

Relapse to smoking

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Abstract

Relapse is by far the most likely outcome of any smoking cessation attempt, even those made with the benefit intensive psychosocial treatment and pharmacotherapy. The present article briefly reviews the epidemiology of smoking and self-quitting, the outcome data for major forms of behavioral and pharmacologic smoking cessation treatments, and what is known about the natural history of relapse and recovery among treated smokers. A recent trend in smoking relapse research has been to study the dynamics of key motivational processes, such as withdrawal symptoms, negative affect, and craving, in the laboratory and in smokers' natural environments. This literature is also briefly reviewed, with an emphasis on how such investigations may reveal the limitations of current cessation treatments. Finally, three significant research themes that are likely to be important in future relapse research are highlighted—the possible “hardening” of the smoking population, the potential for developmental research to deepen our understanding of smoking motivation, and the promise of molecular genetic studies for advancing treatment and our understanding of relapse.

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Cigarette smoking is a remarkably refractory behavior. Despite the well-known health risks of smoking, relatively few smokers quit smoking successfully each year (CDC, 2002). In the past several decades, considerable effort has been devoted to developing intensive smoking cessation treatments, but smoking relapse is the modal outcome for even the best of these interventions (Piasecki, Fiore, McCarthy, & Baker, 2002). Developing an understanding of why smoking is such a “sticky” behavior and devising methods to combat relapse remain the central challenges in tobacco research.

This article begins with a brief review of the epidemiology of smoking and self-quitting, an overview of the outcome data for major forms of behavioral and pharmacologic smoking cessation treatments, and a review the natural history of relapse and recovery among treated smokers. The dynamics of three smoking motivational processes—withdrawal symptoms, negative affect, and craving—are discussed with an eye toward understanding the limitations of existing treatments. Finally, three significant research themes that are likely to be important in future relapse research are highlighted—the “hardening” of the smoking population, the potential for developmental research to deepen our understanding of smoking motivation, and the promise of molecular genetic studies for advancing treatment and our understanding of relapse.

Before reviewing specific findings, a note on terminology is in order. Despite occasional attempts to codify important outcomes in smoking cessation research (Hughes, Keeley et al., 2003, Hughes, Shiffman, Callas, & Zhang,

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2003; Pierce & Gilpin, 2003; Velicer, Prochaska, Rossi, & Snow, 1992), considerable variation remains in the operational definitions of key concepts in empirical work. In general, the term “lapse” denotes a slip back to smoking after a prior period of abstinence. A lapse may be an isolated event that is followed by a renewal of abstinence, or it may evolve into a relapse. “Relapse” typically refers to a period of several days or more of continuous smoking after a period of abstinence or an attempt at abstinence. In treatment evaluation research, “relapse” often has been operationally defined using a dichotomous, point prevalence measure of whether a person has smoked at all (“even one puff”) in the past week. This common criterion may be argued to be either too conservative (because it could count an isolated lapse as a relapse) or too liberal (because it permits persons who smoke repeatedly to be counted as abstinent if they cease smoking just one week before the measure is taken). For this reason, “continuous abstinence” or “prolonged abstinence” measures are sometimes used. A continuous abstinence criterion requires that an exsmoker be totally abstinent from smoking from the target quit date until the follow-up endpoint to be counted as a treatment success. Prolonged abstinence measures are a blend of continuous and point-prevalence approaches; they permit isolated lapses occurring early after cessation (often the first week of quitting), but require a lengthy period of continuous abstinence after the initial grace period before a quitter is counted as a treatment success. Key endpoints for determining “long term” treatment success in clinical trials are most often 6 or 12 months after the target quit date.

Systematic progress in smoking relapse research is possible despite controversy about definitional particulars because smoking is an unusually stable behavior (and because abstinence is an unusually fragile state). Thus, strong linear relations exist among different definitions of key outcomes. Although the border between a “lapse” and a “relapse” may be ill-defined, “lapses” of any definition will tend to strongly predict diverse representations of “relapse”. Point prevalence, prolonged, and continuous abstinence measures may yield different estimates of the cessation rate in a particular study, but they rarely change estimates of the relative efficacy of individual treatments. Statistical definitions of relapse may be constructed broadly enough to include smoking “even a single puff”, but most people counted as relapsed by such definitions have genuinely returned to regular daily smoking at levels of smoking that leave no reasonable inference other than that a quit attempt has failed (or soon will). Relapse rates at longer follow-ups (e.g., 12 months postcessation) will be higher than rates measured at shorter follow-ups (e.g., 3 or 6 months) because relapse is an orderly, insidious process in which abstinence rates erode steadily over time.

For the purposes of this review, the term “lapse” is used to denote a slip to smoking, often the first instance of smoking after quitting (i.e., the “first lapse”). Many or even most lapses may evolve into full-blown relapse, but the concept of a lapse is useful for marking the transition from abstinence to smoking (even when a smoker has only one “lapse” that becomes a “relapse” seamlessly and rapidly). “Relapse” is used in this review to refer to long-term treatment failure in a general sense. The tendencies for quitters to revert to regular smoking and for smoking lapses to grow into relapse are so robust that meaningful generalizations about relapse or treatment failure may be adduced despite variation across studies in the precise statistical definition of a relapse outcome.

1. Epidemiology of smoking, smoking cessation, and self-quitting

In the United States, smoking prevalence has declined markedly over the past 40 years, but declines in smoking prevalence have been modest since the 1990s. Data from the National Health Interview Survey (NHIS; CDC, 2002) reveal that, in 2000, 23.3% of U.S. adults (approximately 46.5 million people) smoked cigarettes on some days or daily. The NHIS data also speak to the grip of nicotine addiction. Approximately 70% of current smokers reported that they wanted to quit smoking completely, and 41% reported trying to quit smoking for at least one day in the past year. However, relatively few of these attempts are successful; only 4.7% of current smokers in 2000 were able to quit for at least 3 months (CDC, 2002).

Smoking is predominately initiated in adolescence, with very few cases of smoking initiation occurring after age 25 (USDHHS, 1994). Although many adolescent problem behaviors are normatively short-lived, smoking experimentation in adolescence is especially likely to carry significant long-term consequences. Relative to other drugs of abuse, tobacco ensnares a relatively high proportion of those who sample it. For instance, data from the National Comorbidity Survey showed that 32% of all people who ever tried tobacco progressed to dependence; comparable statistics for heroin, cocaine, and alcohol, were 23%, 17%, and 15%, respectively (Anthony, Warner, & Kessler, 1994). Analyses of smoking prevalence trends from distinct birth cohorts in the NHIS suggest that the average adolescent who begins smoking today will likely smoke for 16–20 years (Pierce & Gilpin, 1996).

Most smokers who attempt to quit smoking do so without treatment (Fiore et al., 1990). Rates of success at self-quitting are very low. Prospective studies suggest that the majority of self-quitters relapse within the first week of the cessation attempt, and only about 3–5% of self-quitters attain prolonged abstinence at 6–12 months post-quit (Hughes, Keeley, & Naud, 2004). Over-the-counter (OTC) access to nicotine replacement therapies (NRT; gum, patch, lozenge) has likely encouraged self-quit attempts (Shiffman, Gitchell et al., 1997), and OTC NRT approximately doubles long-term abstinence rates relative to unaided self-quitting (Hughes et al., 2003). Despite the relatively low abstinence rates associated with self-quit attempts, the volume of self-quitting—both “cold turkey” and with OTC medication—is enormous, and thus self-quitters account for the largest share of the sustained smoking abstinence attained in any given year (Shiffman, Mason, & Henningfield, 1998). The self-quitting process is remarkably understudied (Hughes, Keeley et al., 2004; Hughes, Stead, & Lancaster, 2004; West, McEwen, Bolling, & Owen, 2001). Future research should characterize the process of relapse among self-quitters and correlates of both quit attempts and sustained abstinence. Such research would not only contribute to our theoretical understanding of smoking maintenance, but would also provide practical information that might aid development of public health campaigns to stimulate self-quitting and/or increase utilization of more potent interventions by motivated self-quitters (e.g., OTC NRT, formal cessation clinics).

