitters using bupropion or nicotine replacement." Human Psychopharmacology **19**(1): 57-61.	Not a cessation outcome study
West, R., S. Courts, et al. (1999). "Acute effect of glucose tablets on desire to smoke." Psychopharmacology **147**(3): 319-21.	Not a cessation outcome study
West, R., P. Hajek, et al. (1990). "Effect of glucose tablets on craving for cigarettes." Psychopharmacology **101**(4): 555-9.	Not a cessation outcome study
West, R., A. Maini, et al. (Unpublished [b]). "Effect of oral glucose on desire to smoke in abstaining smokers: a dose response study."	Not a cessation outcome study

ST JOHNS WORT	
Reviews excluded	***Reason for exclusion***
Dean, A. J. (2005). "Natural and complementary therapies for substance use disorders." Current Opinion in Psychiatry **18**(3): 271-276.	Not a systematic review of RCTs
Studies excluded	***Reason for exclusion***
Franklin, M. (2006). A 2 x 2 phase II randomised controlled trial to investigate the efficacy of St John's Wort versus placebo in smoking cessation and the efficacy of chromium intake in preventing weight gain, ISRCTN, www.controlled-trials.com.	Trial has not started

Appendix D: Evidence tables

Acupuncture

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
White 2006	Meta-analysis	1	+	Smokers wanting help in stopping N=4749	(A) What is the effectiveness of acupuncture, acupressure, laser therapy, and electrostimulation in aiding smoking cessation in comparison to (1) no intervention or waiting list controls; (2) an appropriate placebo; and (3) other smoking cessation treatments with established efficacy? (B) Do these treatments have any specific effect when they are used in combination with other treatments? (C) Is any one of the different acupuncture treatments better than another? Meta-analysis inclusion criteria: Randomised controlled trials Have a suitable comparison groups. Report complete abstinence from smoking, but no minimum follow-up period was required. Lack of biochemical verification of smoking status did not exclude studies.	Early: Short term (0-6 weeks after the quit date) Late: Long-term (6-12 months after the quit date)	No evidence for effectives of any intervention in aiding long-term smoking cessation.	Three studies in UK smokers.	Poor methodology in some included studies. For this reason this meta-analysis scores '+' for quality.
Docherty	RCT	1	+	355 smokers	What is the effectiveness of laser	6 and 12	CO validated	Scottish	Participants'

2003	Double blind (not included in Cochrane meta-analysis)			from a deprived area of Scotland	acupuncture compared to placebo acupuncture on long-term smoking cessation rates Randomly assigned to active (n=145) or placebo (n=210) laser acupuncture. All provided with counseling and had access to telephone helpline. Participants and therapist blind to allocation.	months	abstinence rates for active vs. placebo 6 month: 12.4% (n=18) vs. 11.9% (n=25) 12 month: 10.3% (n=15) vs. 10% (n=21)	study	characteristics unknown. Unknown if continuous of point prevalence abstinence used. Number of sessions and duration of treatment unknown

Allen Carr's Easyway

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Foulds 1996	Cohort	2	-	Dependent smokers motivated to quit (n=19) attending an Easyway stop smoking clinic in South London	To evaluate effectiveness of the 'Easyway' smoking cessation clinic.	1 & 3 months	26% (5) 1 month continuous abstinence (CO validated) 26% (5) 3 month continuous abstinence Intention to treat analysis	Yes – South London study	Small study No validation at 3 months
Foulds 1996	Cohort	2	-	Dependent smokers motivated to quit selected randomly from Easyway clinic records (n=50)	To evaluate effectiveness of the 'Easyway' smoking cessation clinic.	21 months on average	10 agreed to answer questions, 2 (20% or 4%, depending on base) reported not smoking	Yes – South London study	Small sample size, no validation
Csillag 2005, Mosham mer 2007[2]	Cohort	2	-	Dependent smokers motivated to quit. Sample (n=686/515)from cohort of n=1311 who attended an 'Easyway' group based clinic as part of a workplace smoking cessation initiative	To evaluate effectiveness of the 'Easyway' smoking cessation clinic in a workplace setting	2-4.5 years	36%/51% (249/262) self-reported point-prevalence	Probably, and workplace	Non-random sample, unclear abstinence criteria, validation results not used
Hutter 2006	Cohort	2	-	Dependent smokers motivated to quit (n=308) who attended an 'Easyway' group based clinic over a 4 month period in 2002	To evaluate effectiveness of the 'Easyway' smoking cessation clinic in a workplace setting	1 year	40% (122) self-reported point-prevalence Intention to treat analysis	Probably, and workplace	No details of follow-up method and definition of outcome, no validation

