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## Enhancing the Effectiveness of Smoking Treatment Research: Conceptual Bases and Progress

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### Abstract

**Background and aims**—A chronic care strategy could potentially enhance the reach and effectiveness of smoking treatment by providing effective interventions for all smokers, including those who are initially unwilling to quit. This paper describes the conceptual bases of a National Cancer Institute-funded research program designed to develop an optimized, comprehensive, chronic care smoking treatment.

**Methods**—This research is grounded in three methodological approaches: 1) the Phase-Based Model, which guides the selection of intervention components to be experimentally evaluated for the different phases of smoking treatment (motivation, preparation, cessation, and maintenance); 2) the Multiphase Optimization Strategy (MOST), which guides the screening of intervention components via efficient experimental designs and, ultimately, the assembly of promising components into an optimized treatment package; and 3) pragmatic research methods, such as electronic health record recruitment, that facilitate the efficient translation of research findings into

clinical practice. Using this foundation and working in primary care clinics, we conducted three factorial experiments (reported in three accompanying articles) to screen 15 motivation, preparation, cessation, and maintenance phase intervention components for possible inclusion in a chronic care smoking treatment program.

**Results**—This research identified intervention components with relatively strong evidence of effectiveness at particular phases of smoking treatment and it demonstrated the efficiency of the MOST approach in terms both of the number of intervention components tested and of the richness of the information yielded.

**Conclusions**—A new, synthesized research approach efficiently evaluates multiple intervention components to identify promising components for every phase of smoking treatment. Many intervention components interact with one another, supporting the use of factorial experiments in smoking treatment development.

### Keywords

Smoking cessation; quitting smoking; tobacco dependence; cigarettes; chronic care smoking treatment; Multiphase Optimization Strategy (MOST); phase-based model; comparative effectiveness; primary care; factorial experiment; methodology

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Despite considerable advances in smoking treatment research [1–3], greater progress is needed in multiple areas. For instance, counseling effects tend to be modest, and we have little understanding of which counseling contents are effective [4–6]. Further, most smokers still fail to achieve long-term abstinence in their quit attempts even while using multiple pharmacotherapies [7–10]. Finally, translating evidence-based interventions into clinical practice has been slow and limited [11–16]. In sum, we need to improve smoking treatments and increase their translation into practice.

Why has research progress not been greater? First, there has been insufficient recognition that effective smoking treatment requires *chronic care*; i.e., treatment that can be used effectively across all phases of smoking cessation (e.g., with smokers unwilling to quit, smokers willing to set a quit day, and smokers trying to maintain abstinence). Developing an effective chronic care tobacco treatment might enhance both abstinence rates and treatment reach (i.e., offering motivational treatment to the 60–80% of smokers unwilling to make a quit attempt at any point in time should enhance reach: [13, 17–19]). Second, interventions for smoking have often been either difficult to implement or have lacked effectiveness in real-world settings, limiting their translation [20–23]. Third, commonly used research methods have been inefficient, resulting in too few *individual* intervention components being evaluated, and the data these methods yield have been insufficiently informative and useful. For instance, because previous research has rarely tested interaction effects, we have not learned which intervention components work well together, hampering our ability to combine them effectively [24, 25].

The three papers accompanying the present article (viz. [26–28]) describe a complementary set of studies designed to support the development of an optimized chronic care smoking treatment. By *optimized*, we mean that the resulting treatment package comprises intervention components that have each been shown to be promising in screening

experiments; e.g., yielding significant, beneficial main or interaction effects with regard to key *optimization criteria*. We used several frameworks to address this goal. First, a chronic care treatment requires effective intervention strategies for the different phases of the smoking cessation process; we used the Phase-Based Model (PBM) of smoking treatment [2, 24] to help identify the intervention components that should be experimentally evaluated for each phase of smoking treatment. Second, we needed a research framework to guide the efficient and methodologically principled evaluation of the candidate intervention components identified via PBM. We selected the Multiphase Optimization Strategy (MOST [25, 29–31]), an engineering-inspired framework for the development and evaluation of optimized treatments. The three experiments we report are the first to use MOST to screen clinical interventions for smoking that are designed for use in the healthcare setting (cf. [32, 33]). Finally, we used pragmatic research methods (e.g., [34]) to hasten the translation of our research findings into real world use. These three research frameworks are described below.