2. Efficacy of cessation treatments

Smoking cessation treatments have been actively studied since the 1970s, and interest in testing cessation treatments has accelerated since the mid 1980s. The dramatic upsurge in research activity, coupled with rising clinical and public health interest in smoking cessation, has inspired several organizations to undertake systematic reviews of the extant literature and offer practice recommendations based on these reviews (American Psychiatric Association, 1996; Fiore et al., 2000; Silagy, Lancaster, Stead, Mant, & Fowler, 2004; West, McNeil, & Raw, 2000).

The present review relies primarily upon meta-analytic results from the United States Department of Health and Human Service's *Treating Tobacco Use and Dependence* (TTUD; Fiore et al., 2000) because TTUD deals more completely with aspects of practice relevant to clinical psychologists (e.g., particular psychosocial interventions) than do other recent literature syntheses. Practitioners interested in helping their patients quit smoking are encouraged to familiarize themselves with all of the recent practice guidelines.

The TTUD meta-analytic results presented below should be considered with three caveats in mind. First, these data are now several years old, and new smoking cessation trials are reported at a fast clip. Therefore, this discussion of the TTUD analyses is supplemented with consideration of notable new studies. However, there are few “breakthroughs” in smoking cessation research, and the major conclusions of the TTUD analyses are generally consistent with current knowledge. Second, the meta-analyses may not precisely isolate the impact of particular treatment elements owing to practices common in clinical trial design and reporting (Piasecki & Baker, 2001). Cessation trials often use multicomponent behavioral therapies, and the elements of these behavioral therapies are sometimes sketched only vaguely in published reports. Pharmacotherapy trials often combine medication with behavioral treatments, and the behavioral adjuvants may vary widely across studies of the same pharmacologic agent. While the TTUD authors attempted to exclude seriously confounded study arms from the meta-analyses, the tendency for efficacious practices to be alloyed in primary studies somewhat constrains strong inference. Finally, the meta-analyses, perforce, relied on the outcome data reported in the original trials. The majority of studies employed 1-week point-prevalence relapse definitions at 6-months post-quit. Estimated pooled abstinence rates would no doubt be lower if prolonged or continuous abstinence measures and later endpoints had been preponderant in the primary literature.

2.1. Treatment structure

Treatments can be distinguished from one another along 3 broad dimensions: structure, behavioral content, and pharmacotherapy. Treatment structure refers to the manner in which treatments are delivered, including variables such as the number of sessions, their timing, the provider selected to deliver the treatment, the total amount of treatment time, the counseling format, and so on. Treatment structure is the clinical dimension that has received the least systematic research attention. This is unfortunate because structural variables may account for a great deal of the variability in relapse rates across cessation trials (Piasecki & Baker, 2001).

Table 1 summarizes the results of TTUD meta-analyses assessing the impact of various structural elements. As can be seen from the table, there tends to be almost a dose-response relation between the amount of contact the smoker has with the treatment provider and the ultimate abstinence rate. Whether treatment intensity is measured as level of contact, total amount of contact time, or number of person-to-person sessions, abstinence rates tend to increase with extended contacts. A similar phenomenon is seen as the number of treatment formats (i.e., different types of counseling and psychoeducational interventions) increases within a treatment. Other structural variables (e.g., type of clinician, counseling format) had more overlapping confidence intervals and did not appear linearly related to abstinence rates.

Extended treatment contacts might increase abstinence rates by several means. For instance, some lapses may be discouraged simply because the smoker knows s/he is being monitored and will have to admit the lapse at a future contact. Additional contacts also provide opportunities for delivering more of the “active ingredients” of behavioral treatments, such as educational information, coping skill training, and nonspecific factors such as empathy. Thus, even in the absence of a “breakthrough” discovery in either pharmacotherapy or behavioral therapy, the meta-analytic

Table 1
Summary of TTUD meta-analyses assessing impact of various elements of treatment structure

Structure variable	Number of study arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Level of contact (43 studies)			
No contact	30	1.0	10.9
Minimal counseling (<3 min)	19	1.3 (1.01, 1.6)	13.4 (10.9–16.1)
Low intensity counseling (3–10 min)	16	1.6 (1.2, 2.0)	16.0 (12.8–19.2)
Higher intensity counseling (>10 min)	55	2.3 (2.0, 2.7)	22.1 (19.4–24.7)
Total amount of contact time (35 studies)			
None	16	1.0	11.0
1–3 min	12	1.4 (1.1, 1.8)	14.4 (11.3, 17.5)
4–30 min	20	1.9 (1.5, 2.3)	18.8 (15.6, 22.0)
31–90 min	16	3.0 (2.3, 3.8)	26.5 (21.5, 31.4)
91–300 min	16	3.2 (2.3, 4.6)	28.4 (21.3, 35.5)
>300 min	15	2.8 (2.0, 3.9)	25.5 (19.2, 31.7)
Number of person-to-person sessions (45 studies)			
0–1 session	43	1.0	12.4
2–3 sessions	17	1.4 (1.1, 1.7)	16.3 (13.7, 19.0)
4–8 sessions	23	1.9 (1.6, 2.2)	20.9 (18.1, 23.6)
>8 sessions	51	2.3 (2.1, 3.0)	24.7 (21.0, 28.4)
Type of clinician (29 studies)			
No clinician	16	1.0	10.2
Self-help	47	1.1 (0.9, 1.3)	10.9 (9.1, 12.7)
Nonphysician	39	1.7 (1.3, 2.1)	15.8 (12.8, 18.8)
Physician	11	2.2 (1.5, 3.2)	19.9 (13.7, 26.2)
Number of clinicians Types (37 studies)			
No clinician	30	1.0	10.8
One type	50	1.8 (1.5, 2.2)	18.3 (15.4, 21.1)
Two types	16	2.5 (1.9, 3.4)	23.6 (18.4, 28.7)
Three or more types	7	2.4 (2.1, 2.9)	23.0 (20.0, 25.9)
Format (58 studies)			
No format	20	1.0	10.8
Self-help	93	1.2 (1.02, 1.3)	12.3 (10.9, 13.6)
Proactive telephone counseling	26	1.2 (1.1, 1.4)	13.1 (11.4, 14.8)
Group counseling	52	1.3 (1.1, 1.6)	13.9 (11.6, 16.1)
Individual counseling	67	1.7 (1.4, 2.0)	16.8 (14.7, 19.1)
Number of formats (54 studies)			
No format	20	1.0	10.8
One format	51	1.5 (1.2, 1.8)	15.1 (12.8, 17.4)
Two formats	55	1.9 (1.6, 2.2)	18.5 (15.8, 21.1)
Three or four formats	19	2.5 (2.1, 3.0)	23.2 (19.9, 26.6)

Note. Adapted from Fiore et al. (2000), Tables 12–18. Original tables are in the public domain. Odds ratios and abstinence rates refer to long-term (>5 month) follow-up.

results might suggest that relapse rates could be reduced by offering extended contact—giving smokers more time and more of the tools already in the armamentarium. This conclusion needs to be tempered by practical concerns. Increasing contacts is clearly a very expensive enterprise, especially in an environment in which health insurance only rarely covers smoking cessation (Curry, Grothaus, McAfee, & Pabaniak, 1998; Fiore et al., 2000). Moreover, smokers often do not choose to utilize extensive cessation support services, even when they are made attractive, convenient, and free (e.g., Lichtenstein & Hollis, 1992). Such findings raise questions as to whether an investment in extended contact is likely to yield large returns, and may also suggest that the meta-analytic results are biased by selection effects. That is, especially motivated smokers may be among the most likely volunteers for clinical trials with demanding intervention protocols (Hughes, Giovino, Klevens, & Fiore, 1997). Two streams of future research on extended contact seem warranted. One stream might be designed to more precisely isolate the effects of contact per se by cleanly manipulating structural elements, minimizing possible selection effects, and attempting to identify the vital mediating mechanisms. Another stream might focus on practical issues, such as how to best induce smokers to enter treatments with extended contacts and how to reduce the costs of efficacious extended contact protocols.

