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REVIEW

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Medication screening for smoking cessation: a proposal for new methodologies

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Abstract *Rationale:* The purpose of medication screening studies is to quickly and cheaply evaluate the clinical potential of medications, so that promising drugs proceed to large-scale clinical trials and unpromising drugs do not. Screening procedures for smoking cessation medications either are not sufficiently practical or lack clinical validity. Clinical trials have clinical validity but are often impractical as initial tests of efficacy (i.e., screening) or suffer from limited statistical power. The alternative approach of short-term, laboratory-based studies of purported mechanisms of efficacy may overcome some of the practical problems of clinical trials but appear to have limited clinical validity. *Objectives:* This commentary identifies some of the limitations of current short-term screening procedures and provides suggestions for improving such studies. *Results:* Short-term screening studies typically use smokers unmotivated to abstain (i.e., nontreatment seekers) as participants and examine brief medication effects on clinical markers or potential mechanisms of action, including relief of withdrawal and craving during enforced abstinence or on reduction in the reinforcing effects of smoked tobacco. The limitation of these approaches is shown by their insensitivity to effects of nicotine replacement and bupropion, which are effective in clinical trials for smoking cessation. *Conclusions:* The clinical validity of short-term screening studies may improve if these studies simulate some clinical trial procedures within practical limitations. Thus, they should recruit smokers motivated to abstain, emphasize smoking abstinence as a primary index of medication response, examine effects over sufficiently long time periods to encompass the drug's mechanism of action, and assess responses in the natural environment. Whether these changes improve the sensitivity of screening studies is testable. Other research aimed specifically at identifying the mechanisms of therapeutic action of a medication may also profit from using this approach of simulating a short-term clinical trial.

Keywords Smoking cessation · Pharmacotherapy · Medication screening · Nicotine dependence

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Introduction

In recent decades, dozens of drugs have been evaluated in clinical trials for efficacy in aiding smoking cessation. Among these are antidepressants such as bupropion, doxepin, fluoxetine, imipramine, moclobemide, nortriptyline, paroxetine, sertraline, tryptophan, and venlafaxine, as well as the antianxiety drugs buspirone, diazepam, meprobamate, metoprolol, and oxprenolol, along with a variety of other compounds, including ondansetron, clonidine, mecamylamine, naltrexone, lobeline, and nicotine replacement (Benowitz and Peng 2000; Hughes et al. 1999, 2004; Silagy et al. 2004). Still other drugs have been evaluated in clinical trials, but the results of these studies remain unpublished. Yet, the only two clearly successful medications to date (i.e., approved by the US FDA) are the various formulations of nicotine replacement therapy (NRT) and bupropion (Zyban). Although some of these may yet prove effective and the many failed trials may provide information useful to future drug development, these trials also represent an expenditure of limited time and resources that could be devoted to more promising drugs. This apparent

inefficiency in the development of medications for smoking cessation stems in part from the lack of brief and inexpensive screening procedures, i.e., initial tests of medication efficacy in humans, that are predictive of therapeutic response to medication in a large clinical trial. The objective of this commentary is to highlight this gap in clinical research methodology and suggest directions for research aimed at closing the gap.

Medication development first involves preclinical research, including drug discovery and evaluation in nonhuman animals. Subsequent human research prior to seeking FDA approval for marketing the medication involves three phases (Kroboth et al. 1991; Vocci 1996).

Phase I is designed to determine the safety of the drug in humans, focusing on assessments of tolerability, pharmacokinetics, bioavailability, etc., in a few dozen healthy volunteers. Efficacy is usually not a focus.

Phase II is designed to identify potential efficacy of the drug in humans with the disorder for which the drug is intended (see Kroboth et al. 1991). These studies also identify clinically appropriate doses, subject samples, and other treatment procedures. Studies in this phase typically involve fewer than 200 subjects assessed under fairly tightly controlled conditions (Vocci 1996). Moreover, because results of phase II studies determine whether the drug will proceed to large clinical trials, phase II studies need to use indices of efficacy that predict the likely drug effects in a full clinical trial. As stated by Kroboth et al. (1991), "the importance of efficient phase II studies cannot be overemphasized. The decision to continue a drug product into phase III of development is a commitment to expend extensive resources to study the drug in large numbers of patients. Therefore, *the results of phase II studies should permit an unequivocal determination of the efficacy of the product*...." (italics in original; p. 95).

