The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation

NF Woolacott¹*
L Jones¹
CA Forbes¹
LC Mather¹
AJ Sowden¹
FJ Song²
JP Raftery²
PN Aveyard²
CJ Hyde²
PM Barton²

¹ NHS Centre for Reviews and Dissemination, University of York, UK
² Department of Public Health & Epidemiology, University of Birmingham, UK

* Corresponding author

Executive summary

Health Technology Assessment 2002; Vol. 6: No. 16
How to obtain copies of this and other HTA reports
Copies of this report can be obtained by writing to:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.

Or by faxing us at: +44 (0) 23 8059 5639
Or by emailing us at: hta@soton.ac.uk
Or by ordering from our website: http://www.ncchta.org

NHSnet: http://nww.hta.nhsweb.nhs.uk

The website also provides information about the HTA Programme and lists the membership of the various committees.
Background
The health hazards of smoking are significant and well established. Giving up smoking is difficult and therefore needs to be treated as a chronic, but potentially curable, illness. Nicotine replacement therapy (NRT) and bupropion sustained-release formulation (SR) (Zyban®) are two pharmacological agents available to aid smokers in their attempts to achieve smoking cessation.

Objectives
The aim of this review was to assess the clinical effectiveness, cost-effectiveness and adverse effects of bupropion SR and NRT for smoking cessation. The effects of therapy in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit were not assessed.

Methods
Search strategy
Twenty-six electronic databases and Internet resources were searched from inception to May 2001. In addition, the bibliographies of retrieved articles and submissions received from the manufacturers were searched.

Inclusion and exclusion criteria
Two reviewers independently screened all titles and abstracts for relevance and made final decisions regarding the inclusion and exclusion criteria of studies based on full paper copies of manuscripts. Studies were assessed according to predefined criteria. Any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted. Only systematic reviews and newly identified randomised controlled trials (RCTs) of bupropion SR (used alone or as part of a combination therapy with motivational support or motivational support and NRT) or any type of NRT were included in the review of clinical effectiveness. Participants included smokers of any age or gender and studies had to report abstinence (preferably continued rather than point abstinence) as an outcome measure. In addition, the assessment of adverse effects also included non-RCTs, case-controlled studies, uncontrolled studies and surveillance studies, the primary objective of which was the investigation of the adverse effects, tolerability or safety of bupropion SR or bupropion immediate-release (IR) and/or NRT. Case reports and case series were also documented. The economic assessment included evaluations of the cost-effectiveness or cost-utility of bupropion SR and/or NRT.

Data extraction strategy
Data were extracted into an Access database by one reviewer and checked by a second reviewer. Any disagreements were resolved through discussion.

Quality assessment strategy
The quality of each study was assessed using predefined criteria specified according to study design. The assessment was performed by one reviewer and checked by a second reviewer. Disagreements were resolved through consensus and, if necessary, a third reviewer was consulted.

Analysis strategy
Study details, validity and data were reported in structured tables and discussed in the text of the review. For the assessment of clinical effectiveness, where available and appropriate, pooled estimates of effect in the form of odds ratios from systematic reviews are presented. Subgroup and sensitivity analyses are reported where data are available. For the assessment of adverse events and safety the summary was mainly a narrative one. In the assessment of cost effectiveness, evaluations were grouped according to design.

Results
Included studies
A total of 157 studies were included in the review. These comprised three systematic reviews and 13 individual studies of effectiveness; four systematic reviews and 112 individual studies relating adverse events and safety; and 17 economic studies.

Quality of clinical-effectiveness data
The quality of the systematic reviews and individual RCTs included in the review was good.
Quality of adverse-effects data
The nature and quality of the adverse-effect and safety data were very variable. In particular, many of the studies were uncontrolled, with all the inherent weaknesses of such studies. Furthermore, many of the uncontrolled studies were small, but many of the larger ones suffered from poor quality of reporting. Interpretation of surveillance data was limited by a lack of information on the size of the population treated.

Assessment of clinical effectiveness
The effectiveness of NRT as an aid to smoking cessation has been thoroughly investigated. The evidence indicates unequivocally that NRT as an aid to smoking cessation is more effective than placebo. The majority of the data come from studies investigating the use of NRT gum and NRT patches. Despite this, there are no data to indicate that other forms of NRT are less efficacious. There are no data to indicate subgroup differences in the response to NRT.

There is clear evidence that bupropion SR is more effective than placebo. There is evidence from single subgroup populations that bupropion SR is as effective in smokers with chronic obstructive pulmonary disease, cardiovascular disease, and those who have failed in the past to achieve abstinence with bupropion SR, as in the general smoking population.

Evidence to support the superiority of bupropion SR over NRT for smoking cessation is relatively weak, with one double-blind study indicating that the NRT patch is less effective than bupropion SR and another unblinded study finding no difference between NRT gum and bupropion SR. Further double-blind RCTs are required.