2.2. Psychosocial treatment contents

Table 2 summarizes the TTUD meta-analyses of particular psychosocial treatment contents. Five contents were deemed efficacious: intratreatment and extratreatment social support, general problem solving, rapid smoking, and other aversive smoking. Before considering these contents individually, it is important to note that the reference condition for each content analysis was provision of *no psychosocial treatment*. Thus, the results do not directly implicate particular contents as superior to other active treatments. Head-to-head comparisons of distinct psychological interventions are rarely reported in the same cessation trial. It is notable that the confidence intervals for most treatment contents in Table 2 overlap. One potential interpretation of this overlap is that a version of the “Dodo Bird” phenomenon seen in the general psychotherapy literature might also be at play in smoking cessation—any active psychosocial intervention may tend to be better than no treatment, but no active treatment may ultimately prove to be reliably superior to other active treatments (e.g., Luborsky et al., 2002; Wampold et al., 1997).

The social support interventions were heterogeneous across studies, and are best conceived as a loose class of adjunctive procedures that are typically delivered as part of larger multicomponent interventions (Piasecki & Baker, 2001). Protocols coded as containing “intratreatment social support” were unified only by the fact that study authors reported the provision of caring, concern, and encouragement within the treatment environment as a key component of the intervention. This supportive material was sometimes delivered by the clinician (often working from a treatment manual emphasizing support) and sometimes by other members of a therapy group. Protocols coded as “extratreatment social support” were similarly heterogeneous; they shared in common an emphasis on social support in the patients’ natural social milieu (rather than the treatment setting), but this was approached from a variety of directions (e.g., “buddy” systems, training patients to elicit support at home and work).

Table 2
Summary of TTUD meta-analysis assessing impact of various treatment contents (62 studies)

Content	Number of study arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
No counseling	35	1.0	11.2
Relaxation/breathing	31	1.0 (0.7, 1.3)	10.8 (7.9, 13.8)
Contingency contracting	22	1.0 (0.7, 1.4)	11.2 (7.8, 14.6)
Weight/diet	19	1.0 (0.8, 1.3)	11.2 (8.5, 14.0)
Cigarette fading	25	1.1 (0.8, 1.5)	11.8 (8.4, 15.3)
Negative affect	8	1.2 (0.8, 1.9)	13.6 (8.7, 18.5)
Intratreatment social support	50	1.3 (1.1, 1.6)	14.4 (12.3, 16.5)
Extratreatment social support	19	1.5 (1.1, 2.1)	16.2 (11.8, 20.6)
General problem-solving	104	1.5 (1.3, 1.8)	16.2 (14.0, 18.5)
Other aversive smoking	19	1.7 (1.04, 2.8)	17.7 (11.2, 24.9)
Rapid smoking	19	2.0 (1.1, 3.5)	19.9 (11.2, 29.0)

Note. Adapted from Fiore et al. (2000), Table 20. Original table is in the public domain. Odds ratios and abstinence rates refer to long-term (>5 month) follow-up.

Given that supportive interventions were not characterized by a family of precise behavioral technologies, it is somewhat difficult to understand why these treatment components emerged as reliable aids to cessation. It seems plausible that, like extended contact, treatments with an explicit social support element may deliver higher “doses” of nonspecific factors (e.g., empathy) and/or intensive monitoring, and these may discourage lapses. Alternatively, the results may reflect the tendency for supportive treatments to be correlated with other efficacious, ubiquitous contents, such as problem solving/coping training; the simultaneous presence of other contents may have confounded the meta-analytic results. Finally, mention of supportive interventions in research reports may serve as a “quality marker,” separating out trials with a thoughtful approach to behavioral therapy from those using generic or draconian behavioral adjuvants (Piasecki & Baker, 2001).

“General problem solving” denotes a family of psychosocial contents which includes cognitive–behavioral therapy and so-called “relapse prevention” therapy (Curry & McBride, 1994; Marlatt, 1985). Such treatments aim to help smokers identify situations that may place them at high risk for relapse. Smokers are trained to avoid these situations and/or to use specific coping strategies to reduce the chances of relapse in risky situations. Problem-solving approaches are the mainstay of smoking cessation and have been widely studied; this is reflected in the disproportionate number of qualifying study arms for problem-solving in Table 2. In fact, it is increasingly difficult to find smoking cessation trials that *do not* report the use of cognitive–behavioral or problem-solving techniques (Piasecki & Baker, 2001). Many reviews collapse all psychosocial treatments together to estimate the effects of “behavioral support” (e.g., Fiore, Smith, Jorenby, & Baker, 1994; West et al., 2000). Because they predominate in contemporary smoking cessation research, problem-solving techniques may account for most of the variance in such estimates.

Rapid smoking (Danaher, 1977; Lichtenstein, Harris, Birchler, Wahl, & Schmahl, 1973) and other aversive smoking (e.g., satiation, focused smoking; Best, Owen, & Trentadue, 1978; Hackett & Horan, 1978) are older behavior therapy techniques that attempted to use the malaise resulting from oversmoking as a punisher or substrate for conditioned taste aversion. Aversive smoking techniques are rooted in sound behavioral theory (Erickson, Tiffany, Martin, & Baker, 1983) and had a promising track record in empirical studies from the late 1970s through the mid-1980s. Since then, aversive smoking has largely been abandoned by smoking cessation researchers and practitioners. The demise of aversive smoking resulted from a confluence of factors, including the introduction of nicotine polacrilex gum in the mid 1980s and rising concern about the safety of oversmoking techniques (Miller, Schilling, Logan, & Johnson, 1977; Sachs, Hall, & Hall, 1978). The general decline of behavior therapy and the ascendancy of cognitive therapies within clinical psychology during the 1980s also played a role in supplanting aversive smoking with problem solving approaches.

One can understand why practitioners (and smokers) might shy from a potentially dangerous and frankly messy therapy (achievement of emesis was regarded as an important predictor of abstinence; Merbaum, Avimier, & Goldberg, 1979; Norton and Barske, 1977), especially in an era in which effective pharmacotherapies are safe enough to be made available without a prescription. Nonetheless, the aversive smoking literature could provide an important object lesson for designers of behavioral adjuvants. Aversive smoking almost certainly worked via a different mechanism of action than do contemporary verbal cessation strategies such as problem solving, and in fact has been shown to additively complement such treatments (e.g., Tiffany, Martin, & Baker, 1986). Advances in psychosocial treatments for smoking seem more likely to come from the development of new modes of treatment rather than parametric modifications of existing problem-solving techniques. We should strive to design novel treatments that possess the conceptual virtues of aversive smoking, but which are also safer and less onerous than past practices.

