Original Investigation

Assessing the outcomes of prolonged cessation-induction and aid-to-cessation trials: Floating prolonged abstinence

Paul Aveyard, Dechao Wang, Martin Connock, Anne Fry-Smith, Pelham Barton, & David Moore

Abstract

Introduction: A Society for Research on Nicotine and Tobacco working group recommended outcome measures for cessation-induction trials and aid-to-cessation trials. Cessation-induction trials aim to motivate unwilling quitters to make a quit attempt. Aid-to-cessation trials give either medication or behavioral interventions to increase the rate at which willing quitters succeed in their attempts. Nicotine-assisted reduction programs combine features of both types of interventions by giving nicotine replacement to unwilling quitters. Treatment can be prolonged more than a year, quit attempts can occur and succeed early or late in the program, and renewed quit attempts are an inherent part of the program. Conventional outcome measures are tied to a fixed but arbitrary point in follow-up and cannot capture the true outcome: Prolonged cessation anchored to the point at which a person makes a successful quit attempt.

Discussion: We propose that the outcome should be counted from the successful quit attempt that began during the treatment period and continues for a defined period, ideally 6 months. In particular, if a trial compared a short reduction program with a long reduction program, it would not be possible to obtain an unbiased assessment of the outcome of such a trial using a measure tied to a fixed point in follow-up. Floating prolonged abstinence could provide such an assessment and is suitable for either prolonged cessation-induction trial or combined cessation-induction and aid-to-cessation trials.

Introduction

The Society for Research on Nicotine and Tobacco (SRNT) working group for measuring abstinence in smoking cessation proposed

outcome criteria for two types of trials: cessation-induction trials and aid-to-cessation trials (Hughes et al., 2003). Cessation-induction trials aim to get a population of smokers to attempt to stop smoking, many of whom are not planning to stop immminently. Brief advice from a physician to stop smoking typifies such trials. By contrast, most clinical trials in smoking cessation are aid-to-cessation trials, in which smokers who want to stop are assisted to do so with medication or behavioral interventions.

Tobacco control researchers disagree about how to assess the outcome of studies. Some researchers argue that the primary outcome of studies should be point prevalence abstinence, which refers to abstinence lasting for (typically) the past 7 days. This has been the most commonly reported outcome in studies for several reasons. Because it is a more common outcome than alternative measures (Keely, Hughes, & Carpenter, 2001), it enhances statistical power. Continuous abstinence may not capture those who quit later in the process, which is a particular problem in cessation-induction studies (Velicer, Prochaska, Rossi, & Snow, 1992). Most people who achieve point prevalence abstinence in a typical aid-to-cessation study have achieved long-term abstinence (Keely et al., 2001). The point prevalence rate provides an unbiased estimate of the rate of prolonged abstinence (Keely et al., 2001; Stead, Perera, Bullen, Mant, & Lancaster, 2008). For these reasons, the U.S. Public Health Service guideline on tobacco dependence uses point prevalence as the preferred outcome (Fiore et al., 2008). Counterarguments in favor of prolonged abstinence are that the aim of smoking cessation is to get smokers to quit and stay quit forever, the only outcome known to improve health (Peto & Doll, 2006). One third of those who achieve point prevalence abstinence are not long-term abstainers (Keely et al., 2001), and this proportion might be much higher in cessation-induction studies than in aid-to-cessation studies (e.g., Aveyard, Griffin, Lawrence, & Cheng, 2003).

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There also has been disagreement about how to count enrolled participants who defaulted on follow-up. Some researchers advocate counting such people as smokers (Hughes et al., 2003; West, Hajek, Stead, & Stapleton, 2005), and some evidence indicates that in typical aid-to-cessation studies this is the case (Foulds et al., 1993). Others have argued that this assumption is probably not appropriate for cessation-induction studies (Velicer, Prochaska, Fava, Laforge, & Rossi, 1999), although no empirical evidence has identified the smoking status of defaulters to follow-up in cessation-induction studies.

In an effort to reconcile such differences, the SRNT working group examined these issues and the evidence and recommended that prolonged abstinence, meaning abstinence for either 6 or 12 months, be used as the primary outcome in smoking cessation studies (Hughes et al., 2003). In cessation-induction trials, outcomes should be measured at some (arbitrary) point after the start of the intervention. The period chosen should allow enough time for the intervention to induce initially unwilling quitters to begin a quit attempt. In aid-to-cessation studies, abstinence measures are tied to the quit day. West et al. (2005) proposed the Russell Standard measure of prolonged abstinence. The present paper describes a process for defining how prolonged abstinence is measured and what counts as a treatment success, extending the recommendations of the SRNT working group.

