REVIEWS

DOES NICOTINE WITHDRAWAL AFFECT SMOKING CESSATION? CLINICAL AND THEORETICAL ISSUES[1]

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ABSTRACT

Pharmacological theories of smoking relapse emphasize the role of nicotine withdrawal in the maintenance of smoking behavior and general failure of treatment interventions. In this article, prospective studies are reviewed which examine the relationship of nicotine withdrawal to unsuccessful smoking cessation and relapse. The relative effectiveness of smoking treatments that directly address nicotine withdrawal is also discussed. It is concluded that the research to date does not appear to strongly implicate nicotine withdrawal in adversely affecting smoking cessation or maintenance of abstinence. Some major obstacles to our understanding of the predictive validity of nicotine withdrawal are addressed including: (a) measurement problems, (b) exclusion bias, and (c) insufficient research on nicotine withdrawal in certain subgroups of highly nicotine-dependent smokers. Other factors which may account for smoking relapse, including behavioral and psychosocial variables, as well as their possible interaction with nicotine withdrawal, are also considered. Recommendations for further research are offered.

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INTRODUCTION

The high frequency of relapse following treatment for smoking as well as other addictive behaviors continues to be an important and intriguing issue facing clinicians and researchers alike (1–4). Generally, less than one-third of those who enter even the most comprehensive, sophisticated, and efficacious smoking treatments maintain abstinence at one-year follow-up (4,5). Not surprisingly, these long-term abstinence rates remain somewhat disappointing, especially after 25 years of

aggressive behavioral and pharmacological research attacking this lethal addiction (6–8).

Researchers have attempted to study the factor or factors responsible for these poor treatment outcomes. The role of nicotine withdrawal has received increasing attention (9–11), particularly since the 1988 Surgeon General's Report forcefully implicated nicotine addiction as a primary process in the maintenance of smoking behavior and general failure of treatment interventions (12). Research has now firmly established that nicotine is a potent psychoactive drug which may produce substantial behavioral and physiological dependence (12). The classic indicators of physiological dependence include the development of drug tolerance and the presence of distressing symptoms during smoking reduction or abstinence (13).

The majority of smokers meet diagnostic criteria for nicotine dependence, including the development of symptoms during periods of smoking abstinence (14,15). For example, the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* Substance Use Disorders Work Group found that 64% of 829 smokers reported both tolerance and withdrawal (i.e. symptoms or relief) (13). From a clinical standpoint, smokers often attribute their failure to quit or maintain abstinence to unpleasant withdrawal-type symptoms (16,17). Indeed, individuals may tend to self-regulate levels of nicotine to suppress or to avoid feelings of anxiety and other symptoms (18).

Traditional, pharmacological-based theories of smoking relapse emphasize the significance of physiological dependence in the maintenance of smoking behavior and general failure of treatment interventions (12,19–23). Although the need to avoid or reverse withdrawal symptoms is only one of the complex mechanisms which may serve to maintain smoking behavior, these theories assume that nicotine withdrawal is a primary reason why individuals persist in their smoking behavior and are relatively unsuccessful in their smoking cessation attempts (12,19–23). The study of nicotine withdrawal is thus important because it is a hypothesized mechanism by which physiological dependence can affect relapse to smoking. Relatedly, the underlying basis for the benefits of nicotine replacement therapies is the mitigation of withdrawal symptoms (11,24).

In this article, we review prospective studies which examine the relationship of nicotine withdrawal to unsuccessful smoking cessation and relapse. Potential studies were identified through computer searches of Index Medicus and Psychological Abstracts. Studies were chosen if they examined the nicotine

withdrawal/smoking cessation relationship in human smokers; both self- and clinic-quitters were included. Only English language studies were included. Studies were excluded if they contained only retrospective reports of withdrawal symptoms or smoking relapses. In this review, the relative effectiveness of smoking cessation treatments that directly address nicotine withdrawal are also summarized. Furthermore, some major obstacles to our understanding of the predictive validity of nicotine withdrawal in smoking cessation and relapse are addressed. Finally, other factors which may account for smoking relapse, including behavioral and psychosocial variables, as well as their possible interaction with nicotine withdrawal, are considered.

RELATIONSHIP OF NICOTINE WITHDRAWAL TO UNSUCCESSFUL SMOKING CESSATION AND RELAPSE

Although researchers have used differing indicators to define a withdrawal syndrome, the results are generally consistent with the American Psychiatric Association *DSM-IV* definition of nicotine withdrawal (15). The eight withdrawal indicators which are included in the *DSM-IV* diagnostic classification are: anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain; irritability, frustration, or anger; insomnia; and dysphoric or depressed mood. The *DSM-IV* recommends that the presence of nicotine withdrawal be determined in an individual reporting or observed to have four or more of the eight indicators.

Until recently, most of the research examining the relationship between nicotine withdrawal and smoking cessation/ relapse has been retrospective. These studies generally indicate that severity of withdrawal is not consistently associated with failure to maintain smoking abstinence (e.g. 16,25,26). Although these reports provide potentially useful information, the findings are difficult to interpret given the inherent problems of selective recall, the causal linking of unrelated events, and possible reverse causation (27). For example, one study (28) examined gender differences in reported withdrawal severity assessed both retrospectively and prospectively. Withdrawal severity was found to be similar for both genders when assessed prospectively but different when measured retrospectively, with females reporting more symptomatology than males.

