Novel Strategies to Promote Smoking Cessation

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Introduction

Tobacco smoking results in an estimated 480,000 deaths and $300 billion in healthcare costs in the U.S., annually.[1] Smoking kills more people than alcohol, AIDS, car accidents, illegal drugs, and homicide/suicide combined. More than 16 million people currently suffer smoking related illness. Smoking is the leading cause of both coronary heart disease and cancer, which together comprise the two leading causes of mortality. Though the past 50 years has brought about significant public health improvements in tobacco control, the prevalence of smoking has declined only incrementally in recent years, with current national prevalence at 17%.[2] There are clear needs to improve smoking cessation at the individual level and, perhaps more importantly, at the population level.

The basic principles of promoting smoking cessation on a population-wide basis are rooted in the following formula[3]:

$$\text{Impact} = P_{QA} \times P_{\text{Quit Method}} \times P_{\text{success/method}}$$

where P_{QA} is the probability of making a quit attempt (QA), $P_{\text{Quit Method}}$ is the probability of using a specific quit method for that attempt, and $P_{\text{success/method}}$ is the probability of success for that method. The goal of any population-based smoking cessation effort is to increase the probabilities of making a quit attempt, using evidence-based methods, and improving upon those methods. Most clinical efforts focus on the latter; i.e., developing new and improved cessation techniques (behavioral or pharmacotherapy). There are a number of evidence-based treatment options for smoking cessation. USPHS clinical practice guidelines[4] and other meta-analyses[5-7] provide systematic reviews of empirically supported methods for treating tobacco dependence. Chief among these recommendations are that 1) all tobacco users should be offered brief advice to assist them with quitting, and 2) unless medically contraindicated, all smokers should be offered pharmacotherapy. Consistent with the latter, the most widely used medication is nicotine replacement therapy (NRT): patch, gum, lozenge, nasal spray, and inhaler. Among these options, only patch, gum, and lozenge are available over the counter, and thus offer greatest potential for translational effectiveness. NRT medications work to alleviate withdrawal and craving that are so common when quitting,[8,9] thereby increasing the likelihood of long-term success. All are safe, and, as a general rule, will double one's probability of achieving abstinence.[7] Other cessation medications exist (varenicline and bupropion), each with a substantial evidence base,[10-14] but are prescription based and offer reduced availability and access.

Another approach, just as reasonable, is to focus on the former inputs in the above equation; i.e., getting more smokers to try to quit, and moving them to use the best known methods. This has been a greater challenge. The incidence rate of quit attempts (i.e., percent of smokers who make a quit attempt each year) has not changed much in over a decade.[15] Among those who do make a quit attempt, use of pharmacotherapy is low.[16-18] Most smokers attempt to quit on their own, which is the least successful way to quit.[4,19] In fact, epidemiological data as applied to the above formula show that unassisted quitting (i.e., "cold turkey") has the largest population impact overall – not because it so efficacious (it has a very low $P_{\text{success/method}}$), but because it is so predominant (very high $P_{\text{Quit Method}}$). Tobacco control efforts should shift this balance, focusing on an increase of quit attempts using evidence-based treatments.

There are a number of well-established methods to induce quitting among smokers, including both policy-based (e.g., taxation, smokefree legislation) and clinical. Examples of the latter include physician advice and motivational interviewing, both of which have substantial evidentiary basis.[20-22] However, such strategies often rely on persuasive messaging, eliciting reasons for quitting and obstacles to change. While effective for some, many clinicians and smokers can feel frustrated by verbal techniques, and additional options are needed. Our group has been examining concrete, behavioral, and pragmatic strategies to promote quit attempts and use of evidence-based treatment, particularly among those who express unwillingness to do so. Our view of pragmatic strategies is similar to others,[23-25] with an emphasis on methods that are brief, feasible, scaleable, easily understood (by both provider and smoker), and easily disseminated. We believe such novel strategies are needed to address separate elements of the equation above, with a particular focus on increasing the both incidence of quit attempts and usage of evidence-based treatment. Below we document a series of studies along this theme.