Recently, a new approach to treating smokers has been tested in clinical trials. Smokers who did not intend to quit were randomized to either long-term nicotine replacement therapy (NRT) or placebo and given advice on how to cut down on cigarettes. This approach has been termed nicotine-assisted reduction to stop (NARS). The NARS trials enrolled smokers who did not intend to quit imminently, and the primary goal was reduction. Somewhat unexpectedly, the treatment led to a doubling of long-term abstinence rates; hence, the NRT products tested were licensed for reducing to stop (Wang et al., 2008). We speculate that the NRT improved the experience of reducing and eventually stopping smoking so that the smoker who felt unable to stop without NRT felt that it was possible with NRT, although the reason for the efficacy of NRT in these trials is unknown. Program participants made several quit attempts, and the experimental treatment continued despite the failure of the initial quit attempts. In most aid-to-cessation studies, once participants resume smoking, treatment is withdrawn and the treatment on trial is not reinstituted, even if a participant wants to make another quit attempt. NARS trials, therefore, combined features of cessation induction (the reduction phase) and aid to cessation (the use of NRT for some months after achieving abstinence). The treatment in the trials lasted up to 9 (Etter, Laszlo, Zellweger, Perrot, & Perneger, 2002; Hausteine, 2002), 12 (Batra et al., 2005; Rennard et al., 2006; Wennike, Danielsson, Landfeldt, Westin, & Tonnesen, 2003; Wood-Baker, 2001), or 18 months (Bolliger et al., 2000).

We reviewed these trials recently (Wang et al., 2008). In this process, we examined the outcomes used in the trials, which were based on the recommendations of the SRNT working group (Hughes et al., 2003). As a group of epidemiologists, statisticians, health economists, and tobacco control researchers, we considered the pros and cons of the proposed measures in this context. In these discussions, we developed a new method of assessing their outcome, which was not reported in the studies. Because we had access to individual participant data from the

trials, we were able to extract the outcome from most studies using our newly developed measure. In these discussions, we considered the literature on assessing outcome in smoking cessation studies, some of which we reviewed earlier in this section. Here we draw upon this literature and use examples known to us. This paper proposes a variant of prolonged abstinence that fits better with the aim and practicalities of prolonged cessation-induction trials. First, we review the pros and cons of traditional measures of abstinence, use an example to show their particular drawbacks, and then illustrate the benefits of “floating prolonged abstinence.”

Point prevalence abstinence

In prolonged treatment trials, such as the NARS trials, point prevalence captures cessation occurring late in treatment. In NARS trials, the aim was to induce smokers to stop during the whole period of NRT treatment. Point prevalence would capture this; however, point prevalence measures have two disadvantages particular to NARS trials. First, point prevalence is defined as cessation at some arbitrary point in time and is likely to be measured repeatedly throughout a study. There is no rationale for picking up the point in time that should be used as the primary outcome. Second, point prevalence will mix those who have been abstaining for a long period and those who have been abstaining for only a week. This mixing of different periods of abstinence is likely to be much greater in a cessation-induction trial, in which some participants will have quit early and others late, than in an aid-to-cessation trial, in which everyone quit at the beginning. The evidence for this problem is that the ratio of point prevalence to prolonged abstinence appears much greater in cessation-induction studies than in aid-to-cessation studies (e.g., Aveyard et al. [2003] compared with Keely et al. [2001]). This problem is important because the risk of relapse is low in people who have abstained for 6 months and high in people who have abstained for only 7 days (Hughes, Keely, & Naud, 2004). Thus, it is more difficult in prolonged treatment trials than in aid-to-cessation studies to convert point prevalence rates into lifetime abstinence. Hence, it is difficult to convert these rates into life years gained (LYG) or quality-adjusted life years (QALYs). Demonstrating that an intervention generates sufficient gain in QALYs in relation to the cost is a key factor in ensuring that smoking cessation treatments are adopted into health care systems (Raftery, 2006). Finally, patients want to give up smoking for good, not for 7 days, and it would not be possible to use point prevalence to tell patients the likelihood of doing so if they enrolled in an NARS program.

Traditional prolonged abstinence

Traditional prolonged abstinence is the outcome of choice for assessing smoking cessation studies because it shows that smokers have maintained abstinence for a reasonable period (Hughes et al., 2003), and lifetime abstinence rates can be modeled from long-term follow-up studies (Etter & Stapleton, 2006; Stapleton, 1998). In turn, lifetime abstinence can be converted into QALY gain (Wang et al., 2008). However, in typical aid-to-cessation studies, we can anchor the start of the prolonged abstinence to the start of quitting, which is close to the start of the treatment.

