Pharmacologic and Behavioral Withdrawal From Addictive Drugs

Timothy B. Baker, Sandra J. Japuntich, Joanne M. Hogle, Danielle E. McCarthy, and John J. Curtin

University of Wisconsin-Madison

ABSTRACT—***Recent theories suggest that drug withdrawal does not motivate drug use and relapse. However, data now show that withdrawal produces complex changes over time in at least two symptoms (i.e., negative affect and urges) that are highly predictive of relapse. Evidence suggests that falling levels of the drug in the blood and interruption of the drug self-administration ritual both affect these symptoms. Both of these forms of withdrawal motivate renewed drug use in addicted individuals.***

KEYWORDS—***smoking; tobacco dependence; tobacco withdrawal; drug withdrawal***

Addicts have written powerfully about the "abstinence agony" that occurs when they stop using a drug. For instance, Sigmund Freud described quitting smoking as an "agony beyond human power to bear." One would assume from such accounts that drug withdrawal produces a powerful motive to resume or continue drug use. Indeed, movies and other popular accounts of addiction typically emphasize the role of withdrawal. However, current theoretical models of addiction downplay the role of drug withdrawal in the maintenance of addictive behaviors (Robinson & Berridge, 1993). Such models hold that withdrawal symptoms do not motivate relapse; for example, measures of withdrawal severity do not predict who is likely to relapse. Also, these models assert that withdrawal is brief and, therefore, cannot account for relapse that occurs long after drug use. Finally, these models assert that effective addiction treatments do not work via the suppression of withdrawal symptoms. These theoretical views of drug motivation emphasize incentive or reward processes rather than withdrawal.

Address correspondence to Timothy B. Baker, Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health, 1930 Monroe St. Suite 200, Madison, WI 53711; e-mail: tbb@ctri.medicine.wisc.edu.

In contrast to the claims of recent theories, addicted individuals typically report that withdrawal symptoms motivate them to relapse and that fear of withdrawal causes them to maintain drug use. There is now mounting evidence that the addicted individuals are correct—that withdrawal is a crucial motivator of their drug use. While drug use is no doubt determined by multiple factors, there is compelling evidence that, in the addicted individual, withdrawal potently influences the fluctuating course of drug motivation.

We believe that the motivational impact of withdrawal has been obscured by a failure to assess it sensitively and comprehensively. There are two reasons for this failure. One is that withdrawal is multidimensional, and only some elements, such as urges and negative affect, have motivational relevance. Unless studies focus on these symptoms, the motivational impact of withdrawal may be lost. The second reason is that most previous assessments of withdrawal have not adequately captured its dynamic symptom patterns, which may be both highly complex and persistent. These complex symptom patterns provide important clues regarding the nature and determinants of withdrawal. Withdrawal symptoms appear to reflect the effects of two distinct types of deprivation: deprivation of the drug molecule and deprivation of the drug-use instrumental response (such as injecting a drug or lighting and smoking a cigarette). A reduced level of the drug in the body, or *pharmacologic withdrawal*, results in the escalation of symptoms that has traditionally been labeled withdrawal. However, ceasing drug use also deprives the individual of a behavioral means of regulating or coping with escalating symptoms such as negative affect—in other words, it also causes *behavioral withdrawal*. At the heart of this model is the notion that the self-administration ritual per se quells withdrawal symptoms and that the absence of the ritual will actually exacerbate symptoms because of a disruption in symptom-regulatory processes. In theory, this disruption leads to very persistent and complex symptom profiles because symptoms may arise in response to cues that occur months after

discontinuing drug use. This symptom dysregulation will persist until drug cues lose their associative strength (e.g., via extinction) and/or until the individual acquires a coping response that replaces use of the drug.

COMPONENTS OF WITHDRAWAL

Physical Signs

Previous views of withdrawal have been unduly influenced by characteristics of the physical symptoms of withdrawal. Each class of addictive drug produces a withdrawal syndrome that comprises different sorts of physical signs. For instance, ethanol withdrawal produces tremors, exaggerated reflexive behavior, and sometimes convulsions. Opiate withdrawal produces hypothermia, piloerection (gooseflesh), rhinnorhea (nasal discharge), and diarrhea. These signs all tend to follow the same rise-and-fall pattern after the discontinuation of drug use, with symptoms being largely absent within a couple of weeks after cessation.

