SERIES IN ANXIETY AND RELATED DISORDERS

Anxiety and Substance Use Disorders

The Vicious Cycle of Comorbidity

Sherry H. Stewart
Patricia J. Conrod
Editors

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For Laila and Ali

Epigraph

Whose is . . . the anxiety? . . . Those who linger late over their wine, those who are always trying some new spiced liquor.

Proverbs 23: 29–30

Preface

The idea for this book originated with an invitation from Dr. Martin Antony in the fall of 2002 to contribute an authored or edited book on the topic of anxiety disorder co-morbidity with substance use disorder, to his planned series of books on anxiety disorders. This invitation converged nicely with conversations that the two of us (S.H.S. and P.J.C.) had been having around that time of eventually writing a book on different pathways to substance use disorder, one of which our own work indicates involves anxiety-related processes. We decided on an edited book so that each chapter could be written by an expert in the field and so we could feature the exciting work in this field that is taking place around the world. We were thrilled to be able to involve such an outstanding and international set of chapter authors in the process of putting together this volume. We have both worked rather tirelessly in carefully editing the chapters authored by others, and in writing our own sections of the book, over the many months that have passed since first receiving the invitation from Dr. Antony and signing the contract with Springer. We have had the opportunity to work on these tasks together and separately in such diverse and inspiring locations as Paris and Chamonix in France, London in the United Kingdom, Vancouver in British Columbia, Canada, and Halifax and Evangeline Beach in Nova Scotia, Canada. Over the time that this project has developed, we have seen friends, clients, and patients with substance use and anxiety disorders both thrive under currently available treatments models, and fatally deteriorate. The co-morbidity of anxiety and substance use disorders remains a prevalent problem that traditional treatment models fail to address adequately.

The overall purposes of this edited book are to fully (1) review recent literature on anxiety disorder and substance use disorder co-morbidity, (2) present biologic and psychosocial theories that explain their co-occurrence, and (3) cover recent treatment models based on such theories and the literature evaluating their outcomes.

For some time now, research has been accumulating on the prevalence and nature of the co-occurrence between various forms of anxiety disorders and substance use problems. With increased understanding of the nature of these relationships, more recently, new interventions targeting this co-morbidity have been developed and tested. One of the goals of this book is to disseminate

knowledge about the content and efficacy of these newly-developed approaches. Moreover, emerging findings on efficacy of these approaches to co-morbidity and the things we are learning from efficacy trials have led to a further understanding of the inter-relations and the strategies needed to address them clinically. We felt that a critical analysis of this emerging literature is sorely needed to move this field forward, making this volume very timely.

Our intended audience for the volume is quite broad. We have attempted to make the text relevant for researchers, clinicians, academics, and students alike. Those who work in the area at the intersection of substance use and anxiety-related psychopathologies, and those delivering psychosocial or medical interventions for substance use and/or anxiety disorders should find this volume most appealing.

The theoretical basis for this book integrates the biological and psychosocial approaches to understanding anxiety, substance abuse, and their interactions. Various theoretical models within this larger framework are reviewed in relevant chapters, including the tension reduction/self-medication/stress-response dampening models, and models involving substance-induced anxiety intensification. We explore the idea of reciprocal relations between anxiety and substance abuse throughout the course of co-morbidity of these two disorders, with special attention devoted to mechanisms explaining substance-induced anxiolysis, as well as substance-induced anxiogenesis. This book is unique in its attempt to review theoretical and empirical literature on the reciprocal relations between anxiety and substance misuse across a variety of anxiety disorders. The book also explores the conditions under which pathological anxiety motivates problematic substance use, misuse, and even substance avoidance.

The theoretical orientations of the treatments presented in this book are empirically-supported, and largely cognitive-behavioral. All are presented with consideration of the potential reciprocal relations between anxiety and substance use and the biological and psychosocial mechanisms that mediate these relations.

Our approach in compiling and editing this book has been to focus on basic research on the biologic, social, and cognitive factors mediating anxiety and addictive behaviors and their interaction. Treatment approaches reviewed in this book have at least some preliminary empirical support and have largely been derived from the knowledge gained from basic science research. We also take the field a step forward by attempting to integrate different theoretical perspectives on the nature of the co-morbidity in the concluding section of the book. To our knowledge, this book is the first to examine co-morbidity across different forms of anxiety/substance use disorder co-morbidity. This has allowed us to come to some tentative conclusions regarding commonalities and distinct processes within each pattern of co-morbidity and implications for treatment.

The present volume is divided into four parts. Part I is intended to provide an overview of theoretical issues regarding anxiety and substance use disorders in general. In Chapter 1, Kushner, Krueger, Frye, and Peterson provide an

overview of epidemiological perspectives on co-occurring anxiety disorder and substance use disorders. In Chapter 2, McNaughton provides a thorough review of the neurobiological aspects of anxiety with implications for understanding co-morbid anxiety and substance use disorders.

Part II of this volume is intended to provide a review of research findings on the nature, etiology, and functional relations between anxiety and substance use disorders. Each chapter reviews evidence for theories that explain co-morbidity and may include emphasis on both psychosocial and biologic theories. Each chapter focuses on a specific form of co-morbidity. In Chapter 3, Coffey, Read, and Norberg provide a review of the co-morbidity of post-traumatic stress disorder (PTSD) and substance use disorder with emphasis on neuroimaging, neuroendocrine, and psychophysiologic findings on the nature of this form of co-morbidity. In Chapter 4, Tran and Smith provide theoretical insights on the nature of the relationship between social phobia and alcohol use disorders; their chapter provides an up-to-date review of relevant psychopathology research findings. In Chapter 5, Norton, Norton, Cox, and Belik provide a review of the research on the nature and etiology/maintenance of co-occurring panic spectrum disorders and various forms of substance use.

Part III consists of a set of chapters focusing on treatment models and their effectiveness. Once again, each chapter is devoted to a specific form of co-morbidity. The emphasis of each chapter is on a review of empirically-validated treatments. Authors were asked to include case material whenever possible. In each case, authors provide significant detail about the intervention and its implementation. In Chapter 6, Klosterman and Fals-Stewart review the evidence on the treatment of co-morbid obsessive-compulsive disorder (OCD) and substance use disorders. In Chapter 7, Riggs and Foa provide a state-of-the-art review of what is known about effective treatments for co-morbid PTSD and substance use disorders. Chapter 8 consists of a review by Randall, Book, Carrigan, and Thomas of the research evidence on various approaches that have been tested for the treatment of co-occurring social phobia and alcohol use disorders. Toneatto and Rector focus on the treatment of co-morbid panic disorder and substance use disorder in Chapter 9; they first review the treatment outcome literature, and then detail a functional analysis type of approach to treatment of this form of co-morbidity that might usefully be applied to other forms of co-morbid anxiety and substance use disorder. In Chapter 10, Zvolensky, Bernstein, Yartz, McLeish, and Feldner provide a review of the cognitive-behavioral treatment they have developed for patients with co-morbid panic disorder and tobacco dependence. Watt, Stewart, Conrod, and Schmidt provide a review of a novel approach to the treatment and prevention of co-morbid anxiety and substance use disorder in Chapter 11 – i.e., an intervention aimed at the level of personality vulnerability to these disorders. And in the final chapter of this section (Chapter 12), Marshall provides an overview of the medical management of co-morbid anxiety and substance use disorder.

Finally, in Part IV of the current volume, Chapter 13 contains and integration of the material presented in the earlier sections, written by the volume

editors, Stewart and Conrod. In this concluding chapter, we attempt to identify common themes emerging across the chapters and to set an agenda for future research in this area.

We have a number of people, agencies, and institutions to acknowledge and thank for their roles in the shaping of this text. First and foremost, we would like to thank the authors and their colleagues who contributed chapters to this exciting volume. And we wish to extend our sincere thanks to Dr. Martin Antony for providing us with the opportunity to contribute to his series on anxiety disorders. We also owe a great deal to our editor at Springer, Sharon Panulla, and her editorial assistant, Jennifer Hadley, for their assistance, support, and patience throughout the contract, production, and publication process. Both of us would like to acknowledge the contributions of our own present and former students, research assistants, and colleagues who have contributed to the body of research reviewed herein that has increased the understanding of anxiety – substance use disorder co-morbidity to the point that we are now developing effective interventions for treatment and prevention of this devastating dual affliction. We are indebted to our families for their patience and support while we undertook this challenging project. And of course, we need to thank the various funding agencies that have made our own work in this important area possible. One of us (S.H.S.) has been funded for her work in this area by the Medical Research Council of Canada, the Social Sciences and Humanities Research Foundation of Canada, the Canadian Institutes of Health Research, the Nova Scotia Health Research Foundation, and the Mounted Police Foundation. The other of us (P.J.C.) has been funded for her work in this area by agencies including the NHS Research and Development Trust and the Canadian Institutes of Health Research. And the two of us have jointly held grants in this area of research from the National Health Research Development Program, Health Canada and the Alcoholic Beverage Medical Research Foundation. We hope that you will enjoy the volume as much as we have enjoyed the process of pulling it all together.

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Contents

About the Editors

Sherry H. Stewart has an international reputation for her work in the areas of addictions, anxiety disorders, and the co-morbidity of mental health and substance use disorders. She is a professor of psychiatry and psychology at Dalhousie University. She served as the coordinator of the Dalhousie doctoral training program in clinical psychology from 2004 to 2006. Dr. Stewart has a cross-appointment as a professor in community health and epidemiology at Dalhousie; she also holds research appointments at local teaching hospitals in the Halifax metropolitan area. She just completed a year as visiting faculty at the University of British Columbia in Vancouver where she spent her second sabbatical. She received her B.Sc. (honors) in psychology from Dalhousie University in 1987 and her Ph.D. in clinical psychology from McGill University in 1993. She completed her clinical internship at the Toronto Hospital in 1992–1993. Dr. Stewart has been registered as a clinical psychologist in Nova Scotia since 1995. She ran a part-time private practice in the metropolitan Halifax area until 2003, when she left her practice to become a mother. Dr. Stewart is currently the associate editor of the international journals *Cognitive Behaviour Therapy* and *Current Drug Abuse Reviews* and serves on the editorial boards of *Cognitive and Behavioral Practice* and the *Canadian Journal of Behavioural Science*. She has provided reviews for numerous scientific journals and granting agencies. The quality of her research has been recognized through numerous awards including the Young Investigator Award from the Anxiety Disorders Association of America in 1998, the New Investigator Award from the Association for Advancement of Behavior Therapy Women's Special Interest Group in 1998, the President's New Researcher Award from the Canadian Psychological Association in 1998, and the Killam Prize in Science in 1997. This past year she was elected to the Canadian Academy of Health Sciences and she received a governor-in-council appointment to the Board of Directors of the Canadian Centre on Substance Abuse.

Patricia J. Conrod is a BPS Chartered Clinical Psychologist and Clinical Lecturer in the Department of Psychological Medicine and Psychiatry, Institute of Psychiatry, King's College London. Her research focuses on cognitive, personality, and biological risk factors for the development and maintenance of drug abuse and the factors that mediate the co-occurrence of addictive

behaviors with other mental disorders. Her experimental research focuses on factors that make people more susceptible to seek out behavioral reinforcement from drugs of abuse. She has published several studies demonstrating that personality factors determine the type of reinforcement experienced from substances of abuse. More recently, her research findings have led to the development of new approaches to substance abuse treatment and prevention that target personality risk factors and the underlying motivational determinants of drug use in subtypes of substance misusers. Dr. Conrod is a member of the King's College London Research Ethics Committee. She is an Action on Addiction Research Fellow, and a National Institute of Health Research, Biomedical Research Centre Faculty Member. Dr. Conrod is currently the associate editor of the international journal *Current Drug Abuse Reviews* and has guest edited special issues in the *Journal of Mental Health* and the *Journal of Cognitive Psychotherapy*. Her research findings have been featured in the media, including articles in *The Financial Times*, and *The Guardian*, as well as in radio and television interviews for the BBC and Channel 4, UK.

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"You should relax less."

Part I
Theoretical Issues

Chapter 1
Epidemiological Perspectives on Co-Occurring Anxiety Disorder and Substance Use Disorder

Matt G. Kushner, Robert Krueger, Brenda Frye and Jill Peterson

Introduction

The purpose of this chapter is to review the issue of anxiety disorders co-occurring with substance use disorders (SUDs) ("co-morbidity") from an epidemiological perspective. Generally speaking, epidemiology pertains to the study of the various factors influencing the occurrence, distribution, prevention and control of disease, injury and other health-related events in defined human populations. The quasi-experimental methodology of the typical epidemiological study – contrasting the rates of an outcome between naturally occurring groups – is well suited to the problem of co-morbidity.

For instance, epidemiological data collected in representative community-based samples avoid many of the biases built into studies of co-morbidity in institutional/clinical samples. Such data are also more flexible than are clinical data in assigning the status of outcome between co-morbid disorders. From the epidemiological perspective, for example, which co-morbid disorder is designated as the outcome and which as a putative risk factor is analytically arbitrary. By contrast, outcome status in clinical samples is typically fixed (i.e., all SUD treatment patients have an SUD).

The most basic epidemiological question asks to what extent having either an anxiety disorder or SUD (again, the predictor-outcome arrangement is analytically arbitrary) modulates one's risk for the other disorder. Epidemiological studies can also document changes in risk for the later development of a co-morbid disorder (e.g., SUD) conferred by the earlier presence of an index disorder (e.g., anxiety disorder). Beyond the useful service of quantifying the

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extent of co-morbidity under various conditions, such data also have the capacity to both generate and, in a limited sense, test some critical hypotheses concerning the nature of co-morbidity. We explore each of these issues, in this chapter.

First we highlight methodological and theoretical issues related to epidemiological studies concerning co-morbidity. Next we review data from major community-based epidemiological studies related to co-morbidity separated by several variables of interest (e.g., specific anxiety disorder type, specific SUD type). For each variable of interest, we attempt to highlight and interpret findings based on a broad survey of the co-morbidity literature. Finally, we provide a discussion of what we consider to be the primary conclusions that can be drawn from the review and the primary challenges that remain to be resolved in the epidemiological study of co-morbidity.

Methodological Issues

Chance overlap vs. covariation. Epidemiological studies typically quantify the magnitude of co-variation between co-morbid disorders in terms of the odds ratio (OR); i.e., the ratio of the odds of having an index condition (e.g., an SUD) when the co-morbid condition (e.g., anxiety disorder) is present (numerator) vs. absent (denominator). An OR of 1, therefore, indicates that the odds of the outcome occurring (the index disorder) are the same whether or not the putative risk factor (the co-morbid disorder) is present or absent. This would occur when chance alone is dictating the co-occurrence of the two disorders. ORs departing from 1 indicate that the co-morbid disorder increases the risk for the outcome (i.e., for ORs > 1) or decreases the risk for the outcome (i.e., for ORs < 1). Greater departures from 1 indicate proportionally greater co-variation between the co-morbid disorders.

Cross-sectional vs. longitudinal and prospective designs. Cross-sectional epidemiological designs index the degree of co-variation between co-morbid disorders for a specified time span (e.g., "current," "lifetime") as reported at a single data collection point. Therefore, the co-morbid disorders identified in a cross-sectional design may or may not have been active at the same time. In our view (e.g., see Kushner, Abrams, and Borchardt 2000), establishing that such cross-sectional associations exist with a non-trivial magnitude is an important first step in judging the clinical and theoretical importance of co-morbidity.

Once such co-variation is established, additional information about the nature of the association between co-morbid disorders can be gleaned by knowing the temporal relationship of their onsets and remissions. Longitudinal data provide information about change over multiple time points in one or more variables of interest. Retrospective methods can provide longitudinal data by asking individuals at a single time point to recall and report how their status on variables of interest (e.g., symptoms) have changed over a specified time period. For example, individuals can be asked to recall which of two co-morbid

disorders began first. Prospective methods also provide longitudinal information but have the additional advantage of collecting real-time data (i.e., status at the time data are collected) over multiple time points extending into the future. Time effects (e.g., faulty memory) and cohort effects (e.g., changes in cultural and clinical norms over time) are more likely to distort retrospective data than those that are collected prospectively.

Community-based vs. clinic-based samples. Berkson (1949) noted that individuals with multiple disorders are more likely to be referred (by self or others) to treatment than are those with a single disorder. This would serve to inflate the prevalence of co-morbidity in treatment settings relative to the rates that exist in the community. Therefore, large representative community databases yield the most informative (i.e., least biased) epidemiological data regarding psychiatric co-morbidity. These include the Epidemiological Catchment Area (ECA) survey (e.g., Helzer & Pryzbeck, 1988; Regier et al., 1990), the National Co-morbidity Survey (NCS) (e.g., Kessler et al., 1997, 2005) and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (e.g., Grant et al., 2004). The International Consortium in Psychiatric Epidemiology (ICPE) also provides relevant data that is based on studies both in the U.S. and elsewhere (Mexico, Canada and Europe) (Merikangas et al., 1998). Each of these surveys includes sample sizes that range into the thousands and form the core of the data we review below.

Diagnostic specificity and co-morbid associations. Because various drugs of abuse (including alcohol) have profoundly differing pharmacokinetics, psychoactive, legal and cultural characteristics, it would be very surprising indeed to find that the effects of each establishes the same operant dynamic and psycho-physiological effects among individuals with anxiety disorder. Similarly, specific anxiety disorders (e.g., panic disorder, generalized anxiety disorder, social phobia) may vary considerably in terms of their subjective and behavioral manifestations and may well involve unique neuro-anatomical and neuro-chemical substrates that are differentially affected by drugs and alcohol (Kushner, Sher, & Beitman, 1990). Specific anxiety disorders might also vary in terms of the availability of alcohol and the permissibility of drinking found in the circumstances in which symptoms typically manifest (e.g., work vs. parties vs. driving). These issues suggest that more diagnostic specificity will provide more accurate information regarding co-morbidity. However, this issue is ultimately informed by the data and practical constraints on how data are collected and analyzed. We consider each of these issues in this chapter.

Theoretical Issues

Epidemiological data are best interpreted with an understanding of the various possible links between co-morbid conditions. In this regard, the co-occurrence between two disorders could indicate that: (a) distinct underlying liabilities to the

disorders are correlated (i.e., related but not causally so), (b) the same underlying liability is manifested as putatively distinct disorders (i.e., spectrum disorders), (c) either disorder causes each other directly, (d) the "co-morbid" disorder is really a third type of disorder that is distinct from either condition alone, or (e) the co-morbidity emerged for artifactual reasons (e.g., sampling from a segment of the population where co-morbidity is more concentrated than it is in the population at-large) (e.g., Klein & Riso, 1993; Krueger & Markon, 2006; Kushner, Abrams, and Borchardt 2000; Neale & Kendler, 1995).

Within many of these possible associations (models) a variety of theories and mechanisms might apply. For example, SUD might promote the onset of anxiety disorder (model) via psychophysiological perturbations (theory 1) or via environmental perturbations (theory 2). Theory 1 would fit with a "neuro-kindling" process (mechanism 1) resulting from multiple withdrawals (e.g., Kushner et al., 1990) or with a process related to substance-induced disruption in the stress-response system (see chapter 2 mechanism 2). Similarly, the idea that anxiety disorder promotes the onset of SUD (model) could occur via attempts at "self-medication" of anxiety symptoms (theory) via the neuro-depressant effects of some drugs like alcohol (mechanism 1) or via the boost to psychological well-being that can result from some drugs such as cocaine and hallucinogens like ecstasy (mechanism 2). Using epidemiological data, we have limited but important possibilities of considering the "fit" of these various possibilities.

Cross-Sectional Co-morbid Associations

Abuse vs. dependence and alcohol vs. other drugs. The various studies shown in Table 1.1 converge on the conclusion that anxiety disorders demonstrate a greater association in the case of dependence vs. abuse and in SUDs involving drugs vs. alcohol. In absolute terms, knowing whether the SUD is related to drugs vs. alcohol accounts for slightly more predictive variance than does knowing whether the SUD is related to abuse vs. dependence. The bottom row in Table 1.1 shows that alcohol abuse is the weakest predictor of all with average OR of only 1.5. It is also notable that the association with anxiety disorder is slightly stronger for drug abuse (OR = 2.6) then it is for alcohol dependence (OR = 2.4). This is suggestive of an interaction between abuse vs. dependence with drug vs. alcohol in predicting co-morbidity with anxiety disorder.

It is possible that abuse is more associated with externalizing disorders such as anti-social personality while dependence is more associated with internalizing disorders such as anxiety disorders. This is roughly consistent with the viewpoint put forward by Cloninger (1987) who distinguished two alcoholism subtypes along these lines. According to this view, trait anxiety ("harm avoidance") promotes a style of drinking that is more likely to result in dependence while anti-social traits ("novelty seeking") promotes a style of drinking that is

Table 1.1 Drug and alcohol abuse vs. dependence in Co-morbidity

	Drug disorder		Alcohol disorder	
	Abuse	Dependence	Abuse	Dependence
ECA	2.3	2.4	1.0	1.8
NCS	1.4	3.3	1.2	2.1
NESARC	1.7	6.2	1.1	2.6
ICPE-US-Fresno(MAPPS)	3.1	4.0	1.8	2.7
ICPE-Germany(EDSP)	4.4	5.2	1.9	3.2
ICPE-Mexico(EPCP)	2.8	4.6	1.7	2.7
ICPE-Netherlands(NEMESIS)	2.0	5.2	1.0	1.8
ICPE-Ontario(OMHSS)	2.9	3.4	2.2	2.5
Means (any drug vs. alcohol)	**3.5 (Any Drug)**		**2.0 (Any Alcohol)**	
Means (any dependence vs. any abuse)	**3.0 (Any Dependence)**		**2.1 (Any Abuse)**	
Means (abuse vs. dependence by drug vs. alcohol)	**2.6**	**4.3**	**1.5**	**2.4**

ICPE = International Consortium in Psychiatric Epidemiology.
MAPPS = Mexican American Prevalence Services Survey (n = 3,012, Fresno)
EDSP = Early Developmental Stages of Psychopathology Study (n = 3,021, Munich)
EPCP = Epidemiology of Psychiatric Co-morbidity (n = 1,932, Mexico City)
NEMESIS = Netherlands Mental Health Survey and Incidence Study (N = 7,076, 90 municipalities in Netherlands)
OMHSS = Ontario Mental Health Supplemental Survey (n = 6,902)
ECA = Epidemiologic Catchment Area Survey (U.S., n = 20,000)
NCS = National Co-morbidity Survey (U.S., n = 8,098)
NESARC = National Epidemiologic Survey on Alcohol and Related Conditions (U.S., n = 43,093)

more likely to result in abuse. However, some studies have failed to find such distinctions (e.g., Sannibale & Hall, 1998). Another possibility is that much of the anxiety disorder in co-morbidity is a result of physiological and psychological processes associated with dependence-based withdrawal (e.g., Schuckit & Hesselbrock, 1994).

It is interesting that drug-related SUDs are in general more strongly associated with anxiety disorders than are alcohol-related SUDs; especially since the bulk of clinical studies in this area relate to alcohol use disorders (c.f., Kushner et al., 1990, 2000). This is difficult to interpret for two primary reasons. First, there may well be considerable overlap (i.e., co-morbidity) between drug and alcohol disorders. For example, Helzer and Pryzbeck (1988) reported that the odds of having either a drug disorder or alcohol use disorder was increased more than seven fold among individuals with the other. Therefore, data sets examining co-morbidity with anxiety disorder would more optimally be split into those with only a drug use disorder, only an alcohol use disorder and those with both. Unfortunately, none of the studies we reviewed included these subgroups. A second problem with interpreting this effect is that combining all types of drug use disorder (e.g., cocaine, marijuana, hallucinogens) into one category could add noise to that category. However, this potential "noise"

might be expected to reduce rather than elevate the association of anxiety disorder to drug use disorder relative to alcohol use disorder.