## The Phase-Based Model (PBM) of Smoking Intervention

The PBM was developed to spur research progress on the chronic care of tobacco use [35–38]. Specifically, PBM was designed to enhance research progress, but in manner that would directly inform clinical decisions and practice.

Clinicians, and smokers, face multiple smoking related decisions over time, including whether the smoker will take action with regard to smoking, the type of action to be taken, and how that action will be accomplished. The smoking change goal (e.g., quitting vs. reducing) is particularly important and affects the challenges the smoker faces and the opportunities for intervention. For instance, smokers unwilling to try to quit face different motivational challenges than do smokers who are willing to do so; i.e., the change-goal “organizes” challenges and opportunities and therefore, has implications for assessment and treatment. For example, the smoker attempting to quit faces rapidly escalating withdrawal, for which front-loaded treatment designed to ameliorate withdrawal (e.g., combination nicotine replacement therapy: [39]) might be especially appropriate.

PBM currently identifies five goal-related treatment phases (see Figure 1 and Table 1): Motivation, Preparation, Cessation, Maintenance, and Relapse Recovery [2]; the last phase was not addressed in the present research. The time courses suggested for the phases (see Table 1), reflecting their associated challenges and treatment opportunities, have been informed by prior research (e.g., on withdrawal duration, durations of effective treatments: [24])<sup>1</sup>. We believe that future research will yield more informative guidance with regard to optimal durations of phase-targeted treatment. For the individual patient, however, engagement in and duration of, phase-based treatment will often be affected by change-goal decisions made by the patient and/or clinician (e.g., deciding to reduce smoking or try to quit). Below we describe the phases and list examples of challenges and opportunities that are particularly (*but not exclusively or exhaustively*) relevant for each phase (see Table 1 for additional examples).

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<sup>1</sup>Thus, the timing of phases and the challenges and opportunities they offer have been greatly informed by prior phase relevant research (e.g., [40 – 50]).

The *Motivation phase* comprises smokers unwilling to make a quit attempt. The chief goal of Motivation-phase treatment is to increase the rate and probability of successful quit attempts. Representative challenges are low quitting motivation, inadequate coping skills, and high levels of smoking and dependence [2, 24]. Importantly, any smoker unwilling to make a quit attempt should be offered Motivation-phase treatment.

The smoker in the *Preparation phase* is willing to make a quit attempt, but based on clinical judgement, patient preference, and/or evidence of effectiveness, a decision is made to use treatment to prepare the smoker for the cessation attempt. The chief goal is to increase the likelihood of initial abstinence following a quit attempt and one challenge is to intervene effectively within a brief time window: typically 2–3 weeks [40] to prevent quitting motivation from flagging prior to the quit attempt.

The *Cessation phase* comprises the immediate post-quit period (~2–4 weeks after the quit day) when the smoker is actively engaged in cessation intervention and striving to become abstinent. The goal is sustained early abstinence and representative challenges include withdrawal symptoms that escalate and typically peak at this time, lapsing, and a brief timeframe for effective intervention [51–53].

The *Maintenance phase* follows the establishment of initial abstinence in the Cessation phase and is of indeterminate length. The chief goal is the preservation or restoration of abstinence, while representative challenges include flagging motivation, poor adherence to interventions, and the transition of lapses to relapse.

PBM holds that knowledge regarding the challenges and opportunities of the different phases of the smoking cessation process can facilitate decision making (e.g., selection of a change-goal and the treatment to achieve it), treatment evaluation, and the application of theory. PBM calls for researchers to ask: 1) What are the intervention opportunities and challenges for the various phases? And, 2) What interventions are likely to capitalize on those opportunities and address those challenges successfully? Thus, research organized by PBM could ultimately help guide clinical decisions about what change-goal to pursue, when to pursue it, and how to achieve it (i.e. what intervention components to use). Smokers typically undergo numerous transitions with regards to their smoking change-goal [2, 54]; PBM is aimed at making such transitions more strategic and successful. PBM may be most useful as an organizational research tool, and to guide the design and application of clinical interventions. Thus, it is chiefly relevant to planned, clinical intervention versus unplanned self-quitting [54].