The clinical significance of nicotine withdrawal can be evaluated prospectively by testing whether severity of withdrawal predicts smoking cessation and relapse. In Table 1, the results of 15 prospective studies which examined this relationship are summarized (27,29–42). For each study, information is provided on the subjects, withdrawal predictor variables, dependent variables (i.e. smoking outcome), and results. The findings are presented with respect to short-term smoking outcomes (≤ three months), long-term abstinence (six to twelve months), or both short- and long-term success.

Overall, the findings are highly equivocal; neither individual withdrawal symptoms nor total withdrawal frequency and severity scores are consistently related to unsuccessful smoking cessation and/or relapse. Of the 15 studies reviewed, less than half ($N = 6$) reported that withdrawal symptoms were related to either failure to maintain initial cessation or to long-term smoking relapse. The overall findings are discussed below with respect to the time period in which smoking cessation outcomes were assessed. Some studies in Table 1 are discussed in further detail to illustrate particular findings.

Short-Term Outcomes

Eight studies determined the relationship of nicotine withdrawal to short-term smoking cessation; all involved smokers attending a smoking clinic (27,29–35). Most of these studies measured smoking status within the first month postcessation and some included a three-month follow-up assessment. Half of these investigations revealed that withdrawal severity predicted a lower rate of initial cessation or was associated with smoking relapse (29,30,33,35). In a study which included 36 smokers, symptoms of depression, craving, and difficulty concentrating experienced during the first week of abstinence exerted a negative effect on smoking cessation at the one-month follow-up (29). Gunn (30) further showed that both intensity of withdrawal and craving during abstinence was related to smoking relapse at the end of treatment and at three-month follow-up in females, but not males. It is noteworthy that these four reports showing more immediate treatment outcomes comprise the majority of the six studies included in Table 1 that found a positive relationship between nicotine withdrawal and unsuccessful smoking cessation.

On the other hand, some negative findings were reported. Among 50 smokers, Hughes and Hatsukami (31) observed that severe withdrawal scores during the first two days of abstinence did not predict a lower rate of smoking cessation at the four-day follow-up. West et al. (35) found that although withdrawal intensity was related to relapse at weeks two and three postcessation, it was not predictive of smoking status at week four. Moreover, one study assessed withdrawal and smoking status on a weekly basis for twelve weeks postcessation and found that withdrawal scores were unrelated to relapse at any assessment period (27).

Long-Term Outcomes

Three reports focused on smoking status at six months to one year postcessation; all subjects were clinic-quitters (36–38). Persico (37) found that withdrawal intensity and sleep disturbances were predictive of relapse to smoking at the six-month follow-up. However, the two remaining studies showed no relationship between nicotine withdrawal and smoking relapse.

Short- and Long-Term Outcomes

Four studies included both short- and long-term treatment outcomes when evaluating the association of nicotine withdrawal to unsuccessful smoking cessation (39–42). The follow-up periods for determination of smoking status ranged from two days to twelve months postcessation. Two of the studies involved self-quitters as opposed to clinic-quitters (39,40). It has been suggested that such research is potentially important as self-quitters are a larger, more representative, and untreated sample (43). For instance, several interventions (e.g. relaxation) provided in smoking programs may influence abstinence symptoms.

Overall, only one of the four studies showed that withdrawal was related to failure to achieve abstinence from smoking. Among 544 self-quitters, relapsers reported significantly more withdrawal severity than those who were abstinent at the one-, six-, and twelve-month follow-up time points (39). Conversely, Hughes (40) studied 630 self-quitters and reported that except for depression, neither individual withdrawal symptoms nor mean withdrawal severity were associated with relapse across follow-ups spanning seven days to six months. Kenford et al. (42) further observed that withdrawal severity was unrelated to smoking cessation at posttreatment or six-month fol-

TABLE 1

Relationship of Nicotine Withdrawal to Unsuccessful Smoking Cessation and Relapse