[2] These two papers report the results of the same study

Hypnosis

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Abbot 2006	Meta-analysis	1	+	Participants could be any smoker from any background and from any setting who were motivated to quit. N=915	Aim: to examine the efficacy of hypnotherapy compared to no treatment and other therapeutic interventions Meta-analysis: included only randomised controlled trials with suitable control groups, and at least 6-months follow-up. Five different comparison groups: (a) waiting list or no treatment; (b) attention placebo or advice; (c) psychological treatments; d) rapid or focused smoking; e) group therapy with or without	6 months	Hypnosis was not shown to be more effective than other psychological treatments (OR= 0.92, 95% CI: 0.42 to 2.02) or than aversive smoking (OR=1.00, 95% CI 0.32 to 3.11). Odds ratios not calculated for the other comparisons because of significant heterogeneity.	One study was UK based (Fee 1977)	Poor methodology in some studies.

					hypnosis.				
Carmody 2006	RCT	1	+	266 smokers motivated to quit	What is the efficacy of self-hypnosis + nicotine patch compared to a standard behavioural counselling programme + nicotine patch Randomised controlled trial Intervention group (n=145) had 2 x 45 minute session of self-hypnosis + patches Comparison group (n=141) had 2 x 45 minute session of behavioural counselling + phone counselling at 1,2, and 8 weeks	6 and 12 months Self-reports point-prevalence verified with salivary cotinine	Abstinence rates for intervention vs. comparison groups were: 6 month: 26% (n=36) vs. 19% (n=24) 12 month: 20% (n=27) vs. 15% (n=19). Differences were not significant.		Abstract data only
Tindel 2006	RCT	1	-	34 smokers motivated to quit	Is guided imagery plus brief advice more effective than brief advice alone for smoking cessation? Intervention (n=17): 6-session group-based guided imagery programme Comparison (n=17):	6 weeks 12 weeks Seven-day point prevalence abstinence	36% (n=6) vs, 18% (n=3) 30% (n=5) vs. 12% (n=2) in the intervention and control groups respectively. Difference was not significant.		Abstract data only Small sample size

					waiting list control group (who were offered the guided imagery training at the end of 12 weeks). All participants received brief advice to quit by a physician				
Casmar 2002	RCT	1	-	75 adult smokers of at least 10 cigarettes per day. Standardised for level of hypnotisability	Does the addition of suggestion to anaethetise craving to a standard hypnosis procedure for smoking cessation reduce the recidivism rate compared to the standard procedure and control? Participants randomised to three groups (n=25 in each): (1) Speigels standard smoking cessation hypnosis procedure (2) above plus suggestion to anaethetise craving (3) placebo control All sessions lasted 90 minutes	1 month 3 month	Group 1: 16% (n=4) Group 2: 12% (n=3) Group 3: 20% (n=5) Group 1: 16% (n=4) Group 2: 8% (n=2) Group 3: 8% (n=2) No significant differences between groups. Abtsinece rates validated with salivary cotinine at 3 months. Outcome measure not defined.		Small sample size

Valbo 1996	RCT	1	+	Pregnant women still smoking at 18 weeks gestation	Is hypnosis more effective than usual care in achieving smoking cessation? Intevention (n=80): received 2x45 minute hypnosis sessions 2 weeks apart. Control: (n=78) usual care (not described)	Date of delivery (approx. 4 months)	Continuous abstinence rates were 8% (n=10) in both groups (intention-to-treat).		

NicoBloc

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Gariti 2004	RCT	1	+	N=60 highly dependent smokers (62% female) Accu Drop (n=30) vs. placebo (n=30)	Is nicotine blocking substance (Accu Drop) more effective than placebo when added to a cigarette tapering programme and counselling? Randomised double blind placebo controlled trial. Accu Drops or placebo added to cigarette tapering and weekly counselling over 6-weeks.	1 week 1 month 6 months Outcome: 7-day validated point prevalence	Accu Drop vs. placebo 10% vs. 3% 13% vs. 10% 10% vs. 13% Intention to treat analysis No significant differences	Likely to be applicable to UK setting	High drop out (45%)