In practice, studies considered "phase II" often range from short-term initial tests of efficacy in a small group of healthy volunteers ("early phase II") to large single-site clinical trials involving a few hundred patients ("late phase II"; see Vocci 1996). (Sometimes, small initial tests of efficacy are included in phase I studies of safety, and so could be considered "late phase I" studies; Vocci 1996). In any case, research aimed at initial tests of a medication's efficacy in humans, which is how we define "screening" studies, should inform subsequent clinical trials, whether considered phase II or phase III. Thus, drugs shown to be effective in clinical trials should have previously demonstrated clear effects on clinical indices during short-term screening studies. Similarly, drugs that fail in clinical trials should have had weaker support for their efficacy during prior screening. (Of course, ideally, drugs that fail in screening should not even proceed to clinical trials, if screening procedures are effective.).

Phase III involves full clinical trials of medication efficacy, often requiring multiple sites and hundreds of patients seeking treatment. This phase usually constitutes the longest and most expensive phase of development (Vocci 1996).

Phase IV occurs after the medication is approved by the FDA for marketing and focuses on continued evaluation of efficacy, identification of new indications (other conditions for which the medication might be effective), and surveillance for the emergence of adverse effects. Many of the drugs subjected to clinical trials for smoking cessation are those that were previously approved for other indications but exhibit some evidence of efficacy for smoking cessation (i.e., a new indication) in phase IV. Thus, many of these previously approved medications do not receive formal screening for initial efficacy in smoking cessation but proceed to clinical trials. Yet, screening tests of these drugs for efficacy in smoking cessation may still be useful since these evaluations are less costly and time-consuming than clinical trials and may provide information on potential mechanisms of action in addition to initial efficacy evaluation for smoking cessation.

Unfortunately, for smoking cessation and perhaps for most other drug dependence (O'Brien 1997), screening tools currently in use are geared toward elucidating mechanisms of drug action and do not necessarily provide information clearly predictive of medication efficacy in a clinical trial. Consequently, the most common approach to initial evaluations of medication efficacy in humans is to conduct a small clinical trial. While a small clinical trial may have high validity in predicting results of large clinical trials (i.e., phase III), small clinical trials have a number of practical limitations, notably, limited statistical power. Clinical trials preclude the use of within-subjects designs (since those who improve with one treatment cannot then be clearly tested on response to another treatment), and between-subjects designs require the recruitment of many subjects to be randomized to different treatment groups. Because screening studies constitute the first test of efficacy and the clinically effective dose is not known, such studies typically include more than one active dose in addition to placebo. Thus, a "small" clinical trial of initial efficacy would probably require more than two groups. Moreover, the dichotomous nature of smoking cessation outcome—abstinent vs not abstinent—taxes power even further (e.g., Kraemer 1991), in contrast with trials in which the outcome is continuous in nature (e.g., body weight, blood pressure). Another practical issue concerns the duration of such trials in order to provide adequate treatment and assess clinical outcome, which can require at least a few months. Because of these challenges, the smallest clinical trial with the statistical power to test the efficacy of a new medication might require a few hundred subjects each participating for several months, an expensive proposition, in order to find out if a medication has efficacy that warrants further testing. Therefore, short-term procedures requiring fewer participants would provide practical advantages over clinical trials in the screening of medications. As will be noted, however, current short-term procedures applied to smoking cessation medications have questionable clinical validity.

In the present paper, we will first summarize findings from two common approaches taken in short-term studies

aimed at understanding the mechanisms responsible for efficacy of smoking cessation medications. Limitations to these approaches with regard to predicting clinical trial efficacy outcomes will be emphasized, and suggestions will be made for developing methods that can improve this important area of research. Evaluation of medications aimed solely at harm reduction (i.e., reducing but not necessarily quitting smoking; Hatsukami et al. 2004) or relief of temporary withdrawal and not abstinence per se will not be addressed.