Co-morbidity in specific drugs of abuse. The ECA (i.e., Regier et al., 1990) is the only large epidemiological database to publish anxiety disorder co-morbidity rates with SUDs involving specific drug types. Notably, these ORs range from a low of 2.3 (marijuana) to a high of 5.0 (hallucinogens). Others in descending order are 4.5 (barbiturates), 2.9 (both cocaine and amphetamines) and 2.8 (opiates). Again, these categories are not mutually exclusive and they also combine abuse and dependence (a distinction shown in Table 1.1 to be important). Nonetheless, these data would appear to defy a simplistic self-medication view. Apparently, not all individuals (or perhaps not even a majority) with an anxiety disorder prefer the depressant-type drugs (including alcohol) that might reasonably be expected to reduce the physiological manifestations of anxiety. Rather, Regier et al. (1990) find that SUDs involving hallucinogens – a family of drugs not known to have a calming effect on users – demonstrate the strongest association with anxiety disorders.

One possible explanation for these findings is that self medication dynamics may account for more cases of co-morbidity involving drugs with depressing or tranquilizing effects while drugs with stimulating effects are more likely to trigger, aggravate or maintain anxiety disorders (e.g., Kushner, Abrams, and Borchardt 2000). Again, this suggests multiple initiation trajectories into co-morbidity where either condition might cause the other via different mechanisms. On the other hand, even physiological stimulants (e.g., cocaine, nicotine, ecstasy) might include psychological effects related to enhancing generalized self-efficacy, or a personal sense of well-being that could, conceivably, be especially reinforcing among anxiety disordered individuals as per the classical self-medication view.

Co-morbidity in specific anxiety disorders. More than 15 years ago, we noted that the clinical literature revealed variable levels of base rate-adjusted SUD comorbidity among the various anxiety disorder subtypes (Kushner et al., 1990). As noted earlier, however, clinical samples are potentially biased in a number of ways. In fact, Table 1.2 summarizes data from various surveys showing only modest variability between the various anxiety disorders in terms of co-morbidity risk. For alcohol dependence, ORs range from an average low of 2.0 for simple phobia to a high of 3.1 for panic disorder (OR = 3.0 for GAD). This same basic pattern holds up in drug dependence; albeit, with overall higher ORs (as expected from Table 1.1). Considering data from drug and alcohol dependence together (bottom row of Table 1.2), GAD shows the greatest absolute co-morbidity (OR = 5.1), with agoraphobia showing the next greatest associations (OR = 4.7). Simple phobia remains the anxiety disorder with the weakest association to co-morbid SUD (OR = 2.6).

While type of drug seems to affect co-morbidity rates (see above), it was surprising based on our earlier review of clinical studies (Kushner et al., 1990) that the epidemiological data reviewed here did not find greater variability for

Table 1.2 Association of alcohol and drug dependence with specific anxiety disorders

	Any anxiety	GAD	Panic disorder/no Ag ("Panic")	Panic/ with Ag ("Agoraphobia")	Social phobia	Specific phobia
Alcohol dependence						
ECA	2.1		3.8	2.6	2.1	1.6
NCS	2.1	2.8	2.0	1.7	2.2	2.1
NESARC	2.6	3.1	3.4	3.6	2.5	2.2
Means	**2.3**	**3.0**	**3.1**	**2.6**	**2.3**	**2.0**
Drug dependence						
NCS	3.3	3.8	3.8	2.8	2.6	2.5
NESARC	6.2	10.4	7.6	10.5	5.4	3.8
Means	**4.8**	**7.1**	**5.7**	**6.7**	**4.0**	**3.2**
Drug and alcohol dependence combined						
Means	**3.6**	**5.1**	**4.4**	**4.7**	**3.2**	**2.6**

See notes from Table 1.1 for definition of abbreviations.

type of anxiety disorder. It is possible that the apparent disjunction between clinical and community data is the result of referral patterns. For example, the more common anxiety disorders found in alcoholism treatment patients (e.g., social phobia and agoraphobia) might associate with a more severe form of SUD that is, therefore, more likely to lead to treatment. Consistent with this viewpoint, Kushner et al. (2005) found that social phobia and panic with agoraphobia predicted relapse in treated alcoholics better than did other anxiety disorders. That same study also found that GAD was more likely to resolve following SUD treatment than were anxiety disorders such as social phobia and PTSD. These finding suggest that while the epidemiological data may capture the most unbiased associational quantities in co-morbidity, they may also obscure qualitative distinctions in the way specific anxiety disorders come to be associated with and act upon SUDs.

Number of anxiety disorders. It must be considered that over half of individuals with a specific anxiety disorder subtype also have at least one additional anxiety disorder subtype (e.g., Goodwin et al., 2004; Himle & Hill, 1991). Therefore, the number of anxiety disorders (or "psychiatric load") might be another parameter relevant to co-morbidity involving an SUD. Merikangas et al. (1998) examined this issue in a community sample using the ICPE data set showing that more diagnoses, including (but not limited to) various anxiety disorders and depression, increases the SUD co-morbidity risk. For example, the risk (ORs) for alcohol and drug dependence among those with a single psychiatric disorder was 2.2 and 2.4 (respectively) while these risks (ORs) were 5.0 and 7.8 (respectively) for those with more than two psychiatric disorders. These data mesh with clinical studies showing that the number of anxiety disorders is a significant predictor of a worse psychiatric course for co-morbid patients following alcoholism treatment (Kushner et al., 2005).

Gender and co-morbidity rates. Anxiety disorders are more common in women and SUDs are more common in men (e.g., Lewis, Bucholz, Spitznagel, & Shayka, 1996). However, it would be a logical error to conclude that differing base rates of disorder for men and women indicate differing magnitudes of co-morbidity based on gender. Data from the NCS (Kessler et al., 1997) (Table 1.3) shows base rate adjusted co-morbidity rates (i.e., ORs) for men and women across the various anxiety disorders. One thing that stands out in Table 1.3 is that for men, there are no positive associations between alcohol abuse and anxiety disorders while PTSD and GAD both actually have negative associations with alcohol abuse. Men with PTSD are only about half as likely to have alcohol abuse as compared to men without PTSD. Considering all anxiety disorders and alcohol disorders together (right most column in the last two rows of Table 1.3), women with either disorder are approximately one-third more likely to have the co-morbid disorder as compared to men.

The reason for this moderate gender effect is not clear. Perhaps women and men are prone to different subtypes of alcohol disorder (i.e., even within the broader DSM diagnostic categories of dependence and abuse) that are differentially prone to association with anxiety disorder. Cloninger (1987) distinguishes two types of alcoholism, only one of which ("type 1") he believes is related to the "escape" oriented drinking associated with the "self-medication" of anxiety symptoms. In fact, more women than men can be classified as having type 1 alcoholism (e.g., Sannibale & Hall, 1998); however, these researchers and others have found that individuals with alcohol use disorders often do not fall cleanly into one vs. the other of Cloninger's subtypes.

Table 1.3 Comorbidity across specific anxiety disorder by gender

	GAD	Panic (w/o ag)	Agoraphobia	Social phobia	Simple phobia	PTSD	**Any Anxiety**
Men (AlcDep)	3.9	2.3	1.8	2.4	3.1	3.2	**2.2**
Women (AlcDep)	3.0	3.0	2.5	2.6	2.6	3.6	**3.1**
Men (AlcAb)	0.7	0.8	1.3	1.0	0.9	0.5	**1.0**
Women (AlcAb)	1.31	1.6	1.0	1.8	2.2	1.0	**1.8**
Men (any alcohol disorder)	**2.3**	**1.6**	**1.6**	**1.7**	**2.0**	**1.9**	**1.6**
Woman (any alcohol disorder)	**2.2**	**2.3**	**1.8**	**2.2**	**2.4**	**2.3**	**2.5**

From the NCS data set reported by Kessler et al. (1997).

Longitudinal Co-morbid Associations

Order of disorder onset. Among the most common approaches used to assay causal influence in co-morbidity is the retrospective assessment of the order in which disorders first onset. It might or might not be the case that a condition caused an outcome that it predated, but it is certainly the case that a condition did not cause an outcome that it antedated. This logical fact highlights a Popperian opportunity to potentially eliminate incorrect causal theories concerning co-morbidity. That is, causal theories asserting that either SUD or anxiety disorder causes the other in co-morbidity must conform to the implied order of onset to survive (i.e., to remain viable).

Table 1.4 shows that anxiety began first in about three-fourths of the cases in which it was co-morbid with alcohol dependence and in about four-fifths of the cases in which it was co-morbid with drug dependence. What this suggests is that in at least three of four co-morbid cases (involving dependence), we could expect to be able to rule out the possibility that the SUD caused the co-morbid anxiety disorder. However, as noted above, this neither demonstrates that the anxiety problem caused the co-morbid SUD in these 75% nor that the SUD caused the anxiety disorder in the remaining 25%.

Independent vs. induced co-morbid disorders. DSM IV was the first edition of the American Psychiatric Association's diagnostic nomenclature to place importance on and provide a crisp distinction between independent and substance-induced anxiety disorders. To be "independent" by these criteria, an anxiety disorder must: (a) clearly have begun prior to the onset of the SUD; *or* (b) must be found to persist for more than four weeks following the cessation of substance use and withdrawal. We would draw special attention to criterion "b" which goes beyond the simple order of onset criterion (above) by also examining the question of whether a co-morbid anxiety disorder appears to be capable of persisting once active substance abuse and withdrawal cease

Table 1.4 Retrospective assessments of order of Co-morbid disorder onset

	Percent of Co-morbid cases for whom anxiety began first		
Sample	Alcohol dependence	Drug dependence	Any SUD
NCS (Kessler et al., 1996)	81.1	84.4	79.3
ICPE (U.S. Sample, Fresno)	68.6	72.7	–
ICPE (Germany)	56.7	67.6	–
ICPE (Mexico)	63.5	100	–
ICPE (Netherlands)	75.3	75.5	–
ICPE (Ontario)	76.8	77.9	–
NCS	79.4	83.4	–
ECA	–	–	75.0
Mean	**72.0**	**80.2**	**77.2**

See Table 1.1 notes for abbreviation definitions and citations.

(i.e., anxiety symptoms should persist in the case of independent anxiety disorder and should not persist in the case of induced anxiety disorder).

Grant and colleagues (2004) examined the proportion of independent vs. substance-induced anxiety in the NESARC sample using these criteria. They reported that about 11% of the sample had a 12-month diagnosis of anxiety disorder and that only "a few individuals with mood or anxiety disorders were classified as having substance-induced disorders." (p. 807). In fact, only about 0.2% of co-morbid cases (i.e., virtually none) in this sample had an anxiety disorder that failed to demonstrate independence from the causal or maintaining influence of a co-occurring SUD using strictly applied DSM IV criteria. These findings themselves are subject to critique based on the arbitrary choice (empirically speaking) of a four-week waiting period to rule out SUD effects as a cause of the co-morbid anxiety disorder (e.g., see chapter 2 describing the long-term effect substance abuse can have on the stress system). From this perspective an expanded abstinence period might result in a greater proportion of co-morbid individuals falling into the substance-induced category.

Discussion

As noted at the beginning of the chapter, epidemiology is well equipped to systematically assess changes in risk for an index condition under various naturally occurring circumstances. Several large scale epidemiological surveys of psychiatric disorders and SUDs conducted over the last 20 years leave little question that co-morbid disorders are correlated in the general population. Further, these studies point to sub-grouping characteristics that help to refine our understanding of the parameters of co-morbid associations and provide clues as to the nature of these associations. For example, these studies show that anxiety disorders are more likely to co-occur with drug disorders than with alcohol disorders. This finding is provocative because clinical studies of co-morbidity have overwhelmingly focused on alcohol-disordered samples (c.f., Kushner, Abrams, and Borchardt 2000). These studies also suggest that anxiety disorders are more likely to occur with SUDs involving dependence than those involving abuse. Such findings can serve as a wellspring for hypotheses concerning the mechanisms promoting co-morbidity.

For example, Table 1.4 shows that SUD could not be the cause of co-morbid anxiety disorder for the 75% of cases in which the latter precedes the former. Data from the Grant et al. (2004) study take this a step further by showing that even when SUD begins before anxiety disorder, the anxiety disorder typically persists during periods of abstinence of at least one month in duration. As mentioned above, one month of abstinence might not be enough time to be sure that sub-acute and longer-term withdrawal effects have cleared up. On the other hand, if we presume that a non-trivial

proportion of the co-morbid cases in the NESARC sample reported abstinences of considerably more than the one-month minimum, then it is even more surprising that they found so very few cases in which an anxiety disorder resolved during drug/alcohol abstinence.

Although Grant et al. (2004) concluded from their findings that co-morbid anxiety disorder was rarely substance-induced, we would add the possible alternative conclusion that substance-induced anxiety disorders are resistant to spontaneous recovery even when substance intake is discontinued. Notably, the idea of a semi-autonomous anxiety disorder that originally began as a result of an SUD is virtually never discussed in the literature. This is surprising, in part, because the converse idea that a semi-autonomous SUD could have started with a self-medication process is a commonplace idea. That is, it is commonplace to expect that an SUD would not automatically resolve upon treatment of the anxiety disorder that caused it. Yet the vary standard (i.e., DSM) for establishing a substance-induced anxiety disorder is that it resolves with a brief abstinence from pathological substance use. This asymmetry seems to us to be both arbitrary and potentially misleading, especially for the approximately 25% of co-morbid individuals who report that the SUD began prior to the anxiety disorder.

Although beyond the scope of this chapter, the causal implications of these epidemiological data do dovetail into various clinical aspects of co-morbidity. For example, we have argued elsewhere (Kushner, Abrams, and Borchardt 2000) that treating either the SUD alone or the anxiety disorder alone, while observing the impact on the other condition, offered a quasi-experimental approach to quantifying the degree of causal influence between co-morbid disorders. However, if the causal influences were concentrated at the initiation of the co-morbid disorder (vs. the maintaining influences), then treating the causal disorder would not necessarily resolve the co-morbid (caused) condition. On the other hand, the emergence of maintaining factors that are independent of the etiological origins of a co-morbid condition would not necessarily imply that the two conditions have no functional associations. For example, an SUD that emerged either in response to an anxiety disorder or for reasons unrelated to a co-morbid anxiety disorder could still be maintained, in part, through a self-medication process serving as a functional linkage between the co-morbid conditions.

Limitations and Future Work

In addition to a good deal of information, several problems are also highlighted by the epidemiological data reviewed in this chapter. Perhaps the greatest among these is the overwhelming number of combinations that are possible if one were to represent all of the various parameters that are potentially relevant to co-morbidity. Based on this review, this list could include: dependence vs.

abuse, alcohol vs. drug, one type of drug vs. another, one type of anxiety disorder vs. another, number of anxiety diagnoses, number of SUD diagnoses, induced vs. independent anxiety disorder, variants of alcoholism subtypes not represented in DSM, other co-morbid conditions such as depression, and gender. No survey imaginable could possibly accommodate all the various combinations (i.e., main effects and interactions) that would fully account for these variables. Notably, this problem has been largely ignored in the work of clinical researchers focused on co-morbidity. Indeed, the analytical and conceptual mechanics of handling all possible combinations of more than even two categorical conditions are so daunting as to conceivably inspire a conspiracy of ignorance.

Although the effort to model all combinations of anxiety disorders and SUDs appears to be practically impossible, it may not be necessary. Alternatives include statistical and conceptual models capable of simplifying or otherwise resolving large amounts of information into manageable systems. This was the aim of Kushner et al. (2005) in using multiple regression to partition unique from shared predictive variance associated with multi-morbid anxiety and affective disorders in alcoholism treatment patients. By using a competitive entry strategy, these models allowed the single most predictive anxiety disorders to enter the model with any other anxiety disorder entering the predictive model only if it accounted for additional predictive variance.

Alternatively, Krueger and Markon (2006) suggested a correlated liability conceptualization of co-morbidity as an approach that can potentially characterize complex co-morbid cases. In this conceptualization, co-morbidity can be traced to the existence of a smaller number of etiologically coherent liability spectrums (i.e., latent variables) that give rise to manifest psychopathology. In a meta-analysis of relevant articles, Krueger and Markon (2006) conclude that studies support the existence of a broad "internalizing" liability latent variable that confers risk to a diverse array of unipolar mood and anxiety disorders, on the one hand, and a broad "externalizing" liability conferring risk for substance use and antisocial behavior disorders (c.f., Achenbach & Edelbrock, 1984) on the other hand. Moreover, these liability constructs are also genetically coherent. That is, the structure of genetic risk for common forms of psychopathology parallels the observed internalizing and externalizing spectrums (Kendler, Prescott, Myers, & Neale, 2003).

These constructs are also psychologically coherent when one examines the ways in which personality is linked to psychopathology (see Krueger & Tackett, 2003 for a recent review). Specifically, personality traits in the domain of negative emotionality may confer risk for both internalizing and externalizing disorders, but traits in the domain of disinhibition confer risk specifically for externalizing disorders. The net result is that, in the population at large, the internalizing and externalizing spectra appear to be etiologically, phenotypically, and personologically coherent. From this perspective, the broad personality domain of negative emotionality (vs. the various separate DSM conditions that make it up) is a more parsimonious way to

characterize the co-morbidity between anxiety and SUDs noted in this review.

A second problem that is highlighted by this review is the dearth of prospective data investigating temporal patterning in co-morbidity. Clearly, epidemiological researchers see the importance of these issues as evidenced by their attention to the order of disorder onset (Table 1.4) and changes in anxiety disorder status during periods of SUD abstinence (Grant et al., 2004). However, none of these studies were conducted prospectively, due (presumably) to the added costs and time such data collection would entail. Prospective studies that examine the changes in anxiety symptoms given periods of abstinence of varying lengths would be particularly valuable in further illuminating the substance-induced vs. independent co-morbid disorder question.

Concluding Remarks

Epidemiological data reviewed provide clear evidence that co-morbid disorders co-occur more frequently than would be expected by chance. However, it should also be noted that other psychiatric disorders, including antisocial personality (OR = 21), mania (OR = 6.2) and schizophrenia (OR = 4.0), are much more strongly related to SUDs of all kinds (Helzer & Pryzbeck, 1988). Nonetheless, because anxiety disorders are far more common than disorders such as schizophrenia and mania, the former as a risk for SUD have implications for many more people than do these latter conditions. Epidemiological data have provided key information related to the extent and the nature of this association and has the potential to provide more yet. These data sets will allow for novel symptom clustering methods to be evaluated and have the potential to reveal the temporal topography of co-morbid conditions over time. Such studies should inform and be informed by complementary methodologies such as those highlighted in this volume.

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Chapter 2
The Neurobiology of Anxiety: Potential for Co-Morbidity of Anxiety and Substance Use Disorders

Neil McNaughton

Introduction

In this chapter, I focus on the neurobiology of anxieties and phobias and its links to substance use disorder (SUD). I do not cover the neurobiology of SUD itself nor the other mental disorders, which are just as likely to be accompanied by SUD (Krueger & Tackett, 2003).

Anxiety can lead to SUD in the form of self-medication. Conversely, any use of sedative anti-anxiety drugs, which act via receptors of the inhibitory neurotransmitter GABA (specifically $GABA_A$ receptors), can produce dependence and withdrawal that can generate significant anxiety disorder. Positive feedback between self-medication and withdrawal can thus sustain co-morbidity of SUD and anxiety disorder. Consistent with the epidemiological conclusions of Kushner et al. (this volume), neurobiology suggests multiple causal routes (particularly via stress systems) to co-morbidity of SUD and anxiety.

Life events (and particularly their associated cognition) can impact on the settings of biological systems (Kendler, Thornton, & Gardner, 2000). Equally, disorders such as anxiety and depression can alter, adversely, the incidence of particular classes of life events (Harkness, Monroe, Simons, & Thase, 1999). The psychological, and more indirect social, matrices that supply input to neural systems also create extended feedback loops supporting substance abuse and disorder. These are dealt with further in other chapters of this book (e.g., Coffey et al., this volume).

I will group anxiety and fear disorders into a single class: "neurotic disorders". There is high co-morbidity among these disorders driven in part

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by the predisposing personality factor, in the form defined by Eysenck, of neuroticism[1] (Andrews, Stewart, Morris-Yates, Holt, & Henderson, 1990; Eysenck & Eysenck, 1964; Kendler, Neale, Kessler, Heath, & Eaves, 1992). The links between neuroticism and subsequent "neurotic disorder" may be indirect (Bienvenu & Stein, 2003) but the association is strong enough for some, even now, to use the term "neurosis" for such disorders (Tyrer, Seivewright, & Johnson, 2003). However, "neurotic", below, refers only to a common risk factor for DSM "anxiety disorders", other than simple phobia (Marks, 1969), and does not imply that the disorders are variants of a single syndrome, "neurosis". Nonetheless, the disorders should be seen as trait-like (driven by long term sensitivities) and distinct from state anxiety induced by an upcoming surgical operation, for example.

I will distinguish categorically between anxiety (involved in the approach to threat) and fear (involved in the avoidance of threat) and between subtypes of each. Unlike the DSM classification (DSM-III-R, 1987, p 392; DSM-IV-TR, 2000, p 820, p 826), then, I treat anxiety disorders and fear disorders as distinct classes.

I will use terms such as panic and obsession, as states, much as they are ordinarily used. However I will distinguish three ways in which such states can occur: normal, symptomatic, and syndromal. In the normal case, panic (for example) will occur because of the presentation of a very high level of threat in the environment and will be appropriate (in an evolutionary sense) and usually adaptive. In the symptomatic case, the level of threat would be lower but the panic would still be appropriate to the level of (syndromal) fear or anxiety experienced. In the syndromal case the panic response would be excessive for the level of (normal) input to the panic generating systems. On this view, symptoms are not a particularly good guide to syndromes and in many clinical cases there will be co-morbidity of, for example, panic disorder with anxiety disorder.

Drug Treatment of Neurotic Disorders

Drugs vary in their side effects and also in their range of main effects. None is clinically a "magic bullet" targeting just one specific desired effect. But we can gain an academic understanding of the range of systems they are affecting by investigating cases where a drug fails to have an effect. For example, buspirone (a serotonergic anti-anxiety drug that targets "$5HT1_A$" receptors) improves anxiety but not panic and is not sedative or addictive. It shows that the neural systems controlling panic and anxiety, respectively, are at least partially independent. It also shows that anti-anxiety drugs need not be sedative or addictive.

[1] Neuroticism is close to "harm avoidance" (Cloninger, 1986) and "trait anxiety" (Spielberger, Gorusch, Lushene, Vagg, & Jacobs, 1983).

Many classes of drug can treat generalised anxiety disorder but have varying effects on other neurotic disorders (Table 2.1) suggesting that each is controlled by a different brain area (see below). Most obviously, sedative anti-anxiety drugs (such as barbiturates and benzodiazepines) used at anti-anxiety doses, have no anti-panic, antidepressant or anti-obsessive action. At higher doses, they can effect panic (and alprazolam, at least, has antidepressant action); but they do not effect obsession and have varying effectiveness on social anxiety. These drugs act at the $GABA_A$ receptor and, as a result, are anticonvulsant, muscle relaxant and euphoriant. They are also addictive and the links between this dependence and the tolerance that develops to these side effects (but not their anti-anxiety effect) will be discussed later. The serotonergic anti-anxiety drug buspirone acts on the

Table 2.1 Relative effectiveness of drugs in treating different aspects of neurotic disorder (Gray & McNaughton, 2000; McNaughton, 2002; Rickels & Rynn, 2002; Stein, Hollander, Mullen , DeCaria, & Liebowitz, 1992; Stein, Vythilingum, & Seedat, 2004; Stevens & Pollack, 2005; Westenberg, 1999). *Simple phobia* is included for comparison as a fear/anxiety-related disorder that is not linked to neurotic personality. *Abuse potential* is included to emphasise the fact that antianxiety efficacy, *per se*, is not linked to abuse. Different patterns of response in the table can be attributed to the variation in receptor occupancy or interaction by particular drugs in different parts of the brain. No drug or drug class produces a specific limited effect (despite the omission of side effects from the table) but the variation in relative effectiveness across the different aspects of neurotic disorder argues for distinct neural control of each. Critical discrepancies of one class of drug with one or more other classes are bolded (e.g., CMI is more effective at treating obsession than other tricyclics such as IMI, while BDZ are ineffective)

	"antianxiety"			"antidepressant"			
	BDZ_1	**BUS**	**BDZ_2**	**IMI**	**CMI**	**MAOI**	**SSRI**
Simple Phobia	**0**	?	?	**0**	?	(–)	(–)
Generalized Anxiety	–	–	–	–	–	?	–
Social Anxiety	–	**(–)**	**(–)**	**0**	(–)	–	–
Unipolar Depression	**0**	–	–	–	–	–	–
Atypical Depression	**0**	?	?	(–)	?	**–**	?
Panic Attacks	**0**	**0**	–	–	—	–	–
Obsessions/ Compulsions	**0**	(–)	**0**	(–)	**—**	(–)	**—**
Abuse potential	+	0	+	0	0	0	0

Symbols: 0, no effect; – reduction; — extensive reduction; + increase; ( ), small or discrepant effects.