Smoking Reduction

Under the premise that reduction might facilitate quit attempts, we conducted a nationwide, randomized clinical trial (N=616) in which we randomized smokers who did not want to quit into one of three groups: 1) NRT-assisted reduction counseling, 2) time-matched motivational advice, or 3) no treatment control.[26] Our trial was an explicit test of whether reduced smoking per se would serve as a catalyst to cessation among smokers not wanting to quit, not to be confused with the process of gradual quitting among smokers with firm quit plans. Participants were recruited through market research panels and all interventions were administered via phone and mail. Smokers in the reduction group were guided through a structured protocol to reduce smoking by 50%, after which they were prompted with firm advice to quit entirely. The rationale for reduction was simple – that it would provide concrete evidence of success and control over smoking, however incremental, and that this would bolster confidence and strengthen motivation to quit. Outcomes were tracked prospectively for six months, and results supported the main hypothesis: more smokers in the reduction (43%; RR = 2.8; 95% CI: 1.9 – 4.0) and motivational (51%; RR = 3.3; 95% CI: 2.3 – 4.7) conditions made a 24-hour quit attempt over 6 months than smokers in the no treatment condition (16%) but the two active conditions did not differ. Similarly, 18% of participants within the reduction group (RR = 4.0; 95% CI: 2.0 – 8.1), 23% of the motivational advice group (RR = 5.4; 95% CI: 2.7 – 10.7) and 4% of the no treatment group were abstinent (7-day point prevalence) at six months (see Figure 1) and again the two active treatments did not differ.[26] Thus, reduction facilitated quitting

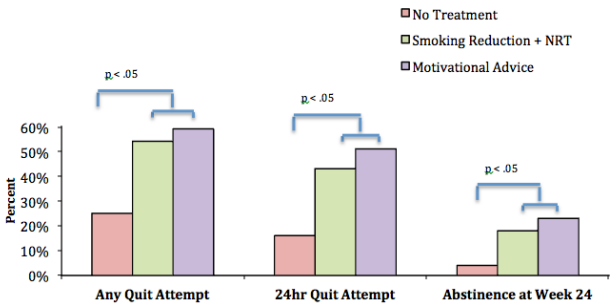

Figure 1. Incidence of quit attempts and cessation

and was as effective as motivational advice, with both options easily disseminable among clinicians. Subsequent literature reviews of smoking reduction, both within our group[27,28] and by others[29-32] provided further support for smoking reduction as a behavioral strategy to induce quit behavior. While our trial results were encouraging for smoking reduction, they were strongly confounded by NRT use. It was unclear whether the effect on cessation was driven by a) the behavioral act of cutting down on cigarettes per day or b) the experiential exercise of using medication. Some evidence within our trial suggested the latter. We subsequently isolated this effect through a series of NRT sampling studies described further below.

Usage, Attitudes, and Perceptions of NRT

We separately conducted two complementary studies that documented attitudes and misperceptions of cessation medication. The first was a qualitative study of perceptions of NRT specifically[33] and highlighted enduring misperceptions about the rationale, development, safety, and efficacy of NRT, all of which likely undermine usage. This study also suggested possible racial/ethnic differences in how cessation medications are viewed, which may in part explain particularly low rates of medication use among African American smokers. Our second study of attitudes towards cessation pharmacotherapy was a phone-based cross-sectional survey of South Carolina smokers.[34] Attitudes towards pharmacotherapy among current smokers (N=697) are presented in Table 1, and show modest endorsement of treatment in general, or cessation medications in particular, and that such barriers may differ by race. From these studies, we believed that greater effort was needed to educate smokers about cessation medication (NRT in particular), and that there was no better way to learn about it than to use it.

