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Conceptual, methodological, and analytical issues in the study of relapse

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Abstract

This article examines conceptual, methodological, and analytic issues in research on relapse to alcohol and other drug use. The review notes the continued move in relapse research from a primary reliance on retrospective assessment of factors surrounding the onset of relapse episodes to an increased focus on the use of new technologies to obtain "near real time" data on proximal factors in relapses. Recent advances in neurobiology have yielded important gains in our understanding of vulnerability to relapse in alcohol and other drug abusers. New statistical techniques are also available to analyze data on relapse. From a theoretical standpoint, there has been an increasing appreciation for the complicated and dynamic interplay of distal and proximal factors in the relapse process. At this point, the strongest and most detailed data on factors in the onset and course of relapse have been generated by studies of smoking relapses that have made use of Ecological Momentary Assessment (EMA) technology. However, there is still limited "near real" time data on proximal factors in alcohol and other drug relapses, and no such data on factors that influence the course of these relapses, once they have begun. Nevertheless, important methodological advances have been and continue to be made in the study of relapse, and our knowledge about the nature and process of relapse has increased considerably over the past 10 years.

Despite advances in the treatment of addictions to alcohol and other drugs, relapse to periods of heavy or uncontrolled use remains a common problem (Donovan, 1996; Witkiewitz & Marlatt, 2004). Even with an increased focus on the prevention of relapse and the improvement of longer-term outcomes, most individuals who seek treatment do not maintain continuous abstinence. For example, in a recent large-scale, multisite comparison of three outpatient treatments for alcoholism, 40% of the participants reported *both* heavy drinking and recurrent problems within 6 months after treatment, and another 19% reported either heavy drinking or recurrent problems at that point (Project MATCH Research Group, 1997). In addition, findings from studies with follow-ups of 2 years or more have indicated that 25–50% of participants moved back and forth between periods of abstinence and heavy drinking or drug use (Dennis, Scott, & Funk, 2003; McKay & Weiss, 2001).

In a review published 6 years ago (McKay, 1999), we examined methodologies used to study relapse in the addictive behaviors. The strengths and weaknesses of three methodological approaches–prospective, retrospective, and near real time assessment–were outlined and discussed, and results obtained with these methodologies were

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compared. The limitations of self-reports of factors in relapse, regardless of how such data are gathered, were also considered. The review concluded that despite their significant differences with regard to strengths and weaknesses, all three methodologies had produced findings that implicated negative affect states, increased craving, diminished motivation, low self-efficacy, interpersonal problems, and lack of coping efforts as factors in relapse. The purpose of this article is to update and extend findings from our earlier review. In doing so, we will focus on three important trends in relapse research over the past 6 years: the increased use of electronic devices to gather data on the relapse process, discoveries from neuroscience regarding vulnerability to relapse, and new statistical methods for the study of relapse.

In order to better evaluate the methodologies that have been used to study relapses in the addictions and the findings that have been generated to date, we will first consider what the "ideal" relapse study might look like. Such a study would be based on a compelling and comprehensive theoretical model of relapse. The influential cognitive–behavioral model of relapse presented in Marlatt and Gordon (1985), and further elaborated in Brownell, Marlatt, Lichtenstein, and Wilson (1986) and updated in Witkiewitz and Marlatt (2004), postulates that one of two processes occurs when a substance abuser encounters a high risk situation, such as negative mood, interpersonal problems, invitations to drink or use drugs, and so forth. If the individual has high self-efficacy, or the belief that he or she can manage the situation without using alcohol or drugs, a coping response is performed and relapse is avoided. However, if the individual has lower self-efficacy, a coping response is not performed and relapse ensues. Therefore, in this model relapse is seen largely as a function of whether one (a) encounters high risk situations, and (b) is able to mount an effective coping response. Other cognitive features of the model include outcome expectancies (i.e., what will happen as a result of either substance use or the exercise of a coping behavior) and attributions for one's behavior.

Over the past 15 years, the cognitive–behavioral model of relapse has been broadened to include enduring personal characteristics, background variables, and life stress, in addition to immediate precipitants and coping responses (Donovan, 1996; Miller, Westerberg, Harris, & Tonigan, 1996; Shiffman, 1989; Sinha, 2001; Witkiewitz & Marlatt, 2004). Recent work has also emphasized biological factors that may moderate risk for relapse, including dysfunction in neurotransmitter systems, deficits in certain brain regions, stress reactivity, and craving (Childress, Ehrman, Rohsenow, Robbins, & O'Brien, 1993; Koob, 2003; Sinha et al., 2003; Volkow et al., 1999). These findings are not incompatible with the cognitive–behavioral model of relapse; rather, they can be seen as complementing that model. For example, the ability of some individuals to mount a successful coping behavior in a high risk situation might be diminished by particularly strong craving or poor impulse control, both of which could be mediated by biological factors. Moreover, recent stressful life events can also reduce one's ability to cope effectively in high risk situations (Sinha, 2001).

However, a comprehensive study of relapse ideally requires an understanding of more than just the etiology of the onset of the episode, as this is only half of the story. Equally important are the factors that influence the course of the episode—for example, whether the episode is short and without serious negative consequences, or spirals into uncontrolled use. To understand course, data are needed on subjective reactions to initial use, coping attempts, beliefs, interpersonal experiences, and biological changes in the minutes, hours and days that follow the onset of use. Moreover, because addiction is a chronic disorder for many individuals (McLellan, Lewis, O'Brien, & Kleber, 2000), relapse episodes are often repeated events and studying within-individual trends over time may be more informative than the study of individual episodes. In this article, we will evaluate how close studies of relapse are getting to the "ideal" relapse study, and identify areas for which good data are still lacking.

At this point, there is still no standard convention on how to define a "relapse" (Maisto, Pollock, Cornelius, Lynch, & Martin, 2003). In many studies, relapse is defined as any use at all after a period of abstinence. However, in some cases, the criteria for relapse has included at least 1 day of "heavy" use (e.g., 5 or more drinks), or a combination of substance use and negative consequences from that use (e.g., missing work, an arrest, interpersonal problems, and so forth). There has also been some debate concerning whether an episode of use represents a "new" relapse or merely the continuation of the prior relapse episode (Miller, 1996). For the purposes of this review, we have labeled any alcohol or drug use in a given period after an intake or baseline assessment as a "relapse". With this definition, relapse is indicated by frequency measures of use that are greater than 0 for a given period (e.g., % days heavy drinking >0) or biological markers of use (e.g., GGT, urine toxicology), as well as by assessments of specific episodes of use (e.g., a first smoking "lapse" after quit date). Using a relatively broad definition such as this makes it possible to include a more diverse group of studies in the review.

1. Distal factors in relapse

Distal, or background factors in relapse are usually thought of as characteristics of the substance abuser and his or her environment that are associated with a heightened vulnerability to relapse at some point in the future (Witkiewitz & Marlatt, 2004). Studies that investigate distal factors use prospective designs, in which variables are assessed at one or more time points, and lagged relations between the putative relapse predictors and substance use status are examined. In these studies, lags have ranged from as short as a few days to 6 months or more. The prospective approach has several strengths. First, participants usually provide information on current or relatively recent thoughts, feelings, and experiences. Therefore, decay of memory over time is not a major issue. Second, self-reports are not influenced by the relapse episode itself, as it has not yet happened at the point at which the data are obtained. However, in most cases it is not possible to ascertain whether the states or conditions that are present at the point of assessment and predict a higher likelihood of subsequent relapse are still present at the onset of the relapse episode. Here, we describe recent prospective studies that make use of self-report data.