BDZ_1 early benzodiazepines, e.g., chlordiazepoxide (Librium) and diazepam (Valium) administered at typical antianxiety doses. Other sedative antianxiety drugs (barbiturates, meprobamate) have similar effects.

BDZ_2 later high potency benzodiazepines, e.g. alprazolam (Xanax). The antipanic effect is achieved at higher doses and this has also been reported with equivalent high doses for BDZ_1 (Noyes et al., 1996).

BUS Buspirone (BuSpar) and related $5HT1_A$ agonists.

CMI Clomipramine (Anafranil).

IMI Imipramine (Tofranil) and other tricyclic antidepressants, but excluding clomipramine

MAOI Monoamine Oxidase Inhibitors, e.g. phenelzine (Nardil).

SSRI Selective Serotonin Reuptake Inhibitors, e.g. fluoxetine (Prozac).

$5HT1_A$ receptor and has little interaction with GABA. As a result, it has essentially opposite side effects to sedative anti-anxiety drugs. Its main effects include, like the sedatives, treatment of generalised and (more poorly) social anxiety. Although, like alprazolam, it has some antidepressant action, unlike alprazolam it does not effect panic and does have some effect on obsession.

In contrast to these "anti-anxiety" drugs, there is a second class of drug typically seen as "antidepressants". While these treat generalised anxiety, they most obviously share anti-panic and antidepressant effects, and treat obsession to varying extents. Critically, some of these (tricyclics, clomipramine) have little or no effect on social anxiety providing some evidence for a neural dissociation between anxiety and fear (or panic) related systems.

To understand the neurotic disorders we require a model that accounts for the extremely varied symptom presentation in the clinic and the significant variation in the capacity of drugs to treat specific types of disorder. But we must also account for the extensive co-morbidity among anxiety disorders seen in the clinic, the wide effectiveness of some of the classes of drug, and the shared neurotic predisposition to these disorders.

A Two-dimensional Neuropsychology of Anxiety

The picture of fear, anxiety and their syndromes and symptoms that I will present (McNaughton & Corr, 2004) is based on the idea, first proposed by Jeffrey Gray (Gray, 1970), of a Behavioural Inhibition System (Gray, 1982; Gray & McNaughton, 2000).

Fear is distinct from anxiety following the work of Robert and Caroline Blanchard (Blanchard & Blanchard, 1990). Fear (controlled by a Fight, Flight, Freeze System) and anxiety (controlled by a Behavioral Inhibition System) differ in "defensive direction". Fear refers to concurrent reactions (e.g., autonomic activation, escape, avoidance) that have evolved to remove us from danger and are sensitive to anti-panic drugs. Anxiety, by contrast, refers to concurrent reactions (e.g., autonomic activation, risk assessment) that have evolved to allow us to approach danger and are sensitive to anti-anxiety drugs. The activation of the autonomic nervous system by fear and anxiety is slow and similar. The behavioral output is fast and distinct.

The Blanchards showed that the specific behavior generated within the separate classes of fear or anxiety also depended on "defensive distance". On any particular occasion, defensive distance is directly related to the distance of an organism (in space or time) from a threat – but is, itself, an internal construct: perceived rather than actual threat. A brave individual will show a specific defensive reaction at a smaller real distance from threat than a cowardly one. Likewise, drugs alter defensive distance not specific behaviors. In a highly anxious individual, showing little movement towards a threat, an anti-anxiety drug will allow risk assessment to appear. In a less anxious individual, already

undertaking risk assessment, the drug will reduce risk assessment and allow non-threat behavior to appear (Blanchard, Blanchard, Tom, & Rodgers, 1990).

The theory (Fig. 2.1) maps this two-dimensional functional picture to a matching neural one. A stream of structures controlling fear (threat avoidance) is shown on the left of the figure and one controlling anxiety (threat approach) on the right. Structures at the bottom of the figure control "quick and dirty" responses (LeDoux, 1994) to the most immediate threats; those closer to the top control progressively slower, sophisticated responses to more distant threats. Each structure could operate alone but normally they are activated together and will interact (LeDoux, 1996). For example, the

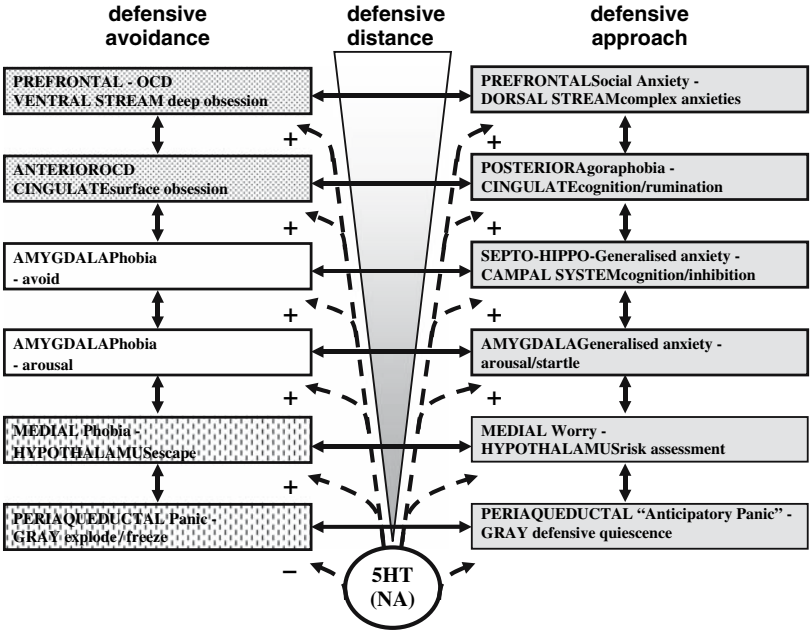

Fig. 2.1 A two-dimensional view of the neural structures controlling defensive reactions involved in anxiety and phobia (McNaughton & Corr, 2004). All the relevant structures receive monoamine input (serotonin, 5HT; noradrenaline, NA). Defensive avoidance (fear; left hand column) and defensive approach (anxiety; right hand column) are controlled by separate neural streams. Structures controlling defensive approach contain receptors ($GABA_A$; $5HT1_A$) for antianxiety drugs and receive subcortical "theta rhythm" input that is altered by antianxiety drugs (shaded structures on right hand side of figure). Structures controlling defensive avoidance vary in the precise nature of 5HT receptor and uptake systems they contain. Thus some drugs, such as clomipramine, can interact with higher levels of the system (stippled structures at top left of figure) to a greater extent than other serotonergic drugs and so be relatively more effective in treating obsessive compulsive disorder (OCD). Some drugs can interact more with lower levels of the system (hatched structures at bottom left of figure) and so be relatively more effective in treating panic. The relatively general effectiveness of drugs such as SSRIs and the relatively general impact of neurotic personality on predisposition to disorder are accounted for by their interaction with monoamine input.

periaqueductal grey (PAG) receives direct, topographically organized, input from prefrontal cortex (Shipley, Ennis, Rizvi, & Behbehani, 1991). This allows complex threat appraisal mechanisms (including traits such as catastrophizing) to produce a panic response if they asses threat as close.

The relation between normal behavior, symptoms and syndromes for all structures can be exemplified by the PAG. It is held to control all instances of panic. Consistent with this, panic is much the same whatever the cause (Barlow, 2002). An extreme threat in a normal person will produce normal (potentially adaptive) panic (Marks, 1988). A weak threat in a pathologically fearful or anxious person will produce an abnormally high input to the PAG and so panic appropriate to the pathological fear (Goisman et al., 1995). Spontaneous activity in PAG (Dantendorfer et al., 1995) could generate spontaneous panic – a neurological syndrome of "pure panic disorder" – as could excessive reaction to input stimuli. This could involve a "suffocation false alarm" from sensitivity to blood carbon dioxide (Klein, 1995); an exaggerated autonomic response (Gurguis et al., 1999) to stimulant drugs or with poor autonomic control (Middleton, Ashby, & Robbins, 1994); or altered central responses to endogenous benzodiazepines (Randall et al., 1995), CCK, or monoamines.

Purely physiological panic is uncommon in the psychiatric clinic (Shear & Maser, 1994) but is detectable in population surveys or cardiology clinics (Carter et al, 1994; Holt, 1990). Current criteria for "panic disorder" require secondary avoidance or anxiety accompanying the panic—and panic itself ceases to be a problem once avoidance and anxiety are treated (Franklin, 1990).

Distinct structures controlling distinct neurotic syndromes accounts for the effects of different drugs (Table 2.1). A single chlorine atom changes imipramine to clomipramine but is enough to cause them to interact with different molecular targets and so different neural structures. Clomipramine, but not imipramine, can target the cingulate cortex and so treat obsession. Drugs that affect both defensive avoidance and defensive approach do so through different mechanisms (e.g., with benzodiazepines the actions appear to be through low affinity and high affinity receptors, respectively, see Table 2.1) both in animals (Griebel et al., 1995) and in the clinic (Basoglu et al., 1994).

The theory also allows for more general effects. For example, monoamines (serotonin, noradrenaline and dopamine) innervate much of the fear and anxiety systems. As a result, tricyclic drugs, clomipramine, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors all increase monoamine function and so have both anti-anxiety and anti-panic effects. (Monoamine systems are also a likely basis for the common factor of neuroticism.) Likewise, many of the structures of the anxiety system (right hand side of Fig. 2.1) show coordinated rhythmic electrical activity ("theta rhythm") controlled from subcortical areas such as the hypothalamus. Theta rhythm is altered by all anti-anxiety drugs including those that are not also anti-panic, such as buspirone (McNaughton & Coop, 1991). So while individual syndromes can depend on individual structures, more general modulatory (and likely predisposing) influences can impact on groups of structures.

Sedative Anti-anxiety Drugs and SUD – Positive Reinforcement

Avoidance of withdrawal can account for the maintenance of abuse of sedative anti-anxiety drugs but not for their initial use. Part of the addictive potential of sedative anti-anxiety drugs appears to derive from an interaction with endogenous opiate systems and, directly or indirectly, with the dopaminergic reinforcement system. Part of the specifically anti-anxiety action of the benzodiazepines may also be mediated by endogenous opiate systems; but this appears to be restricted to behavioural inhibition that lasts only a few seconds (Tripp & McNaughton, 1987; Tripp, McNaughton, & Oei, 1987).

Ethanol, for example, releases both beta-endorphin and dopamine from the mesolimbic system – and ethanol intake is reduced by opiate antagonists (Kostowski & Biénkowski, 1999). Similarly, positive hedonic effects of the benzodiazepine, diazepam, are completely blocked by the opiate antagonist naltrexone (Richardson, Reynolds, Cooper, & Berridge, 2005).

Drug discrimination paradigms show that the perceptual components of ethanol action are made up of distinct opiate and non-opiate components. Opiate antagonists block perception of the initial (~5 minutes) excitatory action of ethanol but not of the later sedative phase (Kostowski & Biénkowski, 1999). Likewise, very low doses of ethanol are perceived as relatively like amphetamine while higher doses are perceived as like a barbiturate. The discriminative effects of ethanol appear to depend on GABA receptors in the dopaminergic nucleus accumbens (Kostowski & Biénkowski, 1999). But they are not entirely mediated by dopamine and so are likely to involve effects of endogenous opioids on non-dopaminergic systems in a variety of brain areas (Van Ree et al., 2000).

The distinct abuse potential of the classic anti-anxiety drugs, as compared to the novel anti-anxiety drugs, may then depend in part on their release of endogenous opiates. These can not only release dopamine but also have a range of dopamine-independent effects on primary, affectively positive, motivational systems. These various opiate-mediated effects can easily account for the initial use, and abuse, of the drugs.

Sedative Anti-anxiety Drugs and SUD – Withdrawal as Negative Reinforcement

The foundation of the above theory is the action of anti-anxiety drugs. It is interesting, therefore, that the sedative anti-anxiety drugs (including ethanol, barbiturates and benzodiazepines) are significantly abused. However, the link between these actions is indirect.

First, let us note that the treatment of neurotic disorders, even with sedative anti-anxiety drugs, requires weeks of treatment (Trimble, 1990; Wheatley, 1990). A single dose of a sedative anti-anxiety drug can alleviate

a state of anxiety produced by an upcoming surgical operation, for example. But (see also section on stress below) single dose effects of these drugs are quite distinct from those produced by the longer term administration needed to alter trait predispositions (McNaughton, 1985; Zhu & McNaughton, 1995).

Second, let us note that serotonergic ($5HT1_A$ active) anti-anxiety drugs are not addictive. They also produce no withdrawal syndrome or signs of dependence (Fontaine, 1987). Indeed, the problem with them is to persuade the patient to take them long enough to obtain a positive effect. Once obtained, their anti-anxiety action is maintained in the long term and this long-term effectiveness is shared by the sedative anti-anxiety drugs. There is, then, some additional short-term action of sedative anti-anxiety drugs that predisposes to abuse – and potentially to their more immediate effectiveness.

The sedative anti-anxiety drugs have quite distinct side effects from novel anti-anxiety drugs: including euphoriant, anticonvulsant, and muscle relaxant action. Abuse potential arises, in part, from rapid tolerance (Roy-Byrne, 2005) to their euphoriant and muscle relaxant (but not anti-anxiety) effects (Wheatley, 1990) – leading to abuse as avoidance of the unpleasant effects of withdrawal (see chapter 5).

The side effects profile varies from drug to drug but is qualitatively the same for all since they act via the $GABA_A$-benzodiazepine-chloride ionophore complex, which may be involved in some anxiety disorders (Roy-Byrne, 2005). Different classes of drugs act at different sites on the receptor (Teicher, 1988) and have so have varying effects, acting differently on different regions of the brain (Pirker, Schwarzer, Wieselthaler, Sieghart, & Sperk, 2005). Their anti-anxiety action is often on the same areas as $5HT1_A$ anti-anxiety drugs, but their side effects are elsewhere and will vary because of regional variations in their interaction with the GABA receptor complex (McKernan et al., 2000).

Each receptor linked to the $GABA_A$-benzodiazepine-chloride ionophore complex must be the target of normally released neuromodulators that alter the action of GABA in relation to both physiological and psychological conditions. Thus, while the benzodiazepine antagonist, flumazenil, has little clinical action (Haefely et al., 1992), it can reduce performance-induced anxiety, probably by antagonizing the effects of an endogenously released (anxiogenic) benzodiazepine receptor ligand (Kapczinski, Curran, Gray, & Lader, 1994) and can elicit panic in panic disorder patients (Randall et al., 1995).

So, we can account for the common anti-anxiety effects of drugs by the presence of the appropriate receptors distributed within the neural structures controlling defensive approach; and we can account for part of the abuse potential of the sedative anti-anxiety drugs by the extent to which they interact, in areas outside the defense system (Pirker et al., 2005), with a specific form of the GABA-benzodiazepine receptor complex that undergoes tolerance and so negatively reinforces abuse through avoidance of withdrawal symptoms.

Anti-anxiety Drugs, Stress and Self Medication

The sedative (addictive) and $5HT_{1A}$ (non-addictive) anti-anxiety drugs also have different interactions with the hypothalamic-pituitary-adrenal axis. Here, abuse of a sedative anti-anxiety drug is most obviously tied to self-medication in response to acute stress or to a neurotic, stress-related or sleep disorder. With alcohol at least, those most prone to such discomfort can show a larger reducing effect (MacDonald, Baker, Stewart, & Skinner, 2000).

Anxiety, produced by simple associative conditioning or other means, releases stress hormones. Initially, sedative anti-anxiety drugs reduce this release but, by contrast, novel anti-anxiety drugs increase it. Further, the hormones act as anti-anxiety drug antagonists and so the immediate anti-anxiety action of the sedative anti-anxiety drugs is increased and that of the novel anti-anxiety drugs decreased by their interactions with the stress system (McNaughton, Panickar, & Logan, 1996). The (opposite) interactions of both novel and sedative anti-anxiety drugs with stress hormones undergo tolerance and so, after long term administration, their actions converge. The sedative anti-anxiety drugs become less effective and the novel ones more effective (Zhu & McNaughton, 1995). The initial difficulty of keeping patients on novel anti-anxiety drugs such as buspirone can be accounted for, in part, by their release of stress hormones, which will increase pre-existing dysphoria.

Interaction with the stress system will also make a significant contribution to the abuse of sedative anti-anxiety drugs. They can immediately decrease the release of stress hormones (as well as producing muscle relaxation). This will decrease pre-existing stress-related dysphoria and so lead to self-medication. As we have already noted, these effects show tolerance. Withdrawal produces rebound and so dysphoria. Continuous self-medication will then be reinforced by avoidance of this dysphoria.

Anxiety-provoking Actions of Non-sedative Drugs of Abuse

So far we have considered drugs of abuse that are primarily sedative and the abuse potential of which stems from a capacity to produce anti-anxiety or euphoriant and muscle relaxant action and then rebound anxiety or panic on withdrawal. Stimulant drugs are also abused and can also influence anxiety but for essentially opposite reasons.

An important link in the positive feedback between anxiety and panic that drives co-morbidity among the neurotic disorders is adrenaline. Anxiety and stress activate not only central monoamine systems but also peripheral systems that release adrenaline into the blood stream. Injections of adrenaline, coupled with perceived threat, can induce panic attacks (Lader & Tyrer, 1975).

This effect of adrenaline is far from specific. Panic can also be elicited by lactate infusion, norepinephrine, and caffeine among other compounds

(Margraf & Ehlers, 1990). Thus, as with spontaneous panic attacks, unexplained physiological disturbance, particularly with stimulant drugs, may produce anxiety and in some cases full blown panic – with different challenges producing different (or no) effects in different individuals.

The stimulant drugs are also, in general, direct monoamine agonists or reuptake inhibitors. They thus have the potential to activate both serotonergic systems (discussed earlier) and noradrenergic systems which, although I have not discussed them, have a similar involvement in anxiety and stress (Tanaka, Yoshida, Emoto, & Ishii, 2000). They can, as a result, have longer-term effects on these systems. For example, cocaine and amphetamine both impair 5HT function (Egan, Wing, Li, Kirch, & Wyatt, 1994) and stimulants that interact with monoaminergic transporters have the potential to produce neurotoxicity of the monoamine systems (Fleckenstein, Gibb, & Hanson, 2000) with potential consequences (depending on the precise site of terminal loss) for a wide range of both fear- and anxiety- related disorders.

The psychomotor stimulants, like cocaine, can also interact with stress hormones. However, in contrast to the effects of anti-anxiety drugs, this interaction is unlikely to be the basis of abuse potential based on withdrawal (but see chapter 5, chapter 10). The stimulant drugs stimulate the release of stress hormones, while sedative ($GABA_A$) anti-anxiety drugs decrease the release of stress hormones. The two classes of drug do so when tested under common conditions of self administration with different drugs of a class affecting stress hormones to different extents (Broadbear, Winger, & Woods, 2005). On this view, stimulants would be addictive because of their dopamine agonist action and anxiogenic or panicogenic as a side effect of the changes they produce in arousal.

A final mention should be made of hallucinogenic drugs. SUD involving these appears particularly likely to be linked to anxiety disorder (see chapter 1). This could well be due to their interaction with monoamine systems or of an effect of changes in these systems on the response to the hallucinogen (Bonson & Murphy, 1995).

Conclusions

I have suggested that, at the neural and general population level, there is a range of quite distinct neurotic disorders, with different patients being effectively treated by different drugs. The mixed clinical picture arises from extensive co-morbidity of the neurotic disorders and the self-selection of mixed cases into conventional clinical samples. In some cases, I have argued, SUD will develop through the use of sedatives (particularly alcohol) as self- or prescription-medication for anxiety. In other cases, the recreational use of sedatives for their short term euphoriant effects can lead to dependence and subsequent symptoms of anxiety on withdrawal – with a self-medication cycle

again providing part of the basis for dependence. Positive feedback between anxiety and abuse is not limited to pharmacological changes – abuse can also increase the incidence of adverse life events (Heikkinen et al., 1994) and so the risk of comorbid neurotic disorder. With stimulant and hallucinogenic drugs, dependence can produce peripheral and central changes that could result in neurotic disorder but, unlike the sedative case, the latter would not reinforce SUD.

If neurotic disorder (whether due to neurotic personality or stress) is the cause of sedative substance abuse, one option for treatment is to find a serotonergic rather than GABAergic compound that can be used to control the original problem. Compliance is a significant issue here, as is medication delivery and selection of an appropriate alternative compound, but gradual introduction of an appropriate serotonergic compound, coupled with gradual (likely later) withdrawal of the sedative, over periods of weeks or months, appears indicated (see chapter 12).

The theory suggests that self-medication with drugs like alcohol will relate to anticipatory anxiety more than fear or panic. Compound psychological treatments of anxiety and avoidance are effective in panic-agoraphobia even when "pure panic" is not eliminated – operating to increase the perceived defensive distance of threats. Although expensive to deliver, such treatments (targeted specifically to anxiety) are likely also to be helpful with SUD involving sedatives. They are likely to help in both the initial transfer of a patient from a sedative to an alternative serotonergic treatment and, potentially, later in transferring the patient to a drug free state. However, it is clear that, in addition to avoidance of withdrawal, sedative abuse is maintained by opiate receptor mediated effects and other positive reinforcing effects that treatment will also have to address.

Stimulant drugs, generating abuse or dependence as a result of their stimulant action, can either trigger states such as panic (in the same manner as physiological arousal) or generate fear and anxiety through processes such as chemical kindling. The changes here are akin to those involved in the interaction of stress with neurotic disorders and should be seen as distinct from those involving sedatives. With these compounds, treatment of the source of primary dependence is likely to be more important than treatment of anxiety. However, if long term changes have occurred in the brain, elimination of dependence will not eliminate residual neurotic disorder, which will then require further treatment.

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Part II
Research Findings

Chapter 3
Posttraumatic Stress Disorder and Substance Use Disorder: Neuroimaging, Neuroendocrine, and Psychophysiological Findings

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Posttraumatic Stress Disorder-Substance Use Disorder Co-Morbidity: Defining the Problem

Posttraumatic stress disorder (PTSD) is an anxiety disorder that results from exposure to a traumatic event. The experience of such an event is the first diagnostic criterion specified by the Diagnostic and Statistical Manual for Mental Disorders – IV (DSM IV-TR; American Psychiatric Association [APA], 2000), and is defined as "the experience, witnessing, or confronting of an event that involves actual or threatened death or serious injury, or other threat to one's physical integrity" (Criterion A.1) accompanied by a reaction which involves "intense fear, helplessness, or horror" (Criterion A.2). Remaining criteria specify that such a traumatic event is followed by a constellation of symptoms including persistent re-experiencing of the event (Criterion B), avoidance/numbing (Criterion C), and increased physiological arousal (Criterion D).

Traumatic exposure is an unfortunately common occurrence, with rates of 60–70% or higher in the general population (e.g., Breslau, Davis, Andreski, & Peterson, 1991; Kilpatrick et al., 2000). However, only a fraction of those who have experienced such a trauma go on to satisfy diagnostic criteria for PTSD. The prevalence of PTSD among those with a Criterion A history range from 16% to 70% depending on trauma type (e.g., Kessler, Sonnega, Bromet, Hughest, & Nelson, 1995), and estimates of the lifetime prevalence of PTSD range from 1% to 12% (e.g., Kessler et al., 1995; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993).