In traditional cessation-induction studies, interventions to induce cessation occur across a period of time. Cessation-induction interventions are often brief and occur over a short period. For example, one early trial of physician advice to patients to stop smoking observed no cessation induction more than 3 months after the advice was given (Russell, Wilson, Taylor, & Baker, 1979). In such a trial (or similar trials), it would be reasonable to count prolonged abstinence from the end of Month 3 to the end of follow-up and tying follow-up to this fixed point will work well.

In the NARS trials, however, no quit date applied and cessation induction was as long as the treatment lasted, up to 18 months. This approach creates several problems. First, the NARS trial protocols defined prolonged cessation as commencing from 6 weeks after enrollment to multiple points in follow-up. It seems unlikely that participants recruited based on their not intending to stop smoking in the next month would begin a cessation attempt within 6 weeks of making such a statement. Consequently, such outcomes were rare (occurring in 1.6% of those in the NRT arm; Wang et al., 2008), and trials using this outcome as the primary one would need to be unfeasibly large to show a difference in abstinence between arms. These studies treated smokers for up to 18 months with a view to inducing abstinence throughout that period. It is illogical to treat someone for 18 months but use an outcome measure that counts as a failure anyone who quit after 6 weeks.

One possible solution is to assess the outcome as prolonged abstinence from the end of the treatment period for a further 6 months. This approach also creates problems.

First, some smokers will have stopped smoking early in treatment, remained abstinent for a year, but then resumed smoking. If only lifetime abstinence counts as a success, then this is not a problem in itself, but it does reduce the absolute abstinence rate that an intervention achieves.

Second, if treatment persists for a year, then successes measured at the 18-month follow-up will be those subjects who have abstained for 6–18 months. Around 20%–30% of people who maintain abstinence for 6 months will relapse in the next 12 months (Stapleton, 1998). This finding has two consequences for such a trial. The sample size is inflated because the outcome (6- to 18-month abstinence) is less frequent than is 6-month abstinence, and, in health economic assessment, lifetime abstinence is the true outcome of interest (Wang et al., 2008). Abstinence lasting 6–18 months is hard to convert to lifetime abstinence because this mixture of abstinence periods makes relapse rates harder to model.

Third, it creates practical problems for researchers. For good reasons, we use a procedure in smoking cessation studies that counts as smokers those who are lost to follow-up (West et al., 2005). Although treatment was offered for 18 months, many participants did not stay with it that long, including many who stopped smoking and used NRT only a few months after stopping, as most quitters do. To be counted as abstinent such a trial participant would need to continue attending the clinic for the sole benefit of the researcher. Persuading participants to attend repeatedly would be difficult and expensive and risk having participants default from follow-up and be counted as smokers when they are in fact abstinent. Evidence indicates that repeated

assessments without therapeutic benefits reduce follow-up rates (Velicer et al., 1999).

An example trial showing the disadvantages of tying outcome measures to a fixed point in time

In one of the NARS trials, participants unwilling to quit in the next month were randomized (a) to receive instructions to cut down more than 1 month and then stop or (b) to cut down more than 6–9 months and then stop (Haustein, 2002). This trial used a 2×2 factorial design (with randomization to NRT or placebo). As with all NARS trials, smoking reduction was the primary outcome. The secondary outcome was 2-month prolonged abstinence between months 2 and 4. If participants in the short reduction arm followed the program instructions and succeeded in stopping smoking, they would be counted as successes. However, those following the 6- to 9-month instructions, while not precluded from stopping smoking, were not instructed to do so until 6–9 months. Thus, the prolonged abstinence measure is biased in this trial toward the 4-week reduction. Point prevalence abstinence would be biased in a similar direction. In our review (Wang et al., 2008), we extracted 7-day point prevalence at 12 months from this study. By 12 months, relapse eroded more quitters from the 4-week reduction than from the 6- to 9-month reduction because the former had been abstinent longer; thus, assessing the outcome with point prevalence was biased in favor of the 6- to 9-month reduction. It is not possible to use a cessation measure tied to real time to measure the relative success of these two approaches to reducing and then stopping.

Floating prolonged abstinence: a solution

The key concept behind floating prolonged abstinence is that a person is counted as a success if that abstinence begins some time during the treatment phase of a study and is maintained for 6 months. This approach is true to the spirit of the SRNT procedures (Hughes et al., 2003) but adapts it to these kinds of trials.