Research has shown that these physical signs are not consistently related to drug motivation (e.g., Baker, Piper, McCarthy, Majeskie, & Fiore, 2004), supporting the idea that withdrawal is motivationally inert. However, the motivational irrelevance of these physical signs should not be surprising as they are so dissimilar across different types of drugs. If withdrawal has a motivational influence that is common to all addictive drugs, it seems sensible to look for this influence among the symptoms that are themselves common across drugs. Negative affect and drug urges are such symptoms.

Negative Affect

Many of the symptoms used to characterize withdrawal are, in fact, affective terms such as "irritable," "stressed," "anxious," and "depressed." Robust correlations are observed between measures of withdrawal and mood, and factor-analytic studies have demonstrated that affective items capture much of the reliable variance in withdrawal measures (Piasecki et al., 2000). Experimental manipulations of tobacco withdrawal in the laboratory prompt increases in self-reported and physiological indicators of negative affect (Hogle & Curtin, in press).

A listing of negative mood adjectives does not do justice to the affective consequences of withdrawal. Addicted individuals commonly report that giving up a drug seems like losing a dear friend or experiencing a death of a family member. We believe that this reflects a crucial part of the withdrawal syndrome: a feeling akin to social loss or separation distress. Indeed, at the neuropharmacologic and experiential levels, withdrawal produces effects similar to intense social loss (Panksepp, Herman, Connor, Bishop, & Scott, 1978). However, the relationship with the drug, once lost, can be reinstated at any time.

There is evidence that the emotional distress of withdrawal differs from other withdrawal elements in terms of both its motivational significance and its physiological substrata. For instance, researchers have shown that brain structures associated with the motivational components of the withdrawal syndrome (e.g., negative affect) show different sensitivity to the opioid antagonist, naloxone, than do brain structures associated with the somatic components (Frenois, Cador, Caille, Stinus, & Le Moine, 2002). In addition, research shows that it is the affective and not the somatic signs of withdrawal that are responsible for its motivational effects (Mucha, 1987; Piasecki et al., 2000). In sum, assessment strategies should target the affective elements of the withdrawal syndrome if the intent is to assess drug motivation or relapse vulnerability.

Urge/Craving

An urge may be viewed as the conscious recognition of the desire to use a drug. Since a variety of influences may stimulate such desire and make it available to consciousness, urges are not uniquely related to withdrawal (as negative affect is not uniquely related). However, urge measures appear to be sensitive indices of withdrawal and rise precipitously in response to abstinence (Baker et al., 2004).

There exist both biological and theoretical reasons to distinguish urges from the emotional components of withdrawal. First, urges and withdrawal-related affectivity appear to be associated with different physiologic substrata (e.g., Curtin, McCarthy, Piper, & Baker, 2006). Moreover, urges show different trajectories in response to drug removal and environmental events (McCarthy, Piasecki, Fiore, & Baker, in press). Finally, as we shall review momentarily, urges appear to exert their own distinct motivational influences.

EXTRACTING MEANING FROM COMPLEX WITHDRAWAL PROFILES

As noted earlier, most studies of withdrawal have assumed a standard pattern across time (waveform) for all symptoms and signs. This was used, either implicitly or explicitly, to justify simplistic measurement strategies. Researchers often used only a single measure of peak or average withdrawal, collapsing all symptoms together, to reflect the potentially meaningful information. Interviews with addicted individuals, however, indicate that they experience strong urges and negative affect many weeks after discontinuing drug use. This suggests that withdrawal patterns should be assessed in a more comprehensive manner. Therefore, we measured profiles of withdrawal symptoms, especially urges and negative affect, so as to capture their average elevation, trajectories (e.g., whether symptoms are worsening or improving), rise times (how quickly symptoms increase following abstinence), durations, and reactivity to stressors and environmental events.