Assessment of adverse events and safety
Overall, the incidence of adverse events with NRT is very low. The main concern relates to potential adverse cardiovascular effects (i.e., the same harmful effects that are the driving force behind needing to ‘treat’ smoking as a chronic illness). There is strong evidence that the effects of nicotine acquired through NRT are no different from those of smoking-derived nicotine. Evidence suggests that the main problem with NRT is that its use can delay the reversal of the adverse effects of smoking normally associated with smoking cessation. There is evidence to suggest that the abuse potential of NRT is low.

There is only very limited overlap of adverse symptoms associated with the different types of NRT. Thus, the qualitative differences of the adverse effects associated with the different types of NRT will determine their effectiveness in different individuals.

None of the common adverse events of bupropion (rash and pruritus, irritability, insomnia, dry mouth, headache, tremor, urticaria) reported in this review are newly identified. The adverse events resulting in withdrawal from treatment with bupropion SR are the same as those for the IR formulation (skin disorders (mainly rash), insomnia, tremor, headache, dry mouth, anxiety), with the exception of motor disturbances, psychological problems, drowsiness, weight loss, headache/nasal congestion, thinking difficulties, dizziness and tachycardia/palpitations. Such differences might be due to differences in dose and duration of treatment, and differences in response between depressed and non-depressed patients. Significantly, the side-effect profile of bupropion SR does appear to be better than that of the IR formulation.

This review identified seizure as the most significant and important potential adverse effect of bupropion SR, as had already been recognised. The crude incidence of seizure is lower with the SR than with the IR formulation; however, the evidence demonstrates that even in populations screened to exclude those at risk, seizures can occur. Significantly, no RCT of bupropion SR in smoking cessation has reported any seizures. This may be related to stricter screening in the clinical-trial setting than occurs in clinical practice.

Assessment of cost-effectiveness
Published economic studies of smoking cessation have adopted different methods and assumptions for estimating effectiveness and costs. However, the results of existing economic evaluations consistently indicate that smoking cessation interventions are relatively cost-effective in terms of the cost per life-year saved. An assessment of results from existing studies suggests that the number of life-years saved per quitter ranges from 1.0 to 3.0. Adding NRT to current practice is cost-effective, with a relatively low (under £1000) incremental cost per quitter. No published studies have evaluated the relative cost-effectiveness of bupropion SR for smoking cessation.
A decision analysis model has been built to compare the cost-effectiveness of four smoking cessation interventions:

- advice or counselling only (including general practitioner advice and more intensive counselling by other health professionals)
- advice plus NRT
- advice plus bupropion SR
- advice plus NRT and bupropion SR.

The results of this decision analysis modelling are broadly similar to those found in previous studies. NRT and/or bupropion SR as smoking-cessation interventions are cost-effective as compared with many accepted healthcare interventions. According to our estimates, the incremental cost per life-year saved is about £1000–2400 for NRT, £640–1500 for bupropion SR and £900–2000 for NRT plus bupropion SR.

The estimated cost of the smoking-cessation programme to the NHS in England and Wales would be about £67 to 202 million per year. Consequently, about 45,000–135,000 smokers would quit, and 90,000–270,000 life-years may be saved. The average cost per life-year is about £750 (range £500–1500).

The incremental cost-effectiveness of bupropion SR is generally better than that of NRT. However, this should be interpreted cautiously because of the very limited available data on the relative efficacy of bupropion SR and because the cost of adverse effects of bupropion SR were not considered in the analysis.

Conclusions

- Both NRT and bupropion SR are effective interventions to assist smoking cessation.
- The relative effectiveness of bupropion SR and NRT still needs further research.

- Information on how to maximise effectiveness in practice is still lacking, but motivational support is probably involved.
- The most significant differences between NRT and bupropion SR relate to the adverse events and safety profiles of these interventions.
- Overall, the safety profile of NRT is more favourable, particularly given the small but real risk of seizure with bupropion SR.
- Irrespective of the methods used or the assumptions involved, the results of existing economic evaluations and the model developed in this review consistently suggest that smoking-cessation interventions, including the use of NRT and/or bupropion SR, are relatively cost-effective in terms of the cost per life-year saved. The worst-case scenarios still provide estimates of cost-effectiveness better than many other medical interventions.

Recommendations for research

Studies that compare the effectiveness of NRT with that of bupropion SR are needed. Ideally, these studies should include a high level of motivational support.

To increase the effectiveness of all smoking cessation agents the questions to be asked include:

- How do we encourage smokers to become motivated to quit?
- How do we effectively maintain smokers in a motivated to quit state until smoking cessation has been achieved?

Publication

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 00/17/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA Programme Director: Professor Kent Woods
Series Editors: Professor Andrew Stevens, Dr Ken Stein, Professor John Gabbay, Dr Ruairidh Milne, Dr Tom Dent and Dr Chris Hyde
Monograph Editorial Manager: Melanie Corris

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report.