One prospective study (Chung, Martin, Winters, & Langenbucher, 2001) investigated the relationship between alcohol subtypes A and B (Babor, de la Funte, Saunders, & Grant, 1992; Babor et al., 1992), coping responses, and 12-month treatment outcome in a sample of 133 alcoholic patients. Coping responses were assessed at baseline, and 6 and 12 month follow-ups, using the Coping Responses Inventory (CRI; Moos, 1993). Results indicated that decreases in cognitive avoidance coping and increased behavioral approach coping predicted better alcohol use outcomes. Patients with Type B alcoholism (i.e., greater impulsivity, hyperactivity, and personality disorders such as antisocial, narcissistic, and borderline) used more avoidance coping than Type A alcoholics, who had lower levels of psychopathology and later onset of alcoholism.

Data from the Collaborative Cocaine Treatment Study (Crits-Christoph et al., 1999) were used to investigate the relationship of cocaine craving in a given week to the likelihood of cocaine use in the following week (Weiss et al., 2003). The longitudinal data were analyzed with generalized estimating equations (GEE) models, which also controlled for cocaine use in the prior week. The analyses indicated that higher levels of craving were strongly predictive of cocaine use in the subsequent week. A second set of analyses indicated that this finding was consistent across three of the four treatment conditions in the study. However, in the condition that demonstrated the best outcomes–individual drug counseling plus group drug counseling–craving scores were not predictive of subsequent cocaine use. These results suggest that this condition was effective in helping patients cope with cravings that did arise.

Several recent prospective studies have used multivariate analytic approaches in an effort to determine the predictor variables that account for unique portions of variance in substance use outcomes. One such study measured motivation, self-efficacy, mood, social support, medical problems, employment, self-help participation, and attendance in treatment at 6, 12, and 18 month follow-ups, and used those data to predict cocaine use in the subsequent 6 month follow-up period (McKay, Merikle, Mulvaney, Weiss, & Koppenhaver, 2001). Results from the multivariate analyses indicated that the strongest and most consistent predictor of subsequent cocaine use was low levels of participation in self-help programs. However, when current cocaine use at the point at which the predictors were assessed was also entered into the model, a slightly different pattern emerged. At 6 months, treatment and self-help participation predicted less cocaine use in the next 6 months. At 12 months, however, employment and higher medical problem severity predicted less cocaine use in the next 6 months, while treatment and self-help were no longer significant. These results suggest that factors outside of treatment may assume greater importance in recovery over time.

Another multivariate study investigated the relation of pre- to post-treatment changes in self-efficacy and coping, and participation in treatment, to alcohol use outcomes at a 12 month follow-up (Maisto, Connors, & Zywiak, 2000). The analyses controlled for patient demographic factors, degree of involvement with alcohol and other drugs, and psychiatric factors. Potential mediation effects were also evaluated. The design of the analyses was guided by the authors' intention to test an overall model of relapse that was based on social learning theory and stress-and-coping research (Maisto et al., 2000). Results indicated that greater involvement with treatment, increases in coping efforts, and increases in self-efficacy predicted fewer drinks per drinking day in months 6–12. Treatment and increases in coping also predicted higher percent days abstinent in months 6–12, and increases in self-efficacy also predicted lower negative consequences from drinking scores at 12 months. However, the mediation analyses indicated that the effect of treatment involvement on subsequent outcomes was not mediated by changes in either coping or self-

efficacy. Moreover, coping effects were not mediated by self-efficacy, contrary to what was predicted by the social learning model (Maisto et al., 2000).

In summary, recent studies of distal factors in relapse that make use of self-report data have yielded findings that are consistent with those reported in our earlier review (McKay, 1999). Specifically, less active coping efforts, lower self-efficacy, craving, and low participation in self-help and treatment all have predicted a greater likelihood of relapse at later points. In addition, the designs of these more recent studies are similar to those used in prior studies, in that the lag between assessment of predictors and substance use or relapse is often around 3 months. Studies that feature shorter lag times, as was the case in the Weiss et al. (2003) study, are relatively rare.

2. Proximal factors in relapse

Rather than determining factors that indicate heightened vulnerability to relapse, studies of proximal factors seek to identify the personal characteristics and experiences that are presumed to have triggered the onset of a *particular* lapse or relapse episode. Therefore, these studies focus on cognitions, beliefs, moods, interpersonal experiences, and other situational factors that are present shortly before or at the onset of a relapse. Until recently, all studies of proximal factors in relapse used retrospective designs. However, new technologies are now available that make possible the "near real time" assessment of circumstances surrounding the onset of relapse.

2.1. Retrospective studies

In retrospective relapse study designs, substance abusers provide data at some point after a relapse episode about factors that contributed to the onset of that relapse. In these studies, the amount of time between the onset of the relapse and the point at which data about it are gathered has ranged from as short as a few days to 6 months or more. The two main advantages of this approach are that it is an easy and relatively inexpensive way to gather data on relapse precipitants and factors that influence the course of relapses once they have begun, and data obtained are often comprehensive and rich in detail (McKay, 1999). However, this approach has serious limitations, including the very real possibility that the occurrence of the relapse itself biases later explanations concerning why it happened, and general decay in the accuracy of memories over time (Hammersley, 1994; Henry, Moffitt, Caspi, Langley, & Silva, 1994; McKay, 1999).

One study retrospectively compared the relapse experiences of cocaine dependent patients with and without Antisocial Personality Disorder (APD), following completion of outpatient treatment (McKay, Alterman, Cacciola, Mulvaney, & O'Brien, 2000). A structured retrospective assessment instrument, the Cocaine Relapse Interview (CRI; McKay, Rutherford, Alterman, & Cacciola, 1996), was used to gather information on experiences during the week prior to first relapse to cocaine use, and initial experiences after the onset of these episodes. The APD and nonAPD patients differed on only one CRI subscale; APD patients reported less interpersonal problems in the week before relapse than nonAPD patients.

A questionnaire designed to retrospectively assess proximal factors in relapse, the Reasons for Drinking Questionnaire (RFDQ), was studied by Zywiak, Connors, Maisto, & Westerberg (1996). A factor analysis of this 16-item questionnaire yielded three factors: negative emotions, social pressure, and craving/cues. In a prospective study, alcoholism treatment clients were contacted every 2 months for a year, and those who had relapsed to drinking in the prior 2 months were asked to complete the RFDQ. Of the 142 clients in the study, 85 relapsed and completed the RFDQ. These first relapses were categorized as negative affect relapses ($n=33$), social pressure relapses ($n=27$), and craving/cued relapses ($n=25$). Almost half the relapses occurred in the first 2 months. Craving/cued relapses occurred only in the first 6 months of the follow-up, whereas negative affect relapses were reported out to 10 months, and social pressure relapses to 12 months (Zywiak, Westerberg, Connors, & Maisto, 2003). As was the case in the McKay, Merikle et al. (2001) study of cocaine relapse, these findings suggest that factors in relapse may change over time.