Waveforms of urges and affective symptoms show dramatic differences from one person to the next and possess motivational relevance (see Fig. 1; McCarthy, Piasecki et al., in press). When researchers measure withdrawal in a way that captures this variability, strong relations with smoking relapse are obtained. For instance, relapse to smoking is consistently and powerfully

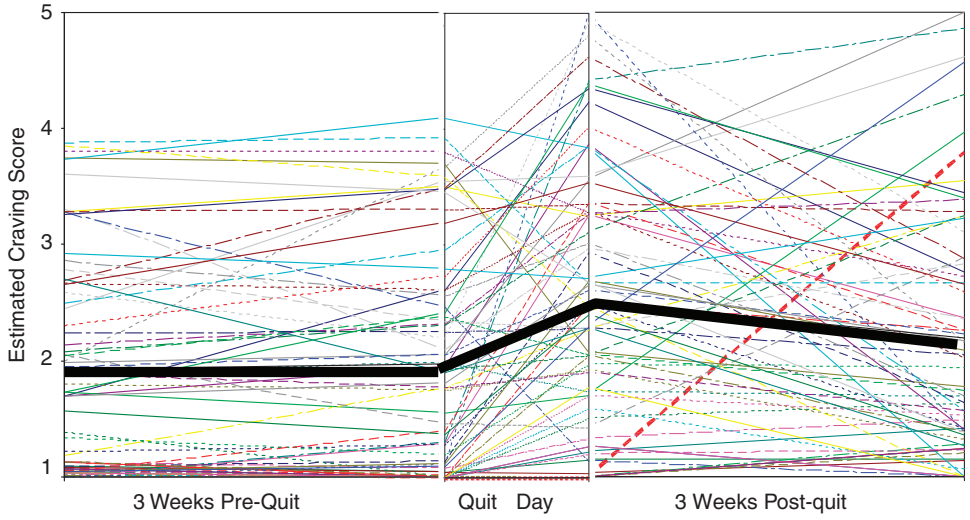

Fig. 1. Estimated cigarette-craving growth curves for 70 adult smokers. Craving ratings were collected multiple times per day for 3 weeks before and after the target quit date. The central panel labeled "Quit Day" reflects the change in craving ratings from just before to just after midnight on the quit day. The heavy black line represents the mean trend in craving ratings across individuals (from McCarthy, Piasecki, Fiore, & Baker, in press).

predicted by such measures as the rise time of craving, the average levels of craving and negative affect, and the duration of high levels of craving and negative affect (Baker et al., 2004). Moreover, such measurement strategies show that withdrawal symptoms are very persistent and predict the occurrence of relapses long after the initiation of the attempt to quit. Finally, these strategies have shown that suppression of withdrawal can indeed account for the therapeutic effects of drug treatments for addiction. For instance, recent studies show that smoking-cessation pharmacotherapies reduce relapse risk, at least in part, by suppressing negative affect and craving (McCarthy, Bolt, & Baker, in press). In sum, when researchers measure the temporal dynamics of urges and affective withdrawal symptoms, the resulting profiles provide insights into why addicted individuals persist in drug use and how treatments can help them quit.

WITHDRAWAL AS CONTROL-SYSTEM DYSREGULATION

The preceding discussion raises several questions. For instance, what could cause the highly variable and prolonged symptoms that are observed, and should these be considered withdrawal?

Dependent drug users cite affect regulation as a major reason for drug use, and research supports their claims. Addicted individuals have learned through repeated pairings of drug use with withdrawal relief that addictive drugs are extremely effective at quelling the affective distress and urges occasioned by withdrawal (Baker et al., 2004). It is not surprising, then, that when addicts stop using a drug they show evidence of symptom dysregulation. Evidence of symptom dysregulation is found in the prolonged and variable affective and urge symptoms noted earlier (e.g., Piasecki et al., 2000) and in smokers' amplified emotional and urge responses to environmental events (see Fig. 2; McCarthy, Piasecki et al., in press). In addition, laboratory research using both psychophysiological and neuroendocrine responses finds that smokers in withdrawal show disturbed patterns of emotion regulation in response to stressors (Hogle & Curtin, in press).