Author (reference #)	Subjects	Withdrawal Predictor Variables	Dependent Variable	Results
Short-Term Outcomes				
Covey et al. (29)	36 clinic clients	Ind'l WD symptoms (including depression) + mean WD intensity during first week postcessation	Smoking status at four-week follow-up	Depression, craving, concentration + mean WD intensity showed a significant negative effect on tx outcome
Gunn (30)	285 clinic clients	Mean WD intensity score + craving during first two to five weeks postcessation	Smoking status at posttx and three-month follow-up	Intensity of withdrawal + craving related to relapse at both time periods for females, but not for males
Hall et al. (27)	68 clinic clients	Weekly total WD score	Smoking status during first twelve weeks posttx	Relapse unrelated to WD scores obtained during week prior to follow-up
Hughes and Hatsukami (31)	50 clinic clients	Total WD score	Smoking status at four-day follow-up	Severe WD scores during first two days of abstinence did not predict a lower rate of smoking cessation
Norregaard et al. (32)	289 clinic clients	Ind'l WD symptoms (including depression) during first three weeks after quitting	Smoking status at three and six weeks, and three-month follow-up	Weight gain predicted abstinence
Robinson et al. (33)	54 clinic clients	Mean WD intensity during first 24 and 48 hours + one-week postquit	Smoking status at one- and two-week follow-ups	Regardless of tx group (buspirone vs. placebo), WD intensity predicted relapse
Stitzer and Gross (34)	9 clinic clients	Ind'l WD symptoms (including depression)	Smoking status at ten-week follow-up	No significant difference between relapsers vs. non-relapsers in WD scores at 24 hours postcessation
West et al. (35)	227 clinic clients	Ind'l WD symptoms (including depression) + mean WD intensity	Smoking status at four weekly follow-ups	Depression + craving during week one predicted relapse at weeks two + three; WD symptoms unrelated to relapse at week four
Long-Term Outcomes				
Hall et al. (36)	255 clinic clients	Weight change at 26 weeks postcessation	Smoking status at 52-week follow-up	Weight gain at week 26 predicted abstinence at week 52
Persico (37)	24 clinic clients	Ind'l WD symptoms + mean WD intensity during first 30-days postquit	Smoking status at six-month follow-up	Mean WD intensity + sleep disturbances predicted relapse to smoking
Swan and Denk (38)	381 clinic clients	Weight change at three-months postcessation	Smoking status at six- and twelve-month follow-ups	Decreases in body weight predicted relapse in males only
Short-Term and Long-Term Outcomes				
Gritz et al. (39)	544 self-quitters	Ind'l WD symptoms (including depression) + mean WD intensity	Smoking status at one, six, and twelve months	Abstainers reported significantly less intense overall WD + craving than relapsers at all follow-ups
Hughes (40)	630 self-quitters	Ind'l WD symptoms (including depression) + total WD score	Smoking status at 7-, 14-, 30-, 90-, and 180-day follow-ups	Ind'l symptoms (except depression) and total WD score did not predict relapse across follow-ups
Hughes et al. (41)	315 clinic clients	Ind'l WD symptoms (including depression) + mean WD intensity	Smoking status at one, six, and twelve months	WD intensity did not predict relapse at any follow-up; weight gain at six months predicted abstinence at twelve months
Kenford et al. (42)	200 clinic clients	Mean WD severity at weeks one and four postcessation	Smoking status at posttx and six-month follow-up	WD severity did not predict unsuccessful smoking cessation or relapse in placebo or active patch tx

Table Notes: Short-Term Outcomes = smoking status at ≤three months; Long-Term Outcomes = smoking status at six to twelve months; WD = withdrawal, Ind'l = individual, tx = treatment.

low-up in clinic subjects treated with either placebo or active nicotine patch therapy.

In summary, there does not appear to be a consistent relationship between severity of nicotine withdrawal and smoking cessation or relapse. When such an association is reported, it has usually been found when assessing short-term, as opposed to long-term, smoking outcomes. Since the average duration of withdrawal symptoms appears to be from three to four weeks (44), it is reasonable that this time period is when withdrawal would most likely affect smoking abstinence. However, even when both short- and long-term outcomes are included in the same study, there is no differential effect of withdrawal on smoking cessation. Furthermore, most of the research has been conducted with smokers attending a smoking clinic. Few studies have included self-quitters, who may represent the majority of smokers attempting cessation.

Role of Individual Withdrawal Symptoms In Smoking Cessation

Although the role of nicotine withdrawal in smoking cessation is debatable, some studies show that specific symptoms are related to unsuccessful smoking cessation or relapse. In particular, considerable attention has focused on the impact of depressed mood during smoking abstinence. Retrospective survey studies of smoking relapse indicate that negative affect states (e.g. frustration, anger, and depression) are cited as precipitants of relapse by a majority of ex-smokers (45). Seven of the 15 prospective studies reviewed in Table 1 attempted to document the validity of depressed mood as a symptom of nicotine withdrawal and to evaluate its relationship to smoking treatment outcomes (29,32,34–36,39,41). This research has yielded inconclusive results. *Depressed mood* is reported to be a valid symptom of nicotine withdrawal (i.e. significantly different during abstinence than during smoking) and to be predictive of unsuccessful smoking cessation and relapse in some studies (29,35,40). For example, one report (40) showed that depressed mood was the only withdrawal symptom associated with failure to remain abstinent across several follow-up periods. However, other research has failed to connect depressed mood with smoking withdrawal, and increases in depressed mood during smoking abstinence are not reliably associated with smoking relapse (32,34,39,41). The duration of abstinence in one of these studies (34) was only 24 hours, which may account for its lack of association.

The role of depressed mood in adversely affecting smoking cessation needs further exploration among smokers with comorbidity of major depression. Clinically depressed smokers report more nicotine withdrawal symptoms when attempting to quit (25) and are more likely to resume smoking following treatment when compared to non-depressed smokers (46,47). Smokers with a history of major depression also tend to report more depressive symptoms when attempting to stop smoking and are less successful in their smoking cessation efforts as compared to smokers without such a history (48,49).