In our earlier review (McKay, 1999), we described a study by Hodgins, el-Guebaly, and Armstrong (1995) that compared prospective and retrospective reports of substance use relapses. These investigators extended this methodology in a study of precipitants of gambling relapses (Hodgins & el-Guebaly, 2004). Because there are few studies that directly compare these two relapse data collection methodologies, we have included this new study in the review, even though it does not focus on alcohol or drug relapses. In the study, half of the participants were randomly

assigned to be interviewed at 3, 6, and 12 months ("retrospective condition"), whereas the other half were assigned to weekly interviews in addition to the regular follow-ups ("prospective condition"). Overall, the most common reasons given for relapsing to gambling were optimism about winning (23% of relapses), need to make money (17%), and unstructured time/boredom (13%). Therefore, these attributions differed from those offered for drug and alcohol relapses, which are more likely to stress negative emotions and interpersonal stress or pressure (Marlatt & Gordon, 1985; McKay, 1999). However, women were more likely than men to attribute their gambling relapse to negative situations or emotions, whereas men were more likely to attribute relapses to the need to make money and unstructured time/boredom.

Twenty participants provided data on mood and financial pressures in the week prior to a gambling relapse and retrospective reports on the same relapse at the next regular follow-up. On average, the lag in the prospective condition between when a weekly report was obtained and when the relapse occurred was 3–4 days. Agreement between prospective and retrospective reports was very good for active and passive negative mood and financial pressure (ICCs > .65). However, agreement was poor for energetic mood (ICC = .05). Bias analyses on the energetic mood scale indicated that greater depressed mood at the retrospective assessment was associated with greater underreporting of energetic mood prior to relapse in the retrospective report, relative to the prospective report (Hodgins & el-Guebaly, 2004).

In summary, fewer studies of relapse are making use of retrospective self-report methodologies, most likely because of increased concerns about the limitations of this approach, coupled with the availability of new methodologies described later in this article. However, recent work by Hodgins and el-Guebaly (Hodgins & el-Guebaly, 2004; Hodgins et al., 1995) with substance use and gambling relapses suggests that retrospective reports of relapse determinants may be less biased than was thought to be the case, at least under some circumstances and for some factors.

2.2. Near real time studies

Recognizing the limitations of both retrospective and prospective designs for the study of relapse, investigators have been moving toward obtaining data on a more frequent basis. One approach involves the use of daily diaries to record information on current substance use and other factors (Carney, Tennen, Affleck, Del Boca, & Kranzler, 1998). Other studies have used automated telephone-based systems to gather information, in which participants provide answers to pre-recorded questions by entering responses using the keypad buttons on the telephone (Collins, Kashdan, & Gollnisch, 2003; Searles, Helzer, & Walter, 2000). This technology is referred to as Interactive Voice Response (IVR) systems. Finally, hand-held computers that can be programmed to randomly prompt participants to provide information have also been used to study relapse (Shiffman & Stone, 1998), particularly in the area of smoking relapse.

2.2.1. Daily diaries

Daily diaries can be an excellent and relatively inexpensive source of data on substance use, mood, cognitions, behaviors, and experiences. For example, Carney and colleagues examined relations between positive and negative daily events, perceived stress, and alcohol use in a sample of regular drinkers, using the daily diary methodology (Carney, Armeli, Tennen, Affleck, & O'Neil, 2000). Results indicated that participants reported greater desire to drink and more actual consumption of alcohol on days when they also reported more positive and negative nonwork daily events. Conversely, participants reported less consumption on days when they reported more positive and negative health events. Previous work by this group had indicated that daily diaries were more useful for accurately assessing patterns of consumption within individuals than retrospective calendars methods such as the time-line follow-back (Carney et al., 1998).

However, there is evidence that some individuals may complete daily diary entries for multiple days at one point in time, after the fact (Hufford, Stone, Shiffman, Schwartz, & Broderick, 2002). Patterns of recording in daily diaries were examined by having chronic pain patients use special diaries that recorded the date and time that they were opened (Stone et al., 2003). The participants were instructed to open the diaries three times per day, at predetermined times, for 21 days, and record information on current levels of pain and other factors. The participants reported that they had been compliant 90% of the time. However, electronic records generated by the diaries indicated that actual compliance was 11%, and the diaries were not even opened on 32% of study days.

Comparable data are not available on true rates of compliance with daily diaries among substance abusers, but some concern appears warranted.

2.2.2. Interactive voice response

Interactive Voice Response, or IVR, has been used to collect standardized information over the telephone on psychiatric symptoms and substance use outcomes in research studies and clinical trials, and a number of popular assessment instruments have been adapted for delivery via IVR (Mundt, Bohn, King, & Hartley, 2002). Typically, this information is obtained through daily telephone calls. The advantages of IVR over more standard outcomes monitoring include more frequently obtained data, immediate electronic storage of information, the potential for data collection at a distance, and the possibility that participants may be more willing to disclose information on undesirable behaviors to a computer than to an actual person (Mundt et al., 2002).

Researchers at the University of Vermont have conducted a creative series of studies in which IVR has been used to obtain daily reports of alcohol use and other factors over periods of a year or longer. For example, one IVR protocol assessed alcohol consumption, current and highest level of intoxication, alcohol related problems, location of drinking, cigarette use, stress, mood, and health. All questions addressed behavior and experiences over the prior day. For respondents who reported no use of alcohol, questions regarding urge to drink and reasons for not drinking were automatically substituted for questions about intoxication and alcohol related problems (Helzer, Badger, Rose, Mongeon, & Searles, 2002). Initial published findings have indicated that IVR methodology generally yields higher estimates of alcohol use–particularly number of drinks per day–than the retrospective, calendar-based Time Line Follow Back approach (Searles, Helzer, Rose, & Badger, 2002; Searles et al., 2000). Compliance also appears to be very high, with over 93% of calls made on the day they were due (Searles et al., 2002).

The combination of daily assessment of information on substance use and potential relapse triggers, plus the extremely high compliance rate for data collection, strongly suggest that the IVR approach could be extremely useful in studying the process of relapse in the addictions. For example, data on stress, mood, urges to use, and reasons for not using could be used to determine if experiences on a given day raise the likelihood of relapse on the next day. Or, trends over several days–such as steady increases in depression or stress–might be linked to higher relapse risk. This methodology could also look at the process through which a "slip" either does or does not progress into a full-blown relapse. At the same time, there are several potential limitations to the IVR approach. In its present form, IVR is used to collect data on a daily basis. In some cases, the key trigger for a relapse may happen on the same day of the relapse. In those instances, IVR reports provided the next day concerning mood and other factors before the relapse on the prior day may be confounded by the fact that a relapse did occur. It is also not clear to what extent participants can provide accurate information on their status and experiences over the prior 24 h once they have started to relapse.

2.2.3. Ecological momentary assessment

Ecological momentary assessment, or EMA (Shiffman & Stone, 1998), makes use of small, hand-help computers, referred to as "electronic diaries", to obtain data on substance use, internal states, situational factors, and other aspects of experience prior to and during lapses and relapses. With regard to the study of relapse to addictive behavior, EMA has been used primarily with smokers, and many of the studies have been done by Shiffman and colleagues. The primary advantage of this approach over other near real time approaches is the tremendous flexibility in data collection that can be written into the software of the units. For example, participants can be signaled on a random basis to enter data on their current internal states, experiences, and coping behaviors. Moreover, they can enter data while experiencing strong urges to smoke or use substances, and after they have started to use. These data make it possible to examine factors in the days or even hours prior to relapse episodes that differentiate these periods from episodes of temptation that did not result in relapse, and from periods of stable continued abstinence.