Substance use disorders (SUDs) include both substance abuse and substance dependence, and refer to a cluster of cognitive, behavioral, and physical symptoms and maladaptive patterns of substance use that result in negative consequences for the individual or for others around them, or in clinical

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impairment (APA, 2000). In a nation-wide survey, Grant and colleagues found up to 14% of the U.S. population meets lifetime criteria for alcohol abuse or dependence (Grant, 1997). A study by Kessler and colleagues (1994) found that approximately 27% of the U.S. population meets lifetime criteria for some kind of SUD (abuse or dependence).

Commonly, PTSD and SUDs are comorbid with one another. In the general population, the literature suggests a substantial portion (as much as 46%) of individuals with one disorder also meet criteria for the other (e.g., Stewart, Conrod, Pihl, & Dongier, 1999), and that a diagnosis of one represents a risk factor for diagnosis of the other (e.g., Chilcoat & Breslau, 1998).

Though the frequency of co-occurring SUD and PTSD is well documented, far less is known about the distinct mechanisms that may link these two disorders. Adequate understanding of the mechanisms underlying these disorders may offer implications for etiology, diagnosis, treatment, and prognosis (see Kessler et al., 1994; Stewart et al., 1999). To this end, theoretical models of comorbidity may help to guide research seeking to test the connectedness of these two disorders. Models of comorbidity are described briefly below.

Models of PTSD-SUD Co-morbidity

Self-Medication Hypothesis. The proliferation of research examining the relationship between PTSD and SUD comorbidity has yielded a number of hypotheses regarding how these two disorders may relate to one another. Some of the predominant theoretical models of association are organized around the primacy of one disorder over another – viewing one disorder as a precipitant to the other. The Self-Medication model exemplifies such a conceptualization, asserting that substance abuse occurs as an effort to cope with (or medicate) distressing affect associated with a traumatic event (see Stewart, 1996).

Studies reporting trauma exposure occurring prior to substance abuse appear to support the Self-Medication Hypothesis (e.g., Kilpatrick et al., 2000; Pfefferbaum & Doughty, 2001). In a recent study, Stewart, Mitchell, Wright, and Loba (2004) found increases in post disaster alcohol use among recovery workers involved in the Swissair disaster of 1998. Increases in drinking were associated both with PTSD symptom severity and symptom frequency. These same PTSD variables also showed strong positive associations with drinking to cope. Though this study examined only changes in alcohol use and not DSM abuse or dependence diagnoses, it does offer support for a self-medication explanation for posttraumatic reactions concurrent with substance misuse.

There also is longitudinal evidence to support the self-medication conceptualization. In a 5-year, prospective study of PTSD-SUD, Chilcoat and Breslau (1998) found individuals with a history of PTSD at baseline to be 4 times as likely to abuse substances at 5-year follow-up as those without such a history. In another longitudinal study examining SUD inpatient treatment-seekers,

Read, Brown, and Kahler (2004) found that at 6-month follow-up, baseline re-experiencing symptoms were prospectively associated with continued PTSD and continued PTSD was associated with fewer days abstinent. Together, these data are consistent with a pattern whereby persons with PTSD, who are perhaps suffering pronounced re-experiencing symptoms, use substances in an effort to avoid trauma-related memories and/or to mute emotional arousal.

High Risk Hypothesis. An alternative view of the PTSD-SUD association is known as the "High Risk Hypothesis." Within this conceptualization, trauma and resulting traumatic stress symptoms are viewed as a function of substance use and abuse (see Chilcoat & Breslau, 1998). For example, those who use substances heavily may put themselves at greater risk for accidents, violence, or other types of trauma which may then result in greater traumatic stress sequelae. Furthermore, SUDs may exacerbate traumatic stress symptoms with more use associated with more symptoms over time (e.g., Saladin, Brady, Dansky, & Kilpatrick, 1995).

In a study of individuals who survived the 1995 Oklahoma City bombing in the U.S., North et al. (1999) found modest evidence for SUD as a pre-existing risk factor for PTSD. Almost a third of individuals with PTSD following the bombing incident had a pre-disaster diagnosis of an alcohol use disorder. Approximately 1 of 10 PTSD individuals carried a pre-disaster diagnosis of another SUD. These data support the idea that SUDs may serve as a risk factor for subsequently developing PTSD following trauma exposure. Interestingly, Pfefferbaum and Doughty (2001) found increased drinking following victimization to this same incident, providing support for reciprocity between the two diagnoses.

Acierno, Resnick, Kilpatrick, Saunders, and Best (1999) examined longitudinal predictors of risk factors for victimization and for posttraumatic stress sequelae in a national sample ($N = 3{,}006$) of women. In this study, drug use was prospectively linked to physical but not to sexual assault victimization. Alcohol abuse was not a risk factor for either type of victimization. However, lifetime alcohol abuse was prospectively linked to the development of PTSD following sexual assault. Again, these data provide support for the hypothesis that SUDs may serve as a risk factor for subsequently developing PTSD. The findings presented here illustrate the complex relations between trauma, PTSD, and SUD, and provide an opportune segue for a brief discussion of some of the challenges inherent in attempting to establish temporal precedence in these two disorders.

Disentangling Symptoms: Complexity and Complications

Clearly, the literature offers evidence for both Self-Medication and High Risk models of comorbidity. This is perhaps because establishing temporal precedence is not a simple process. Many factors complicate researchers' ability to determine the primacy of one disorder over the other. To begin with,

temporality may not always be discernible and as some evidence suggests reciprocity between these two disorders, determining primacy of one disorder over another may have little clinical value once the two conditions co-occur. Reciprocal associations between these two disorders underscore the likelihood that symptoms of one disorder influence those of the other. Moreover, as DSM diagnoses are increasingly viewed as dimensional and continuous rather than categorical, it may be that the relationship between misuse of substances and posttraumatic stress reactions may unfold over time at the symptom level and manifest as subtle shifts in the development of each disorder.

Relatedly, the ubiquity of childhood trauma and victimization make temporal ordering of PTSD and SUD complicated (e.g., Acierno et al., 1999). Thus, it is particularly difficult to establish PTSD symptoms in relation to a particular Criterion A event, when the event may have occurred too early for current functioning realistically to be contrasted with pre-trauma functioning. Further, many persons with trauma histories have experienced not one, but multiple traumas (e.g., Cloitre, Tardiff, Marzuk, Leon, & Portera, 1996), and linking post-traumatic sequelae to any single trauma is difficult if not impossible.

Also worth considering is the distinction between temporal primacy and clinical distress. Patients not only have reported that they believe the two disorders are related, but they also have reported that when symptoms from one disorder either improved or became worse, symptoms from the other disorder would move in the same direction (e.g., Back, Brady, Jaanimägi, & Jackson, 2006; Bremner, Southwick, Darnell, & Charney, 1996; Brown, Stout, & Gannon-Rowley, 1998). Though client *perceptions* about how the two disorders relate to one another are valuable pieces of clinical information, such perceptions do not necessarily confirm either temporal onset or causal associations.

Social Learning Models

An alternative conceptualization of the co-occurrence of PTSD-SUD that moves away from models defined solely by determination of causal associations and temporal ordering may be found in a social learning perspective (SLT; Bandura, 1986). Though this view encompasses elements of the Self-Medication and High Risk Hypotheses, it is somewhat broader, including mediating mechanisms of affect, as well as dynamic, reciprocal associations.

According to SLT, substance use is learned in response to both acute and chronic stressors, and from an individual's interaction with and cognitive interpretation of these stressors (Maisto, Carey, & Bradizza, 1999). According to this theory, a traumatic event serves as an unconditioned stimulus, and all trauma-associated stimuli are conditioned stimuli that elicit conditioned emotional responses. The regulation, amelioration, or avoidance of these

conditioned negative emotions motivates substance use (e.g., Stasiewicz & Maisto, 1993).

Reinforcement that occurs as a result of reduction in trauma-associated affect facilitates the learned use of substances in response to conditioned trauma stimuli. Thus, a cycle emerges in which increased levels of trauma result in increased negative affect (e.g. fear triggered by a trauma memory), providing more opportunities to learn maladaptive behaviors to cope with the negative affect (e.g., substance use). This SLT-based view is consistent with Stewart's (1996) observation that the PTSD-SUD association is a cyclical process, with each phenomenon influencing and being influenced by the other.

Non-Causal Models of PTSD-SUD Comorbidity

In addition to the more direct models described above, some investigators have examined the potential role that shared vulnerability may play in PTSD-SUD comorbidity. These studies have focused less on how one disorder may influence, put an individual at risk, or "cause" another disorder and instead have focused on potential non-causal associations that the two disorders may share. Examination of these pathways as a possible contributing factor is more in line with a "third variable" or shared vulnerability conceptualization of this co-morbidity.

Anxiety sensitivity. One of the most widely studied psychological factors thought to function as a shared vulnerability for PTSD and SUD is the cognitive construct of *Anxiety Sensitivity* (AS), which is the propensity to respond fearfully to anxiety sensations or symptoms. AS has long been associated with PTSD (e.g., Taylor, Koch, & McNally, 1992) and more recently, with SUDs (e.g., Kushner, Thuras, Abrams, Brekke, & Stritar, 2001). For example, individuals with high AS are also quite sensitive to the fear damping effects of alcohol (MacDonald, Baker, Stewart, & Skinner, 2000; Stewart & Pihl, 1994). Sensitivity to both the effects of alcohol and anxiety may place individuals at heightened risk for developing SUDs.

Data that more directly supports the hypothesis that AS is a risk factor for PTSD-SUD is emerging. For example, Conrod and colleagues identified four personality factors among a community sample of substance abusing women: Anxiety Sensitivity, Sensation Seeking, Impulsivity, and Introversion-Hopelessness (Conrod, Pihl, Stewart, & Dongier, 2000). Although PTSD was not assessed by a structured clinical interview in this substance abusing sample, PTSD symptoms, as measured by a self-report measure, strongly loaded on the Anxiety Sensitivity factor. Among treatment seeking substance abusers, Bonin and colleagues have reported similar results. Men and women likely to meet criteria for PTSD, as measured by a self-report questionnaire, reported higher AS scores than individuals that were not likely to meet PTSD criteria (Bonin, Norton, Asmundson, Dicurzio, & Pidlubney, 2000). The literature described

here suggests that AS may be important in the etiology or maintenance of PTSD-SUD co-morbidity and, if so, PTSD-SUD treatments may benefit from the addition of AS coping techniques (see chapter 11).

Neurobiological mechanisms. Other data point to neurobiological processes that are common to the two disorders. Though a more detailed review of these shared neurobiological pathways is presented later in this chapter, examples are presented here.

A number of hyperarousal symptoms associated with PTSD, such as hypervigilance and exaggerated startle have been linked to increased dopamine release in response to stressors. It has been observed that such hyperactivity of dopamine transmission is similar to dopaminergic processes associated with the use of substances such as cocaine, amphetamines, and alcohol (Di Chiara, 1997; Swift, 1999). Research in the area of SUDs has suggested that such increases in dopamine release can serve the function of eliciting a craving for alcohol or other drugs (see Addolorato, Leggio, Abenavoli, & Gasbarrini, 2005 for a review). This suggests that individuals with elevated dopamine reactivity may be at risk for developing both PTSD and SUD. In addition to the dopamine system, the noradrenergic systems, and its role in arousal, may also play a significant role in PTSD-SUD comorbidity (Koob, 1999). Perhaps one of the most promising neurobiological intersects between PTSD and SUD is the hypothalamic-pituitary-adrenal (HPA) axis (see Armony & LeDoux, 1997; Yehuda, 2002). The HPA axis and the dopaminergic and noradrenergic systems, and their possible roles in PTSD-SUD comorbidity, are discussed in more detail below.

In the remaining sections of this chapter, we will briefly review some of the psychophysiological, neuroimaging, and neuroendrocrine literatures of PTSD, SUD, and when it exists, the PTSD-SUD co-morbidity literature. Finally, we will discuss a common theme within the various literatures that may help explain the high co-morbidity of the two disorders.

Psychophysiological and Cue Reactivity

Posttraumatic stress disorder. PTSD has been the focus of a great deal of psychophysiological research. Studies have shown that psychophysiological measures can be used to accurately distinguish PTSD veterans from non-PTSD veterans and nonveterans (see Keane et al., 1998). For instance, Blanchard and colleagues have demonstrated elevated heart rate, forehead electromyography (EMG), and systolic blood pressure responses to combat sounds among Vietnam veterans with PTSD, relative to matched non-PTSD veteran or non-veteran groups (e.g., Blanchard, Kolb, & Prins, 1991). In these studies, between 70% and 95% of the subjects were classified correctly as PTSD or non-PTSD according to their autonomic responses. Similar results have been found in women with PTSD stemming from childhood sexual abuse (Orr et al.,

1998). Increased arousal in response to trauma-related stimuli (e.g., memories, trauma reminders) and a desire to reduce this arousal may place individuals a risk for substance abuse in an effort to reduce PTSD-related arousal.

Recently, several studies have measured the acoustic startle reflex in relation to emotional responding in PTSD individuals. The acoustic startle reflex has been of interest because the reflex, as measured by muscle contraction of the orbicularis oculi muscle (the muscle just beneath each eye), is reliably potentiated during negative emotional states and attenuated during positive emotional states. In a sample of veterans with and without PTSD, Miller and Litz (2004) examined the startle reflex and other psychophysiological measures associated with emotional states (i.e., facial EMG) during a picture viewing task. Following a trauma-stress manipulation (i.e., 5 min presentation of combat-related pictures and sounds) veterans viewed positive and negatively valenced pictures presented on a computer screen. The negatively valenced pictures were not combat-related pictures. PTSD veterans, compared to non-PTSD veterans, evidenced larger startle responses while viewing negatively valenced pictures and greater corrugator EMG activity (a muscle group associated with negative affect) to both positive and negatively valenced pictures. The results of this study suggest that PTSD is associated with abnormalities in emotional processing of trauma-related stimuli which then leads to further abnormalities in negative emotional responding. As negative emotion is a key feature of PTSD and an important component of addiction (e.g., Baker, Piper, McCarthy, Majeskie, & Fiore, 2004), future research along this same line may help us better understand the relation between PTSD and SUD and explain their high comorbidity.

Substance Use Disorder. To better understand the underlying processes that are associated with, and potentially maintain, SUDs many investigators have turned to laboratory-based studies. The advantage of laboratory studies is that phenomenon such as drug or alcohol craving can be studied under controlled, safe conditions. Within the addiction literature, cue reactivity is a term generally used to describe a phenomenon in which individuals with a history of SUD exhibit physiological, verbal, and behavioral responses to cues associated with their preferred psychoactive substance. These elicited responses differ from physiological, verbal, and behavioral responses to non-substance-related control cues and have been observed across a variety of substances (e.g., Childress et al., 1994; Coffey et al., 2002; Coffey, Stasiewicz, Hughes, & Brimo, 2006; Cooney, Litt, Morse, Bauer, & Gaupp, 1997). While there are a broad range of theoretical accounts of this phenomenon, almost all models postulate that basic associative learning processes underlie cue reactivity (see Carter & Tiffany, 1999). These theories postulate that repeated stimulus-drug pairings imbue a wide range of stimuli with the capacity to elicit drug-related conditioned responses (e.g., craving) in the absence of drug consumption.

Studies employing cue reactivity paradigms have provided considerable evidence that both interoceptive (e.g., fear, anxiety) and exteroceptive substance-related cues (e.g., smell of alcohol) may serve as precipitating factors

for increased physiological arousal and substance craving. For example, alcohol-related stimuli, such as the sight or smell of alcohol (i.e., exteroceptive cues), have demonstrated cue reactivity in a number of studies (e.g., Cooney et al., 1997). In addition, reactivity to interoceptive cues, specifically negative emotion, has been empirically demonstrated (e.g., Childress et al., 1994; Cooney et al., 1997). For example, Cooney et al. (1997) demonstrated that alcohol dependent persons who were most reactive to both negative emotion and alcohol cues tended to evidence higher relapse rates. Likewise, Childress et al. (1994) found that induced negative emotion elicited craving in opiate abusers. The relation between negative emotion and substance use craving is important since, as stated above, negative emotion is a core feature of PTSD.

Posttraumatic stress disorder and substance use disorders. To better understand the relation between symptoms of PTSD and SUD symptoms, investigators have conducted similar laboratory-based studies. Coffey and colleagues (Coffey et al., 2002) have provided evidence that imaginal trauma cues increase craving and negative emotion in PTSD-SUD individuals. Both alcohol dependent (AD) and cocaine dependent (CD) men and women with co-morbid PTSD were recruited to participate in a cue reactivity protocol. The first phase of the experiment was the presentation of an imaginal cue. The cue was either a narrative description of the participant's worst traumatic event or a narrative of a neutral event. Immediately following the imagery phase, the second phase involved the presentation of *in vivo* cues, either alcohol or cocaine cues (depending on the preferred substance of abuse), or neutral cues. Participants displayed increased reactivity, including increased craving, to both trauma and substance use cues when compared to neutral cues. Compared to the respective neutral cues, both the trauma cues and substance cues elicited self-reported substance craving and elicited a negative emotional state in participants. In a broader study examining substance dependent trauma survivors with and without PTSD, Saladin and colleagues (Saladin et al., 2003) found that PTSD symptom severity (for the sample as a whole) measured during a psychosocial assessment predicted trauma cue-elicited substance craving during a laboratory-based cue reactivity session. These data suggest a strong interconnectedness between symptoms of PTSD and symptoms of SUD.

Interestingly though, in the Coffey et al. (2002) study, AD and CD participants with PTSD did not report similar levels of craving when presented with a personalized trauma cue. The AD participants evidenced a significantly higher craving response than the CD participants, though both AD and CD participants reported greater craving to the trauma cue compared to the neutral cue. To better understand this differential cue responding, the personalized trauma scripts were examined and many of the scripts were found to contain substance use cues (e.g., the assailant was intoxicated, the trauma occurred during the purchase of drugs or alcohol, etc.). To examine the effect of a substance cue embedded within a personalized trauma cue, the scripts for both the AD and CD participants were dichotomized based on whether a reference to drugs or alcohol was present in the script. Within the PTSD-AD participants, no

differences in trauma script-elicited craving were found between those who provided a trauma script that contained a reference to drugs or alcohol and those who provided a "pure" trauma script. However, among the CD participants, trauma scripts that contained references to drugs or alcohol elicited much greater craving than trauma scripts that did not contain a reference to drugs or alcohol. Because the PTSD-CD participants only reported craving in response to a trauma script that contained a drug cue, and because overall the PTSD-CD participants reported significantly lower cue-elicited craving compared to the PTSD-AD participants, the authors suggest that the mechanisms underlying PTSD-SUD co-morbidity may differ among different substances of abuse. Specifically, negative emotion, the most common relapse trigger for alcohol abusers (e.g., Lowman, Allen, Stout, & The Relapse Research Group, 1996) and a common response when PTSD individuals recall a traumatic event, may have a weaker relation to CD compared to AD. This hypothesis, while speculative, is supported by a non-experimental study that found CD males were less likely to use cocaine when experiencing negative emotion and more likely to use cocaine when experiencing positive emotion. Likewise, males dependent on both cocaine and alcohol were more likely to use alcohol, rather than cocaine, when experiencing negative emotion (Cannon et al., 1992). Together, these data suggest that negative emotion may play a stronger role in PTSD-AD comorbidity compared to PTSD-CD comorbidity. As reported by Coffey et al. (2002), this is a logical explanation when drug class and disorder class are considered. PTSD is an anxiety disorder and cocaine is a powerful stimulant. The stimulatory effects from cocaine intoxication (e.g., increased heart rate) may not be desirable when an individual with PTSD is experiencing PTSD symptoms (e.g., increased arousal, irritability, intrusive memories). This undesirable stimulatory effect may result in little cocaine use intended to modulate PTSD-induced negative emotion and result in only a moderate association between cocaine and trauma cues. Conversely, the anxiolytic properties of alcohol may reduce the acute severity of PTSD symptoms and therefore, reinforce its use when an individual experiences trauma symptoms (see Stasiewicz & Maisto, 1993).

To follow up on the findings described above, Coffey and colleagues (Coffey et al., 2006) tested the hypothesis that alcohol craving elicited by a trauma cue might be attenuated if trauma-elicited negative affect was reduced following trauma-focused imaginal exposure. PTSD-AD volunteers participated in a cue reactivity session much like the sessions described above (i.e., Coffey et al., 2002). Participants listened to a verbal description of their worst traumatic event combined with an *in vivo* cue – either an alcohol cue or a neutral cue. Alcohol craving, negative and positive emotion, and subjective distress ratings were collected following each trial. Subsequent to this initial cue reactivity session, participants were randomly assigned to either 6 sessions of trauma-focused imaginal exposure (Foa & Rothbaum, 1998) or 6 sessions of imagery-based relaxation as a control. Upon completion of the 6 sessions, subjects participated in a second cue reactivity session. When comparing

craving and subjective distress ratings elicited by the trauma-alcohol cue during the two laboratory sessions, neither alcohol craving nor subjective distress changed in the relaxation control condition. However, both craving and distress decreased significantly from the first laboratory session to the second laboratory session in the imaginal exposure condition. Similar results were observed in response to the trauma image-neutral cue (i.e., water) combination suggesting that, in this sample, the negative emotion related to the trauma cue may have been eliciting most of the alcohol craving (i.e., craving decreased despite the presence of an alcohol cue) and when the trauma-related negative emotion was decreased, so too was alcohol craving. In addition, PTSD symptoms decreased across the two laboratory sessions in the exposure condition but not in the relaxation control condition. These data underscore the dynamic and reciprocal association between symptoms of PTSD and SUD described earlier in this chapter.

Neurological differences between individuals with PTSD-SUD and comparison groups have been reported in a few published studies, but to date this literature is still in its infancy. Below we briefly review the literature for PTSD, SUD, and when possible, for PTSD-SUD.

Neuroimaging Studies

Magnetic resonance imaging (MRI), functional MRI (fMRI), and positron emission tomography (PET) have been used to investigate structural and functional brain abnormalities in persons with PTSD, SUD, and PTSD-SUD. MRI allows for the imaging of the brain due to changes at the molecular level when placed in a magnetic field and stimulated by radiofrequency pulses. Signals from photons in water and lipids can be processed to create images showing dark and bright regions that reveal the structure of the brain. fMRI determines regional brain activation during cognitive processing by detecting changes in blood oxygenation level (Mazziotta & Frackowiak, 2000). PET involves administration of compounds containing radioisotopes that emit positrons. The emitted radiation from the different parts of brain is computed to obtain a tomographic image (Mazziotta & Frackowiak, 2000).

Posttraumatic stress disorder. Studies utilizing MRI in trauma survivors have provided a somewhat ambiguous picture regarding association between hippocampal volume and PTSD. The hippocampus is the portion of the limbic system (i.e., emotion system) that transfers new information to memory. A number of studies have shown decreased hippocampal volumes in veterans with PTSD compared to those without PTSD (e.g., Bremner et al., 1997; Gurvits et al., 1996), although whether the decrease is present in the left, right, or both sides of the hippocampus is unclear. Most MRI studies of PTSD have used cross-sectional designs, which do not address whether smaller hippocampal volume serves as a risk factor for, or consequence of, PTSD. To

address this issue, Bonne and colleagues (Bonne et al., 2001) used a longitudinal design and measured hippocampal volume within one week of a traumatic event and again 6 months later. Twenty-seven percent of the participants met criteria for PTSD at 6 months. Hippocampal volume did not differ between the PTSD and non-PTSD groups at 1 week or 6 months and the hippocampal volume did not change in the PTSD group over the course of the study. The results of this study, combined with previous work in this area, suggests that smaller hippocampal volume may not be a risk factor for developing PTSD but instead may develop over time in longstanding PTSD (e.g., chronic PTSD related to combat exposure in Vietnam).

