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Review

Ethical concerns about non-active conditions in smoking cessation trials and methods to decrease such concerns

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ABSTRACT

Many have questioned whether it is ethical to assign participants in a research trial to a non-active control condition (e.g., a placebo or attention-only control) when (a) the disorder under study is serious, (b) validated treatment is available, and (c) harm may occur if treatment is not given. This ethical concern may apply to studies of controlled trials of treatments for drug dependence. The current paper examines this concern for trials of nicotine dependence because there are multiple validated treatments available. The major harm from assignment to a non-active condition in such a trial could occur if failure to quit discourages smokers from trying to quit again. Whether this harm actually occurs is unclear. Potential harms from non-active conditions may be mitigated by (a) provision of more explicit information in the consent process, (b) inclusion of only those who have failed optimal treatment, (c) provision of validated treatment via a different modality, (d) tests of the new treatment as an add-on to standard treatment, (e) use of dose–response design, (f) use of unequal randomization designs, (g) use of stopping rules, (h) provision of optimal therapy to those who fail during the study, or (i) comparison of the experimental treatment vs. standard treatment. Empirical research to inform ethical analysis of non-active conditions in drug abuse research is suggested.

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1. Introduction

Randomized controlled trials (RCTs) using a non-active control (e.g., a placebo or attention-only condition) are thought to be the best test of the specific efficacy of medical or psychological interventions (Spilker, 2000). However, some have argued that it is unethical to assign persons to a non-active control condition when (a) a serious disease is being treated, (b) proven treatment exists, and (c) significant or irreversible harm may occur if treatment is not delivered (Emanuel and Miller, 2001; Forster et al., 2001; US Food and Drug Administration, 2001; Huston and Peterson, 2001; Weiss Roberts et al., 2001; Rothman, 1994; Temple and Ellenberg, 2000; Ellenberg and Temple, 2000; Tollman, 2001; Carpenter et al., 2003). This ethical concern might apply to RCTs of treatments for drug dependence because drug dependence is a serious disorder with validated treatments (Kleber et al., 2006) (www.cochranelibrary.org).

The current paper reviews whether harm from assignment to a non-active condition might occur in RCTs of treatments for nicotine dependence. The author chose this dependence disorder for three reasons. First, smoking cessation is the most important behavioral change an individual can do to improve his/her health (US Department of Health and Human Services, 1990), yet quit rates with treatment are still low (The Clinical Practice Guideline Treating Tobacco Use and Dependence, 2008 Update Panel) thus, continued evaluation of new treatments is essential. Second, seven well-accepted proven pharmacotherapies and four proven psychosocial therapies for smoking cessation have been validated in over 150 RCTs (Hughes, 2003; The Clinical Practice Guideline Treating Tobacco Use and Dependence, 2008 Update Panel). Third, controlled trials of nicotine dependence are very common; e.g., www.clinical.trials.gov lists 689 controlled intervention trials on tobacco use.

The major purposes of the current article are (a) to provide an overview of the ethical concerns about placebos and non-active controls and evaluate their applicability to RCTs of pharmacological and behavioral treatments for smoking cessation and (b) to suggest methods that smoking cessation RCTs can use to mitigate such concerns. This article is not a comprehensive nor systematic review, does not provide a formal ethical analysis using ethical principles such as respect for persons, contracting principles, etc., and is not comprehensive. Many such reviews already exist (Emanuel and Miller, 2001; Forster et al., 2001; US Food and Drug Administration, 2001; Huston and Peterson, 2001; Weiss Roberts et al., 2001; Rothman, 1994; Temple and Ellenberg, 2000; Ellenberg and Temple, 2000; Tollman, 2001; Carpenter et al., 2003). The current paper's contribution is an examination of how these ethical concerns apply to smoking RCTs and a suggestion of methods to decrease these concerns. The paper is written from a scientist-clinician perspective and the conclusions of the paper are based on the author's subjective judgments.

2. Methods

2.1. Definition of non-active conditions

Much of the literature focuses on the use of placebo pills and the term "placebo" has been used to describe behavioral non-active control conditions. The current review will, instead, use the phrase "non-active controls" to refer to attention-only, contact-only, known ineffective, no-treatment, placebo or wait-list conditions to emphasize that the ethical concerns apply to inert (or non-specific) behavioral conditions as well as inert pharmacological interventions. The review defines a "non-active" condition as one that the experimenter and the community of scientists and clinicians believe is not effective due to its specific contents.

2.2. Identification of relevant literature

I searched *PubMed*, *Embase*, and for *PsychInfo* using the words/stems "(smok* OR tobacco OR cigar* OR nicotin*) AND ethic*". This produced 329 citations but only one dealt with non-active groups in smoking cessation RCTs (Shelton, 2001). A similar search for RCTs of alcohol and drug abuse RCTs using "(alcohol* OR drug OR substance) AND ethic* AND (dependenc* OR cessation OR abuse)" produced 285 publications, none of which were relevant. Thus, I decided to collect review articles on the ethics of non-active conditions in RCTs of any disorder and examine how they apply to smoking cessation RCTs. To do this, I searched for "placebo*" or one of the synonyms for non-active conditions used in the Cochrane review on placebo effects (Hrobjartsson and Gotzsche, 2007) "ethic" in the abstract or title. I searched *PubMed* and *PsychInfo* and limited this to editorials, meta-analyses and reviews. This resulted in 236 citations that discussed placebo and behavioral non-active control conditions in studies of alcohol/drug abuse, mental disorders and physical disorders. I also examined what appeared to be relevant articles cited in the bibliographies of these reviews. I located many excellent articles on the ethical issues of using non-active controls in RCTs, but none mentioned smoking cessation or alcohol/illicit drug abuse RCTs (Emanuel and Miller, 2001; Forster et al., 2001; US Food and Drug Administration, 2001; Huston and Peterson, 2001; Weiss Roberts et al., 2001; Rothman, 1994; Temple and Ellenberg, 2000; Ellenberg and Temple, 2000; Tollman, 2001); thus, the discussion below is based on my attempt to apply discussions on the ethics of non-active conditions in RCTs of depression, etc, to the ethics of using them in smoking cessation RCTs.

3. Results

3.1. Benefits of non-active controls

Many articles have argued the scientific rationale for the inclusion of non-active controls (Emanuel and Miller, 2001; Forster et al., 2001; US Food and Drug Administration, 2001; Huston and Peterson, 2001; Weiss Roberts et al., 2001; Rothman, 1994; Temple and Ellenberg, 2000; Ellenberg and Temple, 2000; Tollman, 2001). One major argument for their inclusion is they control for natural remissions of a disorder. Given that many smokers quit without any treatment (The Clinical Practice Guideline Treating Tobacco Use and Dependence, 2008 Update Panel), natural remissions of nicotine dependence are common.

A second argument is that, when a non-active condition is credible (e.g., a time-matched, face-valid behavioral treatment or a placebo), it can control for expectancies and determine whether improvement is due to the actual contents of the treatment and not to "non-specific factors" (O'Leary and Brokovec, 1978). This second