A recent study on smoking relapse by Shiffman and Waters (2004) illustrates the power of this methodology. Data on daily stress (i.e., negative and positive events) and negative affect were obtained from electronic diaries. Results indicated that *day-to-day* changes in stress and negative affect did not predict smoking lapses the next day, even when the participant later attributed the lapse to stress or negative affect. However, data collected via electronic diaries indicated that there were significant increases in negative affect in the *hours* before smoking lapses occurred. This intriguing finding strongly suggests that in order to understand the determinants of a particular relapse, it is necessary to obtain accurate data on internal states and experiences very close in time to the onset of the episode.

Shiffman and colleagues have also conducted two other recent studies exploring the role of self-efficacy in smoking relapses. In the first study (Shiffman et al., 2000), self-efficacy was assessed a week before the targeted quit date via a questionnaire, and then repeatedly via electronic diaries over the 4 weeks following smoking cessation. The results indicated that self-efficacy remained high prior to the first smoking lapse, and decreased after that. Although daily self-efficacy did predict the likelihood of a lapse the next day, this relationship was actually accounted for by individual differences in self-efficacy assessed at baseline via the questionnaire. However, daily self-efficacy, assessed via EMA, did predict the likelihood that lapses would progress to full relapses. It should be noted that in this study, both distal (i.e., prior to quit date) and proximal (i.e., daily) measures of self-efficacy were obtained. The results suggest that distal measures of self-efficacy are a good indication of the likelihood of substance use at some point in the future, whereas proximal measures of self-efficacy predict how severe the next episode of use will be.

The second study (Gwaltney et al., 2002) tested whether strength of self-efficacy for specific situations, assessed via questionnaire prior to targeted quit date, predicted the characteristics of smoking lapse situations assessed via electronic diaries. These authors used profile correlations to compare self-efficacy and proximal lapse factors in six areas: negative affect, positive affect, smoking restrictive situations, idle time, social-food situations, and low arousal. The profile correlation coefficient represents the overall degree of agreement between self-efficacy and proximal lapse factors across all six domains. To determine the specificity of these associations, the same analyses were done with temptation situations that did not result in lapses, and randomly selected non-temptation/non-lapse situations. As predicted, there was a significant profile correlation between self-efficacy scores and proximal episode characteristics in the first lapses ($r = .26$). In other words, low self-efficacy for specific situations tended to predict that subsequent lapses would be immediately preceded by those same situations, and not by other situations for which self-efficacy was higher. Similar results were obtained in analyses that examined proximal factors in the onset of multiple lapses after the first lapse, indicating some consistency in proximal relapse factors over time. Conversely, weaker profile correlations were obtained between self-efficacy and proximal episode characteristics for temptations ($r = -.06$) and non-temptation situations ($r = -.17$).

These recent EMA studies of factors in the onset and course of smoking relapses represent extensions of the initial EMA studies done by Shiffman and colleagues in the middle 1990s. These earlier studies showed that smoking lapses were associated with increased urges and negative affect, environments conducive to smoking, and the failure to perform some sort of coping response (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). Furthermore, this earlier research demonstrated that the progression from first smoking lapse to full relapse was influenced by factors such as urge to "give up" attempts to not smoke, degree to which the lapse was precipitated by stress, and coping efforts (Shiffman, Hickcox et al., 1996).

There is still comparatively little application of EMA technology in the study of alcohol or other drug relapses in treatment populations. However, Swendsen et al. (2000) conducted a novel study that investigated the relation between daily mood and drinking in a sample of moderate to heavy drinkers who were not treatment seeking and did not meet DSM-IV criteria for alcohol dependence. The main purpose of the study was to test the "self-medication hypothesis" of alcohol use, which proposes that some individuals drink alcohol to reduce feelings of anxiety and depression. Data on eight mood states and alcohol use were collected multiple times per day via electronic diaries. Analyses indicated that greater anxiety predicted more alcohol use later in the same day, with the result stronger in men than in women. Conversely, higher scores on the "quiet" mood scale predicted less alcohol use. Scores on the "bored" and "sad" mood scales did not predict alcohol use.

2.2.4. Cellular telephones

A recent report (Collins et al., 2003) describes a pilot study that seeks to combine IVR and EMA approaches, capitalizing on complementary strengths of each approach. Participants carried cellular telephones with them at all times for 2 weeks. They were instructed to call in to a computer first thing in the morning, immediately prior to drinking episodes, and after drinking. For each type of call, the computer administered a series of approximately 30 questions that the participants responded to using the keys of the cell phone. The participants also received four random prompts per day on the cell phones. In response to these calls, they called into the computer and answered 28 questions. The content of the questions addressed areas such as mood, activities, social context, presence of others, and location. The questions in the after drinking interview also addressed number of drinks and reasons for drinking. The results of this pilot study were promising. Compliance with the random prompts was excellent (97% completed). However, compliance with the morning interviews was somewhat lower (81% completed). Of the 10 participants,

8 completed 47 before drinking interviews and 44 after drinking interviews; date and time stamping indicated that 35 of these corresponded to the beginning and end of the same episode. The participants averaged 4 drinks per drinking episode, and 42% of the episodes could be classified as "binge drinking" (i.e., 5 or more drinks). The participants reported drinking an average of about 1 drink prior to completing the "before drinking" interview.

A second pilot study has made use of EMA and cell phones to assess proximal factors in crack-cocaine use, temptation to use, and craving episodes (Freedman, Lester, Roth, McNamara, & Milby, 2004). In this study, 30 homeless crack cocaine addicts who were in an IOP program and had achieved at least 1 week of cocaine abstinence were given cell phones and followed for 14 days. During that period, they were called eight times per day, on a random schedule, and prompted to answer questions on current location, associates, activities, mood, and craving. Other questions addressed recent cocaine use or temptation to use, precipitants of these episodes, and coping attempts. The participants answered an average of 5.7 calls per day, and 80% completed the 14 day protocol. Of the 30 participants, 8 reported some cocaine use, 13 reported significant temptation to use, and 23 reported some cocaine craving.

Results indicated that participants who more frequently reported being in high-risk situations or being with a sex partner or prostitute were also more likely to report using cocaine or being tempted to do so. In addition, participants who went from being alone to spending more time with friends and relatives were less likely to report being tempted to use. These two pilot studies are exciting because they suggests that EMA technology can be used to study relapse in alcoholics and "hard core" drug dependent populations. However, further studies are needed with larger samples and longer assessment windows before any more definite conclusions about feasibility can be drawn.

Despite the obvious appeal of computerized, near-real time approaches to data collection, there are many potential problems in applying these methodologies to the study of alcohol and drug relapses. Because of the chaotic nature of many relapses and the relapser's level of intoxication, compliance with prompts to enter data is likely to decline once the relapse begins. Indeed, some relapsers may be too intoxicated to type information accurately into a computer or telephone keypad, or they might lose the computer during the course of the relapse, thereby preventing downloading of data on relapse precipitants.