Making effective smoking treatment available for each phase should enhance the net benefit of treatment; i.e., by using the most effective intervention components at each treatment phase [24]. This necessitates developing effective interventions for those phases for which effective interventions have not been definitively identified: e.g., preparing for cessation or avoiding relapse [40, 55, 56].

Phase-based treatment should also enhance the net benefit of treatment by enhancing the *reach* of treatment. Given that the majority of smokers are *not* willing to make an aided quit attempt at any given time point [57–59], reach would be enhanced if such smokers entered

effective treatment with a different change-goal, one that ultimately increases cessation (e.g., Motivation phase treatment with a smoking reduction goal).

Unlike the Transtheoretical Model (TTM: [60]), PBM is not a theory of change, but is instead an *organizing framework*, and its chief goal is to help organize *all* data, theory, and research relevant to decisions about smoking treatment goals and interventions so as to support successful change. PBM certainly shares features with the TTM, but it differs from it in several ways. 1) Unlike the TTM, PBM phases are determined largely by the clinician's and patient's strategic selection of change-goals and success in meeting those goals, and therefore, need not unfold in a set order; 2) PBM is directed at the treatment of *tobacco smoking* per se, meaning that any data and theory relevant to smoking and its treatment can be incorporated into the framework, and they need not apply to behavior change in general; 3) PBM is not constrained to view change as occurring via a restricted set of extracted mechanisms (such as the TTM "processes of change" [61]) and therefore, any effective treatments thought to work via any sort of mechanism can be incorporated into the framework; and, 4) In PBM each phase has associated behavioral and clinically relevant smoking change-goals (e.g., smoking reduction in the Motivation phase, maintenance of abstinence in the Maintenance phase). Therefore, PBM represents a unique framework for developing and applying smoking treatment. While matching optimal treatments to theory-based stages of change has proved challenging [62–64]; although cf. [65], PBM may nevertheless prove useful in guiding such treatment matching.

## The Multiphase Optimization Strategy (MOST)

The classic approach to behavioral intervention science has been to identify a set of intervention components, and then assemble them into a treatment package that is evaluated in a two-arm randomized controlled trial (RCT)<sup>2</sup>. This approach has several shortcomings. Because the individual components of the treatment package are never assessed in a controlled, randomized factorial experiment (we use the term "experiment" to indicate the use of a factorial design, versus the nonfactorial RCT), it is impossible in an RCT to determine which components are active ingredients and which are inert. Moreover, interactions amongst intervention components are not examined, so it is unknown whether and how the performance of a particular component may be enhanced or reduced by the presence other components.

### Screening experiments

MOST ultimately encompasses the conduct of RCTs, but it entails considerable research prior to an RCT, including initial, factorial "screening" experiments, so named because they are aimed at screening out poorly performing intervention components by evaluating the performance of individual components and any interactions amongst them. Factorial experiments differ from RCTs in that their objective is to provide estimates of the individual main effects of several experimental factors and interactions amongst them, whereas the

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<sup>2</sup>In MOST, a clinically meaningful, but relatively specific treatment element is termed an *intervention component*; such components can be screened for effectiveness using factorial experiments. As per MOST, those components that are especially effective would then be combined into *treatment packages* or *treatments*.

objective of an RCT is direct comparison of the means of experimental conditions (e.g., Experimental Treatment versus Usual Care: see [66]). The information obtained from factorial screening experiments makes it possible to optimize treatment packages to meet one or more specific criteria (e.g., effectiveness, cost-effectiveness, translation potential) by selecting the appropriate components for inclusion. Our criterion for optimization was simple. In the three companion experiments [26–28], we sought to develop a treatment comprising only components that have promising patterns of effects in terms of the magnitude, consistency, and significance of the main and interaction effects.

In our research [26–28], an intervention component was viewed as promising if it yielded a significant main effect and/or interacted synergistically with other components. Note that assessment of “promise” in screening experiments depends upon an appraisal of evidence across different effects (e.g., across main effects and interactions at different time points), and is not necessarily reducible to a significant effect on a single outcome. This synthesis of information across effects is efficient since it permits the use of all information yielded by the experiment; however, it introduces some subjectivity into the evaluation of the results. In addition, factorial screening experiments can yield tests of numerous main and interaction effects, leading to increased risk of Type I error. (However, it should be noted that with effect coding, all main effects and interactions are essentially uncorrelated [66, 67].) For these reasons, the conclusions yielded by such factorial screening experiments serve the purpose of hypothesis *generation* not hypothesis *confirmation*; they suggest that certain intervention components will perform well as an integrated treatment, a hypothesis that can be evaluated ultimately in an RCT comparing the treatment package developed via screening experiments with a meaningful alternative such as usual care.