Current approaches to short-term evaluations of medication efficacy

Broadly speaking, medications for smoking cessation have been aimed at either or both of two potential mechanisms: (1) relieving the adverse effects of withdrawal and craving that accompany abstinence, and (2) blocking or attenuating the direct reinforcing effects of inhaled tobacco smoke. Different procedures necessarily have been used in short-term tests of these potential mechanisms. For the first, smokers who typically are not trying to quit permanently are required to abstain for some time to allow for the emergence of withdrawal and craving (e.g., self-reported urge to smoke), often under close monitoring to ensure abstinence. Medication is then administered to determine whether withdrawal and craving are attenuated. Enforced abstinence is required, since continued smoking would confound the assessment of craving and withdrawal relief (e.g., Hatsukami et al. 1988). For the second mechanism, smokers not trying to quit are typically administered the medication and allowed to continue smoking. Their smoking behavior and self-reported hedonic responses (e.g., satisfaction) to smoking are assessed to determine whether the medication attenuates smoking frequency and, if so, whether that may be due to a reduction in the pleasurable effects of smoking. While these approaches may have utility for examining mechanisms of medication effects, as will be presented below, neither of these approaches has good clinical predictive value.

Assessing craving and withdrawal relief during enforced abstinence

Clinical trials research on nicotine replacement therapy medications has supported both the clinical efficacy of these products as smoking cessation aids and their role in providing relief of craving and withdrawal (e.g., Martinez-Raga et al. 2003; Jorenby et al. 1995; West and Shiffman 2001). However, short-term studies that have examined withdrawal relief in unmotivated quitters during relatively brief periods of enforced abstinence have provided mixed results with respect to medication-induced relief of craving and especially of withdrawal symptoms other than craving. An early study involving outpatient assessment found that 2 mg nicotine gum vs placebo did attenuate most withdrawal symptoms, but not craving, across 4 days of smoking abstinence (Hughes et al. 1984). However, many laboratory-based studies have not found robust relief of withdrawal due to NRT. Hurt et al. (1998), for example, administered 4 mg gum or 1 mg nasal spray (NS) to smokers during a 2-h session. Significant reductions in craving and withdrawal were found with nasal spray but not with gum. In a more recent study, smokers who abstained overnight were administered intermittent NS, 14 mg NRT patch (to match blood levels with NS), or double placebo over most of a day in the laboratory (Perkins et al. 2004). Both nicotine spray and patch attenuated craving at some but not all time points, compared with placebo, but neither affected withdrawal. Similarly, Teneggi et al. (2002) found reduced craving, but not withdrawal, during treatment with 21 mg nicotine patch vs placebo patch in smokers who underwent 3 days of enforced abstinence. Reduced craving due to nicotine vs placebo patch has also been observed in other laboratory studies that did not assess withdrawal (e.g., Tiffany et al. 2000; Waters et al. 2004), although Havermans et al. (2003) failed to find reduced urge to smoke during treatment with 30 mg nicotine patch vs no patch in smokers who abstained for 12 h.

The mixed results reviewed above suggest that the methodologies employed have not been uniformly sensitive to the expected effects of NRT, particularly with regard to relief of withdrawal symptoms other than craving. Whether this is due to methodology features, such as the use of inappropriate subjects (e.g., smokers not motivated to quit) or inappropriate assessment time frames (e.g., too short), or due to other factors such as the absence of assessment in the natural environment (i.e., in the presence of smoking-related contexts and stimuli), these short-term procedures would not appear to be useful for predicting efficacy of medications whose primary mechanism of action is withdrawal relief. Further, there are other medications such as the FDA-approved cessation medication, bupropion (Zyban), which may have different mechanisms of action than NRT and thus would not necessarily be expected to produce positive results in a short-term test of withdrawal relief. A study by Shiffman et al. (2000) assessed craving and withdrawal in smokers abstaining temporarily while on an inpatient unit for 3 days and found a mixed profile of results. Bupropion (300 mg) attenuated the increase in three withdrawal symptoms (depression, irritability, and difficulty concentrating) but not on three others (anxiety, restlessness, and hunger). A dose of 150 mg bupropion attenuated only one symptom, irritability, and neither dose of bupropion had significant effects on craving.