In addition to depressed mood, other withdrawal symptoms have been analyzed for their relation to smoking treatment outcomes. Nine studies shown in Table 1 examined the predictive validity of *craving* in smoking relapse. Four of these reports showed a positive result (29,30,35,39), while the remaining studies failed to find such an association (32,34,37,40,42). Furthermore, eight studies assessed *difficulty concentrating* in relation to smoking treatment outcomes (29,32,34,35,37,39,40,42), with

only one showing a positive association (29). One study assessed *sleep disturbances* and observed that frequent night awakenings triggered relapse to smoking six months following treatment (37). However, other withdrawal indicators including irritability, appetite, heart rate, impatience, restlessness, and anxiety have not been found to be related to unsuccessful smoking cessation or relapse (29,32,34,35,37,39,40,42).

Paradoxical findings have emerged when examining postcessation *weight gain* as a predictor of smoking relapse (27,32,38,41). Weight gain has retrospectively been reported to be a cause of relapse for a substantial number of smokers (50). However, one prospective study (27) revealed that weight gain following smoking treatment predicted abstinence, not relapse, at the 52-week follow-up. Similarly, Hughes et al. (41) found that higher one-year abstinence rates were predicted by postcessation weight gain. One interpretation of these findings is that dieting, and thus depriving oneself of food as well as nicotine, may promote relapse (51,52). Alternatively, subjects who gain weight after stopping smoking and who do not relapse may have prior experience with increased weight, whereas relapsers may lack experience with weight gain (53). For instance, Hall et al. (27) found that subjects who gained the most weight during abstinence also reported greater past maximum weight. Finally, more motivated smokers may ignore weight gain and concentrate on maintaining smoking abstinence (54).

Efficacy of Nicotine Replacement Therapies

A second and related piece of evidence in the determination of whether nicotine withdrawal functionally controls smoking cessation and maintenance of abstinence is the relative success of therapies that directly address nicotine withdrawal in their treatment of smoking. For example, one recently popular smoking intervention is to supplement nicotine after quit dates using different routes of administration, such as nicotine polacrilex gum (55) or, more currently, the extensively marketed and promoted transdermal nicotine patch (56–58).

As a general rule, there appears to be a considerable advantage of those programs taking account of nicotine withdrawal in their treatment, showing differentially higher smoking cessation and maintenance rates with the nicotine patch (57,58) or gum (59–61). Several recent meta-analyses of double-blind, controlled studies have shown that nicotine replacement via the patch (62,63) or gum (64,65) doubles or triples quit rates, especially when paired with psychological or behavioral counseling (63,66). High-dependent smokers, as compared to low-dependent smokers, appear to particularly benefit from transdermal nicotine (56) or nicotine gum (66). However, with either form of replacement therapy, a high rate of relapse is often observed during the initial weeks of treatment (53,57).

The efficacy of nicotine replacement therapies is commonly attributed to withdrawal reduction (11,24). Indeed, nicotine replacement appears to alleviate most, but not all, nicotine withdrawal symptoms. Nicotine gum appears to reduce several withdrawal indicators, including irritability and total withdrawal discomfort; however, reductions in craving and weight gain are less consistent (44,55,61,67). Transdermal nicotine replacement is also effective in attenuating withdrawal discomfort (68). In particular, many studies have consistently shown craving to be reduced by the nicotine patch (57,66,69,70). However, the nicotine patch does not reliably reduce hunger and weight gain (57,58,62). Interestingly, transdermal administration of nicotine does not apparently ameliorate sleep disturbance during with-

drawal and may even increase it since insomnia, somnolence, and abnormal dreaming are commonly reported (62).

While replacement therapies do provide relief from most nicotine withdrawal symptoms, their effectiveness does not appear to be entirely due to this mechanism. As indicated previously, research examining the relationship between severity of nicotine withdrawal and smoking cessation has yielded highly equivocal results. A further observation is that although treatment outcome results for transdermal nicotine replacement therapy are dose-related, withdrawal symptoms are not reduced in a dose-response manner (57). Hughes (24) cited three non-withdrawal mechanisms which could account for the efficacy of nicotine replacement. First, replacement therapies may be effective because of instructional or "expectancy" factors. Second, by making nicotine intake independent of environmental events, replacement therapies could disrupt the pairing of nicotine intake and environmental stimuli and thereby make it easier for abstinent smokers to not smoke in the presence of these events. Third, by maintaining nicotine levels and tolerance, nicotine replacement may make cigarettes less reinforcing and thus prevent a slip from becoming a relapse. A fourth possibility is that smoking while on the patch may overshoot tolerance, leading to nicotine toxicity (6). This would make smoking aversive. Although these hypotheses provide additional explanations for efficacy, it remains to be determined whether they can be considered full alternatives to the withdrawal suppression hypothesis.

