

Review

Effects of abstinence from tobacco: Valid symptoms and time course

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This article updates a 1990 review of the effects of tobacco abstinence by reviewing (a) which symptoms are valid indicators of tobacco abstinence and (b) the time course of tobacco abstinence symptoms. The author searched several databases to locate more than 3,500 citations on tobacco abstinence effects between 1990 and 2004; 120 of these were used in this review. Data collection and interpretation were based solely on the author's subjective judgments. For brevity, the review does not evaluate craving, hunger, performance, and several other possible outcomes as withdrawal symptoms. Anger, anxiety, depression, difficulty concentrating, impatience, insomnia, and restlessness are valid withdrawal symptoms that peak within the first week and last 2–4 weeks. Constipation, cough, dizziness, increased dreaming, and mouth ulcers may be abstinence effects. Drowsiness, fatigue, and several physical symptoms are not abstinence effects. In conclusion, no major changes are suggested for *DSM-IV* criteria for tobacco/nicotine withdrawal, but some deletions are suggested for *ICD-10* criteria. Future studies need to investigate several possible new symptoms of withdrawal and to define more clearly the time course of symptoms.

Introduction

In 1990, the author and some colleagues published a comprehensive, critical review of scientific studies on the effects of abstinence from tobacco (Hughes, Higgins, & Hatsukami, 1990). The present article updates this review using information from studies published from 1990 through the end of 2004. The article specifically examines the valid symptoms of nicotine withdrawal and their time course. A companion paper reviewed optimal methods for withdrawal studies (Hughes, in press) and another companion paper reviews the etiology, animal models, epidemiology, and significance of tobacco withdrawal.

Since the 1990 review, several review articles on tobacco abstinence effects have discussed theoretical, measurement, and clinical validity issues (American

Psychiatric Association, 2000; Baker, Piper, Fiore, McCarthy, & Majeskie, 2004; Eissenberg, 2004; Hughes, 1994a; Hughes & Hatsukami, 1992; Hughes, Higgins, & Bickel, 1994; Patten & Martin, 1996a, 1996b; Piasecki, Kenford, Smith, Fiore, & Baker, 1997; Shiffman, West, & Gilbert, 2004; Sommesse & Patterson, 1995). In addition, two extended critiques of nicotine dependence have questioned the existence or importance of nicotine withdrawal (Atrens, 2001; Frenk & Dar, 2000). The present review adds to this literature by reviewing a larger dataset of studies in more detail.

Method*Data sources*

The author initially located citations via searches of MEDLINE using two strategies. One used the keywords “nicotine,” “tobacco,” “tobacco use disorder,” and “tobacco use cessation,” crossed with “substance withdrawal syndrome.” The second strategy searched titles and abstracts for the terms or stems “cigarette” “tobacco,” “smok-,” “nicotin-,”

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and “withdrawal.” Similar searches were conducted with PsycInfo, EMBASE, SSCI, and the Centers for Disease Control and Prevention Tobacco Information and Prevention Database. The author also asked for publications from subscribers to the Society for Research on Nicotine and Tobacco (SRNT) e-mail list and from authors of relevant abstracts at recent SRNT, College on Problems of Drug Dependence, National/World Congresses on Tobacco or Health, and Society for Behavioral Medicine meetings.

Study selection and synthesis

The present review includes only published or in press articles because most abstracts do not provide sufficient detail to evaluate their rigor. Also, the published literature appeared to provide sufficient articles to address the major questions. This method may have introduced publication bias (D. J. Cook et al., 1993) but does promote “best evidence synthesis,” i.e., the weighting of evidence based on the methodological rigor of the study producing the evidence (Slavin, 1995). Other criteria were that the study had to (a) describe a prospective study, (b) add new information not covered in the prior review, and (c) involve more than 18 hr of abstinence. This last inclusion criterion was used because it is unclear whether overnight abstinence represents sufficient time to elicit withdrawal symptoms (Hughes, in press). This review examines studies involving only cigarettes because withdrawal appears to be more likely from stopping cigarettes than from other forms of tobacco or nicotine (Hughes et al., 1990).

Finally, the article reviews only studies of the following ten symptoms: Anger/irritability/frustration, anxiety, depression, difficulty concentrating, drowsiness, fatigue, impatience, insomnia, physical symptoms, and restlessness. The article does not review craving (Abrams, 2000; Sayette, 2000; Shiffman, 2000; Tiffany, Carter, & Singleton, 2000), delirium (Mayer et al., 2001), drug use (Carmelli, Swan, & Robinette, 1993; Kos, Hasenfrantz, & Battig, 2005; Murray, Cribbie, Istvan, & Barnes, 2002; Swanson, Lee, & Hopp, 1994), medication levels (Desai, Seabolt, & Jann, 2001; Swanson et al., 1994; Zevin & Benowitz, 1999), pain (Hughes et al., 1990), neonatal withdrawal (Godding et al., 2004), performance effects (Heishman, 2002; Heishman, Taylor, & Henningfield, 1994; Kassel, 1997; Levin, 1992; Levin & Simon, 1998; Rezvani & Levin, 2001; Sherwood, 1993), physiological changes associated with behavioral changes (e.g., brain imaging or neurochemical changes; Gilbert et al., 1999), the precipitation of psychiatric disorders (Glassman, Covey, Stetner, & Rivelli, 2001; Kalman, 1998), or weight gain/hunger/eating (Froom, Melamed, &

Benbassat, 1998; Perkins, 1993, 1994; Varner, 1999; K. D. Ward, Klesges, & Vander Weg, 2001). These outcomes were not included because (a) many of them have been summarized in prior excellent reviews (see above citations), (b) many have literatures spanning thousands of articles each and to comprehensively review each would warrant separate review papers, (c) factor analyses suggest the symptoms included in the present review are correlated with each other but not with the excluded symptoms (Hughes, in press), and (d) the incidence and time course of the excluded symptoms appear to differ from those included; for example, see reviews of craving (Sayette, 2000; Tiffany, 1990; Tiffany et al., 2000), hunger (Froom et al., 1998; Perkins, 1993; Varner, 1999; K. D. Ward, Klesges et al., 2001), and performance (Heishman, 2002; Heishman et al., 1994; Kassel, 1997; Levin, 1992; Sherwood, 1993).