Most functional brain imaging studies of PTSD have employed a symptom provocation paradigm; stimuli such as listening to a traumatic script, seeing trauma-related pictures, or remembering the previously experienced traumatic event often elicit fear, anxiety, and physiological activity (i.e., intrusive symptoms of PTSD). The majority of these studies have found abnormalities of limbic and paralimbic areas during symptom provocation. PET scans have revealed abnormal right amygdala activation (Rauch et al., 1996). Shin and colleagues (1999) compared women with histories of childhood sexual abuse, with and without current PTSD, and discovered that in response to script-driven trauma imagery, regional cerebral blood flow decreases in Broca's area were greater in the PTSD group than in the comparison group. Furthermore, the PTSD group had greater cerebral blood flow increases in orbitofrontal cortex and anterior temporal pole, while the comparison group had greater increases in the anterior cingulate gyrus. Given that the anterior cingulate gyrus has a major role in extinguishing fear-conditioned responses (Griffin & Berry, 2004), the finding that persons with PTSD fail to activate this structure to a similar extent as traumatized, non-PTSD controls, suggests that neural processes mediating extinction to trauma-related stimuli may be impaired in PTSD.

In a study of Vietnam combat veterans with and without PTSD, veterans underwent fMRI while performing the Emotional Counting Stroop, a task that requires individuals to view a set of identical words simultaneously displayed on a screen, count the number of words, and then press a button corresponding to that number (Shin et al., 2001). In separate conditions, veterans counted combat-related, generally negative, and neutral words presented on a screen. Veterans without PTSD demonstrated significant activation in the rostral anterior cingulate cortex during the combat-related condition as compared to the general negative condition. However, veterans with PTSD demonstrated significant activation in bilateral anterior insular cortex and in the dorsal anterior cingulate cortex. The authors hypothesized that lack of activation of the rostral anterior cingulate cortex in PTSD might increase the cognitive processing load, increase behavioral interference, and activate more dorsal regions of anterior cingulate cortex. Studies have found that the rostral anterior cingulate cortex is important for affective processing while the dorsal anterior cingulate cortex is important for cognitive processing. Diminished activation of the rostral anterior cingulate may impair emotional processing,

which may then place a person with PTSD at risk for developing a SUD to cope with these emotions (Shin et al., 2001).

Substance use disorders. Neuroimaging also has been used to better understand SUDs. For example, in an MRI study, De Bellis et al. (2000) found significantly lower left and right hemispheric hippocampal volumes in adolescents who abused alcohol than in the matched controls. Furthermore, total hippocampal volume correlated positively with age of onset and correlated negatively with the duration of the alcohol-use disorder, suggesting the hippocampus may be particularly sensitive to the toxic effects of alcohol during adolescence. This finding also is consistent with findings of reduced hippocamal volumes in individuals diagnosed with PTSD, although understanding these common findings is complicated by the fact that substance use history is not always well-controlled in imaging studies of PTSD (e.g., Gurvits et al., 1996).

Variations in synaptic activity related to cue-induced craving in cocaine dependent participants have been localized using PET (e.g., Kilts et al., 2001; Wexler et al., 2001). For example, Kilts and colleagues used script-guided imagery to generate autobiographical memories for cocaine craving cues and angry and neutral emotional states. Compared with the neutral control condition, the cocaine craving condition was associated with bilateral activation of the amygdala, the left insula and anterior cingulate gyrus, and the right subcallosal gyrus and nucleus accumbens area. Compared with the anger control condition, the cocaine craving condition was associated with bilateral activation of the insula and subcallosal cortex, left hippocampus, and anterior cingulate gyrus and brainstem. Together, these findings demonstrate that cocaine craving activates structures involved in stimulus-reward association, incentive motivation, and anticipation (Kilts et al., 2001). These findings also point to structures implicated in PTSD, including the hippocampus and the amygdala.

Long-term opioid dependence has been linked to decreased prefrontal cerebral blood flow. In addition, left-greater-than-right cerebral blood flow asymmetry has been reported (Pezawas et al., 2002). Greater activation in the right than left hemisphere has been associated with negative moods while greater activation in the left than the right hemisphere has been associated with positive moods (Tucker, 1981). Pezawas and colleagues postulated that opioids may protect individuals from experiencing negative emotions during stressful situations – an SUD-related effect that may be particularly attractive to individuals with PTSD.

Posttraumatic stress disorder-substance use disorder. Few published reports have employed neuroimaging to better understand PTSD-SUD comorbidity. However, Semple and colleagues (e.g., Semple et al., 1996, 2000) have produced a line of research using PET and an auditory continuous performance task with individuals diagnosed with PTSD and a history of SUD (i.e., cocaine and alcohol use disorders). In this series of studies, PTSD-SUD individuals evidenced significantly higher regional cerebral blood flow in the right amygdala and left parahippocampal gyrus than healthy controls during the auditory

continuous performance task. Healthy controls had higher regional cerebral blood flow in the frontal cortex at rest and during the task than PTSD-SUD individuals. The authors suggested that the increased regional cerebral blood flow in the amygdala may be related to the role of amygdala in attention and fear conditioning (see Armony & LeDoux, 1997) and also may be associated with cocaine use. Future studies that compare brain function in individuals with PTSD, SUD, and comorbid PTSD-SUD, are likely to advance our understanding significantly of the relation between PTSD and SUD and why these disorders so commonly co-occur.

Neuroendocrine Studies

There is mounting evidence that some victims of extreme stress experience biological changes, particularly in the neuroendocrine system implicated in the stress response. The HPA axis has been shown to have functional importance during stressful situations. When stress is experienced in a healthy person, a cascade of neurobiological events is triggered. The paraventricular nucleus of the hypothalamus is the primary source of the hypothalamic peptide, corticotrophin releasing factor (CRF), which is the main physiological regulator of pituitary adrenocorticotrophin releasing hormone (ACTH) secretion. Within the anterior pituitary, CRF interacts with a G protein to release ACTH. ACTH stimulates the secretion of glucocorticoid from the adrenal cortex. In humans, the principal glucocorticoid is cortisol. In a classical endocrine feedback manner, when these steroids rise above a certain threshold, they inhibit the synthesis and secretion of CRF within the hypothalamus, which discontinues ACTH secretion, which leads to a discontinuation of cortisol secretion from the adrenal cortex (Turnbull & Rivier, 1999). This process can be referred to as *negative feedback regulation*. Acute stress can produce a transient elevation in plasma cortisol levels and partial resistance to feedback inhibition that persists during and immediately after a stressful stimulus (Charney, 2003). Following stress termination, as glucocorticoid levels decrease, feedback sensitivity returns to normal.

Post-traumatic stress disorder. Neurophysiological abnormalities have been detected in the HPA axis of PTSD patients. Rather than showing the classic stress response described above, the HPA axis appears to be highly sensitized in trauma survivors with PTSD as evidenced by decreased basal cortisol levels and increased negative feedback regulation. Lower basal cortisol levels have been detected in studies of PTSD arising from a variety of traumas (e.g., Glover & Poland, 2002; Yehuda et al., 1995).

A model that characterizes some of the neurobiological alterations seen in PTSD is the *negative feedback model*. This model proposes that PTSD is characterized by chronic or transient increases in the release of hypothalamic CRF due to differences in neuropeptide modulation (Yehuda, 2002). To

examine this model, estimations of hypothalamic release of CRF have been made utilizing neuroendocrine challenge strategies. The CRF challenge test measures ACTH and the adrenal cortisol response to exogenous infusion of CRF and thus provides for an estimate of CRF's effects on pituitary sensitivity. These studies have found blunted ACTH responses to CRF in persons with PTSD (e.g., Yehuda, Golier, Halligan, Meaney, & Bierer, 2004). In addition to the CRF challenge, CRF assessments can also be made using metyrapone stimulation tests. Metyrapone is a drug that temporarily prevents adrenal steriodogenesis by blocking the production of cortisol, and thus, releases the pituitary gland from the influences of negative feedback inhibition (Emilien et al., 2000). Metypone administration allows for a direct examination ACTH release from the pituitary without the potentially confounding effects of differing ambient cortisol levels of glucocorticoid receptor responsiveness (Emilien et al., 2000). Using a metyrapone stimulation test, male veterans with PTSD were found to demonstrate increased pituitary activity in the absence of negative feedback compared to healthy male controls (Yehuda et al., 1996). This finding, coupled with the results from CRF challenge studies, provides support for the hypothesis of enhanced negative feedback in PTSD (Yehuda, 2002).

Activation of the sympathetic nervous system also is an important component of the stress response. In response to stress, processes occurring in the sympathetic nervous system result in increased energy to skeletal muscles, increased heart rate and blood pressure, and release of catecholamines. Elevated catecholamine levels have been found in individuals with PTSD (e.g., Lemieux & Coe, 1995; Young & Breslau, 2004) – findings which are consistent with the arousal symptoms of PTSD (Lemieux & Coe, 1995). Abnormalities in HPA axis functioning and increased arousal may place a person with PTSD at risk for developing a co-occurring SUD in an attempt to regulate arousal and the effects of stress on the nervous system.

Substance use disorders. Preclinical studies have examined specific aspects of the stress response that facilitate drug self-administration. Activation of the HPA axis is known to increase dopaminergic neurotransmission in mesolimbic areas (Piazza & Le Moal, 1996). The mesocorticolimbic dopaminergic system is known as the brain reward pathway, and increases in dopamine in this pathway is imperative for drug reinforcement. Thus, stress co-activates brain stress circuits and reward circuits, providing a common neural substrate by which stress may enhance the drug administration experience. Repeated exposure to a stressor or psychostimulant has been found to increase both the magnitude and duration of dopamine in the nucleus accumbens (Meany, Brake, & Gratton, 2002). This process is known as sensitization. The dopamine transporter in the nucleus accumbens appears to involved in the development of this sensitization. Dopamine transmission is regulated through degradation and reuptake. Reuptake occurs through the dopamine transporter system. Psychostimulants inhibit the dopamine transporter, which produces elevations in extracellular dopamine. Elevated dopamine levels in

response to amphetamine administration have been reported in acutely stressed, maternally-separated rats (Meany et al., 2002). This preclinical study suggests that early traumatic experiences may serve as risk factors for drug abuse and may help explain the high comorbidity between stimulant abuse (e.g., cocaine) and PTSD.

Clinical research appears to be consistent with findings from animal studies. For example, results from clinical studies have found that exposure to stress and drug cue imagery, in comparison to neutral imagery, produces significant drug craving, subjective stress, physiological activation (e.g., increased heart rate), activation of the HPA axis, and activation of the noradrenergic pathways (Sinha et al., 2003). The existence of common neural pathways between stress and drug reinforcement, and the sensitization that may occur in these pathways, suggests a significant role for neuroendocrine functioning in the explanation of PTSD-SUD comorbidity.

Post-traumatic stress disorder-substance use disorders. Koob has posited that the interactions of the CRF and noradrenergic systems may function as a feed-forward system under certain conditions, leading to the progressive augmentation of the stress response with the repeated stress exposure characteristic of PTSD. A feed-forward system may represent one neurobiological link between SUDs and PTSD. Stress may stimulate the release of CRF in the locus coeruleus, leading to activation of the locus coeruleus and release of norepinephrine in the cortex, which then stimulates the release of CRF in the hypothalamus and amygdala (Koob, 1999). The interaction between CRF and noradrenergic systems may mediate the symptoms of hyperarousal seen in PTSD, including the exaggerated startle response. Individuals with PTSD may misuse central nervous system depressants in an attempt to interrupt this feed-forward system by suppressing activity at the locus coeruleus. Related to this model, Bremner and associates (1997) measured cerebral spinal fluid concentrations of CRF in patients with chronic combat-related PTSD and normal controls. Importantly, all of the PTSD participants met criteria for an alcohol use disorder and many also met diagnostic criteria for a drug use disorder. Cerebral spinal fluid concentrations of CRF were considerably higher in the PTSD patients than in the healthy controls.

In sum, the studies reviewed here suggest that drugs of abuse acquire their reinforcing properties through a sensitized reward pathway resulting from chronic stress and/or reductions in anxiety via substance use. However, drugs of abuse result only in short-term anxiety reductions and thus chronic use is needed to maintain the anxiolytic effects. This pursuit of anxiety/arousal reduction, which may be negatively reinforcing, could lead to substance dependence. Furthermore, there is some evidence that elevations in substance use symptoms is associated with worsening of PTSD symptoms (e.g., Back et al., 2006; Brown et al., 1998; Saladin et al., 1995). These findings may help to explain how PTSD symptoms are maintained, and possibly exacerbated, by chronic substance use.

Summary and Conclusions

The literature examining associations between PTSD and SUDs has grown substantially in the past 15 years. This growth has addressed some questions about this comorbidity, but many others still are left unanswered. A review of the literature supports a number of different etiological models of PTSD-SUD comorbidity, including the High Risk and Self-Medication Hypotheses, shared vulnerability, and SLT processes. Additionally, a number of mechanistic variables that may be implicated in this comorbidity also have been identified.

Though the PTSD-SUD literature is indeed complex, at least one dominant theme emerges – the role of negative emotion and affect. Across the clinical and experimental literature, negative affect is a central feature of both PTSD and SUDs independently, and appears to be at least one primary shared pathway in the comorbidity of the two disorders.

Negative affect is diagnostically central to PTSD; it is experienced when reminders of the traumatic event are present and when an individual with PTSD experiences trauma-related nightmares, memories, or flashbacks. Many individuals with PTSD also report irritability that they attribute to their traumatic experience (APA, 2000). In the PTSD psychophysiology literature, negative affect is viewed as such a key component of the disorder that it is almost always measured as a dependent variable in some form. As described earlier, when individuals with PTSD are presented with trauma-related stimuli they report greater negative affect (e.g., fear) and distress in response to the trauma-related cues compared to non-PTSD controls (e.g., Keane et al., 1998; Orr et al., 1998). Physiological arousal, consistent with the experience of negative affect (i.e., fear, distress, anxiety), also is reported in this literature. In the neuroendrocrine literature, individuals with PTSD have consistently shown alterations in stress responding (see Yehuda, 2002). Yehuda suggests that these abnormalities may represent both a pre-existing risk-factor to develop PTSD in the face of extreme stress for some people, but in others, a response that may develop over time due to the physiological demands of living with PTSD symptoms. Whether these abnormalities in neuroendrocrine functioning are related to the marked sensitivity to anxiety (i.e., AS) demonstrated in individuals with PTSD (e.g., Taylor et al., 1992) is unknown. Parallel to neuroendocrine studies, neuroimaging studies of PTSD have also found abnormalities in brain regions thought to be important to emotional processing (e.g., Shin et al., 2001), particularly processing of fear (e.g., Griffin & Berry, 2004). Together, these psychophysiological, neuroendocrine, and neuroimaging studies suggest abnormalities or alterations in emotional responding and processing of negative emotion in individuals suffering with PTSD.

In the SUD literature, the role of negative emotion is equally important (see Baker et al., 2004). Data from experimental studies have consistently shown strong drug-relevant reactivity (e.g., drug craving) to negative emotion manipulations (e.g., Childress et al., 1994; Cooney et al., 1997). These findings

are supported by studies on treatment relapse. For example, in a large study examining reasons for treatment relapse, alcohol dependent individuals listed negative emotion-related situations as the most common relapse trigger (Lowman et al., 1996). Again, looking at the AS literature, recent studies have found that SUD individuals appear to be have high AS (e.g., Kushner et al., 2001) and AS study participants are quite sensitive to the fear damping effects of alcohol (e.g., Stewart & Pihl, 1994). Preclinical neuroendocrine studies have found that stress activates neural pathways commonly activated by drug administration (Piazza & Le Moal, 1996), which suggests that stress may enhance drug administration. Neuroimaging studies have also found important potential links between SUD and negative emotion/stress (Pezawas et al., 2002).

In the PTSD-SUD and related literatures, there is a growing body of work that suggests that the experience and regulation of negative emotion and affect is an important component of PTSD-SUD comorbidity (e.g., Bonin et al., 2000; Coffey et al., 2002; Coffey et al., 2006; Conrod et al., 2000; Koob, 1999; Saladin et al., 2003). Future psychophysiological, neuroendorine, and neuroimaging studies that directly compare PTSD-SUD participants to PTSD, SUD, and healthy control study participants are needed to better understand the relative contribution of PTSD and SUD to PTSD-SUD comorbidity. It is also important that other experimental paradigms (e.g., studies of AS, longitudinal studies of PTSD-SUD symptom covariation) be utilized to better understand PTSD-SUD comorbidity and the role of negative emotion in this complex clinical phenomenon. Further, the role of negative emotion in explanatory models of PTSD has yet to be elucidated. An important direction for future research will also be to determine whether negative emotion associated with trauma and PTSD is a causal mechanism that leads to SUDs (consistent with self-medication), whether it is a third variable that may account for this comorbidity (consistent with shared vulnerability models), or whether it is both cause and effect (as described by SLT). Such delineation of this and other factors which may contribute to the etiology and/or maintenance of PTSD-SUD comorbidity, will inform interventions targeting specific mechanisms of effect, and thus may be of significant clinical utility (see Riggs & Foa, this volume).

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Chapter 4
Co-Morbidity of Social Phobia and Alcohol Use Disorders: A Review of Psychopathology Research Findings

Giao Q. Tran and Joshua P. Smith

Various empirical studies have demonstrated a relationship between Social Phobia (SP) and Alcohol Use Disorders (AUD), with the presence of one disorder increasing the risk of having the other by two to three times in epidemiological samples (Kushner, Krueger, Frye, & Peterson, this volume). Epidemiological findings also show SP to be co-morbid with a variety of other Substance Use Disorders (SUD) (see chapter 1), but the literature on psychopathology and causal explanations of SP's association with specific illicit drugs and nicotine is just emerging (e.g., Baker, 2001; Sontag, Wittchen, Hofler, Kessler, & Stein, 2000). Thus, this chapter review focuses on psychopathology research findings for the co-morbidity of SP and AUD, with the goal of using the existing literature to build a conceptual framework to delineate the SP-AUD specific association that may also be useful in guiding the next generation of research on SP and other SUD.

In this chapter we review the literature on a spectrum of current biological and psychosocial explanations for the co-occurrence between SP and AUD. Our literature review places primacy on investigations conducted with clinical/diagnosed and subclinical samples of SP and AUD to reduce redundancy with a recent comprehensive review of this topic (Morris, Stewart, & Ham, 2005) and to avoid possible distraction by results that may not be specific to our population of interest. To provide a context for our review, we begin with an overview of the literature on SP-AUD co-morbidity rates, highlighting the effects of symptom severity on the relationship between SP and AUD. We review empirical studies testing directly and indirectly the following hypotheses on the mechanisms linking SP to AUD: (1) Individuals with SP and AUD are genetically predisposed to both disorders, (2) Neurochemical disturbances are related to the occurrence of co-morbid SP and AUD, (3) Individuals with SP use alcohol because it has anxiolytic properties, and (4) Individuals with SP

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consume alcohol because they expect that alcohol use will reduce social anxiety and/or lack confidence in their ability to abstain or moderate their drinking in stressful social situations. The initial results in these research areas suggest that both biological and cognitive factors can account for the co-morbid relationship of SP and AUD. Our chapter concludes with a preliminary model of how genetics, neurobiology, cognitive, and social learning experiences might be considered jointly to provide an integrative and more complete understanding of SP-AUD causal mechanisms than can be achieved by focusing on any single causal pathway alone.

Prevalence of Co-morbid Social Phobia and Alcohol Use Disorders

AUD and SP are the second and third most prevalent psychiatric disorders in the United States, occurring at the rates of 14.1% and 13.3%, respectively (Kessler et al., 1994). In the National Comorbidity Survey conducted with epidemiological samples, the lifetime prevalence of alcohol abuse or dependence was about twice as high (24% vs. 14%) among people with SP as among those without this disorder (Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996; see also Kushner et al., this volume). Furthermore, there is an emerging body of data showing that the strength of relationship between SP and AUD is moderated by the severity of the other condition. The following section focuses on data that suggest moderating effects of symptom severity, which have not been previously reviewed.

Severity of Alcohol Dependence

Two investigations with clinical and community samples showed that individuals with SP have higher rates and severity of alcohol dependence than comparator groups, despite little, if any, difference in quantity and frequency of alcohol consumption. Thomas, Thevos, and Randall (1999) found that compared to alcoholics without SP ($n = 397$), individuals with co-morbid SP and alcohol dependence ($n = 397$) endorsed more severe alcohol dependence despite no differences in quantity and frequency of alcohol consumption. Also, in a study comparing treatment-seeking individuals with SP ($n = 54$) or dysthymia ($n = 23$) with normal controls ($n = 27$), typical drinking levels did not differ across groups (Ham, Hope, White, & Rivers, 2002). This finding is notable, considering the research suggesting that SP participants are significantly more likely to be dependent on alcohol compared to dysthymic individuals (e.g., Kessler et al., 1997).

Researchers have suggested several interpretations for these contrasting results for alcohol consumption and severity of alcohol dependence. Thomas et al. (1999) noted that their results may have reflected an artificially inflated severity of alcohol dependence among alcoholics with SP compared to

alcoholics without SP because their alcohol dependence measures (Alcohol Dependence Scale and Alcohol Dependence module of the Structured Clinical Interview for DSM-III-R) were also sensitive to overlapping anxiety symptoms. There was substantial overlap between these measures' alcohol withdrawal symptoms (e.g., anxious feelings, shakes, racing heart, sweating, etc.) and anxiety symptoms that SP individuals experience. In addition, the instruments used to assess alcohol consumption in the above studies may not specifically target the drinking patterns most relevant to socially anxious individuals. Their alcohol use measures assessed overall or typical consumption frequency and quantity rather than frequency of heavy drinking episodes, which is more characteristic of socially anxious individuals' drinking patterns when they do drink.

Investigators have also suggested that the rates and severity of alcohol dependence are not an artifact of the measurement methods, but instead indicate that individuals with co-morbid SP and alcohol dependence are more psychologically dependent on alcohol than alcoholics without SP, in spite of no differences in overall quantity or frequency of use. This position is supported by findings showing that compared to alcoholics without co-morbid SP, those with SP purposively drink alcohol to enhance their social functioning (e.g., Thomas et al., 1999) and reported significantly greater difficulties in controlling alcohol use during their worst lifetime period (Lepine & Pelissolo, 1998). Also supporting the psychological dependence hypothesis is Stewart, Morris, Mellings, and Komar's (2006) finding that coping motives for drinking explained the positive relationship between social anxiety and alcohol problems, despite a lack of an association between social anxiety and drinking levels. Further research is necessary to determine whether method factors or psychological dependence better account for these findings.

Severity of Social Phobia

Two investigations with community samples revealed another counterintuitive finding on the moderating effect of social anxiety severity—that individuals with sublinical social anxiety showed higher risk for alcohol dependence than those who met diagnostic criteria for SP. In their prospective study, Crum and Pratt (2001) found that individuals with subclinical SP ($n = 84$) showed a significantly higher risk for developing an AUD than those with clinical SP ($n = 33$) or no psychiatric disorder ($n = 1044$). Similar findings emerged in the Zurich Cohort Study of Young Adults (Merikangas, Avenevoli, Acharyya, Zhang, & Angst, 2002), which found that the adjusted odds ratio for a co-morbid AUD among individuals with subclinical SP ($n = 70$) was almost double the ratio found among those with clinical SP ($n = 36$). Crum and Pratt (2001) provided two hypotheses to account for these findings: (1) those with clinical SP may be more likely to avoid anxiety-producing

situations that may elicit alcohol use, and (2) individuals with clinical SP may seek treatment more frequently, which could result in early identification and intervention for coincident problem drinking. Future prospective studies are needed to examine these hypotheses and understand why individuals with subclinical SP are more likely than individuals with clinical SP to develop a co-morbid AUD.

Summary and Conclusions

Overall, the prevalence of co-morbid SP and AUD indicates that these disorders frequently co-occur. Interesting findings on the severity of AUD and SP are also noteworthy. First, despite similar levels of alcohol consumption, individuals with SP have elevated rates and severity of alcohol dependence compared to alcoholics without SP. Secondly, individuals with subclinical levels of SP are more likely to have a co-morbid AUD than individuals with clinical SP. These counterintuitive findings are worthy of future research efforts to increase our growing understanding of the complex nature of SP-AUD co-morbidity.

Genetics of Co-morbid Social Phobia and Alcohol Use Disorders

Research highlighting the role of genetics in the etiology of co-morbid SP and AUD can provide a rich empirical resource for delineating the linkage between these disorders. Both twin and family studies have been conducted to investigate the disorders' genetic relationships.