### **MOST and the three experiments**

This series of 3 screening experiments [26–28] evaluated 15 intervention components to identify especially promising components for the Motivation, Preparation, Cessation, and Maintenance phases (Figure 1). The components evaluated were those with promise to address phase-relevant challenges, based on prior positive findings and/or substantive considerations. For instance, nicotine gum and patch were both used in the Motivation phase in the Cook et al., experiment [26]; the gum has been shown in multiple studies to increase abstinence rates amongst those not initially motivated to quit (e.g., [42]), whilst the nicotine patch seemed a theoretically promising substitute for smoking, with the potential to reduce smoking prequit and promote greater success in a subsequent quit attempt (also see [68]).

The factorial designs used [26–28] are highly efficient, in keeping with MOST’s resource management principle; i.e., using available research resources, including research participants, as efficiently as possible [67]. Factorial experiments efficiently produce information needed to optimize a treatment, namely, all main and interaction effects for multiple components. With proper analysis, factorial experiments can maintain a given level of statistical power with only a fraction of the subjects required by alternative approaches (e.g., an RCT [67, 69]).

The resulting experimental data were analyzed primarily with multivariable analyses with effect coding (where the two levels of a factor are coded –1 and 1) rather than with dummy

coding (where coding is 0 and 1). These two approaches yield statistical models that are identical in terms of their overall fit to the data, but yield different estimates of component effects that should be interpreted differently. As noted above, a key virtue of effect coding is that obtained effects are uncorrelated in balanced designs. This permits interpretation of a factor's main effects even when it interacts significantly with (an)other factor(s) [31, 70].

With effect coding, the main effect of a factor represents its effect averaged over all the other factors in the model. As Fisher pointed out, this provides "a wider inductive basis" for any conclusions [71, p.102]. Thus, main effects are especially important in evaluating promise since they reflect robustness across variation due to the influence of other factors.

## Interactions

Relative to main effects, interactions can pose greater interpretive and inferential challenges. Each of the factorial experiments in our research [26–28] entailed the experimental evaluation of 4 or more intervention components. These yielded numerous interaction tests (e.g., 11 in a 4-factor experiment) and higher-order interactions that produced complex patterns of effects. In these experiments [26–28], we interpret interaction effects via practices used in engineering (as per MOST: [25]); i.e., we inspect differences in performance of one or more components across levels of other relevant components, and then relate this information to relevant main effects (see also cf. [72, 73]). We do not conduct simple effects hypothesis tests, in part because they would be gravely underpowered. Well-powered simple effects tests following higher order interactions would require a substantial increase in  $N$ , greatly reducing the efficiency of the factorial experiment (i.e., to test multiple components using relatively small  $N$ 's: [25]). Our approach to interpreting interactions is consistent with the goal of this research being hypothesis generation, not confirmation.

The results of the factorial experiments reported in this issue [26–28] contain examples of synergistic and antagonistic interactions. In a synergistic interaction, the effect of Component A and Component B together is significantly greater than would be expected simply from the additive effects of the two component main effects (i.e., the effects of one experimental factor varies significantly depending on the level of another factor(s)). Conversely, in an antagonistic interaction, the joint effects would be less than expected based upon the additive main effects. A promising component would either produce a beneficial main effect, interact synergistically with other promising component(s), or ideally, do both. However, even if two components interact antagonistically they may both merit inclusion if their main effects are strong and the interaction, modest.

## Pragmatic Research Strategies

Pragmatic criteria were also used to guide this research program [20, 34]: 1) The topic addressed (smoking cessation) is important to key stakeholders (e.g., patients, and payers [74]); 2) the participants were those to be targeted in real-world application: smokers visiting primary care clinics; 3) the research was conducted in primary care clinics; and, 4) the evaluated components and their delivery systems were feasible and appropriate for use in

healthcare settings. This research did not, however, adhere to all pragmatic research criteria ([34]: e.g., research staff were hired to function as clinic-based case managers).

