Assessment of Therapeutic Safety in Systematic Reviews

A systematic review of the safety of Nicotine Replacement Therapy

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Systematic reviews are becoming ever more accepted as important sources of information in the practice of evidence-based medicine, but they fail to address safety and tolerability issues adequately. Of over 2,000 systematic reviews published between 1996 and the end of 2000, only 27% contained safety information and only 4% had safety as the primary objective.[1] Most systematic reviews of clinical topics are based on data from randomised controlled trials (RCTs), as they are considered to provide the most reliable evidence.[2] Unfortunately, in the vast majority of RCTs, evaluation of efficacy is the primary objective, and very little space is given over to the reporting of safety findings.[3,4]

If RCTs are not a satisfactory source of adverse event data, what other resources are available to the reviewer?

We conducted a systematic review of the adverse events and safety of Nicotine Replacement Therapy (NRT) as part of a wider review of the effectiveness of NRT in aiding smoking cessation. The literature search was comprehensive (see Box 1) and studies were included if their primary objective was the investigation of adverse effects, tolerability or safety of NRT.

The number of published studies that specifically addressed the issue of adverse effects and safety was disappointingly small. Of a total of 1,279 references identified by the searches, only 65 references of 63 studies met the inclusion criteria for the review. Many were excluded because they were studies of efficacy.

A summary of the different types of study design included is shown in Figure 1. The studies that met our inclusion criteria were, for the most part, of limited quality. The findings from uncontrolled studies, and to a lesser extent from non-randomised controlled trials were subject to confounding and biases. Even the RCTs that addressed safety issues were of limited quality. Furthermore, many of these studies included only small numbers of participants. Case reports, whilst interesting, can only be used to generate questions rather than answer them.[5] Surveillance studies, though large, are imprecise and are really only useful for identifying safety issues of major significance.[6]

Figure 2 summarises the included studies by focus of safety study. Within the category 'Specific safety aspects' the following aspects were investigated: effects on cardiovascular function; effects on blood lipid profile; effects on endothelial function; effects on glucose tolerance; possible cutaneous inflammatory response; effect on the oral mucosa; effect on body weight change; and the abuse potential of NRT. Synthesising the data by focus of safety study from such a diverse collection of studies was difficult because outcomes rarely corresponded with each other. The generalisability of findings was occasionally limited because some studies investigated the therapy in populations who would not receive it in routine clinical practice.

Overall the data collected from studies whose primary objective was some aspect of the safety of NRT was limited, particularly in terms of incidence. Although many aspects of the safety of NRT had been addressed the overall quality of the studies, and consequently the reliability of the findings was poor. In conclusion, large prospective cohort studies are necessary to provide data on the nature and incidence of adverse events, and when such data are published, all adverse events should be reported not just those selected by the investigators. Potential safety issues should be investigated more systematically, with studies assessing standard outcomes in relevant populations.

Box 1. Search strategy

The following databases and internet resources were searched, from inception to May 2001:

- AMED
- Biosis
- CINAHL
- Cochrane Controlled Trials Register
- Cochrane Database of Systematic Reviews
- DARE
- DH-Data
- EMBASE
- HELMIS
- Index to Scientific and Technical Proceedings
- King's Fund Database
- Martindale Pharmacopoeia
- MEDLINE
- PsycLit
- Science Citation Index
- Social Science Citation Index
- TOXLINE
- Drug and Therapeutic Bulletins website
- Committee on Safety of Medicines website
- Medicines Control Agency website

The literature search was designed to retrieve studies of any design. Bibliographies of retrieved articles and submissions received from the manufacturers were also searched.