In sum, many studies of short-term medication effects focusing on relief of withdrawal and craving in smokers not attempting to quit permanently have yielded inconsistent findings that would not necessarily support the decision to proceed to clinical trials of efficacy for a given medication. The fact that the studies using these short-term models have been conducted with medications clearly shown to be efficacious in smoking cessation highlights the problem of their inadequate predictive utility as medication screening procedures.

Attenuating the direct effects of smoking

A second potential mechanism of effective medications in smoking cessation treatment is attenuation of the reinforcing effects of smoking. A number of studies have pretreated smokers not interested in changing their smoking with various doses of nicotine gum, patch, or a variety of individual or combined NRT products (patch, gum, and inhaler; Etter et al. 2002). The studies then assessed ad libitum smoking behavior (typically, number of cigarettes) over time, often for 1 day but occasionally over a week or longer. None of these studies found significant decreases in smoking behavior at the maximum NRT doses originally approved by the FDA (2 mg gum, 21 mg patch), although much higher doses (4 or 8 mg gum, 44 or 63 mg patch) may produce modest (10–26%) decreases in smoking behavior (Benowitz et al. 1998; Nemeth-Coslett and Henningfield, 1986; Nemeth-Coslett et al. 1987; Pickworth et al. 1994). The relative insensitivity of smoking reduction as an index of medication efficacy is clearly noted by Benowitz et al. (1998), who examined effects of 0, 21, 42, and even 63 mg nicotine via patch on ad libitum smoking behavior among smokers on an inpatient unit. Number of cigarettes smoked was not significantly decreased by 21 mg patch (−6%) or even 42 mg patch (−10%), a dose producing blood nicotine levels of approximately 40 ng/ml, above that typically seen during ad libitum smoking. The decline in smoking was significant only following 63 mg patch (−26%), three times the typical clinical dose.

In regard to bupropion, Cousins et al. (2001) examined the acute effects of 0, 150, and 300 mg bupropion on ad libitum smoking behavior across a 3-h laboratory session in smokers not interested in abstaining. Bupropion 300 mg, the standard dose for cessation, significantly *increased* the number of cigarettes smoked (and expired-air carbon monoxide, or CO) by more than 25%. Bupropion 150 mg did not affect the number of cigarettes smoked but did significantly increase CO. Neither dose affected craving or "smoking satisfaction." Notably, a second study from this paper showed that amphetamine (10 and 20 mg), a well-known drug of abuse not considered as therapy for smoking cessation, had the same effects as bupropion on increasing smoking behavior. In another paper, bupropion 150 mg similarly increased self-reported smoking over the course of a day in the natural environment among smokers not interested in quitting (Zernig et al. 2004). Thus, the effect of bupropion on smoking in these short-term studies was opposite of that expected from a smoking cessation treatment.

Furthermore, recent preclinical research suggests a similar pattern of findings when nonhuman animals trained to self-administer nicotine are pretreated with nicotine and bupropion. For example, virtually complete "replacement" of self-administered nicotine (the clinical goal of NRT) by continuously infused nicotine decreases nicotine self-administration behavior of rats by only 17% (LeSage et al. 2003), comparable to the modest reduction in smoking behavior by smokers exposed to high-dose NRT in the above-mentioned studies. Similarly, bupropion has been shown to increase nicotine self-administration in rats (Shoaib et al. 2003), consistent with its previously noted effect on smoking behavior of humans in two short-term studies. Thus, results of cessation medication effects on nicotine or smoking self-administration appear consistent between preclinical and early clinical (e.g., early phase II) studies despite the difference in species, but results are inconsistent between these early clinical studies and clinical trials (late phase II or phase III) despite both types of studies involving humans. The conformity in findings between preclinical and early clinical studies is not particularly useful if neither predicts the findings from clinical trials, the final and most critical step in determining the clinical efficacy of a medication.

In summary, studies in which smokers were pretreated with medication and allowed to smoke ad libitum show little reduction in smoking due to medication, suggesting either that smoking reward attenuation is not a mechanism of these medications or that the methodology is insensitive to reward attenuating effects. Overall, the results of most short-term studies of NRT or bupropion on withdrawal relief and on ad libitum smoking are inconsistent with their clear efficacy in aiding smoking cessation in clinical trials. It would be difficult to argue proceeding to large clinical trials with these drugs if the decision hinged on these results from short-term laboratory studies.