2.3. First-line pharmacotherapies

Table 3 summarizes TTUD meta-analyses of commonly-used pharmacotherapies for smoking cessation: bupropion and nicotine replacement. These treatments were deemed “first line” therapies by the TTUD expert panel to distinguish them from “second line” pharmacotherapies (e.g., clonidine, nortriptyline) which have empirical support as cessation aids (Covey & Glassman, 1991; Hall et al., 2002), but which do not have an FDA indication for treatment of tobacco dependence and may have more aversive side effects relative to the first-line treatments.

Sustained-release bupropion (Zyban[®]) is the only non-nicotine first-line therapy. Bupropion, originally developed as an antidepressant (Wellbutrin[®]), blocks reuptake of dopamine and norepinephrine and may also act as a nicotine antagonist (Hays & Ebbert, 2003). At the time of the TTUD analyses, only 2 published clinical trials had evaluated

Table 3
Summary of TTUD meta-analyses evaluating first-line pharmacotherapies

Condition	Number of study arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Bupropion (2 studies)			
Placebo	2	1.0	17.3
Bupropion	4	2.1 (1.5, 3.0)	30.5 (23.2, 37.8)
Nicotine gum (13 studies)			
Placebo	16	1.0	17.1
Nicotine gum	18	1.5 (1.3, 1.8)	23.7 (20.6, 26.7)
Nicotine inhaler (4 studies)			
Placebo	4	1.0	10.5
Nicotine inhaler	4	2.5 (1.7, 3.6)	22.8 (16.4, 29.2)
Nicotine nasal spray (3 studies)			
Placebo	3	1.0	13.9
Nicotine nasal spray	3	2.7 (1.8, 4.1)	30.5 (21.8, 39.2)
Nicotine patch (27 studies)			
Placebo	28	1.0	10.0
Nicotine patch	32	1.9 (1.7, 2.2)	17.7 (16.0, 19.5)
Over-the-counter nicotine patch (3 studies)			
Placebo	3	1.0	6.7
OTC nicotine patch	3	1.8 (1.2, 2.8)	11.8 (7.5, 16.0)
Combination NRT (3 studies)			
One NRT	3	1.0	17.4
Two NRTs	3	1.9 (1.3, 2.6)	28.6 (21.7, 35.4)

Note. Adapted from Fiore et al. (2000), Tables 25–29, 32, 40. Original tables are in the public domain. Odds ratios and abstinence rates refer to long-term (>5 month) follow-up.

bupropion's efficacy, and both showed it to be superior to placebo controls (Hurt et al., 1997; Jorenby et al., 1999). A more recent meta-analysis including data from unpublished trials and newer studies estimates an odds ratio of 1.97 for bupropion vs. placebo (Hughes et al., 2004).

Bupropion has now been tested under a variety of clinical conditions, and these warrant some comment. First, bupropion has been shown to be more effective than placebo in a variety of subpopulations thought to be at high risk of relapse, including women (Smith et al., 2003), persons with a history of depression (Hall et al., 2002; Hayford et al., 1999; Smith et al., 2003), and African-Americans (Ahluwalia, Harris, Catley, Okuyemi, & Mayo, 2002). Second, the standard dose of 300 mg per day appears to be superior to a 150 mg daily regimen in the short term, but does not significantly improve long term (i.e., >6 month) outcomes (Hurt et al., 1997; Swan et al., 2003). Third, bupropion produces long-term abstinence rates around 25% in medical management regimens (Hall et al., 2002; Swan et al., 2003) and these outcomes may not be substantially improved by adding intensive group counseling (Hall et al., 2002). Fourth, bupropion and nicotine replacement may be co-administered safely, and combined use may increase abstinence rates relative to use of either drug alone (Jorenby et al., 1999). Fifth, bupropion was not superior to nortriptyline, a lower-cost generic tricyclic antidepressant drug, in a head-to-head comparison (Hall et al., 2002). Finally, bupropion is well-tolerated, and extending bupropion therapy for one year after initial attainment of smoking cessation delays subsequent relapse (Hays et al., 2001).

The efficacy of nicotine replacement therapy, especially gum and patch, has been widely studied. Currently, nicotine gum, patches, and lozenge are available for OTC purchase in the United States. Nicotine nasal spray and inhalers are available by prescription only. The TTUD analyses (Table 3) and subsequent reviews (Hughes et al., 2003; Silagy et al., 2004) are remarkably consistent in suggesting an odds ratio of approximately 2.0 for NRT vs. placebo, regardless of the specific NRT formulation. The tendency for active NRT to double the odds of cessation also appears to translate well across behavioral adjuvants. While adjuvant behavioral support does not affect the magnitude of the *relative* benefit of NRT, it does seem to moderate the absolute abstinence rates attained in NRT trials. As the level of behavioral support delivered with NRT increases, abstinence rates increase. This phenomenon can be appreciated by comparing the results of analyses for the nicotine patch overall and in the OTC environment. The odds ratios for the patch are comparable (1.9 vs. 1.8) but long-term abstinence rates were lower in OTC trials vs. the larger body of controlled studies (11.8% vs. 17.7%). A more recent, comprehensive synthesis of OTC NRT studies estimates the NRT vs. placebo odds ratio at 2.5 and estimates long-term cessation rates at 7% in the OTC context (Hughes et al., 2003).

Since the publication of the TTUD guidelines, one major clinical trial has evaluated the efficacy of a new lozenge form of NRT (Shiffman, Dresler, et al., 2002). In this study, smokers were stratified according to dependence, with smokers reporting smoking within 30 min of awakening classified as high dependence. High dependence smokers were allocated to a 4 mg dose and low dependence smokers were assigned to a 2 mg lozenge. Within each dependence group, half were treated with placebo and half were treated with active lozenges. Minimal counseling was provided (5–10 min of support at 4 visits). In low dependence smokers, the continuous abstinence rate among 2 mg lozenge users was 24.2% (vs. 14.4% for placebo, OR=1.96) at 6 months, and 17.9% (vs. 9.6% for placebo, OR=2.14) at 1 year. In high dependence smokers, the continuous abstinence rate for 4 mg lozenge users was 23.6% (vs. 10.2% for placebo, OR=2.76) at 6 months and 14.9% (vs. 6.2% for placebo, OR=2.69) at 1 year. More trials of lozenge are needed, but these results suggest the lozenge is at least as effective as more established NRTs, approximately doubling long-term abstinence rates.

Patient preference is generally regarded as an important factor in the selection of a particular NRT formulation, since all NRTs appear effective and no evidence cleanly implicates any one form as superior to the others (Hughes, Goldstein, Hurt, & Shiffman, 1999). The one possible exception to this rule is that highly-dependent smokers may benefit more from 4 vs. 2 mg gum or lozenge (cf. Garvey et al., 2000; Herrera et al., 1995; Sachs, 1995; Shiffman, Dresler, et al., 2002). In general, a problem with nicotine gum is that patients tend to under-dose themselves (West & Shiffman, 2001). Thus, some clinicians will recommend that all smokers be started on a 4 mg dose and that the 2 mg dose be reserved for those who cannot tolerate the higher dose.

While all NRTs deliver nicotine, their pharmacokinetic and sensory properties differ somewhat. A chief distinction is that patches deliver steady-state nicotine levels, whereas other NRTs can be self-administered ad libitum (though a fixed dosing schedule is often recommended to avert under-dosing). For some smokers, it may be useful to combine a patch with another form of NRT; the patch may provide a steady baseline of nicotine and the other form may allow more flexible dosing (and a self-administration ritual) that may help the smoker to cope with acute urges and temptations. A few trials suggest that combination NRT regimen is superior to monotherapy (Table 3; Blondal, Gudmundsson, Olafsdottir, Gustavsson, & Westin, 1999; Kornitzer, Boutsen, Dramaix, Thijs, & Gustavsson, 1995).