The present article also does not review changes in cardiovascular risk factors (U.S. Department of Health and Human Services, 1990), long-term (i.e., more than 6 months) behavioral changes (Chassin, Presson, Sherman, & Kim, 2002; Hughes et al., 1990; Mayer et al., 2001; U.S. Department of Health and Human Services, 1990), the similarities and differences between nicotine and other drug withdrawal syndromes (Hughes et al., 1994), the relationship of nicotine withdrawal and nicotine dependence (Cottler et al., 1995), nor the ability of medications (Hughes & Glaser, 1993; Jorenby, 2002; R. West & Shiffman, 2001) or behavioral therapies (Brown et al., 2001; Levin et al., 1993; Ussher, West, McEwen, Taylor, & Steptoe, 2003; White, Resch, & Ernst, 1998) to reduce withdrawal. The review also does not cover several specific questions often asked about withdrawal states, for example, whether withdrawal and tolerance covary, acute physical dependence occurs, withdrawal is cross-tolerant with other withdrawal syndromes, gradual reduction reduces withdrawal, conditioned stimuli can elicit withdrawal, and the like (Hughes et al., 1994). These exclusions were necessary to conform to usual page limitations of journals. Information on these issues can be obtained by contacting the author.

The study selection methods described here resulted in more than 3,500 citations. From these, the author read 792 abstracts that appeared to meet the specified criteria. From these, the author selected 290 articles that appeared to be relevant to read, of which 120 are cited in the present review.

Data extraction and synthesis

The author’s subjective opinion of the methodological rigor of the studies, consistency of results across studies, and magnitude of effects were used to choose which results to include. The prior review concluded

that the evidence was sufficient to state that anger/irritability/frustration, anxiety, difficulty concentrating, insomnia, impatience, and restlessness are valid withdrawal symptoms; thus, for these symptoms, the current review reports only studies after 1990 to determine whether they contradicted the conclusions of the 1990 review. In contrast, the 1990 review did not come to a clear decision on the validity of depression, drowsiness, fatigue, and physical symptoms; thus, for these symptoms, the present review examines all studies, both prior to and since the 1990 review.

Results

Description of abstinence effects

Methodological issues in measuring abstinence effects have been reviewed elsewhere (Colby, Tiffany, Shiffman, & Niaura, 2000; Eissenberg, 2004; Hughes & Hatsukami, 1998; Patten & Martin, 1996a, 1996b; R. West & Gossop, 1994) including the SRNT paper on this subject (Shiffman et al., 2004) and the companion paper by this author (Hughes, in press). These issues are not repeated here. The sections below describe the available evidence on (a) whether abstinence from cigarettes reliably increases a behavioral symptom across

studies, (b) whether the effect is an offset, a withdrawal, or an indefinite effect (Hughes et al., 1990), and (c) whether the time course is known. An offset effect was defined as a unidirectional change after abstinence (Hughes, in press). A withdrawal effect was defined as a biphasic transient change after abstinence. An indefinite effect was said to occur when too little data were available to make this distinction. For the reasons outlined in the methodological reviews mentioned above, this review examined only prospective studies and required preabstinence values to determine valid abstinence effects.

Among the prospective studies reviewed, only 15 comprehensive, experimental studies had adequate methodology and tracked several behavioral symptoms at several time points postcessation so that decisions on type of abstinence effect and time course could be determined for each symptom (Table 1; Gilbert, McClernon et al., 1998; Gilbert, McClernon, Rabinovich, Plath, & Masson, 2002; Gritz, Carr, & Marcus, 1991; Gross & Stitzer, 1989; Hatsukami, Dahlgren, Zimmerman, & Hughes, 1988; Hatsukami, Hughes, Pickens, & Svikis, 1984; Hatsukami, McBride, Pirie, Hellerstedt, & Lando, 1991; Hillemann, Mohiuddin, Del Core, & Sketch, 1992; Hughes, 1992; Hughes, Gust, Skoog, Keenan, & Fenwick, 1991; Hughes & Hatsukami, 1986; Jorenby

Table 1. Comprehensive prospective studies of individual tobacco withdrawal symptoms.

Study	Sample size	Subjects	Follow-ups (days postquit)	Comments
Gilbert et al. (1998)	30	Male smokers not trying to quit	3, 10, 17, 31	Multiple preabstinence values, low attrition
Gilbert et al. (2002)	53	Female smokers not trying to quit	2, 5, 11, 19, 27	Multiple preabstinence values, low attrition
Gritz et al. (1991)	96	Self-quitters	1, 2, 7, 30, 180, 365	No preabstinence values
Gross & Stitzer (1989)	20	Smokers trying to quit randomized to placebo	7, 14, 21, 28, 35, 42, 49, 56, 63, 70	Detailed, long-term time course
Hatsukami et al. (1988)	11	Smokers not trying to quit	1–5	Comparison with gradual reduction
Hatsukami et al. (1984)	20	Smokers not trying to quit	1–4	Inpatients
Hatsukami et al. (1991)	73	Female smokers trying to quit randomized to no treatment	2, 7, 14, 28	Women with weight concerns
Hillemann et al. (1992)	20	Smokers trying to quit randomized to placebo	1–7	
Hughes (1992)	178	Self-quitters	2, 7, 14, 30, 90, 180	Measured via phone
Hughes et al. (1991)	82	Smokers trying to quit randomized to placebo	1, 4, 26	
Hughes & Hatsukami (1986)	50	Smokers trying to quit randomized to placebo	1, 2, 4	
Jorenby et al. (1996)	105	Smokers trying to quit randomized to placebo	7, 14, 21, 28	Low attrition
Robinson et al. (1992)	27	Smokers trying to quit randomized to placebo	1, 2, 7, 14	
Ward, Swan (2001)	46	Smokers trying to quit randomized to no treatment	1, 2, 3, 7, 14, 21, 28	Nonsmoker control group, detailed analyses
West et al. (1991)	61	Smokers trying to quit randomized to placebo	7, 14, 21, 28	