Improving screening studies of medication effects: suggested new directions

The ideal procedure for human screening of medications should produce results that strongly predict medication efficacy in clinical trials. Such procedures should, whenever possible, also retain elements of current short-term studies that provide important practical advantages. Almost by definition, these studies are small in size and brief in duration. Greatly expanding either of these aspects would diminish the cost and time savings of screening studies vs clinical trials. Similarly, screening studies typically use within-subjects designs to maximize statistical power in light of the small samples. As previously noted, such designs are not possible in traditional clinical trials, where outcome after a follow-up period due to one treatment vs another is of interest. However, within these constraints, there may be room to improve short-term tests of medication efficacy.

Simulated (or "practice") quit attempt

The strategy we propose for improving on existing screening procedures is essentially to combine the practical advantages of short-term laboratory studies and the clinical predictive validity of clinical trials. This approach may be viewed as simulating a permanent quit attempt, the focus of clinical trials of cessation medications.

Recruiting smokers motivated to abstain When designing a model useful for directly predicting efficacy in smoking cessation, it would appear prudent to use smokers who are in the appropriate motivational state, such as treatment seekers or smokers preparing to quit soon. An earlier meta-analysis of clinical trials with nicotine replacement (Tang et al. 1994) concluded that its efficacy in promoting abstinence (i.e., the difference between active and placebo) was much greater among treatment seekers ("self-referred") than among those asked to participate in the trials ("invited" from hospital clinics). This finding suggests that abstinence motivation can make a critical difference in medication efficacy. It should be noted that even in studies of a medication's mechanisms, the ability to detect withdrawal relief and/or smoking reduction may also be influenced by the quit motivation of participants.

Potential ethical and practical problems of recruiting smokers who are ready to quit to enroll in a short-term medication study need to be addressed. First, such participation could interfere with their subsequent quit attempt. For example, in a within-subject design comparing different medications, smokers might be asked to abstain during the medication phase and resume their typical smoking patterns during the interim drug washout phase. Smokers interested in quitting permanently may be reluctant to resume smoking temporarily, or resuming smoking may reduce their subsequent motivation to quit permanently. Institutional Review Boards may require additional protections to ensure that participation does not discourage subjects from ultimately quitting. Such smokers could be persuaded that participation may help them prepare for their later permanent quit attempt by allowing them to perceive and learn to cope with the effects of early abstinence. They could also be given cessation treatment materials and other resources to aid that attempt after the end of their study participation. Second, the validity of this strategy could be compromised if smokers willing to delay their quit attempt in this way were not typical of most smokers trying to quit, who may want to quit permanently without delay. However, some evidence suggests this is not the case, as participants in one study involving repeated laboratory assessments prior to a quit attempt were similar to most treatment seekers in terms of smoking history and motivation to quit (Perkins et al. 2002). Third, smokers' stated intent to quit may be volatile over time (Etter and Sutton 2002), complicating the identification of subjects for use in a weeks-long study as those who are intending to quit soon. However, in the same study, we found that 87% of treatment seekers followed through with a quit attempt after the end of their participation in the multisession laboratory study, a full 6 weeks after their initial recruitment (Perkins et al. 2002). Fourth, some short-term studies of medication effects, such as those examining relapse prevention (e.g., testing whether a medication reduces smoking following a brief abstinence period and programmed lapse; Chornock et al. 1992), may not be ethical with quitting smokers, leaving smokers not trying to quit permanently as the preferred subject population. Finally, we hasten to note that smokers unmotivated to abstain are suitable for other kinds of studies, such as those on harm reduction or factors that maintain smoking.

Using smokers who are ready to quit may not be the only procedure to attract smokers motivated to abstain in a short-term study. For example, abstinence motivation levels could be "artificially" raised through the use of a modest monetary reinforcement contingent on abstinence (e.g., Stitzer et al. 1986; Gilbert et al. 1999). Incentive payments can be very effective for promoting short-term smoking abstinence (e.g., Alessi et al., 2004), and payment schedules can be devised that allow abstinence duration to be used as a dependent measure (e.g., Juliano et al., unpublished data). Whether incentive-based vs naturally motivated abstinence would be equally sensitive to medication effects is an empirical question that would need to be addressed. However, if incentive-motivated abstinence does prove to be useful, this would expand the subject pool available for valid medication screening research and facilitate use of within-subject designs.