Even if compliance with the protocol is good in the days leading up to the relapse, results from Shiffman and Waters (2004) suggest that information in the *hours* prior to the relapse may be of particular value. Although initial pilot studies with alcoholics and cocaine addicts have yielded promising results with regard to feasibility, it is not clear whether compliance during the period immediately prior to relapse will be as good in alcohol and other drug abusers as it has been in smokers. Finally, although the frequency with which data are gathered in near real time studies is clearly a major strength of this methodology, the degree to which the data are truly representative of behavior and experiences is not entirely clear. Future studies would benefit from greater consideration of the relative strengths and weaknesses of different experience sampling schedules and strategies.

3. Neurobiological factors in relapse

Explanatory models of relapse that are based primarily on demographic, psychological, behavioral, and environmental factors have been successful in predicting relapse onset, as many of the studies reviewed here have demonstrated. However, large portions of the variance in these models remain unexplained. This may reflect the influence of neurobiological factors on vulnerability to relapse. Over the past 5 years, there have been considerable advances in our understanding of how factors such as neurochemistry, receptor availability, natural reward circuitry, stress reactivity, craving, and attentional bias influence the development of addiction and propensity to relapse. Research in these areas provides potential explanations for why some individuals have stronger craving for alcohol and drugs, or have a more difficult time initiating and sustaining effective coping behaviors when confronted by high risk situations.

Accumulating evidence indicates that the dopamine neurotransmitter system is the fundamental neurobiological substrate of addiction processes. Dysfunction in one or more dopaminergic components (i.e., receptor number or function) and/or in specific brain regions where dopamine is released may increase susceptibility for dependence and probability of relapse. Studies single out the prefrontal cortical area of the brain, and regions functionally and anatomically connected to it, as key players in vulnerability to relapse. However, the neural circuitry underlying addiction processes is far more complex than it may appear from these general statements and we have only begun to understand the role of individual neurotransmitter systems and specific brain regions.

The structures and systems that mediate the maladaptive learning underlying addiction processes are essentially the same as those involved in mediating learned responses to natural reinforcers, such as food or sex. However, the natural reward circuitry is usurped and modified by drugs of abuse (Jentsch & Taylor, 1999; Koob, 2003). A body of evidence suggests that there are two distinct neuroadaptations that increase vulnerability to drug relapse. First, there is a progressive loss of inhibitory control over conditioned or learned associations, which most likely is related to deficiencies in the prefrontal cortex. Second, reminders of drug use become increasingly more salient. Limbic structures such as the amygdala and ventral striatum (nucleus accumbens) are centrally involved in attributing salience to such stimuli.

Frequently, drug users report craving, an intense and overwhelming desire to find and use drug, as the motivating force underlying relapse (Childress et al., 1993; Shiffman et al., 1997). Craving may reflect desire for the euphoric features of alcohol or drugs, or desire to avoid withdrawal. Further, craving may be initiated by stress and/or drug-related cues. These conditioned reminders of drug availability likely engage overlapping, yet distinct neural circuitry. In addition, craving for various psychoactive drugs such as cocaine, heroin, nicotine and alcohol, may recruit different circuitry. Despite these disparities in craving bases and underlying drug-specific neurobiology, addiction researchers generally agree that the neurobiological substrate of craving ultimately converges on one final common pathway.

Human studies imply that low dopamine receptor (DA R) availability in limbic regions may confer biological vulnerability to relapse. Decreased limbic DA R availability predicted a pleasurable response to cocaine-like substances in normal control subjects (Volkow et al., 1999, 2002), and a decreased sensitivity to natural reinforcers (Volkow et al., 2002). Decreased DA R availability was found in cocaine, heroin, alcohol and methamphetamine abusers (Hietala et al., 1994; Volkow et al., 2001, 1996; Wang et al., 1997). One plausible hypothesis is that low DA R availability is a basis for reduced sensitivity to natural rewards, and thus, an increased propensity to depend on pharmacological stimulation to experience reward.

Craving research in humans is rapidly expanding with the emergence of powerful and noninvasive neuroimaging tools. These tools allow a close examination of brain structure, function, and neurochemical composition. The cue reactivity paradigm is most often utilized to unveil the neurocorrelates of cue-induced craving. This paradigm involves exposing drug dependent subjects to stimuli associated with their drug of choice, while assessing neural activation (Breiter & Rosen, 1999; Childress et al., 1999; Garavan et al., 2000). However, neuroimaging is in its infancy, and is therefore fraught with technological and methodological issues that can lead to inconsistencies across studies and across imaging modalities. For example, brain regions that are importantly involved in addiction processes, such as the amygdala and ventral prefrontal cortex, are adjacent to sinuses or tissue/fluid boundaries. These regions of inhomogeneity lead to artifacts which can obscure actual signal.

Each approach to neuroimaging has strengths and limitations. In BOLD (blood oxygen level dependent) fMRI (functional magnetic resonance imaging), the limitations include regions of high signal loss and poor image quality. In positron emission tomography (PET) using oxygen-labeled water, the problem of signal loss near tissue/air boundaries does not exist, but spatial resolution and signal-to-noise ratio are compromised compared to BOLD fMRI. A novel technique, perfusion fMRI is being developed that is based on blood perfusion to the brain tissue. Perfusion fMRI promises to provide enhanced signal-to-noise ratio (Aguirre, Detre, Zahran, & Alsop, 2002). For example, activation of the dorsal lateral prefrontal cortex was observed in a study that presented the same 2 min segments of a compound stimulus set repeatedly but was not activated in a similar study that presented one 10 min compound stimulus set. This difference was attributed to the role of the dorsal lateral prefrontal cortex in explicit episodic memory (Grant et al., 1996; Childress et al., 1999).

Despite differences in these neuroimaging approaches, several interconnected brain regions consistently emerge in cue reactivity literature. A distributed neural circuitry that includes prefrontal sites and interconnected limbic regions (i.e., the amygdala, ventral striatum) is activated by cues for alcohol, nicotine, cocaine and heroin (Brody et al., 2002; Childress et al., 1999; George et al., 2001; Tapert et al., 2003). Further, relationships between self-reported craving and brain activation have been found with alcohol cues (Myrick et al., 2004; Tapert, Brown, Baratta, & Brown, 2004), nicotine cues (Brody et al., 2002), opiate cues (Daglish et al., 2001; Sell et al., 2000), and cocaine cues (Garavan et al., 2000; Grant et al., 1996; Wang et al., 1999). Although craving and neural activation are indisputably correlated, whether this correlation is associated with relapse has not been established.

In recent research, strong links between stress and relapse are emerging. In animals, stress reliably reinstates drug seeking, just as relapse to alcohol and drug use is more likely to occur in individuals experiencing high levels of stress (Shaham, Erb, & Stewart, 2000). Preclinical studies indicate that the hypothalamic–pituitary system is dysregulated in

stress-induced relapse, and that the underlying neural circuitry is different than that of drug- and cue-induced relapse. In humans, stress-induced craving is a relatively new avenue of exploration. Initial studies indicate exposure to stress and drug cues each resulted in significant increases in cocaine craving, ACTH, and cortisol (Sinha, Catapano, & O'Malley, 1999; Sinha et al., 2003). Moreover, acute cortisol administration triggered craving in cocaine abusers (Elman, Lukas, Karlsgodt, Gasic, & Breiter, 2003).