Consider the hypothetical trial and participants illustrated in Figure 1. This trial is typical of NARS trials, with a treatment period of 12 months and last follow-up at 15 months. Participant 1 is a straightforward case. She maintained abstinence for two periods of 2 months and so failed to maintain 6 months of abstinence. Participant 2 is straightforward because he ended the trial abstinent, having been abstinent for 6 months. Participant 3 would count as a treatment failure in a conventional assessment because he ended as a smoker. However, with our proposed outcome, he is a success because he succeeded in achieving 7 months of prolonged abstinence.

Participant 4 is typical of people in an aid-to-cessation trial. He started abstinence early in treatment and relapsed after 5 months. In aid-to-cessation trials, resumed smoking would normally mean the participant, if he quit again, would use either no treatment or treatment obtained elsewhere but not the treatment to which he was randomized initially. (This is one

Treatment period																
	Months of observation															Outcome
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Participant 1	s	s	s	s	Q	Q	s	s	s	s	s	s	s	Q	Q	Failure
Participant 2	s	s	s	s	Q	Q	s	s	s	Q	Q	Q	Q	Q	Q	Success
Participant 3	s	s	s	s	s	s	s	Q	Q	Q	Q	Q	Q	Q	s	Success
Participant 4	Q	Q	Q	Q	Q	s	s	s	Q	Q	Q	Q	Q	Q	s	Success
Participant 5	s	s	s	s	s	s	s	s	s	s	s	s	Q	Q	Q	Failure
Participant 6	s	s	Q	Q	Q	s	s	s	s	s	s	Q	Q	Q	Q	Censored

Figure 1. Possible outcomes from a prolonged treatment trial. s, Smoking; Q, quit.

reason why point prevalence abstinence can give misleading information.) In NARS trials, treatment continues regardless of the success or failure of the first quit attempt. For Participant 4, a resumed quit attempt at month 9 led to 6 months of abstinence; hence, this participant would be counted as a success.

Participant 5 ended follow-up abstinent, but because her quit attempt started after treatment finished, it cannot logically be due to the treatment. We would expect such participants to be spread evenly across the treatment and control groups, but including them as successes leads to random error and will distort the true treatment effect, usually underestimating it. Whether such people should be counted as successes depends on the plausibility that the treatment induced and sustained abstinence after it was completed. We know of no evidence that pharmacotherapy for smoking cessation supports cessation after participants have ceased using it; thus, in our review, we did not count such participants as successes, even if follow-up had lasted 6 months or more after treatment stopped.

Participant 6 started her quit attempt during the 12th month of treatment and is potentially a success, but follow-up ceased in her 4th month of abstinence. It would be wrong to count her as a failure because she might have continued cessation for 6 months, but she also had not yet sustained abstinence for 6 months and so she was not considered a success. We propose dealing with this case by censoring. We would estimate the proportion of 4-month quit attempts that led to 6 months of abstinence and apply this correction factor to all similar participants who sustained 4 months of abstinence before they were censored.

The formula for this process is as follows. Let N_6 represents the potential number of smokers who sustain abstinence for at least 6 months measured from any timepoint during the treatment period. N_6 is calculated in two steps: (a) count the uncorrected number of smokers N_6^u who have sustained abstinence for at least 6 months within the study period (starting at any time within treatment period) and (b) calculate the censored number of smokers N_6^c who would have sustained abstinence for at least 6 months if the follow-up had been sufficiently extended. This censored estimate is the sum of the numbers of subjects abstinent for less than 6 months ($j < 6$) months [N_j] but still abstinent at the end of the study, multiplied by the probability (P_j) they would have gone on to remain abstinent for

at least 6 months. $N_6^c = \sum_{j=1}^5 N_j P_j$, P_j is obtained from the number of smokers who sustained abstinence for at least 6 months N_6^u , divided by the total number of all quits made during the treatment period (excluding those censored [N_j]), that is, $P_j = \frac{N_6^u}{n_j}$, where n_j is calculated as the number of smokers who sustain at least j months of abstinence to the end of the follow-up period, excluding those who are censored. Although the algorithm has been presented for estimating the rate of sustained abstinence for at least 6 months, it can be generalized to estimate the rate of sustained abstinence for at least T months.

Discussion

The true outcome of smoking cessation trials is lifetime abstinence, but because this is not measurable, 6 months of prolonged abstinence is the preferred measurable proxy (Hughes et al., 2003). The floating 6-month prolonged abstinence outcome we propose is consonant with this goal and consonant with the aim of prolonged treatment: to induce abstinence and support it whenever it occurs. However, it does not impose undue burdens on participants or investigators and is statistically more efficient than measuring prolonged abstinence at some arbitrary point in time. It also avoids the bias that can be generated by using fixed follow-up times.