Figure 1. Study designs included in the review

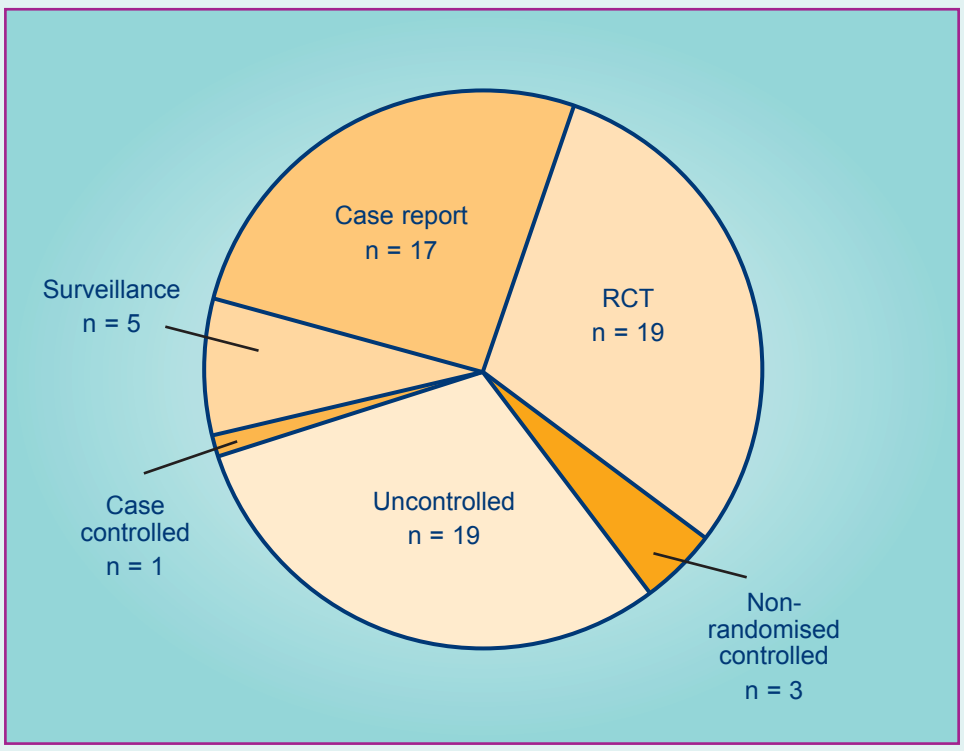
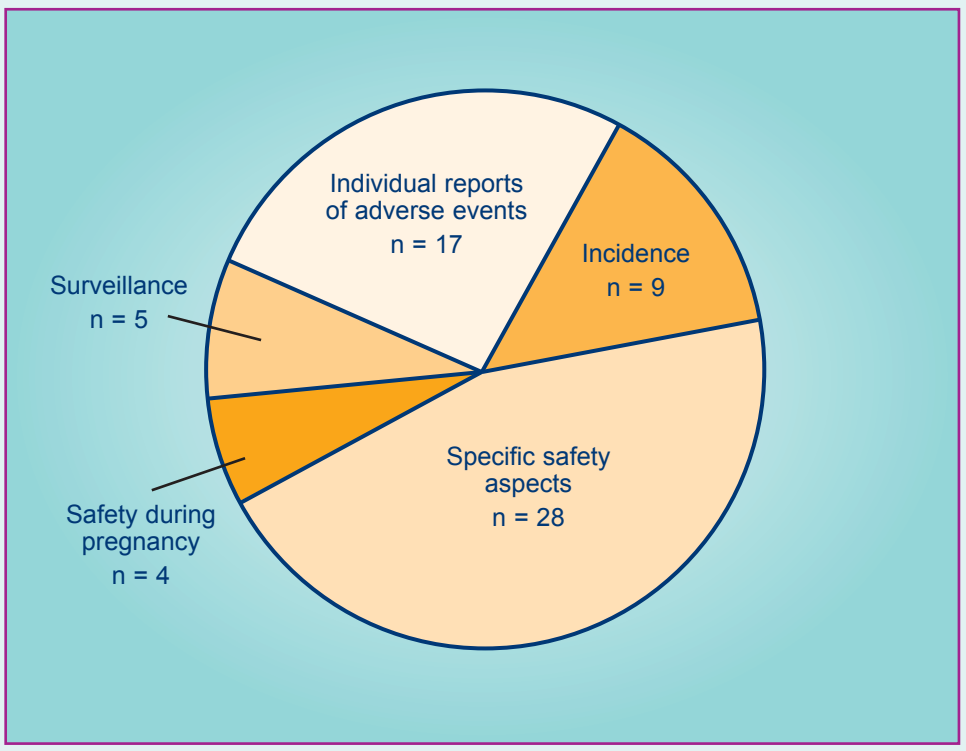


Figure 2. Focus of safety study included in the review



1. Ernst E, Pittler MH. Assessment of therapeutic safety in systematic reviews: literature review. BMJ 2001;323:546

2. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness. 2001. CRD Report Number 4 (2nd Edition)

3. Ioannidis JPA, Lau J. Completeness of safety reporting in randomised trials: An evaluation of 7 medical areas. JAMA 2001;285:437-443

4. Loke YK, Derry S. Reporting of adverse drug reactions in randomised controlled trials – a systematic survey. BMC Clin Pharmacol 2001; 1:3

5. Bland M. An Introduction to Medical Statistics. Oxford University Press Inc New York 2000

6. Jones DG, Langman MJ, Lawson DH, Vessey MP. Review: post-marketing surveillance of the safety of cimetidine – the problems of data interpretation. Aliment Pharmacol Ther 1987;1:167-77

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