Role of Withdrawal in Relapse to Nicotine Versus Other Addictive Drugs

The relatively poor relationship between withdrawal severity and relapse to nicotine does not differ markedly from what has been found for alcohol and other addictive drugs (71). Although it is commonly believed that severity of withdrawal is related to the inability to maintain abstinence from alcohol and drug use, empirical evidence to support this contention is surprisingly weak (3,17,27,72,73). Cappell and LeBlanc (72) reviewed the literature on the role of physiological dependence in alcohol and other drug use and concluded that withdrawal is a sufficient, but not necessary, cause of relapse. A recent study (27) compared the effects of withdrawal symptoms on relapse to alcohol, opiates, and nicotine. For all substances, withdrawal symptoms predicted first drug use following treatment, but only when assessed retrospectively. Alternatively, prospective analyses failed to reveal a link between withdrawal severity and relapse to drug use. Yet, pharmacologic therapies appear to be useful adjuncts in the treatment of alcohol and drug dependence (17,20,74). For instance, naltrexone, an opiate antagonist, has been recently shown to reduce alcohol withdrawal symptoms and to prevent short-term relapse (75). Generally, then, the findings which have emerged in the treatment of nicotine dependence are similar to those observed for other addictive drugs.

In summary, nicotine withdrawal does not appear to be clearly implicated in negatively affecting smoking cessation or abstinence from smoking. But why are these findings not consistent? One possibility is that nicotine withdrawal has not been precisely assessed and documented. Second, as withdrawal symptoms have been linked to unsuccessful smoking cessation and relapse in some studies, perhaps nicotine withdrawal does account for treatment failure in certain individuals, such as highly nicotine-dependent smokers. It is thus useful at this point

to address some major factors that may be associated with the lack of conclusive results in this line of research.

OBSTACLES TO OUR UNDERSTANDING OF THE PREDICTIVE
VALIDITY OF NICOTINE WITHDRAWAL

The following factors are discussed which may have impeded progress in our understanding of the relationship of nicotine withdrawal to unsuccessful smoking cessation and relapse: (a) measurement problems, (b) exclusion bias, and (c) insufficient research on nicotine withdrawal in certain subgroups of highly nicotine-dependent smokers including recovering alcoholics and drug abusers.

Measurement Problems

The inconsistencies in predicting smoking cessation and relapse may be related to how nicotine withdrawal is assessed. In a recent review of the literature on the assessment of nicotine withdrawal, Patten and Martin (76) concluded that widely varying measurement instruments are commonly employed across studies; these instruments are generally characterized by undetermined or relatively unproven reliability and validity. Frequently, only face valid, sometimes single, questions are used when probing subjects for withdrawal symptomatology (e.g. 30,32,37). For instance, depressed mood has typically been assessed by single questionnaire items (e.g. "feel sad") (29,35) even though standardized measures exist for assessing severity of depressive mood (77). Furthermore, only three of the prospective studies in Table 1 included behavioral or observer ratings of nicotine withdrawal (31,40,41). These studies are potentially important to the construct validity (via multi-trait multi-method analysis) and clinical significance of withdrawal symptoms as they provide assessment through an alternative route (43).

A second measurement problem includes the use of total withdrawal scores or factor scores, which may obscure the relationships of individual items to smoking cessation outcomes (e.g. 27,39,42). It may be difficult to capture a potentially volatile set of symptoms with an aggregate score measured over a period of a week or a few days (78). Within each symptom group (i.e. subscale), there is likely to be wide variation in the occurrence and duration of specific symptoms (35). Such variation may be masked by grouping symptoms into general categories (78).

A third issue relates to the timing of assessment of both withdrawal symptoms and smoking status. A high level of precision in the measurement of these variables is critical in any attempt to link withdrawal occurrence and severity to smoking relapse. Unfortunately, as illustrated in Table 1, widely varying intervals have been employed between the assessment of nicotine withdrawal and the evaluation of smoking outcome, ranging from two days to nine months (27,29–42). Moreover, there does not appear to be any consistency across studies as to when and how often withdrawal symptoms are assessed. Thus, the research to date does not allow for the determination as to when nicotine withdrawal most likely affects smoking cessation or relapse, which represents a striking gap in the literature. For example, it is possible that there might be a sudden increase in withdrawal just prior to smoking relapse that could not have been predicted from measures taken the previous week or month.

Future research could address these issues by the systematic manipulation of the timing of nicotine withdrawal and smoking status assessment, using measures that are valid and reliable. An exciting development in the smoking literature is the use of hand-held computers which allow researchers to track daily mood/symptoms as well as smoking status (79,80). These computers have been adapted to both prompt subjects at various times throughout the day and collect and store data (80). Careful self-monitoring of this sort may be useful in detecting transient increases in withdrawal symptoms as well as providing a more exact specification of when withdrawal affects smoking relapse.

A final measurement issue concerns the current research focus on variation in withdrawal severity as a predictor of smoking outcome. Perhaps it may also be important to study variation in smokers' ability to *tolerate* withdrawal discomfort. The inability to endure discomfort may be related to sensitivity of withdrawal and to the likelihood of relapse (81). Along these lines, one study showed that breath-holding (a measure of endurance of physiological discomfort) predicted short-term outcome of a smoking cessation attempt (82). Relatedly, it has been suggested that intolerance of weight gain may be a reason to avoid quitting for some (27,83).