On the other hand, a recent study found that reduced reactivity to stress, as indicated by *lower* cortisol levels after a laboratory stress inducing paradigm, predicted a greater likelihood of early relapse in alcoholic males (Junghanns et al., 2003). This finding is in keeping with research in children, which has shown that reduced basal cortisol concentrations have been associated with aggressivity (Tennes, Kreye, Avitable, & Wells, 1986), hostility (Tennes & Kreye, 1985), and conduct disorder severity (Vanyukov et al., 1993). Moreover, lower cortisol levels in children have been shown to be associated with higher conduct disorder symptom counts and higher antisocial personality symptom counts in their fathers (Vanyukov et al., 1993). It is therefore possible that dysregulation of the hypothalamic–pituitary system, as indicated by either reduced or increased stress-reactivity, could play a factor in relapse. These apparently contradictory findings may reflect differences in the effects of chronic versus acute stress.

Several theories of relapse posit that conditioned responses may increase risk for relapse. Specifically, moods or experiences that become associated over time with substance use can themselves become "triggers" for craving and urges to use (Childress et al., 1993; Rohsenow, 1999). In a study with humans, alcoholic men who admitted to a detoxification program underwent a laboratory procedure in which they were instructed to hold and smell an alcoholic drink (Rohsenow, 1999). Greater salivation during this procedure predicted greater frequency of drinking during post-treatment follow-up. In animal studies, presentation of the conditioned cue following extinction in the absence of drug can reinstate responding, and drug-associated cues increase dopamine and activity in dopaminergic circuits (Ciccocioppo, Sanna, & Weiss, 2001; Crombag, Grimm, & Shaham, 2002; Di Ciano, Blaha, & Phillips, 1998; Franklin & Druhan, 2000a, 2000b; Neisewander et al., 2000; Weissenborn, Deroche, Koob, & Weiss, 1996).

Another neurocognitive factor that may be related to relapse is attentional bias, which refers to a tendency on the part of alcohol or drug abusers to focus attention on stimuli related to substance use to a greater degree than someone who does not abuse substances (Ehrman et al., 2002). One study examined whether smokers exhibit an attentional bias in which they attend to a greater degree to smoking cues (Waters, Shiffman, Bradley, & Mogg, 2003). Attentional bias was assessed with a visual probe task, in which participants are told to respond to a probe that appears on a screen immediately after a picture containing either motivationally salient stimuli (i.e., smoking related) or neutral stimuli is presented. Faster response times to the probe following the smoking related stimuli are consistent with an attentional bias, or greater vigilance, toward that stimuli. The hypothesis of an attentional bias was supported, as smokers responded more quickly and accurately to the probe that followed a smoking picture than to the probe that followed a neutral picture. However, reaction time bias did not predict time to first smoking lapse in a subsequent smoking cessation attempt (Waters et al., 2003).

In summary, results from biological studies are complex and sometimes contradictory. However, it does appear that relapse may be related to a number of factors, including irregularities in the dopamine system, problems in the prefrontal cortex and related regions of the brain, reactivity to stress, conditioned cues, and biases in the processes that govern the degree to which substance use related stimuli are attended to.

4. New applications of statistical methods that facilitate the study of relapse

In this section, we briefly review the data analytic methods used in the studies of distal and proximal factors in relapse. The principal types of outcomes used in relapse studies are longitudinal repeated measures of alcohol consumption, drug use, treatment participation, general functioning, and times to event, where the event is typically a resumption of some abusive activity (e.g., heavy drinking, drug use, cessation of participation in treatment, and so forth). We also describe some other analytic methods that appear to have potential value in studies of relapse but have not been widely used, and some of the challenges provided by the use of "near-real-time" data. A broader review of statistical techniques can be found in McKinnon and Lockwood (2003).

We do not consider methods for the analysis of neuroimaging data in this section, for the following reasons. The basic statistical framework is the general linear model with fixed and random effects (Friston et al., 1995; Marchini & Ripley, 2000; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004), so the area has many similarities with the analysis of repeated measures data. However, the fact that the basic unit of analysis is a series of spatial images, with

the resulting need for special-purpose software to process and analyze the responses, means that the area is somewhat inaccessible to the non-specialist. The most immediate effect of research on the biological and neurocognitive factors in relapse has been to broaden the set of factors that might be used to explain heterogeneity in response in a relapse study. The additional covariates suggested by this research are then accommodated within the analytic framework of longitudinal trials. As a result, the data analytic challenges presented by neuroimaging data are not directly relevant to the design of relapse studies.

Some authors have called for the application of concepts from nonlinear dynamic modeling and chaos theory in the study of the genesis of relapse (Hufford, Witkiewitz, Shields, Kodya, & Caruso, 2003; Warren, Hawkins, & Sprott, 2003; Witkiewitz & Marlatt, 2004). These approaches may be useful, for example, in explaining how a seemingly small change in a particular factor could quickly trigger a relapse episode. However, it is not clear that the applications of these concepts have been developed to the point where they will increase our understanding of the onset and course of relapses, so we prefer to focus on methods that are more closely related to existing approaches.

4.1. Repeated measures

It has become standard practice to analyze longitudinal responses using either mixed-effects models (Verbeke & Molenbergs, 2000) or GEE models (Diggle, Heagerty, Liang, & Zeger, 2003). These methods were used by several articles considered in this review (e.g., Maisto et al., 2000; McKay et al., 2004; Weiss et al., 2003). Particular advantages of these approaches over their predecessors is that they do not require equally spaced time points for the repeated measurements, and do not require all participants to provide data at a common set of time points. In combination with some assumptions on the nature of missing data, these advantages permit more appropriate analyses of data where there is drop-out of participants, and where measurement times are irregular within and across participants. Weiss et al.'s (2003) examination of measurements gathered around repeated relapses provides an example of the value of these improvements. Weiss et al. (2003) also describe how simple additional analyses (pattern-mixture models; Hedeker & Gibbons, 1997) can be used to test for violations of the assumptions on the missing data process.

Most analyses of relapse studies focus on a single response, measured repeatedly across the course of the study. However, it is often the case that there may be more than one outcome of interest. Although these responses might be expected to be correlated, it is usually the case that they are analyzed separately. Multivariate mixed effects models that accommodate combinations of continuous and categorical or count outcomes have been developed recently (e.g., Roy, Lin, & Ryan, 2003; Sammel, Lin, & Ryan, 1999; Sammel, Ryan, & Legler, 1997), and their use in substance abuse studies has been advocated by Rounsaville, Petry, and Carroll (2003). When there are a small number of related responses of the same distribution type, such as the various summaries obtained from calendar assessment methods like the Time-line Follow-back approach, or when alcohol and cocaine use are considered as outcomes in a co-morbid sample, it is possible to perform a multivariate mixed-effects analysis using the same software that is used for the separate analyses (Hox, 2002; Snijders & Bosker, 1999).

When there are many multiple responses, it may be better to consider models that assume an underlying factor structure for the multivariate responses. Muthen and colleagues (Muthen, 1998–2004; Muthen et al., 2002; Muthen & Shedden, 1999) have developed a set of general growth mixture models that incorporate the main features of univariate and multivariate mixed effects models and structural equation models, together with a latent class structure that allows for qualitatively different growth models for different subsets of the data. As an example, latent growth curve models could assume that the multiple observed responses at each time point are indicators of unobserved factors, and that the observed trends over time are best described by changes in these factors over time. When there is considerable heterogeneity in response to treatment, as is typical in relapse studies, these latent classes can provide a useful clustering of a data set into different types of responders. Despite these potential advantages, these methods have not been widely used in relapse research.