Nicobrevin

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Schmidt 1974	Controlled trial	1	-	N=2470 smokers Mean cigarette consumption of 25 cigs/day Recruited via ads on TV and papers Nicobrevin N=200 Placebo N=270	Efficacy of 16 smoking cessation medicines compared to placebo No individual contact, all done by post. Placebo not matched to individual medicines 3 month follow-up by postal questionnaire (N=1824, 74% response rate)	3 months	Nicobrevin: 32% (n=64) Placebo: 21% (n=57)	German study	Not clear how drug was assigned. Self-report and no validation of outcome. One placebo not matched to 16 other interventions
Dankwa 1988	RCT	1	-	N=92 middle aged smokers, 35% female, 55% reported >20 cigs/day Recruit from a hospital. Unclear if inpatients outpatients Nicobrevin N= 44 Placebo N=48	Examined the efficacy of a 28 –day course of Nicobrevin or matched placebo on short-term cessation. Randomised double-blind placebo controlled trail	4 weeks	3-week self-reported point prevalence abstinence: Nicobrevin: 52% (n=23) Placebo: 17% (n=8) Self-reported abstinence on day-28: Nicobrevin: 59% (n=26) Placebo: 27% (n=13)	Swiss study	Active treatment group were older. Participants did not have to quit. No validation of outcome.

Rapid smoking

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Hajek 2006	Meta analysis	1	-	Smokers wanting help in stopping Average age: 34 Average cigarette consumption: 28 N=536 for effect of rapid smoking on long-term abstinence analysis N=475 for effect of other aversive smoking methods on long-term abstinence analysis N=326 for dose response effect of rapid smoking on long-term abstinence analysis	Is rapid smoking more effective than an 'attention placebo control? Are other aversion methods more effective than an 'attention placebo control? Is there are dose response effect of rapid smoking? Meta-analysis Inclusion criteria: Randomised controlled trials Suitable control group At least 6-months follow-up	At least 6 months	Rapid smoking vs. control: OR=1.98 (95% CI: 1.36-2.90) Abstinence rates: 36% vs. 22% (effect size=14%) Other aversive methods vs. control: OR=1.15 (95% CI: 0.73-1.82) More aversive vs. less aversive methods: OR=1.66 (95% CI: 1.00-2.78)	Slightly younger participants and higher cigarette consumption than typically seen in NHS stop smoking services.	Poor methodology in most studies. Publication bias. Note: The quality of this meta-analysis is high. It scores '-' for quality because of the nature of the studies included.

Cytisine

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Paun 1968	Controlled Trial	2	-	N=605 smokers German study Cytisine: N=366 Placebo: N=239	Aim: To assess the efficacy of cytisine compared to a placebo in aiding smoking cessation Non-randomised placebo control trial.	8 weeks	Cytisine: 55% (n=202) Placebo: 33% (n=80) (p<0.001) These data were entered into the 4-8 week meta-analysis. For the Potsdam group the 2-4 month abstinence rates were: Cytisine: 42% (n=15/36) Placebo: 34% (n=81/239) (NS) These data were entered into the 2-6month meta-analysis.		No definition of abstinence No validation All placebo group at one study site (Potsdam)
Scharfenberg 1971	RCT double blind	1	+	Recruited 1452 smokers. Exclusion criteria: hypertension, arteriosclerosis (n=216 excluded) N=1214 randomised (607 each to cytisine and placebo)	Aim: To assess the efficacy of cytisine compared to a placebo in aiding smoking cessation Randomised double blind placebo controlled trial. Medication plus 'intensive psychological treatment'	4 weeks 6 months 2 years	Cytisine: 65% (n=395) Placebo: 41% (n=246) (p<0.001) Cytisine: 30 % (n=185) Placebo: 16% (n=97) (p<0.001) Cytisine: 21% (n=127) Placebo: 13% (n=79) (p<0.001)		2-year follow-up by mail, with a 66% response rate. This is the same study as Benndorf et al (1968). Side effects similar in both groups.

Schmidt 1974	Controlled trial	2	-	N=2470 smokers Mean cigarette consumption of 25 cigs/day Recruited via ads on TV and papers Cytisine N=250 Placebo N=270	Examined the efficacy of 16 smoking cessation medicines against a placebo No individual contact, all done by post. Medicines packed with instructions for use but without labels identifying the medicine. 3 month follow-up by postal questionnaire (N=1824, 74% response)	4 weeks (end of treatment) 3 months	Cytisine: 41% (n=103) Placebo: 31% (n=84) ($p<0.05$) Cytisine: 25% (n=63) Placebo: 21% (n=57) (NS)		Not clear how drug was assigned. Self-report and no validation of outcome. One placebo not matched to 16 other interventions Report few side effects.