Twin Studies

The twin study method is based on the knowledge that monozygotic twins share all of their genes and dizygotic twins share about 50% of them. Any excess degree of similarity between the monozygotic twins when compared to the dizygotic twins should be due to the influence of genes because all twin pairs are assumed to share the same respective family environments. To date there have been two published twin studies that examined co-morbidity of AUD and SP disorder/symptoms.

In a study with 2,431 pairs of female adolescent twins, Nelson et al. (2000) found that SP, AUD, and major depressive disorder (MDD) shared to varying degree a common additive genetic risk factor. However, AUD also had a disorder-specific additive genetic component, indicating that AUD had

a unique genetic risk factor not shared by SP or MDD. The three disorders did not share any common environmental risk factors. Knopik and colleagues (2004) conducted a study with 2,723 pairs of monzygotic and dizygotic twins to determine the genetic effects on alcohol dependence risk after controlling for other psychiatric factors, including social anxiety problems as determined by a non-diagnostic measure. Based on the residual heritability after accounting for genetic and environmental risk factors, the authors concluded that social anxiety, along with other psychiatric problems, played only a minor role in mediating genetic risk of alcohol dependence. The limited data from these two twin studies suggest that genetics may play a role in the co-morbidity of SP and AUD, though the extent and nature of their genetic link remains to be tested with investigations focusing specifically on this co-morbid relationship.

Family Studies

Family studies were created to explore genetic contributions by examining patterns of familial aggregation of a disorder among relatives of affected probands (individuals with the index disorder). To investigate the genetic influences involved with co-morbid disorders, family studies are designed to inspect patterns of co-aggregation of both disorders. The constellation of familial aggregation provides evidence for or against specific mechanisms of co-morbidity (Merikangas, 1990). Results from family studies can suggest one of two potential mechanisms for the development of a co-morbid condition: (1) a cross-transmission mechanism with the occurrence of each disorder representing an alternative manifestation of shared (common) risk factors, or (2) a causal mechanism with one of the co-morbid disorders predisposing an individual to develop the counterpart disorder.

To demonstrate that co-morbid SP and AUD occur based on cross-transmission, probands with pure (non-co-morbid) forms of either disorder must have relatives at risk for (1) the proband's disorder alone, (2) the co-morbid disorder that the proband does not have, and (3) co-morbid SP and AUD. Alternatively, to show that the co-morbid disorders are causally linked and not connected through cross-transmission, probands with either SP or an AUD must (1) have relatives at risk for the proband's disorder alone and (2) have relatives at risk for the proband's disorder plus the co-morbid condition, but (3) *not* have relatives at risk for the counterpart disorder alone (i.e., the disorder that the proband does not have). For example, if probands with SP have relatives at risk for SP and co-morbid SP and AUD, but do not have relatives at risk for an AUD alone, then the results would indicate SP is causally related to AUD as the alcohol-related disorders do not occur outside the presence of SP.

The Yale Family Study on the familial aggregation of anxiety and AUD was designed to evaluate whether a cross-transmission or causal mechanism better accounts for the relatively frequent co-morbidity of these disorders (Merikangas et al., 1998). Results of this study showed a significant risk for SP among relatives of probands with SP, along with a significant 2.4 odds ratio for alcoholism among socially phobic relatives of probands with SP. Notably, the association was stronger for women and alcohol dependence than men and alcohol abuse, respectively. However, SP in the probands did not increase the risk for a pure AUD among their relatives. Taken together, these results suggest that the two disorders do not share common genetic risk factors by the cross-transmission mechanism, and that SP can cause or contribute to the development of co-occurring AUD.

Summary and Conclusions

These twin and family studies provide an intriguing etiological perspective on SP-AUD co-morbidity. Notably, Merikangas et al. (1998) finding that SP was causally linked to the development of AUD is consistent with clinical studies indicating that SP typically predates AUD in this co-morbid condition (see chapter 1). Overall, these results suggest that both SP and AUD are genetically influenced, but the transmission of this co-morbid condition occurs in a sequential SP to AUD pattern. However, further study is necessary to replicate these findings and determine how these disorders are coupled and transmitted in affected individuals and their relatives.

Neurobiology of Co-morbid Social Phobia and Alcohol Use Disorders

Although few studies have been designed to illuminate the neurobiological factors associated with the co-occurrence of SP and AUD, a review of research examining each independent condition provides useful insight into the neurobiological factors common to both. Data from these two bodies of literature implicate serotonin, gamma amino butyric acid (GABA), and dopamine as potential contributors to co-morbid SP and AUD.

Serotonin (5-hydroxytryptamine, 5-HT)

Pharmacological challenge studies, wherein dynamic measurements after administration of a substance are used to probe endocrine or neurotransmitter

functioning, have provided a useful window into the potential role of serotonin in SP. Both m-chlorophenylpiperazine (m-CPP), a partial serotonin agonist, and fenfluramine, a serotonin releasing agent, have been used in challenge studies to evaluate the role of serotonin in SP (e.g., Hollander et al., 1998, $N = 81$). The results of these studies demonstrated an increase in anxiety after administration of the challenge agents, implicating serotonin dysfunction in SP. The potential role of serotonin in AUD has also been illuminated in empirical studies. For example, Schuckit et al. (1999) followed a group of 41 men ages 21 to 35 who showed low alcohol response, a risk factor for alcoholism because it is a precursor to high tolerance, in a 15-year pilot prospective study and found that low alcohol response was also related to serotonin dysfunction.

The role of serotonin in SP and AUD is also shown in several studies wherein selective serotonin reuptake inhibitors (SSRIs), medications designed to increase serotonin levels by blocking serotonin reuptake, alleviated symptoms of SP (e.g., Stein et al., 1998, $N = 187$) and AUD (e.g., Malcolm, Anton, Randall, & Johnston, 1992, $N = 67$). Further, in a small clinical trial ($N = 15$) testing the efficacy of paroxetine in treating co-morbid SP and AUD, Randall, Johnson, et al. (2001) found that paroxetine yielded improvement for each co-morbid disorder and that reductions in alcohol-related symptoms typically lagged behind SP symptom relief. Notably, the differential treatment response suggests that AUD symptom reduction may have been related to relief from SP symptoms. Another interesting finding is that buspirone, a serotonin partial agonist, has been found effective for alcoholism only when the AUD is accompanied by an anxiety disorder such as SP (see Johnson, 2004). Taken together, results of the reviewed studies suggest that serotonin dysfunction is involved in both SP and AUD. Extrapolating from these findings, it can be suggested that serotonin may be functionally involved in the development of co-morbid SP-AUD, as temporary reductions in social anxiety may result from the increased serotonin activity achieved through alcohol consumption.

Gamma Amino Butyric Acid (GABA)

The role of GABA dysfunction in SP is suggested by findings that benzodiazepines such as alprazolam and clonazepam, which are believed to act on the $GABA_A$ receptor, are effective at providing short-term relief of SP symptoms. For example, Davidson et al. (1993) found in a placebo-controlled clinical trial that a large difference emerged in response rates between individuals with SP receiving clonazepam (80%) and those receiving placebo (20–25%). Research has also shown GABA functioning to be related to alcoholism (Nutt & Malizia, 2001). Lingford-Hughes and colleagues (2005) found a

reduced sensitivity of GABA-BZD receptors for an agonist medication, midalozam, among alcoholics ($n = 11$) compared to a control group ($n = 10$), which implicates GABA dysfunction in AUD. Thus, GABA dysfunction is implicated in both SP and AUD. Furthermore, research on GABA has also revealed a potential direct connection between anxiety and alcoholism, as Nutt (1999) recognized that alcohol's capacity for GABA augmentation is related to its anxiolytic effects. Essentially, as alcohol consumption enhances GABA activity, the increase in GABA results in decreased anxiety levels. GABA may be involved in the development of co-morbid SP and AUD through this receptor mechanism.

Dopamine

A large body of research has indicated that dopamine is involved in the reinforcing properties of alcohol consumption. The relationship between dopamine and alcohol consumption has been shown across animal and human experimental studies, as well as clinical studies examining treatment of AUD with dopamine agonists (Tupala & Tiihonen, 2004). Dopamine involvement in SP is suggested by neuroimaging studies (e.g., Schneier et al., 2000, $N = 20$), along with findings that social anxiety is induced by drugs that block dopamine transmission (Mikkelsen, Detlor, & Cohen, 1981, $N = 15$). Research has also shown that dopamine-enhancing monoamine oxidase inhibitors (MAOIs) are efficacious in reducing the symptoms of SP (Liebowitz, Campeas, & Hollander, 1987), though this medication class is not commonly used to treat SP. Across studies, it appears that dopamine dysfunction is related to both SP and AUD. Furthermore, dopamine may be functionally involved in the development of co-morbid SP and AUD, as alcohol consumption increases dopamine activity, which decreases social anxiety.

Summary and Conclusions

A variety of investigations have suggested that the serotonin, GABA, and dopamine neurotransmitter systems may be involved in both SP and AUD. However, future research is necessary to further evaluate whether and how these neurotransmitters are involved in the co-occurrence of SP and AUD. Also, considering that neurotransmitters do not function in isolation but instead are interconnected, additional efforts that examine the interplay of these neurotransmitters may afford a more comprehensive view of their roles in the co-morbidity between SP and AUD.

Effects of Alcohol on Social Anxiety

Research on the co-morbidity between SP and AUD indicates that SP symptoms often predate alcoholism by several years (Thomas et al., 1999; Tran & Haaga, 2002), and that SP is typically primary when the two disorders co-occur (Kessler et al., 1997; Kushner, Sher, & Beitman, 1990). Based upon this typical order of onset, the most popular explanatory models involve some form of a self-medication hypothesis in which individuals with SP use alcohol to reduce their social fears. In particular, alcohol consumption has been proposed as negatively reinforcing to those experiencing social anxiety due to its ability to reduce tension (Conger, 1956) and dampen one's stress response (Sher, 1987). Along these lines, it has been suggested that alcohol exerts its effects by inhibiting an individual's neurological stress response or by disrupting the self-appraisal process (Sayette, 1993). A number of clinical reports and investigations lend credibility to the self-medication hypothesis, as individuals with SP frequently report using alcohol to cope with their anxiety symptoms (Carrigan & Randall, 2003). Also, Kushner, Abrams, and Borchardt (2000) concluded in a recent review that anxiety disorders such as SP can initiate and maintain alcohol use. Yet, despite the converging evidence for the self-medication hypothesis, research evaluating whether alcohol actually reduces social anxiety has produced overall mixed results.

Empirical Studies

To date only three published studies have directly examined the acute effects of alcohol on social anxiety in individuals with diagnosed SP, each using an alcohol versus placebo design and a speech challenge as an analogue social anxiety situation. It is noteworthy that across time, each successive study has improved upon the design of the study preceding it.

Naftolowitz, Vaughn, Ranc, and Tancer, (1994) initiated this line of research in a study with individuals diagnosed with DSM-III (American Psychiatric Association, 1980) SP ($n = 9$) and age- and sex-matched controls ($n = 9$). This study used a within-subject design in which all participants received a low dose of alcohol (approximately .03% Blood Alcohol Concentration [BAC]) prior to a 10-minute speech on the first study day and placebo prior to another speech on the second study day. The results indicated that alcohol did not reduce subjective anxiety ratings, or alter hormone levels, blood pressure or pulse in the expected directions. However, as noted by the authors, several study limitations may have hindered clear conclusions to be drawn from their findings—a lack of counterbalancing of order of within-subject study conditions, insufficient power due to very small sample size, alcohol dosage being too low to elicit anxiolytic effects, limited credibility of the placebo drink, and low external validity of the social anxiety stressor.

The next study, which included 40 individuals diagnosed with DSM-III-R (American Psychiatric Association, 1987) SP, produced similar results (Himle et al., 1999). All participants in this study engaged in two impromptu speeches across a single experimental session. Each participant received placebo prior to the first speech challenge, but prior to the second speech half of the participants received alcohol while the other half again received placebo. The hypothesis that alcohol reduces social anxiety was again not supported, as no evidence emerged in subjective anxiety ratings, heart rate, or negative versus positive cognitions between the alcohol and placebo conditions. This study improved upon the Naftolowitz et al. (1994) study by enhancing power through inclusion of more participants and using a between-subject design. Despite these improvements, some remaining limitations may have reduced the finding of significant group differences; these included use of alcohol dosage (.03% BAC) too low to produce anxiolytic effects, a sample size being too small to detect medium effect sizes, a speech challenge not producing sufficiently high anxiety, and 25% of the participants being on anxiolytics medications that may have reduced alcohol's effects for these individuals.

Abrams, Kushner, Medina, and Voight (2001) conducted the most recent study of alcohol's direct effects on social anxiety. In contrast to previous research, these investigators employed a three- group design with an alcohol group that expected and received alcohol ($n = 20$), a placebo group that expected but did not receive alcohol ($n = 21$), and a control group that expected and received a non-alcoholic beverage ($n = 20$). The use of this design allowed an evaluation of not only the pharmacological effects of alcohol (alcohol group vs. placebo group), but also the expectancy effects of alcohol (placebo group vs. control group). Of the 61 participants in this study, 90% met DSM-IV (American Psychiatric Association, 1994) criteria for SP, and 10% met all criteria except for the criterion that social anxiety significantly interferes with functioning. All participants engaged in three consecutive 45-minute phases, including a pre-beverage speech phase, a beverage phase, and a post-beverage speech phase. The results of this study showed that both the pharmacological and expectancy effects of alcohol additively contributed to a reduction in social anxiety.

The design used by Abrams and colleagues provided the best investigation to date on the acute effects of alcohol on social anxiety. Noteworthy is this study's targeted .05% BAC in the received/expected alcohol condition, a level greater than the average .03% BAC in the two prior investigations; the .05% BAC is an important methodological change because this BAC level typically produces desired alcohol effects of relaxation and tension reduction in moderate drinkers. Furthermore, the speech challenge produced a level of anxiety higher than that found with the study conducted by Himle and colleagues (1999), and the placebo manipulation check indicated that participants reported subjective feelings of intoxication. Finally, the inclusion of a control beverage condition allowed for an evaluation of the contribution of alcohol expectancies (expected

alcohol effects based on the belief that one consumed alcohol) to the effects of alcohol on social anxiety.

Summary and Conclusions

It is difficult to draw any firm conclusions regarding the effects, if any, of alcohol on social anxiety. It is notable that with each successive study the methodology has improved, and that the most recent and most methodologically sound study (Abrams et al., 2001) did reveal a pharmacological effect of alcohol on social anxiety. Further research is needed in this area with additional improvements in research design to investigate more fully the acute effects of alcohol on SP. Following Abrams et al.'s lead, the effects of expectancy on subjective alcohol effects should be considered in future alcohol administration investigations. The next section on the impact of cognitive variables, especially alcohol expectancies, on alcohol consumption in socially anxious individuals further demonstrates the importance of cognitive variables in the co-morbidity of SP and AUD.

Cognitive Variables Linking Social Phobia to Alcohol Use Disorders

Studies testing the hypotheses that cognitive variables moderate and mediate the relationship between social anxiety and alcohol use are recently growing in number (see recent review by Morris et al., 2005), but very few have been conducted with diagnosed/clinical samples of SP and/or AUD participants. Most of these studies were conducted with undergraduate non-clinical samples consisting of participants who varied widely in their social anxiety or alcohol use problems, with the majority having no or few symptoms associated with these problems. These studies examined the role of social-facilitating alcohol outcome expectancies as a moderator that determines the strength and/or the direction of the relationship between non-clinical social anxiety and alcohol use or drinking related problems. In addition to reviewing research on alcohol outcome expectancies, this chapter also considers a broader range of cognitive variables specific to social situations, coping drinking motives, problem-focused coping, and drink refusal self-efficacy where empirical data suggest that these variables might contribute substantively to understanding the roles of cognitive factors linking SP and AUD. In contrast to alcohol expectancies, drinking motives are reasons why people drink (e.g., because it makes social gathering more sociable). Problem-focused coping is the use of cognitive and behavioral strategies in stressful situations to solve a current problem (e.g., coming up with a couple of different solutions to the problem), and

drink refusal self-efficacy addresses one's confidence in his or her ability to resist alcohol consumption in high-risk situations.

Social learning models provide a useful framework for considering the explanatory roles of alcohol cognitive variables in the co-morbidity of SP and AUD. Consistent with more general principles of social learning theory (Abrams & Niaura, 1987), Burke and Stephens (1999) proposed a social cognitive model to explain the relationship of social anxiety to heavy drinking in college students that is also applicable to conceptualizing the relationship between SP and AUD in general. Most relevant to this discussion is the model's proposal that socially anxious individuals are likely to drink heavily when both of the following conditions exist: (1) they believe that alcohol facilitates social interactions, and (2) they lack other strategies to cope with social anxiety, skills to moderate heavy drinking, and/or drink refusal self-efficacy (low confidence in their ability to resist heavy drinking) in social situations. Specifically, this model indicates that the relationship between social anxiety and heavy drinking is moderated or determined by both alcohol expectancies for social facilitation and coping skills/drink refusal self-efficacy specific to social drinking situations.

Non-clinical Studies Testing Alcohol Expectancies' Moderator Effects

Studies with undergraduate non-clinical samples often did not meet criteria required to test a mediator hypothesis because a direct, positive relationship between social anxiety and alcohol use was not found (Baron & Kenny, 1986). Thus, a moderator hypothesis was consequently tested in these investigations. Two separate studies ($N = 229$ and $N = 521$) conducted by Tran and colleagues at a Northeastern university and a Midwestern university in the United States found very similar results indicating a moderating effect of social-facilitating alcohol expectancies on the relationship between social anxiety and alcohol use/problems, but not in the exact direction initially predicted by Tran, Haaga, and Chambless (1997). Specifically, among participants who did not expect alcohol to reduce their anxiety in social situations, high-social-anxiety participants reported *lower* alcohol consumption; high- and low-social anxiety participants who expected alcohol to reduce their social anxiety *did not differ* in their alcohol consumption (Tran et al., 1997; Tran, Smith, Rofey, & Corcoran, 2002). Only part of these results was replicated in studies with undergraduates conducted by three other research groups (Bruch, Heimberg, Harvey, & McCann, 1992; Bruch, Rivet, Heimberg, & Levin, 1997; Eggleston, Woolaway-Bickel, & Schmidt, 2004; Ham & Hope, 2005). Similar to our result for the low expectancy group, other groups found that social anxiety/shyness was associated with less alcohol consumption/problems, when variance accounted for by alcohol expectancies was considered; however, this effect was a main effect of social anxiety/shyness on alcohol consumption/problems in these studies (Ns = 187–543),

rather than as an interaction effect of social anxiety moderated by low level of alcohol expectancies specific to social situations.

This protective function of social anxiety against high alcohol consumption found in non-clinical undergraduate samples contradicts the consistent epidemiological findings that AUD are more prevalent among individuals with clinical and subclinical SP than found in the general population (e.g., Magee et al., 1996). Along with the fact that moderator studies have been extensively reviewed recently, these conflicting findings reinforce our decision to provide a more detailed coverage of investigations that examined cognitive variables in individuals with clinically and subclinically severe SP and AUD symptoms. Including studies conducted with subclinical social anxiety participants in this review is important in light of the two previously-discussed investigations showing higher prevalence of AUD in individuals with subclinical social anxiety compared to those with SP (Crum & Pratt, 2001; Merikangas et al., 2002).

Studies with Socially Anxious Individuals

Ham and colleagues conducted two studies that found support for situation-specific alcohol expectancies, both of which excluded individuals with co-morbid AUD. In the first study, Ham et al. (2002) compared positive alcohol expectancies in adults with SP ($n = 54$) to those with dysthymia ($n = 23$) and normal controls without any psychiatric disorders ($n = 27$). Their results showed that SP individuals reported stronger expectancies of alcohol's social assertion/facilitation effect than dysthymic individuals; however, no group difference was observed on expectancies of general tension reduction. This situational effect found within the domain of tension/anxiety reduction expectancies was also repeatedly found in investigations conducted by Tran and colleagues (Tran et al., 1997; Tran et al., 2002; Tran, Anthenelli, Smith, Corcoran, & Rofey, 2004). In addition, SP participants were also found to differ from normal controls on expectancies of social assertion, general tension reduction, and global positive changes. Ham, Carrigan, Moak, and Randall (2005) replicated the group difference on expectancies of social assertion when they compared undiagnosed socially anxious ($n = 17$) and non-socially anxious ($n = 45$) individuals from the community. Furthermore, partial correlations with social anxiety as covariates showed that higher social assertion expectancies were related to greater alcohol consumption. It should be noted that the socially anxious participants in this study and the next two studies were selected with stringent criteria such that most would likely meet criteria for SP (c.f. Thomas, Randall, & Carrigan, 2003).

Including research participants that partially overlapped with Ham et al.'s (2005) study sample, the research group at the Medical University of South Carolina published two studies on coping motives for drinking using both explicit and implicit cognitive measures. Results from Thomas et al.'s (2003)

study showed that socially anxious community volunteers ($n = 23$) were more likely than non-anxious controls ($n = 23$) to report using alcohol to feel more comfortable, avoiding social situations if alcohol was not available, and experiencing greater anxiety relief from alcohol use. Carrigan, Drobes, and Randall (2004) found that explicit cognitive measures of drinking to cope also predicted response latency to alcohol-related and social-threat words in the Stroop test, an implicit cognitive measure, among community volunteers ($N = 87$) with a wide range of social anxiety and alcohol use patterns. It is evident from the recent publications that leading alcohol and co-morbidity investigators view coping motives as a promising cognitive mediator to account the co-morbidity of SP and AUD.

Studies with Socially Anxious and Problem-Drinking Individuals

To date four studies have been conducted with participants who reported both social anxiety and alcohol use problems, three of which included participants with diagnosed SP and AUD based on structured diagnostic interviews. Thomas et al. (1999) found that treatment-seeking socially phobic alcoholics ($n = 397$) from Project MATCH reported more symptoms of alcohol dependence and more frequent drinking to improve sociability than alcoholics without SP ($n = 1329$). Abrams and Kushner (2004) further demonstrated in a well-controlled experimental study that general tension-reduction alcohol expectancies marginally moderated the association between consumption of placebo beverage and anxiety responding in individuals with SP. This result showing that alcohol expectancies tended to produce an apparent dose-response psychological effect in the absence of a physical alcohol effect confirms the power of alcohol expectancies in motivating drinking behavior. Furthermore, prior studies demonstrating situation-specificity of general versus social tension-reduction expectancies suggest that this relationship between alcohol expectancies and placebo consumption would likely have been stronger if expectancies of social facilitation, rather than expectancies of general tension reduction had been used in the Abrams and Kushner study.

Drawing from cognitive theory of SP (Beck & Emery, 1985) and a social-learning model of AUD (Abrams & Niaura, 1987), Tran and Haaga (2002) compared three groups of community volunteers on coping responses and alcohol outcome expectancies to determine what distinguishes SP individuals with AUD from those without AUD. The comparison groups included SP participants with current alcohol abuse or dependence ($n = 19$), SP individuals without lifetime AUD ($n = 19$), and normal controls without any current psychiatric disorder ($n = 21$). All three groups differed from each other on the strength of their social facilitating alcohol expectancies and the frequency of which they used problem-focused coping in an alcohol-accessible stressful social situations, which is intended to reflect their general coping

style with social fears when alcohol is present. Specifically, SP-AUD individuals reported the strongest social-facilitating alcohol expectancies and the least use of problem-focused coping, while SP-only individuals scored between normal controls' and SP-AUD individuals' scores on the expectancy and coping measures. Together with Ham et al. (2002, 2005) results, Tran and Haaga's findings suggest that having elevated social anxiety puts one at risk for developing an AUD through decreased ability to use problem-solving strategies in social situations and greater expectations for alcohol's social-facilitating and social-anxiety-reduction effects. Additional support for the social learning model of AUD came from Tran et al. (2004) investigation showing that compared to hazardous drinkers with low social anxiety ($n = 76$), those with high social anxiety ($n = 76$, 51% with subclinical and 49% with clinical symptoms) reported stronger beliefs that alcohol facilitates their social interactions and less confidence in their ability to resist alcohol use in situations when others are drinking. Again demonstrating the situation-specificity predicted by the social learning model, the two groups also did not differ on alcohol expectancies and drink-refusal self-efficacy related to general stress reduction.