et al., 1996; Robinson et al., 1992; M. M. Ward, Swan, & Jack, 2001; R. West, Hajek, & McNeill, 1991). Among these 15 studies, all but one had preabstinence values and reported results as changes from preabstinence, most ($n=11$) were published after the prior review, most ($n=11$) examined smokers trying to stop permanently, and most ($n=11$) had several assessments within the first week of abstinence. In the majority of studies ($n=9$), data were obtained from control groups in randomized, controlled trials (RCTs). On the other hand, few studies ($n=2$) had control groups, used generalizable samples ($n=2$), had large (>90) sample sizes ($n=3$), had multiple precessation values ($n=3$), or had low attrition ($n=5$).

This review relies mostly on the results of these 15 more rigorous studies to draw conclusions. A formal meta-analysis was not conducted because of the methodological heterogeneity of studies (Egger, Smith, & Altman, 2001). For example, studies varied in which withdrawal scale they used, when symptoms were measured, whether smokers were trying to stop for good, and the like.

Anger/irritability/frustration. Irritability is one of the most commonly endorsed symptoms when abstaining from drugs of dependence and other reinforcers (Gilbert, Gilbert, & Schultz, 1998; Hughes et al., 1994). Also, nicotine appears to decrease anger in nicotine-naive nonhumans (Redoiat, Oterino, Carrasco, Berry, & Brain, 2000), suggesting abstinence should increase anger. The prior review concluded increased anger-frustration and irritability were true withdrawal effects. Anger has been measured not only via withdrawal scales but also via the anger-hostility scale of the Profile of Mood States (POMS; McNair, Lorr, & Droppelman, 1992). Unfortunately, no recent studies have used available objective measures of anger (Cherek, 1981).

The more rigorous studies since the last review replicated the conclusions of the prior review (Gilbert, McClernon et al., 1998; Gilbert et al., 2002; Hatsukami et al., 1991; Hughes, 1992; Hughes et al., 1991; Jorenby et al., 1996; Robinson et al., 1992; M. M. Ward, Swan et al., 2001; R. West et al., 1991). All studies suggested anger peaks within the first week (Gilbert, McClernon et al., 1998; Gilbert et al., 2002; Gritz et al., 1991; Hughes, 1992; Hughes et al., 1991; Jorenby et al., 1996; Robinson et al., 1992; M. M. Ward, Swan et al., 2001; R. West et al., 1991). The duration of increased anger is unclear; studies described a duration of 2 weeks (Hatsukami et al., 1991; Hughes, 1992; Hughes et al., 1991; Jorenby et al., 1996; Robinson et al., 1992; M. M. Ward, Swan et al., 2001; Welsch et al., 1999), 3 weeks (R. West et al., 1991), or 4 or more weeks (Gilbert, McClernon et al., 1998; Gilbert et al., 2002). In summary, the evidence still indicates

that anger/irritability/frustration is a withdrawal symptom.

Anxiety. Anxiety is also one of the most common symptoms of drug withdrawal syndromes (Hall, 1984). In addition, some evidence suggests nicotine is an anxiolytic agent (Gilbert, 1996; Kalman, 2002; Kassel, Stroud, & Paronis, 2003). If this is true, it would be reasonable to expect abstinence to increase anxiety. However, other evidence suggests nicotine is an anxiogenic agent; thus, abstinence might be expected to decrease anxiety (Kalman, 2002; Parrott, 2003).

The prior review concluded that anxiety was a true withdrawal symptom. Since the prior review, several studies found anxiety increased in the first 1–3 days postcessation and most reported a duration of about 2 weeks (Gilbert, McClernon et al., 1998; Gilbert et al., 2002; Hughes, 1992; Jorenby et al., 1996; M. M. Ward, Swan et al., 2001). However, one study not included in Table 1 found a decrease in anxiety using two well-validated scales and using only smokers who had been well validated as completely abstinent (R. West & Hajek, 1997). This study hypothesized that prior studies had found increased anxiety because of their inclusion of intermittent smokers who were anxious about going back to smoking. Unfortunately, even though several objective measures are available to measure anxiety in humans (e.g., autonomic functioning, response to carbon dioxide; Zvolensky, Feldner, Leen-Feldner, & McLeish, 2005), tobacco abstinence studies using these measures have not been published. In summary, the weight of the evidence continues to indicate anxiety is a true withdrawal syndrome.

Depression. Depression is a common symptom of drug withdrawal syndromes (Gilbert, Gilbert et al., 1998; Hughes et al., 1994). In fact, some theorists believe negative affect is a core symptom of tobacco and other withdrawal syndromes (Baker et al., 2004; Piasecki et al., 1997). Also, several lines of indirect evidence suggest nicotine has an antidepressant effect (Gilbert, 1996; Hughes et al., 1994); thus, abstinence should increase depression. Other data suggest nicotine could make depression worse (Parrott, 2003); thus, abstinence could improve depression.