NRT Sampling: Study 1

Our experiences above led us to investigate whether sampling of cessation medication, and NRT specifically, would facilitate quit attempts and cessation among smokers not yet ready to quit. There are several mechanisms by which sampling could promote downstream changes in smoking behavior. One is through improved self-efficacy. As smokers gain confidence in controlling smoking, they may be more likely to believe that total abstinence is possible. Second, medication sampling might heighten motivation. Whereas abrupt quitting is often daunting, gradual exposure to cessation, particularly when that experience is made easier through NRT, might remove some of the perceived barriers to quitting. Third, simply trying a medication without any firm commitment for long-term use may dispel misperceptions and increase familiarization, directly addressing barriers as suggested in Table 1. Finally, sampling may increase autonomy, promoting self-control over smoking and the process of quitting. Collectively, these principles are wholly consistent with self-determination theory;[35,36] i.e., the rationale that smokers will be more successful if they are invested in, knowledgeable of, and motivated for quitting if they decide for themselves the goals, pace, and strategies for changing tobacco use. NRT give-away programs are common within quitlines, with demonstrated success.[37-39] However, quitlines are underutilized[40] and by definition generally reach smokers who are actively seeking out and receptive of treatment. Our goal was to take these same principles and apply them more broadly.

We first conducted a randomized clinical trial (N=849) testing the concept of NRT sampling to induce cessation behavior among smokers unmotivated to quit.[41,42] Smokers were again recruited nationally via online channels for a phone-based intervention trial, and were assessed for six months. Treatment consisted either of 1) NRT sampling, within the context of a practice quit attempt (PQA), or 2) PQA alone. The PQA intervention was a behavioral exercise, within which smokers could (or could not) sample nicotine replacement. The PQA was designed to increase motivation, confidence, and coping skills. The added value of NRT samples (nicotine lozenges) was hypothesized to familiarize smokers with NRT, promote wider acceptance of it, and ultimately to enhance motivation and confidence even further. Though participants were provided with a brief overview of medication and supporting rationale, a repeated theme was on self-determined use: to use NRT "if and how you wish." Uptake of NRT during the sampling period was strong: 73% of smokers used the product, for an average of 9 days. Cessation outcomes were very promising, with significant increases in quit attempts and some measures of abstinence (Figure 2). Follow-up mediational analyses[43] revealed that the added influence of NRT sampling worked largely as intended, through hypothesized mechanisms above.

NRT Sampling: Study 2

The trial above was based on unmotivated smokers only. We next completed a separate semi-randomized pilot trial of smokers across three groups (N=157), testing: smokers motivated to quit, given 2-week samples of both nicotine patch and lozenge (Motivated/NRT), vs. unmotivated smokers, either randomized to

Table 1. Attitudes towards Cessation Medications: Current Smokers[1]

	African American	Caucasian-American	p
How well do medications work to help smokers quit?	42%	50%	.03
How concerned are you about medication safety?	51%	46%	.17
How concerned are you that you might get addicted?	30%	23%	.03
How concerned are you about cost?	55%	60%	.22
How much treatment of any kind do you need to quit?	50%	60%	.008
How much do you need medication to help you quit?	44%	51%	.07

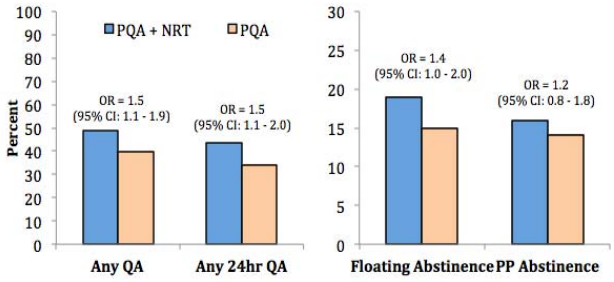

Figure 2. Rates of A) any quit attempt (QA), B) 24hr quit attempt, C) floating abstinence (7 days, no smoking, at any point in study), and D) 7-day point prevalence (PP) abstinence at Week 26, among smokers engaged in a practice quit attempt (PQA), with or without NRT samples.