As most smokers report multiple quit attempts before they succeed (20), it is plausible that individuals eventually learn to endure the symptoms of withdrawal. However, some factors may be associated with decreased likelihood to tolerate withdrawal discomfort. In particular, a deficiency in coping responses or a general lack of ability to endure stressful circumstances may heighten sensitivity to nicotine withdrawal (83,84). For example, cardiovascular reactivity to general stressors (85) or to smoking-specific stimuli (3) has been shown to be predictive of short-term smoking relapse. Smokers with psychiatric comorbidity may also be less likely to tolerate withdrawal due to inadequate resources for coping or to a higher level of baseline discomfort (i.e. depressed mood) (86,87). Coping strategies such as relaxation, distraction, or seeking social support may serve to moderate the stress of nicotine withdrawal (80) as well as other drug withdrawal syndromes (87,88). Niaura et al. (3) have suggested that affect induction techniques may be useful for assessing coping responses prior to smoking cessation.

The relative contributions of genetic and environmental influences in smokers' ability to tolerate withdrawal discomfort needs further exploration. It is possible that individual differences in reactivity to nicotine withdrawal and difficulty quitting could be related to biologically-based differences in temperament or personality. For example, Eysenck demonstrated that smokers tend to score higher on his measure of neuroticism than non-smokers (89). According to Eysenck and colleagues (90), neuroticism measures emotional instability and identifies individuals who are prone to psychological distress, unrealistic ideas, excessive cravings or urges, and maladaptive coping responses. Cloninger (91) has advanced a similar aspect of temperament and character known as "harm avoidance." This is viewed as a heritable bias in the inhibition or cessation of behaviors, including pessimistic worry in anticipation of future problems, passive avoidant behaviors (i.e. fear of uncertainty), and rapid fatigability (91). Such aspects of personality or temperament may account for some of the variance in withdrawal severity and/or difficulty in quitting smoking.

Exclusion Bias

A major problem with studies of nicotine withdrawal is that ratings are typically completed only by subjects who have stopped smoking (27,29–42). However, it is possible that smokers with the most severe withdrawal return to smoking and are not included in the analyses (43). Thus, it is conceivable that for these previously excluded and possibly most heavily nicotine-dependent smoking cessation failures, severity of withdrawal may strongly predict unsuccessful smoking cessation and relapse (92). Unfortunately, few studies have independently focused on these high-rate/high nicotine-dependent and continuing smokers (93).

Nicotine Withdrawal in Highly Nicotine-Dependent Smokers

Nicotine dependence has traditionally been assessed through such indicators as cigarettes smoked per day, number of previous quit attempts, and Fagerstrom score (94). Unfortunately, however, there is no universally agreed upon definition of nicotine dependence or method of assessing this construct (94). Despite these limitations, some studies have examined the relationship between severity of nicotine withdrawal and smoking cessation in highly nicotine-dependent smokers. Generally, the findings are inconsistent. Some research indicates that highly dependent smokers may need to be considered differently from a treatment standpoint. Killen et al. (95) demonstrated that heavy smokers had more difficulty with stopping smoking and reported more withdrawal symptoms than did lighter smokers. Furthermore, baseline measures of nicotine dependence, including Fagerstrom score, and serum levels of nicotine and cotinine are often predictive of smoking treatment failure (96).

On the other hand, some findings suggest that highly dependent smokers do not experience more severe withdrawal or more difficulty in quitting smoking than low dependent smokers. For instance, baseline measures of nicotine dependence are only weakly associated with severity of withdrawal ratings during smoking abstinence (39,41). In addition, traditional measures of nicotine dependence have not consistently predicted smoking outcomes. For example, Kenford et al. (42) observed that measures of physiological dependence, including number of cigarettes smoked per day and baseline serum nicotine and cotinine levels, showed no consistent relationship to smoking outcomes in subjects treated with active or placebo patch therapy.

It is apparent that the literature is inconclusive with respect to the relationships between nicotine withdrawal, smoking cessation, and relapse in highly nicotine-dependent smokers. However, little research exists among certain subgroups of highly dependent smokers such as recovering alcoholics/drug abusers and individuals with other psychiatric morbidity (97,98). Most studies of nicotine withdrawal and smoking cessation in general exclude individuals with these conditions (99).

The prevalence of smoking in alcoholics, whether in recovery or not, is substantial, with estimates ranging from 80% to 95% (99). From the perspective of treatment, an even bleaker picture is apparent; these smokers tend to be the most heavily addicted to nicotine and the most resistant to treatment (100). Recovering alcoholics may also tend to experience more severe withdrawal during quit attempts than other smokers. In our smoking treatment program, Project SCRAP (Smoking Cessation for Recovering Alcoholic Persons), symptoms of depres-

sion and emotional withdrawal are commonly reported as significant nicotine reductions are undertaken and are especially prevalent during the postcessation period (101). Perhaps in contrast, however, Hughes (102) observed that smokers with a history of alcohol problems did not have a greater increase in withdrawal symptoms upon cessation than those without such a history. Clearly, further research is needed to clarify whether and how nicotine withdrawal affects smoking cessation and relapse in recovering alcoholics and in those with other substance abuse histories.

