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New insights into smoking cessation question the effectiveness of nicotine replacement therapy

Stanley and Massey's [1] recent analysis of a Cochrane systematic review on smoking cessation is an important addition to the ongoing debate around the efficacy of nicotine replacement therapy (NRT) and other pharmaceutical interventions in helping smokers to quit. Proponents of NRT, including leading clinical and professional bodies in the United States [2], the United Kingdom [3], and Australia [4] base their position on randomized clinical

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trials (RCTs) which typically report that the use of pharmacotherapy increases cessation success rates, compared to placebo or no assistance, by as much as 50−70% [5].

Such confidence in NRT, however, has come under scrutiny. The reality is that most ex-smokers have quit without assistance [6]. This discrepancy is explained by the fact that results returned by RCTs are not replicated at a population level because trial conditions are far removed from the ''real-world'' settings in which smokers attempt to quit [4]. In addition, much of the research apparently demonstrating impressive results for cessation using NRT (including studies analyzed in Cochrane systematic reviews) has been funded by pharmaceutical corporations that produce cessation products, raising concerns about conflicts of interest [4,7]. Despite this, Cochrane reviews remain a key source of evidence cited by NRT proponents [8].

The significance of Stanley and Massey's study is that it moves beyond the current discourse around trial vs. ''real-world'' results and related concerns about industry funding of research, to a consideration of the validity of the findings of Cochrane reviews. Their meta-regression analysis of more than 100 clinical trials [5] incorporated tests for sources of bias generally not included in systematic reviews. Once these sources of bias are taken into account, they found no statistical evidence that NRT is effective in helping smokers to quit; this finding differs significantly from the 50% to 70% increase in smoking cessation for NRT over placebo reported in the Cochrane review [5]. Furthermore, Stanley and Massey's study is important evidence indicating that the value of NRT as an effective means of smoking cessation has been overstated and that clinical bodies recommending its use should reconsider their advice to medical and health care workers and the public.

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Considerations of statistical power and risk of bias question the strength of nicotine replacement therapy's effectiveness

We are happy to learn that our findings about the limited evidentiary value of the large number of existing randomized controlled trials (RCTs) of nicotine replacement therapy (NRT) are consistent with broader epidemiological evidence and public health concerns [1]. But, we must caution readers that our meta-analysis of NRT RCTs does not ''prove'' that NRT has no clinical value. Scientific study can never ''prove'' the absence of some effect or phenomenon [2,3], and we do not wish to imply otherwise. Nonetheless, we find clear evidence that those RCTs which have greater risks of bias or use smaller, and thereby less reliable, samples report larger positive effects from NRT [4]. Conversely, studies with larger samples and low risks of bias tend to show smaller effects. Our findings merely cast doubt on the strength of the evidence of NRT's clinical efficacy as has been typically reported [5,6]. Although we do not wish to claim that NRT has no effect, we are confident that the size of NRT effect is substantially less than the 50−70% increase in quitting claimed by recent Cochrane Reviews [5,6].

Permit us to address a criticism that others are likely to make, especially in response to this letter by Mac Kenzie and Rogers [1]. The failure to find convincing evidence for a positive clinical effect from NRT need not depend on any meta-regression model of selective reporting bias (aka, ''publication'' bias). Not all meta-analysts have embraced these meta-regression methods to accommodate

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