Clearly, significant strides have been made in the treatment of tobacco dependence. However, it is notable that even the most potent pharmacotherapies, coupled with the most intensive psychosocial treatments, yield long-term abstinence rates of 30% or less. Relapse remains the most likely outcome of any given cessation attempt.

3. Relapse, recovery, recycling, and reduction

Relapse occurs quickly for the majority of treated smokers. Many smokers fail to attain even 24 h of continuous abstinence after a target quit date (Spanier, Shiffman, Maurer, Reynolds, & Quick, 1996; Westman, Behm, Simel, & Rose, 1997). Survival curves from smoking cessation trials tend to show a characteristic pattern in which a majority of relapse occurs during the first 5–10 days of the cessation attempt. After this period, relapse incidence slows, but new relapses occur steadily. In fact, new relapses continue to be observed for several years after the initial quit attempt (Blondal et al., 1999; Hays et al., 2001). In general, effective cessation treatments show an advantage over control treatments very soon after the quit date, within the 5–10 day window in which the relapse risk is highest. After this time, relapse curves from treatments and control groups tend to be parallel. This may suggest that the determinants of early and late relapse are qualitatively different, and that we have not yet identified treatments that are optimized for combating relapse risks that arise relatively late in the cessation attempt (Piasecki et al., 2002).

Quitters sometimes recover from an occasional lapse to smoking after the quit date, but lapses are very risky; any smoking behavior after quitting is a very strong predictor of eventual relapse (Kenford et al., 1994; Westman et al., 1997). Acute instigators of first lapses to smoking include negative affect, urge/craving, alcohol consumption, the presence of other smokers in the immediate environment, and being in situations in which cigarettes are readily available (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). Building or unremitting withdrawal symptoms may precede first lapses, and the lapse tends to alleviate the symptoms (Piasecki, Jorenby, Smith, Fiore, & Baker, 2003a). Approximately 90% of persons who lapse progress to have another lapse, and these second lapses often occur within the same day or even the same hour (Brandon, Tiffany, and Baker, 1986; Shiffman, Hickcox, et al., 1996). The progression from lapses to daily smoking is somewhat variable and slower than the onset of second lapses (Shiffman, Hickcox, et al., 1996), but most lapsers eventually do return to daily smoking.

Some data suggest that relapse is quite discouraging, and may provoke “defensive cognitive restructuring” through which some relapsers come to view smoking as less risky to health and more psychologically beneficial (e.g., Chassin, Presson, Sherman, & Kim, 2002). However, relapse is not necessarily a chronic outcome and discouragement is not universal. One recent study of persons who failed to attain even 24 h of abstinence during an initial quit attempt found that 46% reported quitting for at least a day in the ensuing 6 months (Spanier et al., 1996). The vast majority of smokers enrolling in smoking cessation trials report a history of past quit attempts, and most have already failed at least once while using a pharmacologic cessation aid (Durcan, White, et al., 2002; Shiffman, Dresler, & Rohay, 2004). Some “recycling” studies, in which relapsers are quickly recruited for a second course of treatment, have produced disappointing results (Gourlay et al., 1995; Silagy et al., 2004; Tonnesen, Norregaard, Sawe, & Simonsen, 1993; Tonnesen, Mikkelsen, Norregaard, & Jorgensen, 1996). However, relapsers who try to quit a second course of bupropion (Gonzales et al., 2001), or who switch to a new pharmacotherapy after a treatment failure (Durcan, White, et al., 2002; Shiffman, Dresler, et al., 2004) may fare quite well in the new cessation attempt.

In many older smoking cessation trials, reduction in the number of cigarettes smoked per day was considered to be an important secondary outcome for relapsers. In the 1980s, methodologic conventions shifted, and absolute abstinence rates began to be considered the only important measure of a treatment’s efficacy. This shift was probably predicated on beliefs that (1) most relapsers escalated back to baseline smoking levels relatively quickly, and (2) absolute abstinence was the only sure way to prevent the health consequences of smoking (Hughes, Cummings, & Hyland, 1999). Research into smoking reduction is experiencing something of a renaissance. Recent studies suggest that many smokers are able to maintain smoking reductions after a relapse, and that reduced smoking is a predictor of subsequent quit attempts (Hughes, 2000). Attempts to cut down smoking are prevalent in the general smoking population and are viewed by smokers as preparatory steps toward quitting (West et al., 2001). Clinician-assisted smoking reduction may ultimately prove a valuable complement to existing cessation treatments (Cinciripini et al., 1995; Riggs, Hughes, & Pillitteri, 2001).

4. The dynamics of smoking motivation

Relapse researchers have long been interested in how motivational processes, such as withdrawal, urge/craving, and negative affect contribute to the maintenance of smoking. As a general rule, motivational theories have posited that such motives are inherently dynamic, and that relapse risk will vary in concert with the waxing and waning of internal states (e.g., Baker, Morse, & Sherman, 1987; Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Shiffman et al., 1986; Solomon & Corbit, 1973). A notable trend in relapse research has been the increasing use of research designs that permit fine-grained examination of these dynamic processes, both in the laboratory and in smokers’ natural environments. Such research is yielding new insights into smoking motivation, and is also revealing important limitations of our cessation treatments.

4.1. *Withdrawal*

Abrupt cessation of tobacco results in a withdrawal syndrome that chiefly consists of negative affects, such as sadness, irritability, anxiety, and frustration, but also includes changes in sleep quality, appetite, and heart rate (Hughes, Higgins, & Hatsukami, 1990). There is some controversy as to whether urge/craving should be considered a valid withdrawal symptom; urge craving is discussed separately below. There is substantial evidence that smoking withdrawal symptoms are at least partially pharmacologically mediated. For instance, they arise soon after cessation (Hughes & Hatsukami, 1986) and are reversed by nicotine administration (Hughes et al., 1984).

Withdrawal symptoms have historically been viewed as important instigators of relapse in theories of drug motivation, but early clinical studies found little evidence that withdrawal severity was a good predictor of smoking relapse (Patten & Martin, 1996). These equivocal results were obtained from studies that used ratings of withdrawal from a single occasion (or a mean across repeated occasions), usually very early in the quit attempt, as the sole relapse predictor. Predicting relapse from a “snapshot” of withdrawal taken early in the quit attempt makes sense under a narrow set of assumptions, viz., that withdrawal unfurls in a stereotyped fashion across all smokers and that its peak (the period of maximal relapse risk) occurs early in the cessation attempt. These assumptions may be in error. Early investigations of the smoking withdrawal syndrome noted that it was highly variable across persons (e.g., Shiffman & Jarvik, 1976). This observation should not be surprising, since the cardinal symptoms of withdrawal are negative

affects and affects may be responsive to a host of pharmacologic and nonpharmacologic instigators. Moreover, numerous theories of withdrawal contend that withdrawal symptoms may become entrained to interoceptive and exteroceptive cues through associative learning (Baker et al., 1987; Baker, Piper, et al., 2004; Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000; Solomon & Corbit, 1973). Such theories would predict individual smokers should display unique withdrawal time courses if their environments differ in the density of provocative cues.

The time course of withdrawal symptoms is remarkably stereotyped—but only when group means are examined. Analyzed in the aggregate, withdrawal symptoms increase rather sharply upon cessation, and then decrease gradually back to baseline within 3–4 weeks. However, this mean pattern masks considerable intra- and interindividual variability. Many smokers report symptom profiles that are chaotic, prolonged, or even increasing over an 8-week period (Piasecki, Fiore, & Baker, 1998; Piasecki et al., 2000; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003b). When this configural information is taken into account in prediction models, withdrawal experience is a reliable predictor of relapse. Relapse is predicted by multiple, semi-independent parameters of the withdrawal experience, including the mean elevation of symptoms, day-to-day symptom volatility, the slope of symptoms across time, and the magnitude of acute symptom relief associated with lapses to smoking (Piasecki et al., 2003a). Elevated or acutely spiking withdrawal symptoms tend to precede the first lapse to smoking (Piasecki et al., 2003a).