The 1990 review concluded it was unclear whether abstinence increased depression; thus, this section includes studies prior to 1990. The present review first looks at studies that examined the symptom of depressed mood or “negative affect” that this article describes as “dysphoria.” Dysphoria was indexed by withdrawal scales and the depression-dejection scale of the POMS. This section then reviews studies of changes in depression scales such as the Beck Depression Inventory (BDI) or Center for

Epidemiological Studies Depression (CES-D) scales. This review does not cover whether abstinence increases the probability of the occurrence of major depressive disorder (MDD). Unfortunately, none of the studies used objective measures of depression (Hughes, Pleasants-Novak, Pickens, & Hatsukami, 1985).

Most of the more rigorous studies in Table 1 reported that dysphoria increased with abstinence (Gilbert, McClernon et al., 1998; Gilbert et al., 2002; Hatsukami et al., 1988; Hatsukami et al., 1984; Jorenby et al., 1996; M. M. Ward, Swan et al., 2001), whereas two early trials did not (Hughes, 1992; Hughes & Hatsukami, 1986). Other well-done trials have (Piasecki, Fiore, & Baker, 1998; R. West et al., 1991) or have not (Brown et al., 2001; Lerman et al., 2004; Levin et al., 1994; Tate, Stanton, Green, & Schmitz, 1996) found increases in dysphoria. In the positive trials, dysphoria showed a transient increase peaking 1 week (Hatsukami et al., 1984; M. M. Ward, Swan et al., 2001), 2 weeks (R. West et al., 1991), or 3 weeks (Jorenby et al., 1996) postcessation. In two other trials, dysphoria remained elevated for 30 days (Gilbert, McClernon et al., 1998; Gilbert et al., 2002). Some negative trials found a decrease in dysphoria postcessation (Brown et al., 2001; Hillemann et al., 1992; Lerman et al., 2004; Levin et al., 1994). Other trials reported that positive affect decreased with cessation (al'Absi, Amunrud, & Wittmers, 2002; J. W. Cook, Spring, McChargue, Borrelli et al., 2004; J. W. Cook, Spring, McChargue, & Hedeker, 2004). Some studies found cessation increased scores on the BDI or CES-D scales (Allen, Hatsukami, & Christianson, 2003; Levin et al., 1994; Pomerleau, Namenek Brouwer, & Pomerleau, 2001), but others did not (Brown et al., 2001; Hall et al., 1996; Kinnunen, Doherty, & Garvey, 1996; Levin et al., 1994). The positive trials found increases that appeared to peak at day 3 (Allen et al., 2003) and 1 week (Levin et al., 1994) in two studies and lasted for at least 2 weeks in a third study (Pomerleau et al., 2001). One study found the CES-D score increased but only in those with a history of MDD (Niaura et al., 1999).

In summary, the evidence that dysphoria is a withdrawal symptom is surprisingly mixed. A comparison of negative and positive studies suggest differences do not appear to be related to measurement scale, being in a treatment setting, level of nicotine dependence, or assignment to a placebo group. However, a history of MDD may predict postcessation depression. Unfortunately, most studies did not present precessation mood measures; thus, whether precessation mood is a moderator is unknown. Overall, the data from the more rigorous trials and the weight of the evidence suggest dysphoria is a true withdrawal symptom, but its

reliability appears to be less than that of other symptoms. The time course of depression needs further clarification.

Difficulty concentrating. Difficulty concentrating is a common drug withdrawal symptom (Gilbert, Gilbert et al., 1998; Hughes et al., 1994). Although evidence suggests nicotine can improve performance in naive nonhumans, nonsmokers, and nondeprived smokers, this conclusion is debatable (Heishman, 2002; Heishman et al., 1994; Kassel, 1997; Levin & Simon, 1998; Rezvani & Levin, 2001; Sherwood, 1993; R. West, 1993). However, if this conclusion is true, abstinence should decrease performance. Self-reports of difficulty concentrating were measured by single-item ratings or by the confusion-bewilderment scale of the POMS (McNair et al., 1992). Other reviews have concluded abstinence impairs performance (Heishman, 2002; Heishman et al., 1994; Kassel, 1997; Levin, 1992; Sherwood, 1993), which may be thought of as an objective measurement of difficulty concentrating.

The prior review concluded abstinence increased difficulty concentrating and this was a withdrawal effect that peaked at 2–3 days and lasted 3–4 weeks. The systematic studies since then have found that difficulty concentration peaked in the first few days (Gilbert, McClernon et al., 1998; Gilbert et al., 2002; Hatsukami et al., 1991; Hillemann et al., 1992; Hughes, 1992; Robinson et al., 1992; M. M. Ward, Swan et al., 2001; R. West et al., 1991); however, the duration of this symptom varied from 1 week or less (Hughes, 1992; Robinson et al., 1992), to 2 weeks (Hatsukami et al., 1991), to 3 weeks (R. West et al., 1991), to 4 weeks or more (Gilbert, McClernon et al., 1998; Gilbert et al., 2002; Hughes et al., 1991; M. M. Ward, Swan et al., 2001). Abstinence induces several different types of performance deficits, the most common being a slowing of simple performance tasks (Heishman, 2002; Heishman et al., 1994; Kassel, 1997; Levin & Simon, 1998; Niaura et al., 1999; Rezvani & Levin, 2001; Sherwood, 1993). In summary, difficulty concentrating appears to be a withdrawal symptom; however, the deficits to which smokers are referring when they report difficulty concentrating and its time course are unclear.