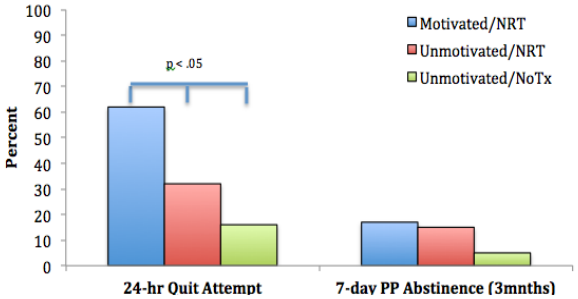

Figure 3. Rates of 24-hr Quit Attempts and Point Prevalence Abstinence among groups of smokers who: A) endorsed motivation to quit and received samples of nicotine patch and lozenge (Motivated/NRT), B) did not endorse motivation to quit but got same treatment (Unmotivated/NRT), and c) did not endorse motivation to quit and got no treatment (Unmotivated/NoTx).

the same treatment (Unmotivated/NRT), or not (Unmotivated/NoTx).[44] The rationale for combination NRT was fourfold. First, a number of studies demonstrate their efficacy when used singularly.[4] Second, they are both over the counter, increasing their dissemination appeal within in various populations. Third, whereas the patch provides a steady dose of nicotine throughout the day, the lozenge is used ad libitum and provides acute nicotine administration. These two mechanisms might appeal to smokers differently. Fourth, two trials[45,46] and a separate review within our group[47] have shown that combined use of patch + lozenge is superior over placebo and single NRT products. We expected superior outcomes (higher incidence of quit attempts and cessation) within Motivated/NRT Group, since they expressed motivation to quit and were given tools to do so, and we anticipated inferior outcomes within Unmotivated/NoTx Group, since they had neither. The main focus was on the Unmotivated/NRT Group, who shared commonality with first (active sampling of medication) and last group (unwillingness to quit). Rates of incidence for quit attempts through three months were ordinal:[44] 62% vs. 32% vs. 16% (Figure 3), while rates of abstinence (7-day point prevalence at final follow-up) were generally comparable between Motivated/NRT and Unmotivated/NRT Groups (17% vs. 15%), a 3-fold increase over Unmotivated/NoTx Group (5%; all pairwise comparisons not statistically significant but still clinically meaningful).[44] Our results provide further support for the concept of sampling medication as a method to induce quitting. Results also indicate that while initial motivation to quit enhances outcomes (Motivated/NRT vs. Unmotivated/NRT), it is not a necessary precursor to success (Unmotivated/NRT vs. Unmotivated/NoTx).

NRT Sampling: Study 3

The collective evidence above suggests a role for medication sampling to promote quit attempts and abstinence among smokers. Overall effect sizes are moderate, but when applied in a larger context, the population impact could be large. Our third trial is a cluster randomized trial of NRT sampling within real-world, primary care settings (N=1160; 20 clinics). The study is inclusive of all smokers regardless of motivation to quit, which may or may not become a potential moderator of treatment outcome. NRT sampling is particularly well suited to any number of medical settings, much like within a dental setting where patients are given product samples at the end of each visit, in that it is brief (i.e. incurs no extra demands on a busy provider or staff) and has intuitive face validity. As throughout above, messaging emphasizes self-determined use: ~"as your provider, we think these medications can help, even if you're not ready to quit. Try them and see for yourself." Outcomes will be assessed through six months, and are focused across three levels: a) individual smoker outcomes, as defined above (also: further use of medication, use of behavioral support including quitlines), b) provider outcomes (e.g., satisfaction and confidence in cessation counseling), and c) aggregate clinic outcomes (e.g., screening and treatment of all smokers, including those not within study). The trial is ongoing and expected end date is late 2017.

Role of Alternative Tobacco Products to Promote Quitting

The proliferation of alternative tobacco products gives rise to parallel research questions along this same theme: what effect will they have on quitting? The market of potentially safer products has vastly expanded in recent years, and though there is wide variation within this market, most new products are non-combustible and thus offer reduced harm to the individual user. For example, low nitrosamine smokeless tobacco (LNSLT) has been popular in Scandinavian countries for years, where rates of lung cancer have significantly decreased.[48-50] LNSLT, also known as snus, differs from traditional smokeless tobacco in that it is pouched, spitless, flavored, and marketed directly to cigarette smokers as a substitute product. As such, whether and how snus changes smoking behavior is a compelling public health question. Snus could conceivably help smokers quit cigarettes, or, alternatively, it could maintain dependence, allowing them to circumvent smoking restrictions, engage in long term dual use, and thus undermine smoking cessation. Only a few randomized clinical trials of snus exist,[51-54] and all are cessation-focused, i.e., recruiting smokers wanting to quit and explicitly testing snus as a strategy to do so. These studies generally show positive effects on snus on cessation. However, these studies do not address the naturalistic population impact of snus on smoking behavior, and this remains an important gap in the literature.