Thus, both self-report and physiological measures point to withdrawal-induced dysregulation of negative affect (Hogle & Curtin, in press; McCarthy, Piasecki et al., in press). If withdrawal varies in intensity, trajectory, and duration across individuals, is there a common mechanism that accounts for this variability? We believe that prolonged symptom dysregulation following withdrawal occurs because addicted individuals are withdrawn from both the self-administration ritual and from the drug molecule. That is, such individuals experience behavioral withdrawal as well as pharmacologic withdrawal. Pharmacologic withdrawal may be largely responsible for the characteristic rise and fall in withdrawal symptoms that occurs in the 1 to 2 weeks after initial drug abstinence, but we assert that behavioral withdrawal accounts for prolonged symptom persistence, the volatility and variability of symptoms, and exaggerated symptomatic reactivity to environmental events. In theory, the loss of a highly practiced and effective symptomatic control strategy should exert effects that occur again and again over a lengthy post-cessation period: Effects that persist until the organism has acquired new regulatory strategies or until once-evocative stimuli (e.g., drug cues) no longer elicit withdrawal responses. The organism may attempt to use nondrug coping strategies in response to symptomatic distress, but lack of practice may lead to inadequate affect regulation as compared to drug use.

The absence of a self-administration coping response leads to dysregulated symptomatic expression for several reasons. First, the lack of the drug per se leaves pharmacologic withdrawal

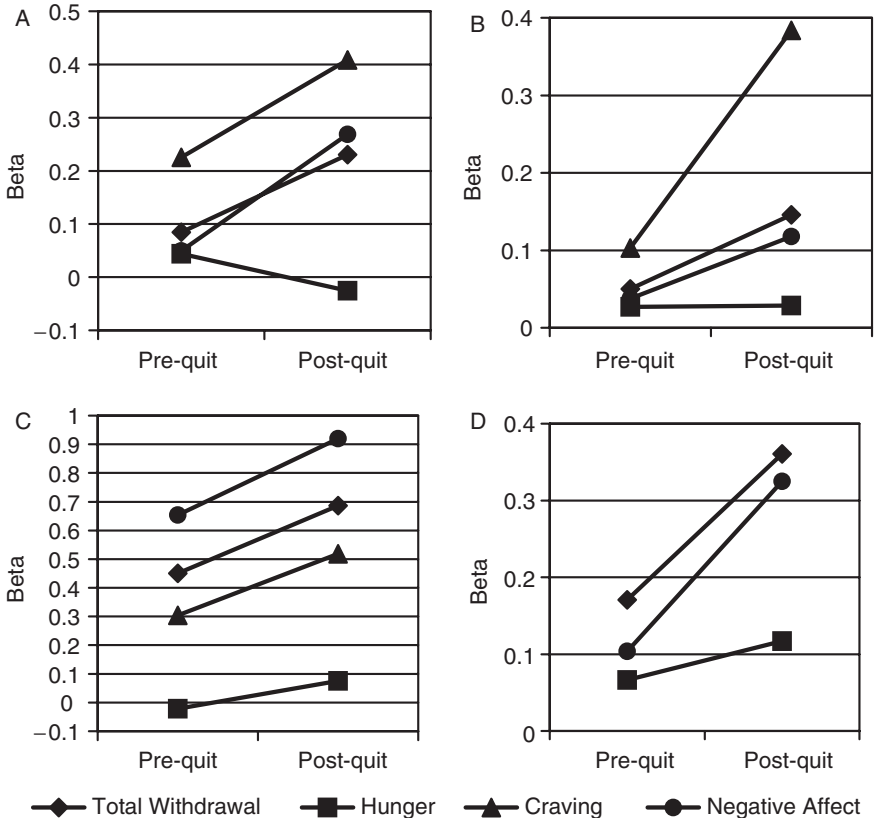

Fig. 2. The degree of association between four episodic events—smoking in the past 15 minutes (A), exposure to others' smoking since the last report (B), occurrence of stressful events since the last report (C), and occurrence of a strong urge or temptation to smoke since the last report (D)—and withdrawal symptoms. Episodic event coefficients (beta values) reflect changes in overall withdrawal summary scores (collapsed across specific symptoms) and hunger, smoking-urge (craving), and negative-affect (sadness, worry, and irritability) ratings associated with each of the events; these were estimated separately in the pre-quit and post-quit periods.