The validity of the floating 6-month outcome as a proxy for lifetime abstinence depends on relapse rates. Are people who achieve 6 months of abstinence through a prolonged treatment course as likely to sustain abstinence for life as those who achieve this length of abstinence in a normal aid-to-cessation study? This is an empirical question to which no definitive answer can be given for all time and in all circumstances. We believe, however, that it is reasonable to presume that relapse rates are independent of the means by which abstinence was achieved. A meta-analysis showed that relapse after NRT and placebo occurred at the same rate (Stapleton, 1998), something observed in the recent phase III trials of varenicline, in which relapse was identical in the varenicline, bupropion, and placebo arms after the end of treatment (Cahill, Stead, & Lancaster, 2007). Finally, in the nicotine-assisted reduction trials, we observed subjects who had achieved 6 months of abstinence for an additional 5 months on average. The observed relapse rate was 19%, about as expected (Stapleton, 1998).

An unusual aspect of floating abstinence is that some people counted as treatment successes may be smoking by the end of follow-up. We are not arguing here that those who relapse are truly successes. We assume, as is common in the field, that lifetime abstinence is the primary goal of treatment. We can estimate that approximately half of those who sustain abstinence for 6 months will sustain it for life (Etter & Stapleton, 2006; Stapleton, 1998). If we continue to follow such individuals, as some were followed in the NARS studies, among the half who relapse prior to their deaths, some will be observed to relapse. What we are proposing is not unusual. It is akin to counting someone as a 6-month prolonged abstinence success who relapses between 6 and 12 months and is thus a failure at 12 months. The practical advantage is that, unless 12-month follow-up is planned, a smoker who is abstinent for 6 months can be discharged from further follow-up, even if others in the trial are being followed longer.

The other unusual feature of what we propose is the censoring of observations. This is not an inevitable component of our suggestion to use floating prolonged abstinence. The need to use censoring arises only if the period in which abstinence could plausibly be due to the intervention ends fewer than 6 months prior to the end of follow-up. Because three of the NARS trials were designed with fewer than 6 months between end of treatment and follow-up, we adopted this process as an expedient solution to our reanalysis (Wang et al., 2008). Allowing for censoring can make an important difference to the outcome, however. In our review of the NARS trials, 4.96% of quit attempts were observed to last 6 months but allowing for censoring gave an estimated 6-month prolonged abstinence rate of 6.75% (Wang et al., 2008).

We are not proposing changing the conventional approach in which those who are lost to follow-up are counted as smokers. Censoring would apply only if the investigators ceased follow-up, not if the participant ceased to return the investigators' calls. An analogous but different approach is proposed in the Russell Standard (West et al., 2005), in which those who move to untraceable addresses or die while abstinent can be discounted from the denominator. Discounting people from the denominator is an alternative procedure, but it is less satisfactory because it biases the quit rates downward.

Although this discussion focuses on trials of prolonged pharmacotherapy, it applies equally to most cessation-induction studies in which the induction period is lengthy. For example, interventions based on the transtheoretical model are aimed at both cessation induction and aid to cessation. Most trials have relatively short intervention periods of 6 months (e.g., Aveyard et al., 2003), in which case tying follow-up to real time is not particularly disadvantageous. In a few trials, the interventions were prolonged, as in the NARS studies, up to 18 months (e.g., Velicer et al., 1999). Debate exists about how to treat smokers lost to follow-up in cessation-induction trials, where there is little or no therapist-patient relationship and where loss to follow-up is typically higher than in aid-to-cessation studies (Lancaster & Stead, 2005). For example, in Aveyard et al. (2003), Meyer et al. (2008), Velicer et al. (1999), and similar studies, greater intensity of assessment and intervention is associated with greater loss to follow-up. In personal communication, Meyer et al. reported that some of their lost participants were nonsmokers who had long ceased to think of themselves as smokers and were annoyed at being repeatedly contacted and defaulted as a result. In cessation-induction studies, those who commence abstinence status early can be retired from follow-up after 6 months, and thereafter counted as treatment successes, whereas others who have yet to commence abstinence can continue to be followed. This procedure would ease the main problem in interpreting these kinds of studies.

In summary, floating 6-month prolonged abstinence provides a practical and rigorous outcome measure that is consonant with the aim of treatment in either prolonged cessation-induction trials or trials that combine cessation-induction and aid-to-cessation studies where treatment is prolonged.

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