Abstinence as a primary dependent measure Because relief of withdrawal and craving may not be necessary or sufficient to produce abstinence (e.g., Hatsukami et al. 1996), medication effects on these indices may not predict the medication's efficacy in promoting abstinence. Thus, short-term screening procedures for smoking cessation medications may be more predictive of clinical efficacy if they assess the medications' effects directly on abstinence as a primary outcome. For example, number of days abstinent or continuous abstinence during a week of medication vs a week of placebo treatment might relate more closely to that medication's likely efficacy in a clinical trial, compared with measures such as withdrawal, craving, or amount of ad libitum smoking. Abstinence as a dependent measure necessarily requires a sample motivated to abstain, as noted previously. A study sample that is heterogeneous with regard to abstinence motivation may provide an insensitive test of medication effects, as those able but unmotivated to quit could not be distinguished from those unable to quit despite motivation to do so. A potential practical problem with this measure is its largely dichotomous, nonparametric nature (i.e., abstinent vs not abstinent) in a short-term study and the resulting impact in reducing statistical power, compared to continuous measures of withdrawal, craving, number of cigarettes per day, etc. However, this problem could be partially alleviated by using for analysis continuous measures such as total abstinence duration or longest duration of continuous abstinence.

Duration of medication exposure Most short-term studies of medication effects involve very brief exposure to medication, sometimes 1 day or less, while clinical trials provide subjects with medication for at least several weeks during a quit attempt. We propose that effective short-term evaluations of medication efficacy may require administration of medication for at least a week because their effects may change over time. These changes could result

from a slow rise in drug concentration to therapeutic levels, changes in pharmacological properties of the medication, or changes in naturalistic factors that influence cessation and relapse. For example, the impact of a medication for which the mechanism of action is to block nicotine reinforcement may change over time, becoming more relevant during later stages of a quit attempt after acute withdrawal has dissipated. By contrast, effects of a withdrawal-relieving medication, such as NRT, may be maximal during the first few days of cessation, when peak levels of withdrawal and craving are apparent, but may weaken later as withdrawal and craving abate (Hatsukami et al. 1998). However, because a basic tenet of medication screening procedures is that they need to be relatively brief and inexpensive, such studies will inevitably provide only a limited opportunity to examine the full time course of medication effects. Nevertheless, effective medications demonstrate efficacy within a few weeks after quitting (e.g., Hurt et al. 1997; Transdermal Nicotine Study Group 1991), and so a week or two should be sufficient to identify whether or not a medication for cessation warrants study in a clinical trial.

Context of abstinence assessment Medications tested in short-term studies of enforced abstinence may attenuate cessation-induced withdrawal and craving in the natural environment, when smokers are confronted by familiar smoking cues and other stimuli associated with smoking, but not in artificial research contexts that lack smoking-associated stimuli. For example, 2 mg nicotine gum attenuated withdrawal in smokers abstaining temporarily and assessed as outpatients over several days (Hughes et al. 1984), in contrast with the weak effects of NRT in laboratory-based assessments of withdrawal (described previously). Advances in electronic diary assessments allow for reliable and frequent measurement of withdrawal, craving, and smoking behavior in the natural environment (Stone and Shiffman 2002), precluding the need for most assessments in the laboratory or clinic. Thus, short-term medication screening studies may benefit from assessing measures in the natural environment whenever it is practical to do so.

The potential value of these design features as improvements for medication screening in short-term studies—using smokers motivated to quit, abstinence as the primary outcome measure, longer medication administration, and outpatient assessment—are exemplified in a study by Hatsukami et al. (1998). This study examined effects of nicotine (15 mg) vs placebo patch over the initial 2 weeks of abstinence in smokers who were motivated to quit but were also paid for compliance with remaining abstinent during the study. In contrast to the mixed and unreliable effects of NRT on withdrawal symptoms in most of the previously described short-term studies, these authors found reduced withdrawal, assessed on an outpatient basis over the first week of an actual quit attempt, although the nicotine patch dose was relatively low. Abstinence could not be evaluated as an endpoint in this particular study because the payment procedures employed produced uniformly high abstinence compliance rates.