Drowsiness/decreased alertness or arousal. Nicotine is typically classified as a stimulant drug; thus, one would expect that decreased arousal or alertness would occur with cessation. Several prior reviews have described the effects of smoking cessation on objective tests of cognition and performance that could be measures of arousal (Heishman et al., 1994; Kassel, 1997; Levin, 1992; Levin & Simon, 1998; Rezvani & Levin, 2001; Sherwood, 1993; R. West,

1993); however, this review focuses on subjective ratings of arousal and alertness.

The prior review concluded that the effect of abstinence on self-reported drowsiness/alertness could not be stated because of wide variance in study results. As a result, the present article reviews all prior studies, including those examined in the earlier review. Several adjectives appear to overlap with "alertness." This review includes research on "arousal" and "alertness" in this section but not research on "active," "fatigue," and "tired," which are covered in the section on fatigue. This review also does not include scores on the vigor-activity scale of the POMS because the POMS manual describes this as a positive affect scale (McNair et al., 1992).

Among the 15 more comprehensive studies, 2 found that alertness decreased in the first few days but the studies could not determine the time course (Hillemann et al., 1992; M. M. Ward, Swan et al., 2001). Two others found that alertness transiently increased, not decreased (Gilbert, McClernon et al., 1998; Gilbert et al., 2002); three studies found no effect of cessation on alertness (Hatsukami et al., 1984; Hughes et al., 1991; Hughes & Hatsukami, 1986). Among other studies not listed in Table 1, two found that alertness decreased (Levin et al., 1994; Shiffman, Paty, Gnys, Kassel, & Elash, 1995), and several others found no effect (Levin et al., 1994; Prorise, Bonnet, Berry, & Dickel, 1994; Tate et al., 1996; R. J. West, Jarvis, Russell, Carruthers, & Feyerabend, 1984; Weybrew & Stark, 1967).

Three studies have examined objective measures of drowsiness. Two studies examined the prevalence of work and traffic accidents on the United Kingdom's No-Smoking Day. One study found an increased number of accidents (Waters, Jarvis, & Sutton, 1998), but this finding was not replicated in a second study (Knowles, 1999). One study of smoking abstinence found that it decreased sleep latency, suggesting it decreased alertness (Prorise et al., 1994).

In summary, the data on whether decreased alertness is a symptom of tobacco abstinence remains contradictory. One possible explanation is that individuals are poor at reporting alertness. Two of the three objective tests of arousal did show an abstinence effect; thus, further testing using objective measures is indicated.

Fatigue. Fatigue or tiredness is a common symptom in drug withdrawal syndromes. Nicotine appears to decrease fatigue from boring cognitive tasks (Heishman et al., 1994; Kassel, 1997; Levin, 1992; Levin & Simon, 1998; Rezvani & Levin, 2001; Sherwood, 1993; R. West, 1993), but whether nicotine reduces fatigue from muscular efforts or reduces more chronic fatigue has not been well tested. When examining fatigue, some scales do and

some do not distinguish between mental and physical fatigue. This section focuses only on the latter and examines symptoms such as "tired" and "lack of energy." None of the studies used objective measures of fatigue (Hughes, Crow, Jacobs, Mittelmark, & Leon, 1984). The prior review concluded that abstinence does not increase fatigue. Among the four more comprehensive studies conducted since that review, three found no effect of abstinence on fatigue (Gilbert, McClernon et al., 1998; Gilbert et al., 2002; Hughes & Hatsukami, 1986; M. M. Ward, Swan et al., 2001). Thus, fatigue does not appear to be an abstinence effect.

Impatience. Impatience is not commonly used in describing drug withdrawal syndromes (Hughes et al., 1994) and is not included in the *DSM-IV* or *ICD-10* criteria for tobacco or nicotine withdrawal. Impatience usually refers to (a) problems waiting, (b) problems enduring irritation or being annoyed, and (c) restlessness. This would suggest substantial overlap with the symptoms of anger/irritation and restlessness. In the single analysis of the overlap among impatience and restlessness or irritation in abstinent smokers, the three were modestly correlated ($r = .42-.52$; Hughes, 1994a). Other data suggest these are different constructs; for example, the *DSM-IV* diagnosis of attention deficit disorder treats impatience and restlessness as two independent constructs (American Psychiatric Association, 2000).

The prior review concluded impatience was a withdrawal symptom. Only three new studies have presented detailed information on impatience, and all reported a transient increase that lasted 3-4 weeks or more (Gritz et al., 1991; Hatsukami et al., 1991; Jorenby et al., 1996). Thus, although impatience is clearly a true withdrawal symptom, more studies are needed to determine if impatience should be treated as a separate withdrawal symptom or aggregated with restlessness or anger/irritability.

Insomnia. Two lines of evidence suggest tobacco abstinence should worsen sleep. First, insomnia is one of the more common drug withdrawal symptoms (Hughes et al., 1994). Second, smoking is associated with depression (Hughes, 1999), which is associated with insomnia and several specific sleep abnormalities (e.g., rapid eye movement [REM] abnormalities, sleep fragmentation, and deficits in slow wave sleep; Wetter et al., 1999). Since the effect of abstinence on sleep was not completely clear in the last review, this review examines studies both prior to and after the 1990 review. Several studies have examined both self-report and objective measures of insomnia.

This section does not review (a) global reports of insomnia, (b) sleep quantity, (c) sleep quality, (d) sleep latency, (e) sleep duration, or (f) sleep stages.

Instead it focuses only on sleep fragmentation and dreaming (with one exception). This is because (a) the effects of abstinence on the former six symptoms were less consistent, (b) these six sleep problems may be the consequences of sleep fragmentation, (c) a recent qualitative review has examined these sleep effects (Colrain, Trinder, & Swan, 2004), and (d) brevity is required. Readers who wish more detail on the six omitted outcomes may contact the author.