In addition to the recovering alcoholic/drug abuser, studies are needed among individuals with other psychiatric morbidity (97). Estimates of smoking prevalence among psychiatric inpatients and outpatients range from 52% to 88% (103). Some studies suggest that psychiatric patients are more highly addicted to nicotine and are less likely to stop smoking than smokers without psychiatric problems (48,49). Despite these findings, there has been little research examining the association between nicotine withdrawal, smoking cessation, and relapse in individuals with psychiatric morbidity (48). The recent accreditation standards from the Joint Commission on the Accreditation of Health Care Organizations (104) offer an opportunity to accelerate research in this area. These standards are intended to restrict smoking to a minimum in hospitals, with the eventual goal of establishing a smoke-free environment. Hospital units including psychiatric and chemical dependency treatment units may no longer provide patients with smoking rooms to continue their use of nicotine. Thus, the relationship of nicotine withdrawal to smoking cessation and relapse could be evaluated in these smokers during hospitalization and following hospital discharge.

In summary, it is possible that for some individuals, smoking cessation and maintenance of abstinence is disrupted by the need to avoid or reverse severe withdrawal discomfort. However, the demonstration of this relationship may be impeded by the relative lack of attention to measurement issues and the exclusion of certain subgroups of highly dependent smokers.

Although attention to these factors is useful for further study, it is clear that the research to date does not strongly implicate nicotine withdrawal in the success or failure of smoking cessation programs. Thus, pharmacological theories which emphasize the role of nicotine withdrawal in the maintenance of smoking behavior appear to play a relatively minor role in smoking cessation and relapse. Paradoxically, the provision of nicotine replacement has a clear advantage in enhancing long-term smoking abstinence rates. Shiffman (105) noted that perhaps nicotine withdrawal is not a direct precipitant of relapse episodes but merely sets the stage for relapse to occur. Nicotine dependence certainly has a pharmacological basis, but it also exists in a particular individual operating in a particular environment (106). Research is therefore needed to evaluate whether and how nicotine withdrawal interacts with other factors, including behavioral and psychosocial variables, in predicting relapse. Accordingly, we now briefly consider behavioral and psychosocial variables which may account for smoking relapse. The reader is referred to several recent review articles for a more extensive discussion of smoking relapse models (3,20,53,92,107).

INTERACTION OF NICOTINE WITHDRAWAL WITH BEHAVIORAL AND PSYCHOSOCIAL VARIABLES IN SMOKING RELAPSE

Behavioral Theories

The various conditioning theories emphasize the role of environmental cues associated with the reinforcing actions of

nicotine as important factors in smoking relapse (108). Nicotine has a variety of pharmacological and behavioral effects that may be directly reinforcing, even in the absence of physiological dependence (109,110). Drug-seeking behavior has been demonstrated for nicotine, alcohol, and other addictive substances in animals using both self-administration and conditioned place preference procedures (106). In humans, the pharmacological rewards of nicotine include a subjective state of pleasure, appetite and weight reduction, and enhancement of certain psychological functions (e.g. concentration) (106,111).

Often stimuli associated with drug self-administration, such as the taste and smell of smoke, may become conditioned phenomena which elicit powerful cues for the urge to smoke (108). The severity and occurrence of withdrawal from nicotine and other addicting drugs is thus a complex interaction of dose and environmental setting (22,88,106). This implies that the sudden absence of the drug is necessary but may not be sufficient to explain the phenomenon of relapse (3,110).

The role of physiological dependence in affecting long-term smoking outcomes is intriguing in that if nicotine withdrawal is a factor in long-term relapse, there must be some mechanism whereby its expression can be preserved over time despite cessation of cigarette smoking or other drug use (72). Wilker (112) explicated such a mechanism for relapse to alcohol and opiate use based on conditioning theory. This theory posits that abstinence symptoms can be classically conditioned to environmental stimuli with which they are repeatedly paired and elicited by those stimuli long after physiological dependence is no longer being maintained by drug administration. Siegel's (113) theory of compensatory conditioned responses is similar in that counterdirectional conditioned responses (i.e. abstinence symptoms) may occur in response to environmental cues that are highly predictive of drug administration. Smoking to relieve conditioned withdrawal is explained in terms of operant conditioning, the withdrawal symptom being a negative reinforcer which is terminated by the resumption of smoking (114). Yet, whether this process accounts for long-term relapse to smoking remains to be determined (3).

Psychosocial Theories

Social learning and cognitive–behavioral based theories emphasize the importance of situational variables and coping responses as factors in relapse to smoking and other addictive drugs (115). Situations posing the highest risk for relapse are those perceived as stressful and in which the individual has inadequate resources to cope with situational demands (83,116). Failure to attempt coping in a high-risk situation is a major cause of smoking relapse (83,116). Likewise, the successful management of high-risk situations is correlated with the number of coping responses attempted (26,45). According to Shiffman (105), perhaps persistent or severe withdrawal symptoms lead, over time, to exhaustion that depletes resources for coping with high-risk situations. Thus, nicotine withdrawal may have an indirect or mediating role in relapse by affecting responsivity to stressors.