Summary and Conclusions

Most of the available literature on cognitive variables linking SP to AUD was based on studies investigating alcohol outcome expectancies. The most apparent result that emerged from this body of investigations is that SP individuals hold specific social-facilitating alcohol expectancies that distinguish them from normal controls and individuals having disorders with overlapping symptoms, including major depression and panic disorder. Also, situation-specificity of alcohol expectancies was demonstrated by consistently different patterns of results for expectancies of social facilitation (social anxiety reduction) and general tension reduction. In addition, recent studies also highlight coping drinking motives, self-efficacy, and problem-focused coping as potentially important cognitive variables to consider in accounting for the relationship between SP and AUD. Given the infancy of research on the latter cognitive variables in the SP-AUD co-morbidity literature, further investigations to refine their constructs and measurements with respect to drinking in social situations and in response to social fears would likely facilitate future research on their roles as moderators and mediators of the association between SP and AUD. The finding that the mean scores of SP individuals who have not developed AUD were between the scores of SP-AUD participants and normal controls suggests that these cognitive vulnerabilities may exist on a continuum, putting individuals with SP at increased risk for developing AUD compared to those without SP.

While the above conclusions based on cross-sectional findings are important for developing a working model for how cognitive variables influence the

development of co-morbid SP and AUD, they remain working hypotheses without prospective and further experimental studies that can empirically test causal relationships among social anxiety, potential cognitive mediators, and alcohol use problems in subclinical and clinical populations. Considering prior research indicating a negative or non-significant association between social anxiety and alcohol use in non-clinical undergraduate samples (e.g., Tran et al., 1997; Eggleston et al., 2004), it would be more conceptually sound and statistically appropriate to test for cognitive mediator effects in research samples consisting of individuals with both social anxiety and alcohol use problems.

General Conclusions and Future Directions

Review of the literature shows initial support for the hypotheses that genetics, neurobiology, and cognitive factors are involved in the co-morbidity of SP and AUD. As with any new areas of research, causal interpretations of the empirical data are limited by the small number of investigations in each research domain and methodological limitations, especially the use of cross-sectional methods. Given the correlational and cross-sectional designs that have been largely used to date, these findings remain working hypotheses to be tested in prospective and experimental investigations.

It is clear from the literature reviewed that much remains to be done in explicating the causal mechanisms for SP-AUD co-morbidity. Both model development and empirical studies are needed to facilitate this effort. Traditionally, biological and cognitive models to explain causal mechanisms are developed and tested independently. Such independent testing does not provide an integrative and complete picture of factors that may jointly influence development of AUD in SP individuals. On a practical level, recruitment of co-morbid research participants whose prevalence rates are lower than the singly diagnosed can be challenging and would benefit from collaborative efforts of investigators studying different causal contributors to the SP-AUD relationship. Based on the current data, we propose a preliminary model of how these variables might be considered jointly. Figure 4.1 provides a schematic representation of this model. In this model, genetics, neurobiology, and cognitive factors are hypothesized to contribute directly to the development of SP-AUD co-morbidity. Genetic factors are expected to influence neurobiological and possibly cognitive factors that further increase the vulnerability of SP individuals to problematic drinking. Consistent with the limited body of genetic findings, a causal mechanism from SP to AUD is proposed to explain their co-morbidity. Furthermore, any genetic influences on cognitive factors are expected to be moderated by social learning experiences. In particular, socially anxious individuals who have developed alcohol expectancies for social facilitation through vicarious learning or direct experience with alcohol's reinforcing effects may drink to cope with their social anxiety and have a low

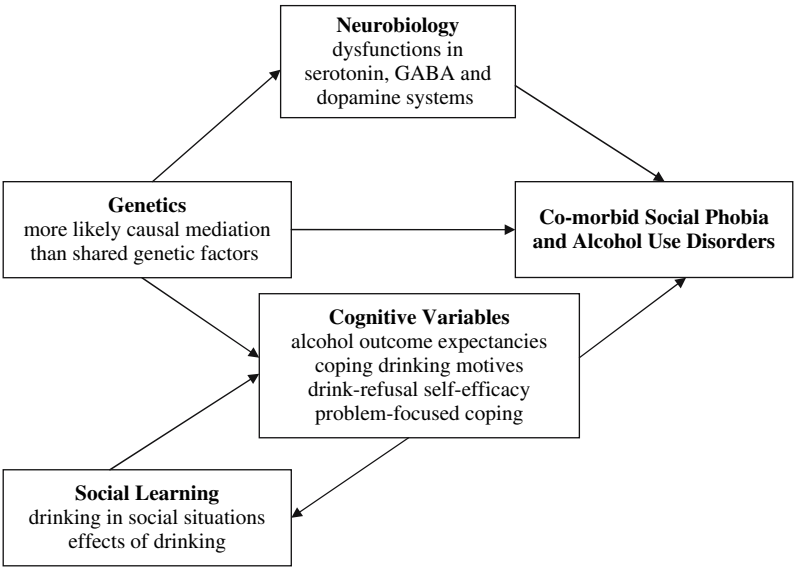

Fig. 4.1 Biopsychosocial model for co-morbidity of social phobia and alcohol use disorders

confidence in their ability to resist using alcohol in social situations. Within the context of this general model, well-developed specific models on how SP is linked to AUD can be developed and empirically tested. Furthermore, our model may provide a framework for building systematic research on the causal mechanisms linking SP to other SUDs. Specific biopsychosocial models of psychopathology may also inform development of comprehensive and ideally integrative treatment for individuals with or at risk for developing co-morbid SP and AUD (for review of current treatments, see chapter 8). Examining co-morbid causal relationships in the context of an integrated biopsychosocial context is consistent with the current trend for interdisciplinary research promoted by the National Institutes of Health, the primary funding source for innovative and scientifically important research on psychopathology and treatment of psychiatric and substance use disorders in the United States.

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Chapter 5
Panic Spectrum Disorders and Substance Use

G. Ron Norton, Peter J. Norton, Brian J. Cox and Shay-Lee Belik

Introduction

There is beguiling evidence that panic spectrum disorders and substance use disorders co-aggregate (see Kushner, Abrams, & Borchardt, 2000; Zvolensky, Feldner, Leen-Feldner, & McLeish, 2005; Zvolensky, Schmidt, & Stewart, 2003 for reviews). Most, but not all, research shows that people with panic spectrum disorders smoke more cigarettes (e.g., Pohl, Yeragani, Balon, Lycaki, & McBride, 1992), drink alcohol more frequently (e.g., Regier et al., 1990), may drop out of alcohol (e.g., Labounty, Hatsukami, Morgon, & Nelson, 1992) and smoking cessation clinics (e.g., Covey, Hughes, Glassman, Blazer, & George, 1994) more frequently, and experience more severe withdrawal symptoms (e.g., Breslau, Kilbey, & Andreski, 1991) compared to people who do not have a mental disorder.

Panic attacks are intense emotional reactions that may include: (1) physical symptoms such as a racing heart and difficulty breathing, and (2) psychological symptoms such as feelings of going crazy. For these emotional reactions to be classified as panic attacks they must either occur "out of the blue" or be excessive to a perceived threat. Panic disorder may be diagnosed when a person experiences "recurrent, unexpected panic attacks followed by at least 1 month of persistent concern about having another panic attack" (American Psychiatric Association [APA]; 2000, p. 433). Panic disorder may or may not include agoraphobia, a marked tendency to avoid situations where the person fears he or she may have a panic attack. For the purposes of this chapter, panic spectrum disorders include panic attacks (a symptom of this category of disorders), panic disorder, and agoraphobia with or without panic attacks. Panic attacks may occur infrequently or very frequently. Unless panic attacks occur frequently, or cause extensive worry and disruption to a person's everyday life, they are not considered to be

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a symptom of a psychological disorder. When panic attacks do produce these problems the person may meet criteria for panic disorder especially if some of the attacks occur "out of the blue." Several of the studies reviewed in this chapter use the term "agoraphobia" as a stand alone diagnosis. Since agoraphobia without panic attacks occurs infrequently (< 5%) in clinical settings (APA, 2000), we are assuming that when agoraphobia is used as a diagnosis it refers to panic disorder with agoraphobia.

This chapter will focus on empirical research assessing the relationship between panic spectrum disorders and: (1) alcohol use and abuse, (2) cigarette smoking, and (3) other substance use and abuse. We will focus on alcohol and smoking because (a) there are large, high quality data sets for both, and (b) they are the two most prevalent substance use disorders.

For each category of substance use, we will assess the research showing its relationships to panic spectrum disorders. We will also attempt to describe the research around substance use, including infrequent use, abuse, and dependence. Substance abuse is defined as "a maladaptive pattern of substance use leading to clinically significant impairment or distress" (APA, 2000, p. 199). Substance dependence includes either the need for larger quantities to achieve the desired effects, or marked psychological and/or physiological symptoms when use of the substance is discontinued. DSM-IV (APA, 1994) criteria require that a person experience symptoms of substance abuse and/or dependence during the past 12 months. DSM-III (1980) criteria only required that symptoms of substance abuse last for one-month. These differences in criteria may have markedly affected prevalence rates, and thus co-morbidity rates as well.

We will examine research showing: (1) prevalence of co-morbidity between substance use and panic spectrum disorders, and (2) when possible, the temporal relationship between substance use and panic spectrum disorders.

Panic Spectrum Disorders and Alcohol Usage

Co-morbidity of Alcohol Use and Abuse and Panic Spectrum Disorders

Several types of studies have estimated the prevalence of co-morbidity between alcohol use and panic spectrum disorders. However, we will focus on clinic-based studies and community surveys. According to a review of the relationship between anxiety disorders and alcohol use disorders by Kushner et al. (2000), the (sometimes marked) differences in prevalence rates may be the result of different ways of assessing panic-related disorders and substance use disorders. As mentioned earlier, it is important to know which diagnostic criteria were used. An additional factor that may lead to differences in prevalence rates is additional co-morbidity. According to Kessler (1997), over 90% of people who

have panic disorder and/or drug dependence are co-morbid with at least one other Axis I disorder.

Clinical research. Bibb and Chambless (1986) conducted one of the first studies to assess the prevalence of alcohol use disorders in patients with agoraphobia with panic attacks. They reported that 22 of their 254 patients (9%) also met Michigan Alcoholism Screening Test (MAST; Selzer, 1971) criterion for alcoholism (5 or more on the MAST). Also, using DSM-III (APA, 1980) criteria, they obtained similar findings: 10% of their patients met criteria for alcohol abuse and 12% for alcohol dependence. In addition, they were able to obtain age of onset data from 16 patients. Of those, 56% reported that agoraphobia began prior to their alcohol problems, 31% reported alcohol problems came first, and 13% stated that the two disorders' onset concurrently. Thyer and colleagues (1986) reported similar findings. They evaluated alcohol abuse in 156 patients who met DSM-III criteria for agoraphobia with panic attacks, panic disorder, simple or social phobia, or generalized anxiety disorder. Patients with agoraphobia had significantly higher MAST scores compared to patients with panic disorder or generalized anxiety disorder.

In one of the first studies to assess panic attacks in patients with alcohol related disorders, Cox, Norton, Dorward, and Fergusson (1989) administered a battery of self-report questionnaires to 144 people attending an inpatient alcohol treatment program. Panic attacks were assessed using a modified Panic Attack Questionnaire (PAQ; Norton, Dorward, & Cox, 1986). Ninety (62.5%) participants reported experiencing one or more panic attacks in the past year and 50.7% reported a panic attack in the past three weeks. Twenty-five percent of those reporting panic attacks in the past three weeks reported that they had been treated for panic disorder in the past. Of those reporting panic attacks, 65% reported experiencing three or more panic attacks in the past three weeks, the minimum required for a DSM-III diagnosis of panic disorder (APA, 1980). Women reported experiencing more frequent and more severe attacks. The majority (83.1%) of those experiencing panic attacks reported that they used alcohol to prevent or reduce the intensity of panic attacks. Finally, 38.9% of those who had experienced panic attacks reported that they began experiencing panic attacks prior to drinking heavily.

In a follow-up study, Norton, Malan, Cairns, Wozney, and Broughton (1989) obtained similar results in a group of 102 male inpatients receiving treatment for alcohol-related problems. Fifty percent of patients reported one or more panic attacks in the past year, with 28% meeting DSM-III criteria for panic disorder. Almost half of those reporting panic attacks experienced panic attacks prior to heavy drinking, with the other half reporting that they began experiencing panic attacks only after they had begun drinking heavily. It is interesting to note that the reported age of onset of heavy drinking was significantly later for those who reported panic attacks prior to heavy drinking ($M = 23.9$ years) compared to those who began heavy drinking prior to experiencing panic attacks ($M = 19.6$ years).

Although the two studies by Norton and colleagues reported higher rates of co-morbidity than did Bibb and Chambless (1986) or Thyer et al. (1986), their data must be considered with some caution. The self-report PAQ, when compared to structured interviews, has been shown to overestimate the number of actual attacks (Brown & Deagle, 1992; Norton, Pidlubny, & Norton, 1999). In addition, the PAQ did not determine if the panic attacks were associated with alcohol withdrawal. Research has shown that acute intoxication and/or withdrawal symptoms in people with alcohol-related disorders are very similar to symptoms of panic attacks (APA, 2000). It is possible that withdrawal symptoms are being misperceived as panic attacks or impending panic attacks which could promote self-medication with alcohol and other substances creating a vicious cycle (George, Nutt, Dwyer, & Linnoila, 1990). More recent clinical studies have produced mixed results with some showing co-morbid alcohol- and panic-related disorders, and others not finding this relationship. For example, in a Spanish study, Segui and colleagues (2001) found that approximately 25% of patients with alcohol, but not drug disorders, met criteria for panic disorder. For those patients with co-morbid panic and alcohol use disorders, the age of onset for alcohol use ($M = 18.7$ years) was significantly younger than age of onset of panic ($M = 28.5$ years). In addition, when the co-morbid patients were compared with those without panic disorder, it was found that those with co-morbidity had more additional Axis I disorders and showed greater clinical severity.

Community surveys. The Epidemiological Catchment Area Survey (ECA) was one of the first major community-based studies to use appropriate sampling procedures and structured interviews to determine the prevalence of mental disorders. Using the ECA data, Regier et al. (1990) were able to estimate the odds of people with panic disorder (and other mental disorders) having a serious alcohol disorder. Diagnoses were made using DSM-III criteria. They found that people having any anxiety disorder were at increased odds of having an alcohol related disorder (Odds Ratio; OR = 1.5) compared to controls. As well, those diagnosed with panic disorder were over three times more likely (OR = 3.3) to also be diagnosed with alcohol dependence. This shows that 35.8% of those with panic disorder also had an alcohol use disorder. They were also over 4 times (OR = 4.4) more likely to be diagnosed with drug dependence. Interestingly, people with panic disorder were not at an elevated risk for drug or alcohol disorders in the absence of dependence. However, Himle and Hill (1991), using the same ECA data, found that people with agoraphobia were twice as likely to meet criteria for alcohol abuse.

Kessler et al. (1997), using data from the National Co-morbidity Study (NCS), obtained data similar to those reported by Regier et al. (1990). Using DSM-III-R criteria, they found that people diagnosed with panic disorder were much more likely than controls to meet diagnostic criteria for alcohol dependence, but not alcohol abuse. For women with panic disorder the Odds Ratio was 2.9 and for men it was 2.3.

Recently, Grant et al. (2004) reported co-morbidity results from the National Epidemiological Survey on Alcohol and Related Conditions (over 40,000 participants). This is the first major survey that has used DSM-IV independent diagnostic criteria. This is notable because, as noted earlier, the symptoms of acute intoxication and/or withdrawal can be very similar to those of anxiety and panic attacks. It was only with the publication of DSM-IV that clear rules were set out for establishing mood and anxiety diagnoses *independent* of symptoms that occur during acute intoxication and/or withdrawal. According to the rules laid out in DSM-IV, independent mood and anxiety diagnoses can be made in one of two ways. First, the mood or anxiety disorder is established before substance use. Second, an independent diagnosis can be made if the mood or anxiety disorder persists for more than four weeks after the cessation of intoxication or withdrawal.

Using these criteria for independent diagnoses, Grant et al. (2004) found that among people diagnosed with a 12-month substance use disorder, 1.5% met criteria for panic disorder with agoraphobia and 2.9% met criteria for panic disorder without agoraphobia. This compares to 0.5% and 1.4% respectively for participants without a substance abuse disorder. This shows that people diagnosed with a substance use disorder in the past year were 3.1 times as likely to meet criteria for panic disorder with agoraphobia, and twice as likely to be diagnosed with uncomplicated panic disorder when compared to those without a concurrent substance use disorder diagnosis. Their results further show that people who met criteria for panic disorder with agoraphobia (OR = 1.4) but not those with uncomplicated panic disorder (OR = 0.8) were significantly more likely to also meet criteria for alcohol abuse. The prevalence rates were even higher for those meeting criteria for alcohol dependence. People who had panic disorder (OR = 3.4) and those with panic disorder and agoraphobia (OR = 3.6) were significantly more likely than those without panic disorder to meet criteria for alcohol dependence. These prevalence figures are based on the use of independent diagnostic criteria and, therefore, may be seen as "true values."

Zimmermann and colleagues (2003) conducted a very interesting longitudinal study of German adolescents and young adults. They followed a sample of approximately 3000 participants over a four-year period of time. The youths were evaluated using DSM-IV criteria for substance use problems, panic disorder, and several other anxiety disorders. They found that panic attacks and panic disorder at baseline significantly predicted alcohol abuse and dependence four years later. Other baseline anxiety disorders were not predictive.

Conclusions

The evidence from most, but not all, clinical research studies and community surveys shows that people with panic disorder with or without agoraphobia are

more likely to also meet criteria for alcohol dependence, but not necessarily alcohol abuse. Unfortunately, many studies may have inflated co-morbidity rates because diagnoses were obtained during periods when the respondents may have been experiencing acute intoxication or withdrawal symptoms. This is especially likely for those studies conducted at facilities for treating people with substance use problems. The only study that we are aware of to use independent, DSM-IV diagnoses suggests that, although people with panic spectrum disorders are more likely to meet criteria for alcohol dependence, co-morbidity is lower than found in other studies and lower than for most other anxiety disorders (Grant et al., 2004).

Future research evaluating coaggregation of anxiety disorders, particularly panic spectrum disorders, and substance use disorders should carefully follow the DSM-IV guidelines for obtaining independent diagnoses using structured interviews for both disorders (see Grant et al., 2004) to assure that individuals with substance use disorders truly do have co-morbid independent anxiety disorders.

Smoking and Panic Spectrum Disorders

It is important to determine the relationship between cigarette smoking and anxiety disorders because, aside from the obvious health risks of smoking, large numbers of individuals smoke, and attempts to quit smoking are usually not successful (Centers for Disease Control and Prevention, 2002). Zvolensky et al. (2005) suggest that one possible reason for failure to quit may be linked to panic-like experiences during withdrawal. This section reviews the relationship between cigarette smoking and panic spectrum disorders. See chapter 10 for information on treating co-morbid anxiety disorders and nicotine dependence.

Clinical research studies. Several studies evaluating co-morbidity between cigarette smoking and panic disorder have been conducted in general psychiatric clinics and specialty anxiety disorders clinics. The results of these studies, which are described below, have come to markedly different conclusions. The first two studies found that participants who had either panic disorder or agoraphobia had higher rates of cigarette smoking than did people with other psychiatric disorders, especially other anxiety disorders. The studies described next compared smoking rates of people with panic disorder, but compared their smoking to either non-smoking controls or to population rates. Finally, the last group of clinical research studies found that people with panic disorder don't differ appreciably from those with other mental disorders, especially other anxiety disorders, in terms of smoking rates.

In one of the first studies to evaluate the prevalence of smoking in people who were receiving treatment for psychiatric disorders, Himle, Thyer, and Fischer (1988) used chart reviews of patients with anxiety disorders, and

found that 47% of people with panic disorder and 57% of those with agoraphobia were current smokers. These rates were significantly higher than those with all other anxiety disorders except specific phobia. Unfortunately, the criteria for making diagnoses were not clearly specified in their article.

McCabe et al. (2004) obtained similar results. They examined rates of smoking in 155 patients attending an anxiety disorders clinic in Ontario, Canada. Participants were included if they met DSM-IV criteria solely for panic disorder, social phobia, or obsessive compulsive disorder. Patients were excluded if they were co-morbid for either of the other two anxiety disorders (e.g., panic disorder patients were required not to be co-morbid for either social phobia or obsessive compulsive disorder). Their results showed that significantly more patients with panic disorder (40.4%) were current smokers than were those with social phobia (19.6 %) or obsessive compulsive disorder (22.4 %). They also reported a greater history of lifetime heavy smoking compared to people with social phobia or obsessive compulsive disorder.

Pohl et al. (1992) compared smoking behavior in patients admitted to two treatment centers in the Detroit area. Participants were compared to age and gender matched controls recruited through a telephone survey. They found that 51.6% of the patients with panic disorder were smokers at the time their panic attacks began (an average of 10 years prior to the study) compared to 38.3% of the control subjects who reported on their smoking behavior 10 years earlier. This difference in smoking rates was only marginally significant ($p = .07$). When men and women were evaluated separately, more women (39.7%) with panic disorder were current smokers compared to female controls (24.5%). Males with panic disorder did not differ from male controls on current levels of smoking.

Amering et al. (1999) evaluated 102 consecutive patients with panic disorder with or without agoraphobia attending a treatment clinic in Austria. They found that significantly more (56%) of those with panic disorder were current smokers compared to the general population (27.5%). It is interesting to note that 72% of the patients reported they were smokers at the onset of their panic attacks.

The last two clinical research studies showed that people with panic related disorders have smoking rates that are equivalent to those of some, but not all other anxiety disorders. Lopes et al. (2002) determined the prevalence of smoking in 277 outpatients in Brazil. Their results showed that the percentage of smokers per diagnosis was very similar for those with panic disorder (30%), major depressive disorder (28%), and social phobia (29%). Baker-Morissette, Gulliver, Wiegel, and Barlow (2004), using a retrospective chart review to determine rates of smoking in 581 patients attending an anxiety disorders treatment clinic, obtained similar results. They found that current smoking rates in people with panic disorder with or without agoraphobia (19.2%) did not differ significantly from those with generalized anxiety disorder (17.2%)

and major depressive disorder (25.0%), but were higher than for other anxiety disorders. However, patients with more than one diagnosis were heavier smokers than people with a single diagnosis.

Community-based studies. Covey et al. (1994), using data from the ECA, evaluated 2,980 individuals in North Carolina who were selected using a stratified multistage sampling procedures. Diagnoses were based on DSM-III criteria. Cigarette smoking was determined using a single question asking if the participants had ever smoked cigarettes for a month or more at any point in their lives. Their results showed that 2.8% of males with a life-time diagnosis of panic disorder and 10.1% with a diagnosis of agoraphobia endorsed the smoking question. For women, the rates were 2.8% and 4.7% for those with panic disorder and agoraphobia, respectively. Smoking rates were also low for most other mental disorders. The low rate of endorsing smoking may be due to the use of a single item evaluating smoking behavior. Using similar criteria for defining smoking, Nelson and Wittchen (1998) focused on nicotine dependence in a sample of 3,021 adolescents and young adults in Germany. The authors compared the prevalence of panic attacks, panic disorder, and agoraphobia in participants who endorsed a yes/no question about ever smoking versus those who did not (non-smokers), and those who met criteria for nicotine dependence. The proportion of non-smokers meeting criteria for panic attacks was 2.4% compared to 4.0% of smokers, and 11.3% for those with nicotine dependence. The percentages for those meeting criteria for a diagnosis of panic disorder were 0.7%, 1.8%, and 2.2%, and 1.6%, 2.5%, and 6.4% for those meeting criteria for a diagnosis of agoraphobia.