We first conducted two pilot studies, both randomized tests of smokeless tobacco[55,56] which generally showed reductions in smoking and increases in motivation to quit compared to control groups. Next, following much of the methods of the NRT sampling studies above, our group conducted what we believe is the largest (N=1236), longest (1-year), and most direct

(randomized design) study of snus among U.S. smokers. Smokers unmotivated to quit, recruited nationwide, were provided a six-week sample of snus vs. not, followed by periodic assessment for an additional 12 months. Sampling of snus was entirely self-determined. The primary outcome was incidence and duration of quit attempts, and secondary outcomes were point prevalence abstinence from cigarette smoking, at 6 and 12 months, smoking reduction, and associated measures of quitting; no support from the tobacco industry was provided. The trial is recently completed and results are forthcoming elsewhere. The results will add to the literature on snus and will provide an important contribution to the clinical and regulatory debate as to how these products fit within the landscape of tobacco control.

More recently, the exponential growth of electronic (e-) cigarettes has dramatically shifted the focus of alternative products. Models of e-cigarettes span a wide spectrum, from disposable cartridges to highly sophisticated tank systems including ones that allow the user to control the amount, dose, and power of nicotine delivery. The basic operation of any e-cigarette involves the heating and vaporization of nicotine; there is no combustion. E-cigarettes attenuate craving to varying degree,[57] but this is likely dependent upon type of e-cigarette product. Like LNSLT, growing evidence[58,59] suggests that e-cigarettes are safer than conventional cigarettes, delivering significantly reduced levels of tobacco-specific nitrosamines; i.e., primary class of carcinogens within tobacco. How e-cigarettes alter behavior is unclear. Only three randomized studies exist.[60-62] All come from abroad, and most are cessation-driven (use of e-cigarettes to help smokers quit) and not naturalistic. Results are generally supportive that use of e-cigarettes might facilitate quitting, which supports some but not all indirect (i.e., non-randomized, cross-sectional) evidence elsewhere.[63-68] Our group is now testing e-cigarettes much like we have done for NRT and snus sampling studies above: using randomized designs but still focusing on naturalistic, self-determined use. One placebo-controlled crossover study is recently completed, another prospective study is ongoing, and a larger trial is planned. In time we believe these studies will guide understanding of the clinical and population impact of electronic nicotine delivery systems.

Conclusion

Many smokers remain unable or unwilling to quit. Among those who try to quit, unaided attempts are the most common, yet least effective strategy. Many evidence-based treatments, including those that are the most accessible, remain under-used by smokers. Promoting active treatment to all smokers, even if they do not wish to quit, offers a strong opportunity to increase cessation at the population level. Increasing both the incidence of quit attempts and the use of evidence-based treatment for those attempts offers strong potential to move smokers away from unproven (unassisted) ways of quitting and thus offers an opportunity to dramatically increase the impact of smoking cessation. Allowing smokers to sample cessation medication on their own terms increases quit attempts and quitting, often among those resistant to do so. Sampling of medication, particularly NRT, is easy to disseminate within any number of real-world medical settings, reaching large numbers of smokers. The role of alternative tobacco products to promote quitting is less clear. There is strong need for large scale, randomized, but still naturalistic studies of products, particularly e-cigarettes, which may or may not promote quit attempts and cessation. Dr. Carpenter is grateful to the South Carolina Academy of Science for acknowledgment of his work, and is deeply indebted to the many individuals who have collaborated and supported this research.

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