A feature of most relapse studies is that there will be many abstainers at any given time point, and that a significant proportion of the sample will remain abstinent through the course of the study. This leads to the phenomenon of "zero-inflation", which is a challenge for standard data analytic techniques, but is also of clinical interest. The general growth mixture models can accommodate such zero inflation, and can therefore incorporate one major source of heterogeneity in response. In addition, the models allow the inclusion of covariates as predictors of the latent classes, or of the observed responses. As an example, this permits the testing of hypotheses about how covariates may

influence abstinence versus use, and how different covariates may influence level of use among non-abstainers. These models have not been fully exploited in the relapse literature, although some examples have appeared (DeLucchi & Bostrom, 2004; Muthen & Muthen, 2000).

4.2. Time to events

Interpreted literally, the study of relapses involves investigating the occurrence of onsets of use, after periods of abstinence, so it is natural that time-to-event data have been widely investigated. The most typical such analysis is almost entirely carried out using the Cox proportional hazards regression model (Hosmer & Lemeshow, 1999), and considers the time to the first relapse. Combined with the use of stratification and time-varying covariates, this model allows the testing of a wide range of hypotheses on time to initial relapse. Given the interest in questions of whether factors relating to relapse differ across multiple relapses within the same subject, it is surprising that little use seems to have been made of extensions of the Cox model to multiple relapses. Wang, Winchell, McCormick, Nevius, and O'Neill (2002) discussed the application of the three main multiple relapse models to alcohol data. A method described by Andersen and Gill (Andersen, Borgun, Gill, & Keiding, 1992) regards all events as being of the same type, in that it does not distinguish between first events, second events, and so forth. A counterintuitive implication of this approach is that subjects are regarded as being at risk for a later event even when they have not yet experienced an earlier event. The model is well suited to questions about the effect of covariates on the overall rate of recurrent relapses, but is not suited to questions about whether hazard rates, or covariate effects, differ between first relapses and later relapses.

The "conditional" models of Prentice, Williams, and Peterson (1981) differ from the Anderson and Gill model in that a subject is regarded as being at risk for a later relapse only when they have experienced all earlier relapses. Finally, the "marginal" models of Wei, Lin, and Weisfeld (1989) are similar to the Anderson and Gill model, in that all subjects are at risk for all events, but these models do make use of strata to distinguish between first, second, and subsequent events. Clearly, the research question being addressed would dictate the choice of model to be used. An advantage of the conditional and marginal models over the Anderson and Gill model is that they allow for covariate by strata interactions. Thus, they permit tests of whether covariates have different effects on earlier and later relapses. For example, McKay, Merikle et al. (2001) reported that attendance at treatment and self-help meetings predicted relapse relatively early in a follow-up, but at later points, employment status was a stronger predictor of relapse. The conditional and marginal models would allow a formal test of this effect, while the Andersen and Gill model would assume constant effects across relapses.

It should be noted that these models do not replace the usual time to first relapse models. The recurrent event models examine average times to any relapse, or consider different strata of relapses. Comparisons between a time to first event analysis, and a time to recurrent events analysis, will necessarily show differences, as different questions are being tested. In some respects, it is of more interest to compare recurrent event models to the usual repeated measures models for consumption over time. In particular, when there are many relapses (say more than 5 or 6 for many people), it is not clear that the recurrent event models are very different from the repeated measures models. Finally, many relapse studies show that patients will spend several days using drugs (particularly alcohol) once they relapse to use. Intuitively, if the time spent in a relapse episode is long relative to the time spent between episodes, then the data seem less appropriate for a recurrent events analysis. In that case, it may be that multi-state models (Hougaard, 1999), where the focus is on the times spent in various states of abstinence or use, and on transition rates between the states are more appropriate. These models would permit the testing of hypotheses about covariate effects on duration of abstinence, or on duration of relapse. Once again, this raises the question of how "relapse", or "use-episode", should be defined.

4.3. Diary data

Bolger, Davis, and Rafaeli (2003) provide a detailed description of the use of "diary", or near real time assessment methods. In particular, they consider the suggested guidelines of Stone and Shiffman (2002) for the design and implementation of studies using such methods, and describe some data analytic approaches. The data obtained from a "diary-based" assessment will be in the form of nested repeated measures, where each subject provides a daily set of repeated measures of affect and smoking, for each of several days. Viewed in this way, the question of whether affect

has an influence on relapse can be addressed using affect as a time varying covariate, with relapse as response, in either a mixed-effects or GEE model (Shiffman et al., 2002; Shiffman & Waters, 2004). The particular hypothesis being tested is whether, on average, levels of affect are related to levels of relapse, where the averaging is over all the days on which diary data were gathered.

As an example of a more complex use of real-time data, consider the question of how the daily relationship between level of affect and relapse is mediated by another factor, such as coping skill. This is an example of what Kenny, Korchmaros, and Bolger (2003) define as "lower-level" mediation, since the mediation is occurring at the lowest level of the nested design. An interesting feature of their analysis of a similar example was that they allowed the "links" defining the lower-level mediational structure to vary randomly across the higher-level units, i.e., extent of mediation could be different on different days and for different people. Clearly, other questions could be asked and addressed. For example, a treatment could be developed in which participants would use EMA-based assessments to provide data on imminent risk of relapse directly several times daily to their therapist, who would use that information to monitor the patient and shape the delivery of services. This approach to relapse prevention could then be compared to a more standard relapse prevention approach, in which data collected weekly during the therapy sessions are used to shape the treatment. Kenny et al. (2003) are explicit in stating that they regard their approach as merely a first step towards a complete analytic framework, and that further developments are very likely.

5. Discussion

At the beginning of this article, we provided a brief description of an ideal study of relapse, and the kinds of data such a study would generate. At this point, there has been a substantial amount of research on psychological, behavioral, and environmental factors that increase vulnerability to relapse, and recent neuroscience research has identified a number of biological factors that also appear to contribute to risk for relapse. However, several aspects of the relapse process in alcohol and other drug abusers are still clearly in need of further study.

5.1. How should relapse be defined?

As was noted in the introduction, there is as yet no standard convention on how to define a "relapse" (Maisto et al., 2003). Differing definitions of relapse can clearly have an effect on the answers that are obtained to some research questions. One of the most obvious of these is the time that elapses between a point in time (e.g., baseline, end of treatment) and the occurrence of a relapse episode. In a sample of adolescent substance abusers, Maisto et al. (2003) found that time to relapse varied from 26 to 90 days, depending on whether the definition of relapse incorporated any use, heavy use, or a combination of use and negative consequences. Similarly, McKay, Alterman et al. (2001) found that time to relapse in a continuing care study was 355 days, 474 days, or 540 days when relapse was defined as 1, 2, or 3 consecutive days of cocaine use, respectively.

There may be some advantages to the adoption of a standard definition of relapse that would be clearly different from a "lapse" by virtue of severity and clinical significance. However, the criteria used in this definition might differ across substances. For example, one might consider any use of crack cocaine or IV heroin as a "relapse", whereas a can of beer consumed at a wedding, or a single cigarette smoked in the basement might be seen as a "lapse". Further study of differences between episodes of use that end quickly, before serious negative consequences are experienced, and those that continue to escalate is warranted (see below).