Sleep fragmentation includes awakenings at night, sleep stage shifts, time awake after falling asleep, and the like. The prior review concluded that abstinence increased sleep awakenings but could not conclude whether this was a withdrawal or an offset effect. In more recent sleep EEG studies (Prosise et al., 1994; Wetter et al., 2000; Wetter, Fiore, Baker, & Young, 1995; Wetter et al., 1999) and clinical studies included in Table 1 (Hughes, 1992; Jorenby et al., 1996), cessation and deprivation consistently increased measures of sleep fragmentation, and the effect appeared to be a withdrawal pattern in most (Hughes, 1992; Wetter et al., 2000; Wetter et al., 1995; Wetter et al., 1999), but not all (Hughes, 1992; Jorenby et al., 1996), studies with a duration of 5–14 days.

In the prior review, one study reported increased dreaming but a second did not. Studies since then have reported increased recall of vivid dreams (Hajek & Belcher, 1991; Persico, 1992). In one study, many of these were dreams of smoking; were followed by panic, guilt, or the like; and occurred for several months (Hajek & Belcher, 1991). The type of abstinence effect (withdrawal vs. offset) was unclear. These recalls of increased dreaming may be a byproduct of increased sleep fragmentation because dreaming occurs during REM sleep (i.e., the sleep stage closest to awakening); thus, increased awakening should increase recall of dreams.

Another outcome important to mention is REM sleep latency. Some researchers hypothesize that smokers smoke to self-medicate depression (Gilbert, 1996). This hypothesis would predict that sleep during abstinence should be similar to that of sleep during a MDD (i.e., a shorter time to REM latency; Kupfer, 1976). However, REM studies do not confirm this prediction (Prosise et al., 1994; Wetter et al., 2000; Wetter et al., 1999).

The above conclusions are consistent with those from the recent qualitative review (Colrain et al., 2004). This review also noted that sleep fragmentation from other causes often results in cognitive and affective problems and hypothesized that sleep problems during tobacco abstinence may cause or exacerbate other tobacco abstinence symptoms. In summary, the current review concludes that abstinence causes a specific sleep problem (i.e., sleep fragmentation). Other sleep problems (e.g., increased

dreaming) are hypothesized to be a result of sleep fragmentation. However, empirical data on this hypothesis are lacking.

Physical symptoms. Sometimes withdrawal syndromes induce new physical symptoms (e.g., seizures). The prior review concluded that abstinence had not been found to increase any physical symptoms. Several studies found an increase in composite measures of physical symptoms during the first few days of abstinence (Gilbert et al., 2002; Hatsukami et al., 1991; Hughes et al., 1991), but other studies did not share this finding (Gilbert, McClernon et al., 1998; Hatsukami et al., 1984; Hughes & Hatsukami, 1986; M. M. Ward, Swan et al., 2001).

In terms of individual symptoms, all studies have been negative for headaches (Gross & Stitzer, 1989; Hatsukami et al., 1991; Hughes et al., 1991; Hughes & Hatsukami, 1986; Price, Robins, Helzer, & Cottler, 2005; Ussher, West, Steptoe, & McEwen, 2003; M. M. Ward, Swan et al., 2001), sweating (Gross & Stitzer, 1989; M. M. Ward, Swan et al., 2001), heart racing/palpitations (Gross & Stitzer, 1989; M. M. Ward, Swan et al., 2001), tremor (Gross & Stitzer, 1989; M. M. Ward, Swan et al., 2001), and skin rash (M. M. Ward, Swan et al., 2001). Two studies reported that dizziness had a transient withdrawal pattern (M. M. Ward, Swan et al., 2001; R. West et al., 1991), but another study did not share this finding (Gross & Stitzer, 1989). Although most studies have not found gastrointestinal symptoms (Gross & Stitzer, 1989; Hughes et al., 1991; Hughes & Hatsukami, 1986; M. M. Ward, Swan et al., 2001), one study found a transient increase in nausea (M. M. Ward, Swan et al., 2001) and one study reported increased constipation (Hajek, Gillison, & McRobbie, 2003), which appeared to be an offset effect. This latter finding is plausible given that tobacco initially increases intestinal movement. However, another study did not find this effect on constipation (M. M. Ward, Swan et al., 2001). One study found an increase in mouth ulcers, which appeared to be an offset effect (McRobbie, Hajek, & Gillison, 2004). Again this finding is plausible given that several studies have shown smoking cessation transiently decreases IgA immunoglobulin (associated with oral ulcers; Griesel & Germishuys, 1999; Ussher et al., 2004). However, another study did not find this effect (M. M. Ward, Swan et al., 2001).

Surprisingly, although increased coughing has long been described anecdotally as an abstinence effect, this review could find only one study that examined cough per se in a prospective study. This study did find that cessation increased coughing (Ussher, West, Steptoe et al., 2003). The authors believed this effect was not related to rebound mucociliary action because studies testing ciliary

function have not found it to be influenced by abstinence. One study reported no increase in sore throat (M. M. Ward, Swan et al., 2001), but another reported increased cold symptoms including sore throat, cough, sneezing, and deafness (Ussher, West, Steptoe et al., 2003), but not runny nose, fever, chills, muscle aches, flu symptoms, earache, or fever. Prospective studies using more objective measures (e.g., medical leaves at work, or doctor's visits, in the first weeks postabstinence) could not be found.

In summary, several physical symptoms do not appear to be abstinence effects (dry mouth, headaches, heart racing, skin rash, sweating, and tremor). Other symptoms (constipation, cough, dizziness, and mouth ulcers) were found in some studies but not others. One possible explanation for these contradictory findings is that the studies designed specifically to examine a symptom are more likely to detect the symptom; thus, more carefully designed studies that focus specifically on detecting a symptom are needed, especially tests that use objective measures.