One objective of pragmatic research is to develop treatments that are easy to implement and maintain over time [20, 34]. We tried to achieve this via use of intervention components appropriate for real-world healthcare, and use of a chronic care management model widely used in healthcare (e.g., to manage diabetes, asthma, [75, 76]). The latter involved a team approach with clinic managers, medical assistants (MAs), and BA-level case managers identifying, recruiting, referring, and treating smokers. This team effort was coordinated and guided by an enhanced electronic health record (EHR). The EHR is increasingly widely used and can leverage up-front developmental costs into long term, systematic intervention support [77–80]. In this research, the EHR guided the identification of smokers by clinic MAs and provided them with a script to assess interest in smoking treatment and to offer treatment. The MAs then used the EHR to seamlessly refer interested smokers to study treatment personnel for screening and treatment enrollment. All in-person treatment was delivered at the patient’s primary care clinic [81, 82].

## What We Have Learned

The accompanying screening experiments address the Motivation [26], Preparation/Cessation [27], and Maintenance [28] phases of chronic care smoking treatment. The results are promising. First, we successfully conducted this research in a manner largely consistent with pragmatic research criteria: e.g., recruiting three nonoverlapping samples of smokers and treating them in their primary care clinics. Second, there was evidence that a *phase-based* chronic care approach to smoking treatment can pay clinical and scientific dividends (e.g., by including an option for smokers to reduce their smoking via a Motivation phase treatment, we increased the proportion of smokers attending routine primary care visits who entered smoking treatment by about one-third [26]). Third, we demonstrated the feasibility of factorial experiments for the experimental analysis of multiple clinical interventions; enabled by database prompting, across three experiments [26–28] case managers adherently delivered 80 different combinations of intervention components. Of course, in clinical practice, case managers would deliver only the components included in an optimized treatment.

Scientifically, this research provided informative comparative effectiveness data on multiple components across four phases of smoking treatment. Figure 2 lists especially promising components. As per PBM, the components were evaluated using primary outcomes designed to be sensitive to treatment effects at the targeted treatment phase; i.e., smoking reduction in the Motivation phase [26], end-of-treatment abstinence for the Preparation and Cessation phases [27], and 12-month abstinence for the Maintenance phase [28]. All experiments involved analyses of assessments both at a time point proximal to treatment delivery to maximize sensitivity to treatment effects [24], and at a long-term time point to maximize public health relevance.

This research yielded additional meaningful findings. For instance, it showed numerous interaction effects amongst intervention components (cf. [83]), underscoring the importance



of examining interactions prior to combining components into treatment packages, a step rarely taken in prior treatment development. It is important to note that while interactions amongst naturally occurring person factors and treatments (e.g., Aptitude X Treatment interactions: [84]) may be highly unstable (e.g., because of sampling error), the interactions reported in these factorial experiments are different because the intervention components are experimentally manipulated in a controlled setting, and therefore are fairly standardized from one participant to the next. Moreover, with effect coding, the standard errors associated with our reported interactions are essentially identical in magnitude to those associated with main effects, and power for detecting the two types of effects is equivalent (see [31, 85]). Nevertheless, interactions of randomized intervention components, especially interactions that are not stipulated *a priori*, should be viewed as tentative until replicated. Finally, this research leads to questions about why such interactions occurred. Are interacting components exerting synergistic or antagonistic effects on targeted treatment mechanisms, or are they instead producing their combined effects in other ways, such as increasing distraction or burden in the case of antagonistic interactions [83]?

This research also raises questions about why relatively few intervention components produced strong main effects. This might be because some components were of low intensity (to make them appropriate for healthcare: [86]) or because these factorial experiments attempted to isolate the effects of relatively discrete, individual intervention components, which may have smaller effects than do the packages of components that are often tested in RCT's (e.g., [42]).

In sum, this research identified intervention components that were clearly effective when delivered at particular phases of smoking treatment. Moreover, it demonstrated the efficiency of the MOST approach, not only in terms of the number of intervention components tested, but also in terms of the richness of information yielded (the independent and interactive effects of all components). Because of our integration of MOST and PBM, we now have greater knowledge about what components work, and when they work (which phase). Finally, the numerous statistical interactions amongst components illustrate that a component can have different effects depending upon the components with which it is combined. The success of smoking treatments in the past may have been hampered by assembling treatments in the absence of such data. The information obtained through factorial experiments ultimately will provide a coherent body of knowledge about what works for smoking treatment and what hinders it.