5.2. How do distal and proximal factors interact to produce relapse?

The more widely accepted theories of relapse (Brownell et al., 1986; Donovan, 1996; Shiffman, 1989) postulate that relapse is a function of relatively enduring personal characteristics and background factors, which determine overall vulnerability to relapse; immediate precipitants, which trigger specific relapse episodes; and coping behaviors, which can counteract these other factors and prevent relapse. Witkiewitz and Marlatt (2004) have recently attempted to take into account the complicated, dynamic relationships between these factors in a reformulation of the original Marlatt and Gordon (1985) model of relapse. The new model specifies feedback loops among relapse factors and reciprocal causation between variables such as coping skills and substance use. Despite the intuitive appeal of these comprehensive and dynamic models, limitations in relapse research method-

ology have so far made it difficult, if not impossible, to adequately test many of the components in these models. Studies are needed that feature the use of well-validated self-report measures of distal factors along with newer technologies to assess both distal and proximal factors.

5.3. What is happening in the hours before the relapse begins?

Despite the obvious importance of distal factors that increase relapse vulnerability in a general fashion, the real key to understanding why a particular relapse episode occurs likely lies in experiences and events in the hours and minutes leading up to the onset of that episode. Unfortunately, obtaining accurate information during this period presents enormous methodological problems. Traditional prospective studies are not designed to collect data immediately prior to relapse, and information on this period generated through retrospective studies is of questionable accuracy at best. The "near real time" approaches that make use of IVR or EMA technology hold out the best hope for obtaining accurate data from the hours prior to relapse. However, at this point only the relapses of cigarette smokers have been well-studied with these methodologies.

5.4. What happens once the relapse has begun?

From the work of Shiffman and colleagues (Shiffman et al., 1997; Shiffman, Gnys et al., 1996; Shiffman, Paty et al., 1996; Shiffman & Waters, 2004), we have some understanding of the factors that are associated with the course of smoking lapses, including the role that cognitions, self-efficacy, stress, and coping play in determining whether initial lapses progress into full relapses. However, less is known about how these and other factors influence the course of alcohol and other drug relapses. Marlatt & Gordon (1985) have proposed that the Abstinence Violation Effect (AVE) determines whether an initial "slip" stays a slip or develops into a relapse, but there are no data–other than from retrospective reports–to support this theory. What is needed are near real time data on internal states, behaviors, and experiences in the hours after the initial use of alcohol or drugs, gathered with automated systems of some sort.

Unfortunately, it is possible that the relapser will find it increasingly difficult to accurately use touch tone or hand-held computer technology to enter data as level of intoxication increases. Alternately, relapsers might be able to provide verbal answers over the telephone to a series of questions that are generated by a computer, after a relapse has begun. The technology is now available and is widely used to simply record such verbal answers, or to use them to select further questions which are in turn posed to the caller. For example, a relapser could provide verbal answers over a telephone every hour or so once a relapse had begun to questions concerning craving and euphoria levels, mood states, amount of alcohol or drugs consumed, social interactions, current location, and so forth.

5.5. Is there consistency across multiple relapses?

Most studies of relapse focus on a specific relapse episode or substance use status over a specific window of time (e.g., 6–12 months post baseline). However, many substance abusers experience multiple relapses between treatment episodes (Dennis et al., 2003). At this point, there is very little information on the degree of within-individual consistency in the nature of the distal and proximal factors that contribute to the onset of relapse episodes over time. For example, if a first relapse can be attributed to rapid increases in negative mood in the hours prior to onset (Shiffman & Waters, 2004), is it likely that subsequent relapses will also follow that pattern? Or, is the next relapse just as likely to be due to some other factor, such as a chance encounter with an old friend who has cocaine? Preliminary evidence from the work of Gwaltney et al. (2002) suggests that the circumstances that immediately precede a series of smoking lapses do tend to correspond to areas of low self-efficacy assessed prior to smoking quit date. On the other hand, results from McKay, Merikle et al. (2001) and Zywiak et al. (2003) suggest that key precipitants of relapse may change over time.

5.6. Does study methodology influence results?

If methodology really matters, one would expect to see at least some significant differences in results generated by studies that make use primarily of retrospective, prospective, near real time, or biological assessment designs. In reality, it is difficult to determine whether this is indeed the case, because studies with different methodologies tend to

look at different questions. Take, for example, the role of negative affect in the onset of relapse. Studies of relapse that make use of retrospective assessment methodologies have consistently found that substance abusers report high levels of negative mood prior to relapse (Marlatt and Gordon, 1985; McKay et al., 1996). Furthermore, prospective studies indicate that higher levels of negative mood predict relapse at subsequent follow-ups, several months later (Miller et al., 1996). On the other hand, other prospective studies have found that negative mood does not predict relapse within the following week (Hall, Havassy, & Wasserman, 1991) or on the following day (Shiffman & Waters, 2004). However, relapse was associated with increases in negative mood within several *hours* of the event (Shiffman & Waters, 2004). Research also suggests that level of negative affect after a relapse may effect the degree to which negative affect is stressed in retrospective reports of relapse precipitants (Hodgins & el-Guebaly, 2004; Hodgins et al., 1995; Shiffman et al., 1997).

One might conclude from these studies that study assessment methodology influences findings regarding the role of negative affect in relapse onset. However, the lack of consistency in findings could easily be due to different lag times between the assessment of negative affect and relapse onset. In effect, these studies all ask somewhat different questions.

6. Final comments

The studies reviewed here suggest that the "state-of-the-art" study of relapse in the addictions would use a variety of assessment techniques to capture each phase of the process. Distal factors would likely be assessed via self-report questionnaires and interviews with strong psychometric properties, as well as with laboratory-based procedures that provide data on neurological and biological vulnerability factors. Proximal factors in the onset of relapse would be assessed with near real time and real time techniques such as IVR and EMA, and possibly through simulation studies in a laboratory (i.e., neuroimaging of craving following exposure to relapse cues). Factors that influence the course of the relapse, once an initial "slip" has occurred, would be assessed with newer technology that digitizes and records information that is spoken over a telephone, rather than entered via touch tone buttons or key pad.

In closing, we would like to suggest that as relapse research moves increasingly toward "high tech" methodologies, there is still a place for "low tech" approaches, including retrospective assessment, in the study of relapse. In many relapses there is a moment of truth, so to speak, in which the substance abuser makes a final decision–whether consciously or not–to go ahead and have that drink or take that drug. Unfortunately, none of the cutting edge methods described here is really able to capture what is going on in the substance abuser's mind at that moment. The only way to obtain fairly detailed information on the thought processes, moods, and experiences of the relapser in the moments before the lapse or relapse commences is through interviews conducted after the fact. Such data are likely to be biased, and to contain numerous inaccuracies (Hammersley, 1994; Henry et al., 1994). They are also never more than the subjective perceptions of the substance abuser concerning why the relapse occurred, and should be seen and understood as such. However, these reports still may be the best way to explore an important part of the relapse process, which cannot be studied with IVR or EMA. Obviously, such retrospective reports are likely to be more accurate and complete when they are obtained shortly after the relapse has begun, and will be considerably more useful when combined with more cutting edge assessment methodologies. Therefore, despite all the advances in assessment methodologies available to study relapse, there is still a convincing rationale for not abandoning the practice of asking the substance abuser how a relapse episode came about—as long as this is not the only source of data obtained.

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