Restlessness. Restlessness is a common symptom of drug abstinence syndromes (Gilbert, Gilbert et al., 1998; Hughes et al., 1994). Nicotine initially increases motor activity in nonhumans, but over time nonhumans develop tolerance to this effect and even show a decrease in motor activity (Stolerman, 1988). Thus abstinence from nicotine should initially increase motor activity. Although some studies have used objective measures (Battig, Kos, & Hasenfratz, 1994); these have examined only overnight abstinence.

The prior review concluded that restlessness reliably occurred with cessation and was a withdrawal effect. Four more recent studies have confirmed this conclusion and report a peak at days 1–3 of abstinence and a duration of 2–4 weeks (Hatsukami et al., 1991; Hughes, 1992; Jorenby et al., 1996), but one study found a duration of 1 week (M. M. Ward, Swan et al., 2001). Finally, as stated above, whether restlessness and impatience should be treated as a single outcome or as two outcomes of withdrawal is unclear. In summary, restlessness is a withdrawal symptom, but more studies are needed to determine whether restlessness should be lumped with impatience or irritability. In addition, objective studies of motor activity in humans during abstinence periods of more than 1 day are needed.

Time course

The time course of the individual symptoms has been described above; however, a somewhat different question is how long the entire syndrome lasts. The prior review indicated the withdrawal syndrome begins within the first 1–2 days, peaks in the first week, and

lasts 3–4 weeks (Hughes et al., 1990). Time course studies since the last review suggest that after about 2 weeks the total withdrawal score is either back to the precessation level or very near to it; if still slightly elevated, the score is back to preabstinence by 3–4 weeks (Hatsukami et al., 1991; Hughes, 1992; Jorenby et al., 1996). Thus the exact duration of the syndrome appears to be unclear. Perhaps the most accurate statement is to say that it lasts 2–4 weeks. Neither this review nor the prior review produced conclusions about the time of onset of tobacco abstinence effects because of the methodological difficulties in distinguishing the onset of withdrawal onset from the offset of acute effects of a given cigarette.

The above studies reported the average time course. Two studies indicated the prototypical pattern, in which withdrawal abates after 2–4 weeks, occurred only in a subset of smokers (Piasecki et al., 1998; Piasecki et al., 2000). For example, in two studies, three different time courses were found, and 38% and 61% of smokers did not have the prototypical pattern. Instead, their symptoms either (a) declined and then increased 3 weeks postabstinence or (b) showed no decline over time. These different trajectories had different correlates and, importantly, conveyed different risks for relapse. Additional analyses also showed that the time course can best be described by specifying “the intercept (mean severity), linear slope (direction and rate), quadratic trend (curvature), volatility (scatter), and among lapsers, a cigarette coefficient (smoking related deflections of symptoms)” (Piasecki, Jorenby, Smith, Fiore, & Baker, 2003, 3).

In summary, despite the wishful thinking by many tobacco advocates that withdrawal is short lived, it is not. However, despite the occurrence of prolonged withdrawal states (i.e., 6 months or more) with many drugs of dependence (Satel, Kosten, Schuckit, & Fischman, 1993), this does not appear to occur with cigarette withdrawal (with the possible exception of craving and hunger; Hughes, 1994b). A recent study (Shiffman et al., 2006) suggests that due to bias in retrospective reports, the above estimates of the duration of withdrawal may be significantly overestimated.

Discussion

Assets and limitations of this review

One asset of the present review is its comprehensiveness. Over 3,500 citations were searched, and 290 articles were read. One liability is that data collection and synthesis were based solely on the author's subjective judgments. This liability is mitigated somewhat by the presubmission circulation of the review to experts in the field (see Acknowledgments). A second liability is the exclusion of craving, hunger,

and performance, which makes this a less-than-comprehensive review. The rationale for these exclusions was described earlier.

Valid symptoms of tobacco abstinence

Based on the above findings, this article proposes four categories of symptoms of tobacco abstinence (Table 2). First, valid withdrawal symptoms from stopping tobacco include anger, anxiety, depression, difficulty concentrating, impatience, insomnia, and restlessness. Second, several symptoms may be abstinence effects but have not been replicated in large studies: constipation, cough, dizziness, increased dreaming, mouth ulcers, nausea, and sore throat. These symptoms are clearly worthy of further study. Third, data are lacking for inclusion of several proposed abstinence symptoms or these symptoms have not been found to be consistent abstinence effects: drowsiness, fatigue, and several physical symptoms. Fourth, several symptoms and behavioral signs not covered in the present review appear to be valid abstinence symptoms based on other reviews: craving (Abrams, 2000; Sayette, 2000; Shiffman, 2000; Tiffany et al., 2000), decreased heart rate (Hughes et al., 1990), electroencephalographic changes (Gilbert et al., 1999), hunger and weight gain (Froom et al., 1998; Perkins, 1993), impaired

cognitive performance (Heishman, 2002; Rezvani & Levin, 2001), increased monoamine oxidase (MAO) levels (Gilbert et al., 2003), and changes in medication levels (Desai et al., 2001). Whether changes in craving, heart rate, electroencephalograms (EEGs), performance, hunger, cognitive performance, and weight gain are withdrawal or offset effects is unclear. Changes in MAO levels and medication levels appear to be offset effects. Two outcomes that could change with tobacco abstinence have not been reviewed by either this or other reviews: (a) alcohol or drug use and (b) delirium. Validity tests of three of the symptoms in Table 2 (depression, drowsiness, and physical symptoms) produced mixed results. Although, for the reasons outlined above, the present review did not conduct a meta-analysis of these symptoms, a random-effects meta-analysis that requires fewer assumptions (Egger et al., 2001) might allow a more firm conclusion about these symptoms.