A recent study extended this work by tracking smokers' withdrawal for several weeks both before and after a cessation attempt (McCarthy, Piasecki, Fiore, & Baker, 2004). Results showed that symptoms were much more variable after quitting than before, suggesting that smoking may buffer or constrain aversive symptoms, which are then "unleashed" by cessation. Results also showed that, for many smokers, withdrawal symptoms increase systematically even before the quit date, perhaps in anticipation of reinforcement loss, and the magnitude of such increases predicts short-term smoking relapse. This finding may have practical implications—smokers showing rising symptoms before the quit date might be targeted for stepped-up behavioral or pharmacologic treatments before they experience a potentially demoralizing treatment failure (cf. Smith et al., 2001). The fact that "withdrawal" can change significantly even before quitting highlights the overlap between negative affect and withdrawal.

Pharmacotherapies for smoking cessation are often presumed to work by reducing withdrawal symptoms (Hughes, 1993). The withdrawal literature had culminated in an interesting puzzle for clinical researchers. On the one hand, prominent pharmacotherapies (i.e., NRT) both reduced withdrawal symptoms and reliably boosted abstinence rates. On the other hand, there was scant evidence that withdrawal posed serious relapse risk. Selection bias may have accounted for some of this puzzle—studies attempting to predict relapse from withdrawal measures often eliminated lapsed smokers from the prediction models, on the assumption that any smoking after the quit date would lower withdrawal scores and confound the analyses. In fact, lapsed smokers report systematically higher withdrawal scores despite low-level smoking (Piasecki et al., 2003b), and they are at extremely high risk of ultimate relapse (Kenford et al., 1994). Thus, eliminating lapsed smokers from prediction analyses may have excluded from the models precisely those individuals most likely to reveal a withdrawal-lapse relation. Underappreciation of the variable course of withdrawal symptoms may also have contributed to this conundrum. During a quit attempt, bupropion and the nicotine patch each reduce the mean level of withdrawal, but they appear to have no effect on other relapse-related symptom components, such as the slope or variability of symptoms over time (Piasecki, Jorenby, Smith, Fiore, & Baker, 2003c). A recent laboratory study demonstrated that the nicotine patch reduces the elevation of background negative affect that attends smoking deprivation, but does not blunt the acute increase in affect provoked by smoking cue exposure (Tiffany, Cox, & Elash, 2000). Thus, current pharmacotherapies may only ameliorate one component of a multifaceted affect/withdrawal response system.

4.2. Negative affect

Negative affect is widely believed to be a motive for smoking, but relations between affect and smoking are complex (see Kassel, Stroud, & Paronis, 2003, for a detailed review). In retrospective studies, smokers commonly cite a desire for relief from negative affect as a chief reason for smoking (Brandon & Baker, 1991; Piper et al., 2004), and often attribute relapses to acute negative affects (Brandon et al., 1986; Shiffman, 1982).

Several naturalistic studies in which continuing smokers carried palmtop computers to record states and behaviors in near-real time have revealed that, in contrast to smokers' stated beliefs, there is little or no systematic correlation between affect and smoking behavior (cf. Delfino, Jamner, & Whalen, 2001; Shaprio, Jamner, Davydov, & Porsha, 2002; Shiffman, Gwaltney, et al., 2002; Shiffman, Paty, Gwaltney, & Dang, 2004). Smokers' beliefs about negative

affect may also be driven by their experiences during failed quit attempts (Shiffman, Gwaltney, et al., 2002) or by experiences with affect-laden withdrawal symptoms (Parrott, 1999). A recent reformulation of negative reinforcement theories of addiction posits that negative affect may, in fact, be the fundamental motive for ongoing drug use even though there is a desynchrony of self-reported mood and smoking behavior (Baker, Piper, et al., 2004). According to this account, interoceptive cues which signal impending negative affect or withdrawal come to serve as discriminative stimuli capable of preconsciously prompting smoking. This mechanism is hypothesized to prevent the emergence of strong affects in the prototypic context of ongoing use, and thus may prevent detection of affect-smoking linkages in self-report data.

In contrast to results from studies of ongoing smoking, daily monitoring studies of persons attempting to quit clearly implicate negative affect as an immediate antecedent of smoking lapses. For instance, Shiffman, Paty, et al. (1996) compared reports of immediate experiences during random moments, highly tempting situations, and first lapses to smoking in a sample of quitters. A linear relation was found between the type of assessment and negative affect ratings; first lapses were characterized by high negative affect, temptations involved somewhat less negative affect, and random moments were characterized by the lowest affect ratings. Moreover, approximately 20% of first lapses to smoking occurred at moments when negative affect was extremely high (approximately 2.5 SD above the mean). Negative affect is not only a good marker of lapse risk, but it may also be remembered by smokers as an especially salient lapse instigator. When lapsed smokers from the same study were asked to retrospectively describe the characteristics of their first lapses 12 weeks later, they tended to systematically increase their estimates of negative moods during the lapse (Shiffman, Hufford et al., 1997). This finding underscores the importance of continuing to incorporate near-real-time measurement strategies in the study of relapse episodes.

Major depression and depressive affect have often been studied as moderators of smoking relapse. Lifetime diagnosis of major depression is inconsistently related to relapse (Hitsman, Borelli, McChargue, Spring, & Niaura, 2003), but a major depressive episode may emerge in as many as 15% of history-positive smokers making a quit attempt (Kahler et al., 2002). Even very low levels of depressive symptomatology at the outset of a smoking cessation attempt predict dramatically lower long-term abstinence rates (Niaura et al., 2001).

Among the first-line pharmacotherapies, the antidepressant bupropion would seem to be a natural candidate for reducing post-cessation negative affect. In fact, bupropion does tend to ameliorate negative affect (Jorenby et al., 1999; Shiffman, Johnston et al., 2000). This effect appears to mediate bupropion's clinical efficacy, but this effect is not especially strong (Lerman, Roth et al., 2002). Interestingly, although bupropion may be especially beneficial for smokers with a history of depression (Smith et al., 2003), it does not appear to have reliable effect on post-quit depressive symptomatology per se (cf. Ahluwalia et al., 2002; Hurt et al., 1997; Jorenby et al., 1999). Cognitive-behavioral therapies with a mood regulation component have been shown to be especially effective for smokers with a depression history (Hall, Munoz, & Reus, 1994). Interestingly, one recent study suggests that such treatments may actually provoke increased negative affect after the quit date (Kahler et al., 2002). At present, it is unclear whether this finding is spurious or replicable. If this phenomenon is ultimately shown to be reliable, it would raise questions about the positive outcome data for CBT; one possibility might be that CBT encourages increased exposure to cues which provoke negative affective responses. Such exposures might have a short-term cost (negative affect) but if smoking is avoided, these episodes may facilitate extinction of associative learning or promote other salutary modifications of emotional memory structures (e.g., Baker, Piper, et al., 2004; Foa & Kozak, 1986). A similar process-outcome dissociation was seen in a recent study of cue exposure therapy. Although the goal of therapy was to reduce craving, subjects whose craving acutely *increased* during cue exposure session differentially benefited from the treatment (Niaura et al., 1999).