Glucose

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
West 1998	RCT	1	+	N=308 smokers seeking treatment	To assess the effectiveness of glucose, compared to placebo, on short term abstinence and carving relief Randomised double-blind placebo-controlled trial 4 groups: 1) glucose (3g) + active patch (15mg/16hr) 2) glucose + placebo patch 3) placebo (sorbitol) + active patch 4) placebo + placebo patch 6-session group based behavioural support	4 weeks Intention to treat analysis	4-week CO validated continuous abstinence rates for each group were % (n): 5) 49% (38) 6) 44% (35) 7) 36% (29) 8) 30% (21) Glucose vs. placebo: 46% vs. 33%; (p<0.01) (Effect size: 13%) Active vs. placebo patch: 43% vs. 37% (NS) No effect of glucose on craving	Applicable to UK population, and all smokers, except those with diabetes	
West 2006	RCT	1	+	N=928 smokers seeking treatment	To assess the effectiveness of glucose, compared to placebo, on 6-month abstinence	Primary end point: 6 month continuous abstinence	4-week CO validated continuous abstinence: Glucose 37% (169) Placebo: 33% (158)	Applicable to UK population, and all smokers, except those with diabetes.	Additional medication was provided half way through recruitment because NRT and

					Randomised double-blind placebo-controlled trial 1) Glucose (3g tablets) (N=452) 2) Placebo (sorbitol) (N=476) 452 participants received no additional medication; 255 received NRT; 188 received bupropion; 31 received both	Secondary end points: Continuous abstinence at week 1, 2 3, and 4. Intention to treat analysis	6-month CO validated continuous abstinence: Glucose 15% (66) Placebo: 13% (64) In the group that received additional medication the glucose vs. placebo rates were 18% vs. 13% ($p<0.05$). In the group that received no additional medication the glucose vs. placebo rates were 11% vs. 14% (NS).		bupropion became reimbursable on NHS prescription.

St Johns Wort

First author	Study design	Research Type	Research Quality	Study population	Research question & design	Length of f/up	Main results	Applicability to UK population & settings	Confounders/ comments
Becker 2003	RCT	1	-	N=45 smokers motivated to quit	Effect of SJW on withdrawal symptoms Randomised to nicotine patch + SJW oral spray OR placebo oral spray	1 month Symptoms assessed over 2 weeks	Craving, anxiety, restlessness, & sleepiness lower in SJW users No difference in 1 month abstinence rates (33%)		These data were collected from an abstract only. An attempt to contact the authors was made, but there was no response. Not clear if withdrawal was reported for total sample or just abstainers
Barnes 2006	Randomised trial	No grade assigned	No grade assigned	N=28 smokers motivated to quit. Randomised to 300mg or 600mg SJW/day	Compare effects of 2 doses of SJW on smoking cessation	3 & 12 months	3 months: Overall 18% (n=4 300mg; n=1 600mg) 12 months: 0% Abstinence rates were continuous and CO validated.	Yes (UK study)	Small sample No control group

Dankwa, E., L. Perry, et al. (1988). A double-blind, placebo-controlled study to determine the efficacy of Nicobrevin anti-smoking capsules. Br J Clin Pract. **42:** 359-63.
Dobreva, D. and N. Danchev (2005). Tabex - overview, A natural alternative for giving up smoking and for treatment of nicotine dependence.
Etter, J.-F. (2006). Cytisine for smoking cessation: a literature review and a meta-analysis (RPOS3-59). Society for Research on Nicotine and Tobacco, 12th Annual Meeting. Orlando, Florida.
Ferguson, J., L. Bauld, et al. (2005). The English smoking treatment services: one-year outcomes. Addiction. **100 Suppl 2:** 59-69.
Gariti, P., A. I. Alterman, et al. (2004). Adding a nicotine blocking agent to cigarette tapering. J Subst Abuse Treat.
Gonzales, D. H., S. I. Rennard, et al. (2006). A pooled-analysis of varenicline, an alpha 4 beta 2 nicotinic receptor partial agonist vs. bupropion for smoking cessation (PA9-2). Society for Research on Nicotine and Tobacco, 12th Annual Meeting. Orlando, Florida.
Hajek, P. and L. F. Stead (2006). Aversive smoking for smoking cessation [Systematic Review]. Cochrane Database of Systematic Reviews. **1:** 1.
Royal College of Physicians (2000). Nicotine Addiction in Britain. London, Royal College of Physicians.
Schmidt, F. (1974). Drug support during breaking of smoking habit - report about experiment with over 5000 smokers (double blind experiment). Munchener Medizinsicher Wochenschrift. **116:** 557-564.
White, A. R., H. Rampes, et al. (2006). Acupuncture and related interventions for smoking cessation. Cochrane Database of Systematic Reviews**:** CD000009.
Zatonski, W., M. Cedzynska, et al. (In Press). An uncontrolled trial of cytisine (Tabex) for smoking cessation. Tobacco Control.