The above conclusions are consistent with the current *DSM-IV* formulation of nicotine withdrawal (American Psychiatric Association, 2000), with some exceptions (Table 3). One difference is that *DSM-IV* does not include craving. The major rationale for excluding craving is that often craving does not increase postcessation (Hughes, 1994a). The *DSM-IV* also includes the sign of decreased heart rate but not other valid signs probably because they are

Table 2. Summary of findings.

Symptom category	Synonyms or related symptoms	Type of symptom
Valid symptoms covered in this review		
Anger	Irritable, frustrated	Withdrawal
Anxiety	Nervous, tense	Withdrawal
Depression	Dysphoria, depressed mood	Withdrawal
Difficulty concentrating	Confusion	Withdrawal
Impatience	Restlessness	Withdrawal
Insomnia	Awakening at night	Withdrawal
Restlessness	Impatience	Withdrawal
Possibly valid symptoms covered in this review		
Constipation		
Cough	Flu symptoms	
Dizziness		
Increased dreaming	Nightmares	
Mouth ulcers		
Symptoms reviewed but not validated		
Drowsiness	Decreased alertness or arousal	
Fatigue	Tired, less active, less vigor	
Physical symptoms	Dry mouth, flu symptoms, headaches, heart racing, skin rash, sweating, tremor	
Symptoms not reviewed but probably valid		
Craving	Desire, need	Unclear
Decreased heart rate	Bradycardia	Unclear
Electroencephalographic changes	Evoked response	Unclear
Hunger	Increased appetite	Unclear
Impaired performance	Slower task speed, vigilance decrements	Unclear
Increased medication levels		Offset
Monoamine oxidase levels		Offset
Weight gain		Offset
Symptoms not reviewed that may or may not be valid symptoms		
Alcohol/drug use		
Delirium		
Neonatal withdrawal		

Table 3. American Psychiatric Association (*DSM-IV-TR*) and World Health Organization (*ICD-10*) criteria for nicotine or tobacco withdrawal syndrome.

<i>DSM-IV-TR</i> nicotine withdrawal ^a	<i>ICD-10-DCR</i> tobacco withdrawal ^b
Anxiety	Anxiety
Difficulty concentrating	Difficulty in concentrating
Dysphoric or depressed mood	Dysphoric mood
Increased appetite or weight gain	Increased appetite
Insomnia	Insomnia
Irritability, frustration or anger	Irritability or restlessness
Restlessness	—
Decreased heart rate	—
—	Craving for tobacco (or other nicotine-containing products)
—	Increased cough
—	Malaise or weakness
—	Mouth ulceration

Source. American Psychiatric Association (2000); World Health Organization (1993). *Note.* ^aAlso requires “daily use of nicotine for at least several weeks;” that symptoms “cause clinically significant distress or impairment in social, occupational, or other important areas of functioning;” and that “symptoms are not due to a general medical disorder and not better accounted for by a another medical disorder” (American Psychiatric Association, 2000, 266). ^bAlso requires “clear evidence of recent cessation or reduction of tobacco use after repeated, and usually prolonged and/or high dose, use of tobacco” and “tobacco symptoms and signs are not accounted for by a medical disorder unrelated to substance use, and not better accounted for by another mental or behavioural disorder” (World Health Organization, 1993, 58).

harder to measure in a clinical setting. The “Associated Features” section of *DSM-IV* recognizes that abstinence produces “slowing on EEG, decreases in catecholamine and cortisol levels, rapid eye movement (REM) changes, impairment on psychological testing, and decreased metabolic rate, ... increases in the blood levels of ... medications ..., dry or productive cough, decreased heart rate, increased appetite or weight gain ...” (American Psychiatric Association, 2000, 267). The results of the present review and the other reviews cited above are consistent with these findings, with the exception of the data on REM changes.

Results of the present review also are consistent with the *ICD-10* criteria for tobacco withdrawal (World Health Organization, 1993), with some exceptions. The *ICD-10* includes increased cough and mouth ulcers, which the present review states are worthy of further study. The *ICD-10* also includes malaise or weakness. The present review could find no studies of these two symptoms and suggests they be deleted from the *ICD*.

One outstanding issue with the *DSM-IV* and *ICD-10* criteria is how to describe abstinence-induced insomnia. The present review suggests that insomnia induced by abstinence is of a specific type (i.e., increased awakening and accompanying reports of increased dreaming); thus, the present review suggests a *DSM-IV/ICD-10* wording change from “insomnia” to “increased awakenings or intense dreams.” Neither the *DSM-IV* nor *ICD-10* versions include impatience as a criterion. The present review concluded that impatience is a withdrawal symptom but sufficient data could not be located to determine whether impatience should be a separate item, a synonym for restlessness, or a synonym for anger/irritability. To be conservative, the present review suggests impatience

not be added to *DSM-IV* or *ICD-10* as a separate symptom until sufficient evidence indicates it is distinct from other symptoms.

The above conclusions also are similar to those in the only prior review that specified valid versus nonvalid symptoms (i.e., the SRNT review on tobacco abstinence effects; Shiffman et al., 2004), with two exceptions. First, the SRNT review concluded anxiety should not be considered a valid symptom. However, in the present review, the fraction of studies that failed to find an increase in anxiety postcessation was not any greater than the fraction that failed to find an increase in other symptoms. Second, the SRNT review did not include impatience.

Finally, the present review suggests four types of future studies. First, several promising symptoms (i.e., constipation, cough, dizziness, increased dreaming, and mouth ulcers) should be included in all withdrawal studies and scales so that their validity can be evaluated. Second, future studies should determine if impatience should be a symptom by itself or added as a synonym to other symptoms. Third, future studies should determine if all the effects of withdrawal on sleep are related to sleep fragmentation. Fourth, future studies should better describe the time course of withdrawal symptoms.

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