For many smokers, negative affective states also represent major obstacles to quitting and serve to trigger relapse among ex-smokers (26,107,117). Generally, retrospective studies have consistently found that negative mood states are the most frequently reported precipitant of relapses across a range of abused substances (118). Individuals who smoke more often in negative affect situations and have poorer skills for managing neg-

ative affect are at increased risk for relapse (84). Thus, to the extent that nicotine is employed to regulate affect, poor outcomes in smoking cessation may reflect a lack of skills for managing affect. It is uncertain whether and how nicotine withdrawal mediates or interacts with negative affect in promoting relapse, as poor mood is also a symptom of nicotine withdrawal (18). Nevertheless, the experience of withdrawal symptoms in a high-risk situation may act in a synergistic manner to dampen an individual's ability to cope and resist relapse (119).

Various social influences such as drug use by family or acquaintances have also been implicated in relapses to smoking, alcohol, and other addictions (20,116). For example, the workplace provides a social context that may reinforce or discourage smoking behavior. Workplace smoking restrictions have exerted a marked effect on reducing employee smoking prevalence and consumption (120). Interestingly, we observed that California workers who stopped smoking when employed in a smoke-free worksite relapsed to smoking when moving to a worksite that had no smoking restrictions (121). A smoke-free environment may serve to promote abstinence by removing cues associated with smoking and/or nicotine withdrawal symptoms.

In summary, smoking cessation and relapse appears to be affected by numerous factors, including behavioral and psychosocial influences. Attention to these variables may be useful in future studies to enhance smoking treatment outcomes. However, further research is needed to confirm the predictive validity of these variables and their possible interaction with nicotine withdrawal in smoking cessation and relapse.

CONCLUSION AND RECOMMENDATIONS

In conclusion, the literature does not strongly implicate nicotine withdrawal in negatively affecting smoking cessation and/or maintenance of abstinence. This appears to be consistent with findings regarding the role of withdrawal in relapse to other substances. This review highlights several factors that may account for the disparate findings regarding the predictive validity of nicotine withdrawal including measurement problems, exclusion bias, and insufficient research on nicotine withdrawal in certain subgroups of highly nicotine-dependent smokers. The literature also indicates that models of smoking relapse should incorporate not only withdrawal predictor variables but also behavioral and psychosocial factors.

This review suggests several directions for further research. First, consistent, methodologically rigorous nicotine withdrawal assessment procedures should be utilized. The self-report instruments that are used to document abstinence effects should be valid and reliable. Observer ratings could also be employed as an alternative assessment mode. In addition, the role of individual withdrawal symptoms in predicting relapse to smoking needs further examination.

A second recommendation is that measures be developed which focus on smokers' ability to tolerate withdrawal symptoms as a predictor or mediator of relapse. Furthermore, biologically-based differences in personality and temperament as well as environmental influences in reactivity to nicotine withdrawal and difficulty quitting need further exploration.

Third, the timing of assessment of both withdrawal symptoms and smoking status must become more refined and consistent. Relapse to smoking should be predicted from withdrawal measures that are assessed in close proximity to the determination of smoking status. This may be facilitated by the use of recent methodologies such as hand-held computers, which allow for the systematic daily tracking of both withdrawal symptoms and smoking status.

Fourth, it is recommended that studies target a variety of smokers and quitters in smoking treatment programs. Research is critically needed to demonstrate relationships between the nicotine withdrawal syndrome and acute and chronic smoking abstinence and relapse in relevant populations of nicotine-dependent smokers, including recovering alcoholics and smokers with psychiatric comorbidity. Further studies are also indicated which examine the role of withdrawal in smoking relapse among self-quitters, who represent the majority of smokers attempting cessation.

A fifth recommendation is that the role of behavioral and psychosocial factors in smoking relapse needs further exploration and confirmation. In particular, models of smoking relapse need to take account of the indirect or mediating effects of nicotine withdrawal on these variables in predicting relapse. Relatedly, little is known regarding the mechanisms that underlie the efficacy of nicotine replacement therapies. Although nicotine withdrawal does not appear to be directly related to unsuccessful smoking cessation, perhaps the attenuation in withdrawal severity produced by these treatments works in an indirect manner by facilitating the use of coping skills in high-risk situations or through some other process.

Finally, findings from these studies must be incorporated into smoking treatment methods that will significantly enhance our success in altering chronic and compulsive patterns of tobacco use, especially in high disease-risk individuals. Specifically, the efficacy of coping skills training and affect regulation therapies as adjuncts to smoking cessation treatment needs further examination. The conclusion that withdrawal severity is unrelated to smoking relapse might imply that pharmacological treatments are unwarranted. However, given the success of pharmacologic therapies in smoking cessation, this is not likely the case. Nevertheless, as with other addictions, the relapse rates for smoking have remained relatively unchanged. This implies that more intensive and innovative interventions may be needed, combining pharmacological, behavioral, and psychosocial methods to enhance long-term smoking abstinence.

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