4.3. Craving¹

Cravings had been de-emphasized by addiction scholars in the past because they were viewed as “mental way stations” unnecessarily interposed between external stimuli and drug self-administration behaviors. Theorists also

¹ The terms “urge” and “craving” are used interchangeably here. Although some theorists have conceptualized these terms as referring to distinct constructs (Kozlowski & Wilkinson, 1987), assessments using each term intercorrelate very strongly ($r > .95$; Shiffman, Enberg, et al., 1997) suggesting that smokers do not make such a distinction and that both terms are fungible common-language descriptors of a drug-acquisitive drive state.

questioned whether self-reported urge/craving showed strong enough relations with drug self-administration behaviors or physiological indices of drug motivation to warrant serious consideration (Baker et al., 1987; Tiffany, 1990). Recent research suggests that craving may, in fact, be one of the most sensitive and consistent predictors of smoking behavior and smoking relapse.

Urge/craving is sometimes considered to be part of the smoking withdrawal syndrome, but theorists often consider it separately. Theories of craving differ in their particulars, but most models tend to view urges as more directly tied to appetitive motivational systems (i.e., as an indicator of drug approach) than other withdrawal effects are (Baker et al., 1987; Shiffman, 2000; Tiffany, 1990). Relative to other withdrawal features, urge has a distinctive time course; whereas most withdrawal symptoms increase sharply upon cessation, urge is often found to be higher during ongoing smoking than after cessation (Hughes, 1992; Shiffman, Enberg, et al., 1997). In fact, craving appears to be a near-ubiquitous concomitant of naturally occurring smoking behavior in adult smokers (Shapiro, Jamner, Davydov, & Porsha, 2002; Shiffman, Gwaltney, et al., 2002; Shiffman et al., 2004). This finding may reflect chronic pharmacologic priming of appetitive motivational systems by ongoing use (Stewart, deWit, & Eikelboom, 1984). However, it is important to distinguish between “background” or tonic craving and “pulsatile” or phasic craving responses (Shiffman, 2000). Craving is episodic and exquisitely responsive to environmental and pharmacologic manipulations. Even though general background levels of craving fall after quitting, quitters experience intermittent, strong temptation events associated with elevated craving that are superimposed over the lower, background craving levels (Shiffman, Enberg, et al., 1997).

Craving can be reliably provoked in the laboratory by smoking deprivation (Zinser, Fiore, Davidson, & Baker, 1999), in vivo smoking cues, urge- and affect-related imagery (Drobes & Tiffany, 1997; Tiffany & Drobes, 1990), smoking availability (Wertz & Sayette, 2001), and alcohol consumption (Burton & Tiffany, 1997). In fact, when addicts of any substance are presented with drug-related cues, craving is the most reliable and sensitive response channel (Carter & Tiffany, 1999). Many of the same stimuli that provoke craving in the laboratory are present in the immediate environment when first lapses to smoking occur, and craving is a robust concomitant of first lapses (Shiffman, Paty, et al., 1996).

Craving is a fact of life for the smoker, perhaps permanently for many. Craving frequency decreases after a lengthy period of abstinence, but it may never fully disappear. In one study, smokers who maintained abstinence for 4–5 years, 52% reported craving cigarettes at least occasionally (Daughton et al., 1999).

Craving is an important target for smoking cessation treatment, but existing therapies may not control craving adequately. The nicotine patch is capable of reducing background craving, but it does not affect the magnitude of acute spikes in craving provoked by smoking cues (Tiffany et al., 2000). Craving may exhibit important diurnal rhythms, with morning craving perhaps being an especially good predictor of relapse (Shiffman, Enberg, et al., 1997). Nicotine patches are available in 16- and 24-h dosing forms; use of the 24-h formulation may be better at suppressing waking urge (Shiffman, Elash, et al., 2000; Teneggi et al., 2002), but may still leave some variability in urge uncontrolled (Teneggi et al., 2002). It is not clear whether bupropion has reliable effects on craving (cf. Durcan, Deener, et al., 2002; Shiffman, Johnston, et al., 2000).

Craving is at least partly under associative control (Lazev, Herzog, & Brandon, 1999). This suggests that cue exposure therapies, which focus on extinguishing craving responses to provocative cues, could be an important component of an overall smoking cessation treatment plan. However, cue exposure treatments may be difficult to implement effectively because there are an overwhelming number of candidate cues, because extinction generalizes poorly across contexts, and so on (Brandon, Piasecki, Quinn, & Baker, 1995). Cue exposure did not appear to contribute unique benefits in a recent, controlled trial (Niaura et al., 1999). However, as noted above, increased craving during cue exposure sessions predicted better clinical outcomes; this intriguing finding may deserve further study.

5. Themes to watch

5.1. The “hardening hypothesis”

As noted above, smoking prevalence has declined markedly over the past several decades, but its rate of decline has flattened considerably since the 1990s (CDC 2002; Giovino, 2002). This pattern may imply that the current smoking population represents an increasingly “hard core” for whom quitting smoking may be especially difficult

(Hughes, 1996). There is some supportive evidence for “hardening” apart from the broad epidemiologic trends in smoking prevalence. Historical analyses of clinical trial outcomes suggest that standard interventions such as multicomponent skills training (Irvin & Brandon, 2000) and NRT (Irvin, Hendricks, & Brandon, 2003) have yielded lower abstinence rates over time. Moreover, average nicotine dependence scores among smokers tend to be higher in countries with lower smoking prevalence, suggesting that as smoking is discouraged, differential quitting may leave a “hardened” residual (Fagerstrom et al., 1996). Data from the National Comorbidity Survey suggest that members of younger birth cohorts are progressively less likely to initiate smoking. However, once smoking was initiated, members of younger cohorts progressed more rapidly from smoking experimentation to nicotine dependence (Breslau, Johnson, Hiripi, & Kessler, 2001). Thus, differential selection into smoking initiation by “dependence prone” youth might also be contributing to the hardening of the smoking population.

The hardening hypothesis has been the focus of some debate because it is based on suggestive, correlational data that are open to multiple interpretations (Warner & Burns, 2003). The hardening hypothesis revives old tensions in the tobacco control community, such as whether public health or clinic interventions should get resources, and whether harm reduction strategies aiming to reduce tobacco exposure should supplement treatments which view absolute abstinence as the only goal (Emery, Gilpin, Ake, Farkas, & Pierce, 2000; Niaura & Abrams, 2002; Shiffman et al., 1998; Warner & Burns, 2003). Whatever the merits of these debates, the potential hardening of the smoking population warrants monitoring. If hardening is occurring, it would suggest that relapse will come to be even more prevalent and more resistant to our first-line cessation treatments. Although developing more potent cessation and relapse prevention treatments has long been a goal of smoking researchers, a hardening trend would suggest these goals will become more imperative than ever; the rate of innovation in smoking treatment may need to accelerate to offset expected increases relapse rates. Research suggests that the average smoker must make several serious quit attempts before attaining long-term abstinence (Cohen et al., 1989; Hughes et al., 2004). Hardening may imply that the number of failed initial attempts at cessation will increase for the modal smoker. More intensive research attention may need to be focused on the motivational impact of these failure experiences and on optimal ways to rapidly “recycle” relapsers to shorten the interval between serious cessation attempts.

5.2. *Smoking motivation in developmental context*

Theories of addiction have long posited that drug use induces systematic changes in motivational systems, and these changes, in turn, account for the tenacity of relapse (e.g., Baker et al., 1987; Solomon & Corbit, 1973). Until relatively recently, most human research on drug motivation has focused on the end of the drug use career. For instance, studies of smoking motivation have tended to focus on adult smokers who are either attempting to quit (clinical studies) or who exceed minimum thresholds on dependence measures (laboratory studies). Our focus on adult users—and our relative ignorance about what their lives were like before they became adult users—may have prevented us from fully apprehending the scope and significance of the motivational changes experienced by the smoker across the smoking career. Drug motivational theories have tended to posit motivational effects that are essentially short-lived and reversible—associative learning that can be extinguished, neuroadaptations to the presence of drug that are readily repaired by sustained abstinence, and so on.