## Next Steps

As per MOST, this program of research will proceed by further exploring the comparative effectiveness of the components via additional factorial screening or refinement experiments and by evaluating packages of the most promising components via RCTs. For instance, most effective Motivation-phase treatments have been at least 6 months long [42]; the treatment period in our Motivation phase experiment was only 6–12 weeks [26]. Thus, we will examine Motivation-phase intervention components delivered over longer time periods to see if we can obtain stronger effects. In addition, while the Schlam et al. experiment [28] identified two intervention components that produced promising effects across the Cessation

and Maintenance phases, at present, we know relatively little about how to intervene effectively with recent relapsers. We will undertake a Sequential Multiple Assignment Randomized Trial (SMART [87]) that evaluates multiple intervention components targeted at the Relapse Recovery phase. We will also begin to conduct RCTs that evaluate packages of intervention components identified as promising in the factorial experiments. Ultimately, once especially effective components are identified for all phases of smoking treatment, we will evaluate an integrated, phase-based chronic care treatment as an alternative to usual care in multiple healthcare systems. Of course, we will conduct further secondary analyses on data from these experiments to identify moderators and mediators of treatment effects, to identify sensitive phase-based surrogate endpoints, and to explore the causes of the observed interaction effects. In sum, this program of research has efficiently identified promising intervention components and clarified the need for additional screening experiments to meet the goal of developing a comprehensive, evidence-based chronic care treatment for smoking that can be implemented in real-world clinical settings.

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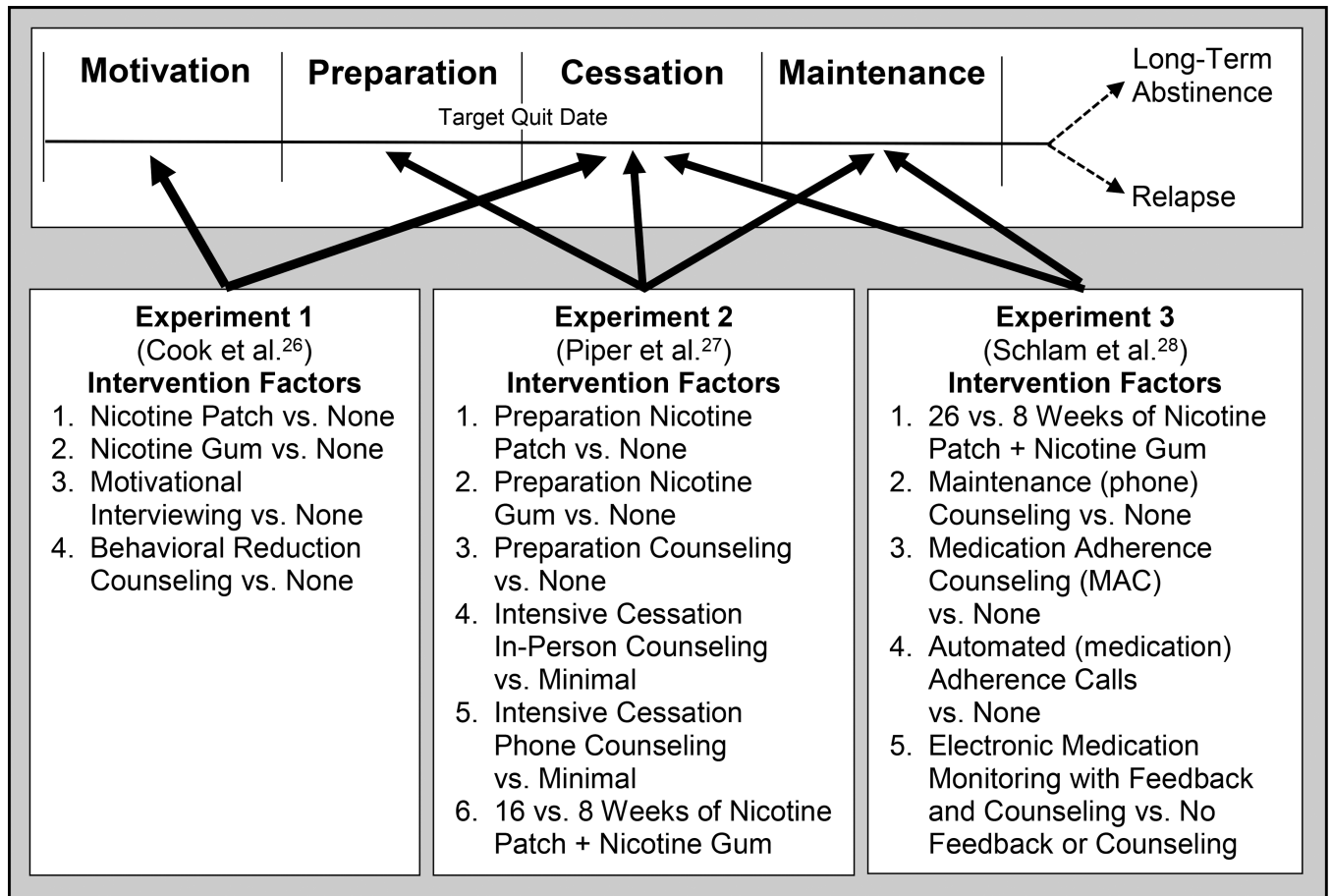
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**Figure 1.** The Phase-Based Model of Cessation and the Phase-Specific Intervention Factors Evaluated in the Three Accompanying Experiments<sup>26,27,28</sup>