Research on mechanisms of action

Procedures in short-term screening studies of medications may also be useful for identifying mediators of abstinence. Further, to the extent that robust mediators are identified, these may serve as proxy measures predictive of abstinence. As noted previously, craving has shown some sensitivity in short-terms studies of NRT, even in smokers unmotivated to abstain. Craving early in a quit attempt predicts long-term abstinence outcome (Killen and Fortmann, 1997). Thus, craving measures may warrant more attention in short-term studies of medication evaluation. However, the direct relationship between craving, or other possible proxy measures assessed under these conditions, and likely abstinence in a clinical trial is unknown. Thus, one immediate direction for research is to determine whether there are any short-term, continuous proxy measures such as craving that are closely predictive of long-term abstinence. Other potential measures may be:

Negative affect Negative affect is a particularly important symptom of withdrawal that may account for virtually all of withdrawal's clinical value in predicting long-term abstinence in quitting smokers (Kenford et al. 2002). Negative affect relief as an index of clinical efficacy has received little attention in short-term medication studies, although most studies noted above, which found little effect of medications on withdrawal, did assess negative affect as a component of withdrawal. Yet, the failure of some antidepressants to improve cessation rates suggests that negative affect per se is unlikely to be any more sensitive than other withdrawal symptoms as a measure of a medication's clinical efficacy for smoking cessation (Hughes et al. 2004). Further emphasizing this point is the observation that bupropion was subjected to clinical trials for cessation not on the basis of its antidepressant actions but on the basis of anecdotal observations of spontaneous abstinence among depressed smokers already taking the drug as Welbutrin (Martinez-Raga et al. 2003; see also Lerman et al. 2004). Similarly, relief of anxiety, another common withdrawal symptom, has provided the justification for clinical trials of a few anxiolytic medications, but none has shown efficacy for smoking cessation (Benowitz and Peng 2000).

Responses to conditioned smoking stimuli The role of smoking-related stimuli, such as the sight and smell of a lit cigarette, in the maintenance of smoking behavior has become increasingly apparent (e.g., Caggiula et al. 2001). Controlled exposure to such stimuli may allow for a quick test of a medication's ability to attenuate conditioned responses to stimuli. Typically, these "cue reactivity" studies show increases in physiological responses, including heart rate, and in self-reported urge in response to smoking-

related stimuli (Carter and Tiffany 1999). However, the relationship between a smoker's responses to smoking-related stimuli and other outcomes in a cessation attempt has not been reliably demonstrated. Niaura et al. (1989) did find that greater phasic heart rate deceleration, rather than increased heart rate, in response to seeing someone light a cigarette predicted relapse 3 months after treatment. Other responses, including electrodermal activity and self-reported anxiety, did not predict outcome. We are not aware of other research showing that responses to smoking cues before quitting reliably predicts post-quit outcome. Moreover, transdermal nicotine, while reducing general levels of abstinence-induced craving, has no effect on acute cue-induced craving, either in smokers not interested in quitting (Tiffany et al. 2000) or in smokers preparing to quit (Waters et al. 2004). Behavioral treatments to extinguish responses to cues also have not proven to be clinically effective (Conklin and Tiffany 2002). Thus, the clinical relevance of responses to smoking-related stimuli, as well as their promise in procedures for screening medications, remains very uncertain at this time.

Subjective responses to medication Little research has examined whether direct responses to medication itself, rather than medication-induced changes in withdrawal, craving, or smoking behavior, may relate to the medication's efficacy in promoting abstinence. Kaufmann et al. (2004) found that greater positive subjective responses (e.g., "good or pleasurable 'buzz'," "good or 'high' feeling") to Nicotrol nasal spray before quitting predicted abstinence at 6-month follow-up in subjects given the spray to aid cessation. Adherence to spray use during the quit attempt did not explain this association. However, there was no placebo spray condition. It is not clear how far this analogy would extend since not all smoking cessation aids have readily detected direct effects. Nevertheless, medications, or other substances that elicit pleasurable responses, may be effective substitutes for smoking, thus aiding abstinence (Johnson et al. 2004).