In contrast, newer theories of addiction, arising from neuroscience research, posit more profound and lasting derangement of motivational systems (e.g., Goeders, 2004; Koob & LeMoal, 1997; Robinson & Berridge, 1993). Moreover, both human and animal research suggests that drug motivational phenomena may be best understood within a developmental framework (Jamner et al., 2003; Kassel et al., 2003).

Animal research attests to the motivational changes that might accompany smoking exposure and smoking cessation. Most smokers begin smoking during this adolescence, a period that is characterized by significant remodeling of the brain (Jamner et al., 2003). Recent animal research suggests that adolescence may be a “critical” or “sensitive period” during which nicotine exposure produces long-lasting changes in brain and behavior, including an increased susceptibility to nicotine self-administration and increased negative emotionality in adulthood (Adriani et al., 2003; Slawecki & Ehlers, 2002; Slawecki, Golder, Roth, & Ehlers, 2003; Slotkin, 2002; Smith, 2003). Adult rats treated with nicotine show slightly decreased reward thresholds (indicating enhanced reward system functioning), but when nicotine is removed, these same rats show prolonged elevations in reward thresholds, perhaps indicative of a dysphoric state (Skjei & Markou, 2003). Thus, even for rats, the world may be a

bit “brighter” under the influence of nicotine and more distressing when the party’s over (Baker, Brandon, & Chassin, 2004; Baker, Piper, et al., 2004).

Smoking rapidly introduces new motivational processes into adolescents’ daily experience. Withdrawal symptoms begin to emerge early in the smoking career, and susceptibility to withdrawal may be an important determinant impediment to cessation even among adolescents (Prokhorov et al., 2001; Rojas, Killen, Haydel, & Robinson, 1998). Craving to smoke emerges early, and is the most prevalent withdrawal symptom endorsed by adolescent smokers (Prokhorov et al., 2001; Riedel, Robinson, Klesges, & McLain-Allen, 2003; Rojas et al., 1998). Negative affect may be a particularly salient instigator of smoking early in the smoking career. Negative affect is a much more prominent part of daily life in adolescence than in adulthood (Whalen, Jamner, Henker, & Delfino, 2001). Although adult smokers show little relation between smoking and mood during ongoing smoking, fairly robust linkages between negative moods and smoking behavior are found in adolescents (Henker, Whalen, Jamner, & Delfino, 2002).

Studies of the psychiatric correlates of smoking reveal an interesting disjunction between the adult and adolescent smoking literatures. Externalizing disorders (e.g., conduct disorder, oppositional defiant disorder) and traits (e.g., rebelliousness) are the most consistent and powerful predictors of smoking initiation (Baker et al., 2004; Kassel et al., 2003). Yet these disorders and traits are almost never the focus of study in smoking cessation research; internalizing problems (especially depression) are much more prominent topics of study.

There are several possible explanations for why adolescent researchers focus on externalizing problems but smoking cessation researchers do not. For instance, smoking initiation and persistence may fundamentally different processes with different correlates (Heath & Martin, 1993; Koopmans, Slutske, Heath, Neale, & Boomsma, 1999). Externalizing problems may “mellow” by the age at which smokers present for cessation treatment (e.g., Moffitt, 1993), making an association between externalizing and smoking more difficult for clinicians to detect. Moreover, when externalizing behaviors are present, they may be seen as more clinically urgent, such that smoking takes a diagnostic “back seat”. While such explanations are plausible, we should remain open to another possibility: that externalizing disorders predispose youth to smoking initiation, and then the pharmacologic effects of smoking (and perhaps other substances sampled in adolescence) trigger physiologic adaptations that culminate in spiraling distress (e.g., Koob & LeMoal, 1997; Parrott, 1999). That is, smoking may superimpose internalizing problems on top of pre-existing externalizing tendencies, and these internalizing problems may grow more prominent over a long career of drug use. Smoking cessation researchers may concentrate on dysphoria because this is the natural end state of the externalizing/smoking combination. This idea is clearly speculative and requires longitudinal tests, but drug-provoked modification of brain motivational systems might represent a mechanism that accounts for the broad epidemiologic correlations between externalizing and internalizing forms of psychopathology (Krueger, 1999; Krueger, Caspi, Moffitt, & Silva, 1998).

We should be sensitive to the possibility that smokers’ entire motivational architecture may be profoundly altered across the smoking career. Because most smokers begin to smoke in adolescence, people attempting to quit have little substantial, practical experience living as adults without smoking. Moreover, pharmacologic factors, other residues of dependence (e.g., associative learning, long-lasting neural adaptations) and the sudden need to maintain rigorous self-control may substantially alter smokers’ daily experiences as they move from the relative comfort of ongoing smoking into a quit attempt. These changes may not just be transient nuisances, but rather enduring problems to which the smoker must effortfully adapt. Construing the process of cessation in this way may help us to understand why relapse is so common. Smokers may not simply surrender a narrow behavior; their whole lives may change in unfamiliar ways. As we develop a more nuanced understanding of the ontogeny of smoking motivation, we will be better able to devise effective treatments.

5.3. *Rise of molecular genetic approaches*

Twin studies have demonstrated (1) that smoking is heritable, (2) that there are etiologic linkages between smoking and common comorbid disorders, and (3) that smoking initiation and persistence may differ in their genetic underpinnings (e.g., Heath & Martin, 1993; Koopmans et al., 1999; Swan, Carmelli, & Cardon, 1997; True et al., 1999). This last finding is of interest for relapse research because, given the fact that most smokers want to quit smoking and make occasional quit attempts, “smoking persistence” is likely a proxy for failed cessation. Thus, there may be genetic factors which contribute relatively specifically to risk for relapse (as opposed to liability for smoking experimentation or the development of dependence).

Although twin studies will undoubtedly continue to make important contributions to our theoretical understanding of smoking behavior, they have relatively few practical implications—simply put, knowing that something is heritable cannot change clinical practice unless we know something about how it is inherited and what to do about it. In principle, molecular genetic association studies—which attempt to link particular genotypes to smoking behaviors—are capable of providing such information.

Recent studies suggest that polymorphisms which affect dopamine regulation may moderate craving and affective responses to smoking-related cues (Hutchison, LaChance, Niaura, Bryan, & Smolen, 2002), discriminate successful quitters from relapsers (Lerman et al., 2003), and identify smokers most likely to benefit from nicotine replacement therapy (Yudkin et al., 2004). Studies of genes affecting other major neurotransmitter systems, nicotinic receptors, and nicotine metabolism are likely targets of future research (see Lerman & Niaura, 2002, for a review).

In principle, such studies may ultimately guide the development of innovative pharmacotherapies for smoking. They may also help us to match smokers to tailored treatments, a long-unrealized goal for smoking cessation researchers (Piasecki & Baker, 2001). Of course, attaining these clinical gains will require the identification of replicable gene \times treatment interactions, which may prove elusive. The inherent difficulties of genetic association studies (Sullivan, Eaves, Kendler, & Neale, 2001) and recent experience in the smoking field (Lerman & Swan, 2002; Vandenberg et al., 2002) suggests that there are likely to be many false positives and failures to replicate on the road ahead. Clinical gains will also require that clinicians have at their disposal the means to test smokers' genotypes and the training to make clinical decisions based on the results. For these reasons, it is unlikely that we will witness the adoption of gene-based treatments in the immediate future. Over the long term, however, molecular genetic research may ultimately revolutionize smoking cessation practice and our understanding of the causes of relapse.

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