<b>Motivation Phase</b>	<b>Preparation Phase</b>	<b>Cessation Phase</b>	<b>Maintenance Phase</b>
<ol style="list-style-type: none"> <li>1. Nicotine Gum for Smoking Reduction</li> <li>2. Behavioral Reduction Counseling</li> </ol>	<ol style="list-style-type: none"> <li>1. Preparation Nicotine Patch or Nicotine Gum</li> <li>2. Preparation Counseling</li> </ol>	<ol style="list-style-type: none"> <li>1. Intensive In-Person Cessation Counseling</li> <li>2. Nicotine Patch + Nicotine</li> </ol>	<ol style="list-style-type: none"> <li>1. 26 Weeks of Nicotine Patch + Nicotine Gum</li> <li>2. Maintenance Counseling</li> </ol>

**Figure 2.**  
Relatively Promising Intervention Components Identified in the Three Accompanying Factorial Experiments<sup>26,27,28</sup>



**Table 1**

Goals, Time Frame, and Challenges of the Smoking Cessation Treatment Phases of the Phase-Based Model

Phase	Motivation	Preparation	Cessation	Maintenance
<b>Main Goals</b>	To encourage smoking reduction and increase the likelihood of a successful quit attempt	To increase the likelihood of initial abstinence following the quit attempt	To produce sustained abstinence early in the quit attempt	To preserve or restore abstinence
<b>Time Frame</b>	While smoker is unwilling to make a quit attempt: may range from weeks to years	~Several weeks prior to quit attempt	~2–4 weeks after quit attempt	~1–12 months after quit attempt
<b>Especially Relevant Challenges</b>	<ol style="list-style-type: none"> <li>1 Low motivation to quit</li> <li>2 Low self-efficacy</li> <li>3 Heavy smoking and dependence</li> <li>4 High density of smoking cues</li> </ol>	<ol style="list-style-type: none"> <li>1 Heavy smoking &amp; dependence</li> <li>2 Limited time for quitting preparation</li> <li>3 Imminent withdrawal</li> </ol>	<ol style="list-style-type: none"> <li>1 Escalating or peaking withdrawal</li> <li>2 High lapse likelihood</li> <li>3 Lapse related decreases in self-efficacy</li> <li>4 Limited time for intervention prior to lapsing</li> </ol>	<ol style="list-style-type: none"> <li>1 Flagging motivation/fatigue</li> <li>2 Risk of transitioning from lapses to relapse</li> <li>3 Recurrent withdrawal</li> <li>4 Lack of social support and/or partner support</li> <li>5 Nonadherence to treatment</li> </ol>

Note. The time frames are rough estimates that are useful for treatment planning and evaluation; patient and clinician decisions will often affect phase durations (deciding to quit, whether to use a Preparation treatment). Also, the “challenges” listed are intended to be illustrative, not exhaustive for each phase, nor exclusive to a particular phase.