untreated. Second, failure to use the self-administration ritual produces intense response conflict resulting in strong urges, frustration, and feelings of helplessness as the individual fights the urge to use the tried-and-true self-administration ritual (Curtin et al., 2006). Conflict between the well-learned drug-use response and a substitute response should elicit intrusive and effortful cognitive-control processes as well as frustration. Finally, the individual does not benefit from the positive conditioned associations (including anticipatory and placebo effects) that are activated by the ritual (Sayette et al., 2003).

If there is a behavioral withdrawal, there should be evidence that the self-administration ritual per se can suppress withdrawal symptoms in addicted individuals. Indeed, there is evidence that mere practice of the self-administration ritual, without any actual drug delivery, effectively suppresses withdrawal symptoms. For instance, heroin withdrawal is suppressed by injections of saline, and nicotine withdrawal is suppressed by smoking nicotine-free cigarettes (Butschky, Bailey, Henningfield, & Pickworth, 1995). Such effects are remarkably persistent and resistant to extinction. This is consistent with observations that organisms persist in the drug self-administration response long after the response ceases to deliver the drug (Caggiula et al., 2001). We believe this occurs because the self-administration ritual quells distress via learned associations. Consistent with this hypothesis, there is evidence that the self-administration ritual itself activates brain reward and incentive systems (Balfour, 2004). This hypothesis also accounts for the finding that drug replacement (e.g., nicotine patch and methadone) without the self-administration ritual only partially suppresses the drug withdrawal syndrome even with very high drug-replacement doses. The behavioral-withdrawal hypothesis suggests some novel predictions: For example, if the drug is administered without the self-administration ritual (e.g., via passive infusion), withdrawal will be less prolonged, persistent, and variable than it will be if the self-administration ritual is routinely reinforced. This explains the observation that the passive receipt of opiates by hospital patients tends not to lead to intense withdrawal or addiction: Such patients are withdrawn only from the drug, not from a highly ingrained self-administration ritual.

Viewing withdrawal as dysregulation helps to explain the apparently anomalous finding that withdrawal symptoms persist

as long as they do: The addicted individual undergoes behavioral withdrawal each time he or she experiences spikes in negative affect or urges (regardless of the cause) and does not or cannot revert to drug use to cope. This perspective has implications for treatment. For instance, it suggests that pairing drug replacement with the self-administration ritual (e.g., using the nicotine patch and smoking nicotine-free cigarettes) will effectively quell withdrawal distress and promote successful cessation of drug use. In addition, it suggests that addicted individuals might be helped by practicing symptomatic regulation strategies well before they attempt to quit, in order to reduce the intense response conflict that occurs upon cessation.

SUMMARY

Modern theories of addiction motivation suggest that withdrawal is not a potent motivator of drug use and relapse. However, addicted individuals routinely attribute relapse to withdrawal distress. We believe that the motivational role of withdrawal is clear once withdrawal is conceptualized appropriately and accordingly analyzed. First, researchers should focus on a subset of withdrawal symptoms that possess motivational relevance: negative affect and urges. Second, when addicted individuals stop using drugs, they withdraw from both the drug molecule and from the self-administration ritual. Falling levels of the drug in the body certainly produce a rise-and-fall pattern in withdrawal symptoms. However, the absence of the drug self-administration ritual exacerbates negative affect and urges, making such symptoms especially prolonged, volatile, and intense. Research shows that when assessments focus on the motivationally relevant elements of withdrawal and capture the complex patterns of withdrawal over time, withdrawal is indeed an important influence on drug motivation and relapse. Therefore, according to the present model, withdrawal may be defined as response dysregulation that occurs due to decreased levels of the drug in the body and discontinuation of the self-administration response.

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