Measures of smoking reinforcement Ad libitum smoking behavior in smokers unmotivated to abstain is insensitive to the effects of NRT and bupropion, as previously reviewed, but other procedures for assessing smoking reinforcement might be more sensitive. Among these are laboratory-based behavioral choice procedures, such as those that involve a choice between smoking and an alternative reinforcer (Johnson et al. 2004), or operant procedures requiring extensive responding for opportunities to smoke (e.g., progressive ratio; Perkins et al. 2004). One recent study by Rukstalis et al. (2005), using a choice strategy developed by Perkins et al. (1996), showed attenuated choice of nicotine-containing vs a denicotinized cigarette as a result of pretreatment with naltrexone but not bupropion. These results are somewhat inconsistent with the demonstrated clinical efficacy of these drugs in smoking cessation and thus not especially promising for sensitivity of the procedure, but do demonstrate feasibility of an innovative strategy for testing medication effects on smoking reinforcement.

Summary and conclusions

Efficient screening of new medications for smoking cessation requires measures of medication response that predict the likely therapeutic efficacy of the medication in a large clinical trial. Current screening approaches consist primarily of conducting small clinical trials, which may have high clinical validity but also many practical problems. An alternative approach is short-term tests of medication mechanisms, notably assessing withdrawal and craving relief during enforced abstinence on the assumption that this is the primary mechanism of action for cessation aids, or of looking for a reduction in ad libitum smoking among smokers unmotivated to abstain as a measure of effects on smoking reinforcement. Both measures are relatively insensitive to effects of NRT and bupropion, the two currently FDA-approved medications for smoking cessation. Thus, these approaches appear to lack predictive clinical validity, and new approaches or measures are needed.

We suggest that one way to improve medication screening procedures is to combine the best features of these approaches to obtain the practical advantages of short-term tests and the clinical validity of small clinical trials. We recommend that screening studies:

- Use abstinence as the primary outcome measure
- Recruit those planning to quit soon into a short-term simulated or practice quit trial, or otherwise increase participants' motivation to abstain, at least temporarily
- Extend the duration of exposure to medication in order to account for different potential mechanisms of action (i.e., withdrawal relief vs reinforcement attenuation)
- Assess responses in the natural environment rather than in a laboratory research setting
- Yet maintain the practical advantages of the screening study, such as its relatively small size, brief duration, and within-subjects design

Aside from these procedural changes, screening studies may benefit by including other proxy measures (acute responses to medication), such as negative affect relief, other measures of smoking reinforcement, and responses to environmental stimuli associated with smoking. However, more evidence is needed to show that these responses predict clinical outcome, especially long-term abstinence.

Each of these features can be tested empirically to determine the conditions under which medications known to be clinically efficacious produce robust effects in a short-term screening protocol. On the other hand, because the therapeutic effects of even the best available medications are relatively modest, the recommended procedural changes may not succeed in enhancing the observed therapeutic effects of such medications in small screening

studies, and initial tests of efficacy may require larger studies with greater statistical power.

In any event, once the conditions associated with greater sensitivity to medication effects are identified, they may form the basis of a procedure for screening novel medications likely to prove successful in clinical trials, the ultimate objective of this effort. Medications known not to be effective in smoking cessation would also be useful to examine in such a procedure in order to verify the specificity of the procedure (i.e., its ability to distinguish between medications likely and unlikely to succeed in clinical trials). In addition, success in improving screening procedures for smoking cessation medications may provide directions for improving procedures for screening medications to treat other abused substances, an area of clinical research with problems parallel to those in the smoking cessation area (e.g., O'Brien 1997). Moreover, although the focus here has been on screening medication therapies, it is possible that these suggested procedures may be helpful in short-term evaluations of nonmedication, behavioral treatments for smoking cessation.

The development of short-term medication screening procedures in humans that predict clinical trial results could dramatically improve the speed and efficiency by which new medications are brought to bear on the worldwide public health problem of persistent cigarette smoking (Ezzati and Lopez 2004), a problem likely to become more, rather than less, intractable (Irvin and Brandon 2000). Such screening procedures could also be useful for studying the mechanisms by which medications known to be effective exert their therapeutic effects. The objective of this commentary was to point out the limitations of current screening approaches and to suggest directions for research and development of more effective procedures.

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