Breslau et al. (1991) evaluated three groups of people: (1) non-smokers, (2) mild dependence smokers, who were defined as having three or four withdrawal symptoms but no interference with social, occupational or recreational functioning; and (3) moderate dependence smokers, who were defined as experiencing five or six withdrawal symptoms, or at least three symptoms when one or more is interfering with the person's normal life. Participants were interviewed by trained raters using the Diagnostic Interview Schedule (DIS; Robins, Heltzer, Colter, & Goldring, 1989). They found that 2.4% of those with "no dependence", 4.8% with "mild dependence", and 6.6% of those with "moderate dependence" met diagnostic criteria for lifetime panic disorder. The two dependent groups differed significantly from the non-dependent group, but not from one another. These findings, combined with those of others (e.g., Nelson & Wittchen, 1998) suggest that panic spectrum disorders are more likely to occur in smokers primarily when they experience nicotine dependence. This could be the result of bodily or cognitive changes that occur during periods of non-smoking or to reduced oxygen levels during smoking (Zvolensky et al., 2005) which may produce panic like symptoms (Klein, 1993).

Lasser et al. (2000), using data from the NCS, assessed daily smoking in 4,411 participants using a structured interview, the Composite International Diagnostic Interview (CIDI; World Health Organization, 1993). Their results

showed that 38.1% of people who experienced lifetime panic attacks, but did not meet criteria for panic disorder, were current smokers. This is very similar to the current rate of smoking for those with for lifetime panic disorder (35.9%) and agoraphobia (38.4%). These rates were significantly higher than rates of current smoking among those without a lifetime mental disorder (22.5%). However, these rates were equal to or less than current smoking rates in individuals diagnosed with lifetime major depressive disorder (36.6%) or drug abuse (49.0%). When panic-related disorder diagnostic status was based on the last month, the rates of current smoking were higher than when lifetime diagnostic criteria were used, with 46.4% of people experiencing panic attacks, 42.6% of those with panic disorder, and 48.1% of those with agoraphobia reporting current smoking. Thus, current panic-related disorders were more closely linked than lifetime panic-related disorders with current smoking behavior.

Goodwin and Hamilton (2002) utilized data from the Midlife Development in the United States Survey, which was a representative household survey of 3,032 participants ranging in age from 25 to 74 years. Data were obtained by telephone using CIDI short form scales. They found that a past year history of panic attacks was associated with a higher rate of smoking (OR = 1.9). This relationship was statistically significant after controlling for co-morbid mental disorders, but not after controlling general neuroticism, which was associated with the co-occurrence of smoking and panic attacks.

Finally, Breslau, Novak, and Kessler (2004) evaluated daily smoking and subsequent onset of mental disorders using the NCS data. Participants were classified as "Past smokers" if they quit smoking at least one year before the onset of a mental disorder. "Current smokers" were defined as smokers who smoked daily at least one year prior to the onset of a mental disorder. Current smokers were more likely to develop panic disorder (OR = 2.6) and agoraphobia (OR = 4.4) after controlling for gender, educational level, and ethnicity. Moreover, when these groups were further broken down as to whether or not they were nicotine dependent (current or past), in the case of both panic disorder and agoraphobia, there were significantly higher odds ratios in current than past daily smokers, independent of nicotine dependence. These findings persisted after controlling for preexisting mental disorders and demographic characteristics.

Prospective community studies. Breslau and Klein (1999) used participants from two separate data sets, the Epidemiological Study of Young Adults (1,007 participants) and the National Co-morbidity Study (4,411 participants). The participants from the young adult study were initially assed in 1989 using a structured interview and again in 1990, 1992, and 1994. Their results showed that daily smokers were almost four times more likely to experience panic attacks and 13 times more likely than nonsmokers to develop panic disorder. These findings were obtained after statistically controlling for major depression and gender. When Breslau and Klein compared individuals who had quit smoking to those who continued to smoke, they found that current smokers

had a greater risk for experiencing panic attacks and for developing panic disorder. In fact, there was no difference in experiencing panic attacks between smokers who had quit smoking and nonsmokers.

In a similar study, Johnson et al. (2000) initially interviewed 688 participants in their homes. At the time of the initial interview, the participants averaged 14 years of age. They were assessed two other times at 16 and 22 years of age, respectively. The results showed that participants who were smoking 20 or more cigarettes per day at the initial assessment were at greater risk than non-smokers for developing panic disorder, agoraphobia, and generalized anxiety as young adults. However, the reverse was not found. Participants who met criteria for an anxiety disorder at time 1 did not evidence increased risk of smoking at a later time.

Finally, Isensee, Wittchen, Stein, Hofler, and Leib (2003) used a prospective, representative study of German youths and young adults (ages 14 to 24 at time 1) who were evaluated over a four-year period in two-year intervals. Their results at time 1 showed that dependent smokers had the highest rates of subsequent panic attacks, panic disorder, and agoraphobia when compared to non-smokers and non-dependent smokers.

Conclusions

Both clinically-based and community-based studies are in general agreement in showing that people who smoke are more likely than those who do not to experience panic attacks and develop panic disorder and agoraphobia. This is especially true for nicotine dependent smokers. There is little evidence that preexisting panic attacks or panic disorder increases the risk of future smoking in nonsmokers. There is evidence, however, that quitting smoking reduces the risk of subsequently experiencing panic spectrum disorders. Although some of the earlier studies did not control for other theoretically relevant variables, such as additional psychopathology and substance use, some of the more recent studies did, showing that the smoking/panic spectrum effect is not likely due to third variables other than neuroticism.

The prospective studies are particularly important for demonstrating the linkage from smoking to the development of panic spectrum disorders. Could the sequence from smoking to panic spectrum disorders be an artifact of when smoking and panic related problems "normally" begin? Daily smoking typically begins between the ages of 15 and 20 years and rarely after 25 years (Breslau et al., 1991) whereas the median age of onset for panic disorder is about 24 years of age (Burke et al., 1990). However, Zvolensky et al. (2005) argue that the onset of panic attacks is much earlier in life. For example, Zgourides and Warren (1988) report that the median age for having the first panic attack is 13 years of age, several years earlier than most people start smoking.

Other Substance Use and Abuse and Panic Spectrum Disorders

In two recent papers, Zvolensky and his colleagues have stated that much of the previous research on the relationship between panic spectrum disorders and cannabis (Zvolensky et al., 2006) and psychedelic drug use (Bonn-Miller, Bernstein et al., 2005) may not accurately reflect their coaggregation. In both papers, they state that much of the earlier research failed to (a) use representative samples, (b) adequately distinguish anxiety symptoms from panic attacks, and (c) statistically control for other relevant variables that could have accounted for the observed associations. We have certainly seen this in early work evaluating the relationship between panic and alcohol use and abuse (e.g., Cox et al., 1989) and panic and cigarette smoking (e.g., Himle et al., 1988). Thus, this section will focus on studies that (a) are based on representative samples, (b) use accepted methods for diagnosing panic attacks and substance use and, (c) have statistically controlled for other theoretically relevant variables.

Recent research suggests that most illicit substances are not frequently used by patients with panic disorder. For example, Sbrana et al. (2005) evaluated the frequency of illicit substance use in psychiatric inpatients and out patients. They found that, with the exception of cannabis, fewer than 10% of patients with panic disorder had ever used illicit drugs. Those who had used drugs, such as inhalants, cocaine, opioids, and hallucinogens, had done so only once or occasionally. The use of illicit drugs by people who met criteria for panic disorder was far less common than for people with bipolar disorder, OCD, or for non-psychiatric controls. This suggests that people with panic disorder may be infrequent users of illicit drugs possibly because many of these drugs produce symptoms similar to panic attacks.

Cannabis use and abuse. Cannabis is one of the most commonly used recreational drugs in the world (Patton et al., 2002). For example, it has been estimated that at least 21 million Americans have used cannabis at least once their lives and over 50 thousand adolescents initiate cannabis use on a yearly basis (Office of Applied Studies, Substance Abuse and Mental Health Services Administration, 2002). Several studies have suggested that regular cannabis use may precipitate anxiety and panic attacks (e.g., Hollister, 1986).

Zvolensky et al. (2006), using data from the Colorado Social Health Survey (CSHS), evaluated the relationship between panic attack history and cannabis use in a representative sample of 4,745 adults living in Colorado. Cannabis use was defined as self-reported use of cannabis on at least five occasions. Cannabis dependence was defined as lifetime use and at least three symptoms including the need for larger amounts to achieve the same effect, and cannabis use causing considerable problems with lifestyle. The definition of panic attacks was consistent with DSM-IV criteria. Their results showed that, compared to participants with a lifetime history of panic attacks and cannabis use, those panickers who did not meet criteria for cannabis use did not begin experiencing panic

attacks until 27.6 years of age on average. In contrast, those panickers who met criteria for cannabis use had a mean panic onset of 19 years of age. This was the same mean age they began using cannabis.

Using hierarchical logistic regression analyses, which allowed them to control for variables such as age, gender, and poly-drug use, Zvolensky et al. (2006) found that cannabis use did not contribute additional variance to the prediction of a lifetime history of panic attacks beyond that explained by the covariates. However, when cannabis dependence was entered as the predictor variable, cannabis dependence increased the odds of a lifetime history of panic attacks above and beyond that of the covariates. Adding major depression to the equations did not change the odds of having lifetime panic attacks.

The authors also regressed cannabis use and dependence on a measure of major depression. Neither cannabis use nor dependence increased the odds of having major depression beyond that of the covariates. An earlier study by Katerndahl and Realini (1999) did not find a relationship between cannabis abuse, defined using DSM-III criteria, and panic spectrum disorders. However, the number of participants meeting criteria for cannabis abuse was very small in their sample.

In conclusion, based on a recent and very well-controlled study of a large number of participants (Zvolensky et al., 2006), it appears that cannabis dependence, but not use, markedly increased the odds that a person would also experience panic attacks, above and beyond theoretically relevant variables such as a history of poly-drug use and depression. It also appears that cannabis use is associated with an earlier onset of panic attacks.

Psychedelic use/abuse and panic attacks. According to the Office of Applied Studies of the United States Department of Health and Human Services (2004), over 10% of Americans over the age of 12 have used LSD at least once. In addition, they report that at least 131,000 Americans initiated PCP use in 2003. Presumably, similar patterns exist for the use of other psychedelics. Psychedelic drugs usually refer to phencyclidine (PCP), lysergic acid diethylamide (LSD), mescaline, peyote, psilocybin, and dimethyltryptamine (DMT). All of these drugs, even though they vary in many aspects, produce marked changes in sensory-perceptual processes (National Institute of Drug Abuse; NIDA, 2001). It is remarkable, given the extensive use of these drugs, that there is so little solid scientific research on the psychiatric effects of ingesting these drugs—especially over a long period of time.

Bonn-Miller, Bernstein, et al. (2005), in the most comprehensive study to date of psychedelics, used the data obtained from the 4,745 participant Colorado Social Health Survey (CSHS) to assess co-morbidity of panic attacks and psychedelic use, abuse, and dependence. They defined three groups of psychedelic drug use: psychedelic use, psychedelic abuse, and psychedelic dependence (see the section on cannabis use for definitions of use and dependence). Abuse was defined as lifetime psychedelic use and either (a) psychedelic use caused considerable problems with family, friends, job, school, or police; or (b) psychedelic use caused health or psychological/emotional problems. Using

hierarchical logistic regression to control for theoretically relevant variables, such as age, gender, and poly-drug use, they found that psychedelic use was not associated with a unique change in the odds of a lifetime history of panic attacks above and beyond the covariates. However, both psychedelic abuse (OR = 2.1) and dependence (OR = 4.6) were associated with increased odds of a lifetime history of panic attacks. They also used logistic regression to determine if psychedelic use, abuse, or dependence was predictive of major depression. It was not, suggesting that psychedelic abuse and dependence was not associated with general psychiatric distress.

Cocaine use and panic attack. As early as the mid-1980s, cocaine has been suspected of precipitating panic attacks and possibly panic disorder (Aronson & Craig, 1986). However, the first epidemiological estimates of the relationship of cocaine and panic attacks did not occur until 1989. Anthony, Tien, and Petronis (1989), using ECA data from almost 9,000 young adults, found that the relative risk of cocaine users having a panic attack was over 3 times that of non-cocaine users. However, as acknowledged by Anthony and his colleagues, theoretically relevant variables which might explain the increased risk of panic attacks among cocaine users were not controlled. More recently, O'Brien, Wu, and Anthony (2005), using National Household Surveys on Drug Abuse (NHSDA) data from 1994 through 1997, used a case-crossover approach to assess the relationship between cocaine use and panic attacks. From a total of over 50,000 adults aged 18 or older, they identified 1,071 people who had had a panic attack within the month. In this study, however, panic attacks were assessed by two quite general questions. They then identified 13 cases where people had used cocaine (including crack cocaine) on one or more occasions and had a panic attack in the past month, but not in the prior 11 months. These people were compared with 44 "controls" who had used cocaine one to 11 months prior to the assessment period, but not during the month they were assessed. After adjusting for interval periods (i.e., one month vs. 11 months), they found that those who used cocaine in the month they were assessed were three times more likely to experience a panic attack than were the controls. Ten of the 13 participants were "rookie" cocaine users who had either never used cocaine or who had used it very few times more than a year before being assessed. The authors repeated the comparison between the 13 indexed participants and the 44 controls for cigarette smoking, alcohol use, and a variety of other illicit drugs. The only substance that showed differences in the risk of panic attacks was cocaine.

Although the relative risk of having a panic attack following cocaine use found by O'Brien and colleagues was consistent with that obtained by Anthony et al. (1989), the results of the O'Brien study must be viewed somewhat skeptically due to the small number of participants and the assessment of panic attacks using only two general questions. Future research should utilize standardized structured interviews for assessing both panic attacks and cocaine use.

Conclusions

When we evaluated the co-occurrence of panic spectrum disorders and substance use and abuse, most, but not all, studies found that substance use (most often substance dependence) was associated with an increased odds of experiencing panic attacks. This held true for alcohol, cigarette smoking, psychedelics, cannabis, and cocaine. Unfortunately, the authors of this chapter were unable to find adequate epidemiologic data assessing the relationship between panic attacks and other substances such as inhalants and tranquillizers. However, we believe that more research is needed. It has been long known that benzodiazepine usage can lead to serious risks, such as dependence, for people with anxiety disorders (e.g., Tyrer, 1980).

The studies we evaluated that attempted to determine order of onset of substance use and development of panic attacks found that substance use usually began before the onset of panic attacks except possibly for alcohol related problems. This suggests that substance use may often provoke the onset of panic spectrum problems. There are several possible reasons why substance use might be panicogenic. First, Zvolensky and his colleagues (e.g., Zvolensky et al., 2005) have suggested that substance use and/or withdrawal may provoke bodily sensations and cognitions similar to those experienced during panic attacks. These sensations and cognitions may then lead to anxiety about the sensations/cognitions provoking full-blown panic attacks. A second hypothesis, suggested by Kushner and his colleagues (2000), is that substance use disorders and panic attacks may share the same neurobiological mechanisms, such as perturbations in the norepinepherine system. More research is necessary to determine how substance use/abuse and panic spectrum disorders are temporally related and the mechanisms underlying this relationship. One possible factor might be anxiety sensitivity (Reiss, 1991). There is very good evidence that anxiety sensitivity, a cognitive factor associated with individual differences in fear of anxiety symptoms (e.g., a racing heart is interpreted as a heart attack), is associated with increased substance use (Stewart, Samoluk, & MacDonald, 1999) and is predictive of the development of panic disorder (Schmidt, Lerew, & Jackson, 1999). In fact, the extant data suggests that the relationship between anxiety sensitivity and substance use and abuse generally parallels that of panic spectrum disorders and substance use and abuse (e.g., Zvolensky et al., 2005). Finally, it is possible that a third factor, such as neuroticism (e.g., Goodwin & Hamilton, 2002), may increase the likelihood of both substance use and panic attacks.

Unfortunately nearly all of the studies assessing co-morbid substance use and panic spectrum disorders are cross-sectional and do not provide information on causal directions. Future research should attempt to emulate the longitudinal methods used by Zimmermann et al. (2003), who found that panic disorder and panic attacks at baseline were a risk factor for the development of alcohol use disorder four years later. Finally, future research should follow

DSM-IV's recommendation in assuring that substance disorders and panic attacks are truly independent by determining that panic attacks occurred prior to the onset of the substances use (or at least heavy usage) or that panic attacks persist several weeks after substance use has been discontinued and withdrawal symptoms are no longer occurring.

It is important to note that relative order of onset and longitudinal studies only help establish initial causal relations between disorders. It is possible that once the two disorders are established that the two mutually maintain one another, or even exacerbate one another leading to a vicious cycle. For example, in a patient with co-morbid panic disorder and alcohol dependence, regardless of whether the panic or alcohol misuse began first, once the two disorders are established, the patient may continue using alcohol in an attempt to self-medicate for his panic symptoms (see Norton et al., 1989). But his frequent experiences of alcohol withdrawal may exacerbate his panic anxiety, creating a vicious cycle (George et al., 1990).

Understanding the functional inter-relations between the panic spectrum and substance use disorder at each stage in the course of the development of co-morbidity has important implications for treatment because it suggests that both disorders may need to be a focus of treatment for best outcomes. Chapter 9 describes a functional analysis approach to treating patients with co-morbid panic spectrum and substance related disorders, and chapter 7 describes a novel approach to the treatment of co-morbid panic disorder and tobacco dependence, in particular.

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Part III
Treatment Strategies

Chapter 6
Treatment of Co-Morbid Obsessive-Compulsive Disorder and Substance Use Disorders

Keith C. Klostermann and William Fals-Stewart

Introduction

Results of recent epidemiological surveys reveal that obsessive compulsive disorder (OCD) and substance use disorders (SUDs) are both among the most prevalent psychiatric conditions in the general population. More specifically, OCD afflicts 2.5% of the population, thus making it the fourth most common psychiatric condition. Yet, this figure is dwarfed in comparison to that of SUDs, which are (collectively) the most common disorders in the general population, with a lifetime prevalence rate exceeding 14% (Grant, 1997; Grant, Peterson, Dawson, & Chou, 1994). When one considers the comparatively high prevalence of OCD and SUDs, respectively, it comes as no surprise that there is a significant subset of individuals who meet criteria for both disorders. Perhaps more importantly, many patients who have both conditions may eventually seek treatment, entering through either the mental health system (to address obsessions and/or compulsions as the primary complaint) or the substance abuse treatment system (to address substance abuse as the primary complaint).

In certain respects, the bifurcation of treatment delivery for mental health problems versus substance abuse heightens and exacerbates the complexities inherent in treating patients with both OCD and substance abuse problems; professionals ensconced in one system (e.g., mental health) often do not have the requisite expertise, by training or experience, to address problems and issues common in the other system (e.g., substance abuse). This is particularly problematic for OCD and SUDs because the most widely used interventions for these disorders in practice, as we will discuss in this chapter, have little in common. Thus, while many have advocated that treatment providers in both systems learn to identify patients with co-morbid OCD and SUDs accurately

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and to develop intervention approaches that take into account both disorders (e.g., Fals-Stewart & Lucente, 1994), the practical implementation of this recommendation is far more difficult than it may, at first, appear.

Yet, efficacious intervention approaches for patients with OCD and co-morbid SUDs have been developed and tested. Thus, the overarching goal of this chapter is to describe a simultaneous assessment and treatment approach for patients identified as having OCD and an SUD that has proven to be efficacious in a well-controlled randomized clinical trial, followed by a case example to illustrate the assessment and intervention methods outlined.

Brief Description of OCD

Once considered a rare and largely intractable condition, OCD is now recognized as among the most prevalent and, in many respects, treatable psychiatric disorders (e.g., Stein, 2002). Generally, OCD is characterized by a reciprocal interrelationship between the presence of intrusive thoughts and images (obsessions), which increase anxiety, and stereotyped ritualistic actions (compulsions), which decrease anxiety. As emphasized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association [APA], 1994), compulsions can be observable behaviors or mental rituals. Perhaps most poignantly, patients with OCD typically realize that their obsessions and compulsions are irrational or excessive, but are unable to prevent or contain them.

The most frequent symptom presentations of OCD are (a) contamination fears with cleaning rituals and (b) fears of harm to self or others coupled with checking (Leckman, Zhang, Alsobrook, & Paul, 2001). However, OCD assumes a variety of forms; many types of obsessions and compulsions have been identified, including precision and symmetry concerns and arranging rituals, hoarding, scrupulosity, and so forth. Although the symptoms of OCD were once conceptualized and understood as manifestations of deep unconscious conflict, OCD is now more commonly regarded as a neuropsychiatric disorder mediated by neurological pathways and closely related to disorders with well-established neurological underpinnings, such as Tourette's syndrome and Sydenham's chorea (e.g., Stein & Stone, 1997).

OCD is equally common among men and women, which is in contrast with most other anxiety disorders, in which the prevalence is usually higher in women than men. Age of onset tends to have a bimodal distribution. Although most patients describe an insidious onset of OCD symptoms prior to age 25 (Eichstedt & Arnold, 2001), there is also a group of patients who report a later onset, for example, after pregnancy, miscarriage, or parturition (Gellar, Klier, & Neugebauer, 2001; Williams & Koran, 1997). Symptoms are usually described as chronic, with some waxing and waning of symptoms, but few spontaneous remissions (e.g. Skoog & Skoog, 1999).

OCD is under-diagnosed and under-treated because patients are very secretive about their symptoms or lack insight about their illness (see Steketee, 1993). Moreover, many treatment providers are unfamiliar with OCD and its manifestation. Consequently, OCD patients often go years without receiving help; the average amount of time between the onset of OCD symptoms and procurement of appropriate treatment is 17 years (Jenike, 2004).

Co-Morbidity of SUDs and OCD

Given the high prevalence of both psychoactive SUDs and OCD in the general population, one would suspect, based on probability alone, a comparatively high co-morbidity of these disorders. Yet, there are vastly conflicting reports in the extant literature about the co-morbidity of OCD and psychoactive SUDs. Several studies have found an elevated prevalence of all anxiety disorders among substance-abusing patients *except* OCD (Quitkin, Rifkin, Kaplan, & Klein, 1972; Smail, Stockwell, Canter, & Hodgson, 1984; Weiss & Rosenberg, 1985). Conversely, other investigators have reported that OCD is 4–5 times more prevalent among substance-abusing patients than observed in the general population (Fals-Stewart & Angarano, 1994; Hoffman, 1991). These disparate findings beg the question, "Why is there such a large discrepancy in these reports?"

As argued by Fals-Stewart and Lucente (1994), there are two primary reasons to suspect that OCD is often under-detected among substance-abusing populations, making it difficult to evaluate accurately its prevalence among these patients. First, symptoms of OCD are very often overlooked among substance-abusing patients and are often not adequately assessed during intake interviews for treatment entry; counselors and other evaluators in substance abuse treatment programs typically do not have the requisite expertise or experience to recognize co-morbid OCD. Second, and perhaps most importantly, OCD is usually hidden by its sufferers; many OCD patients experience shame and embarrassment in connection with their symptoms and find it upsetting that they cannot control or banish what they conceptualize as irrational behavior. Thus, the combination of counselors who are not trained to detect OCD and patients often intent on hiding their symptoms very likely culminates in significant under-reporting of OCD-SUD co-morbidity.

Yet, accurate identification of OCD among substance-abusing patients is not merely of epidemiological significance; the presence of OCD among alcoholic and drug-abusing patients has important treatment implications. There is empirical evidence to suggest that addressing both disorders concurrently results in better treatment outcomes than addressing only the SUDs. In a randomized clinical trial, Fals-Stewart and Schafer (1992) randomly assigned 60 patients (aged 21–48 years) entering treatment for substance abuse and dually diagnosed with OCD to one of three treatment

conditions. One group of patients received a combined intervention that concurrently addressed their obsessive-compulsive symptoms (i.e., behavioral treatment consisting of exposure and response prevention [ERP]) and their substance abuse. A second group received only standard substance abuse treatment provided by the program; a third (attention control) group of patients received training in progressive muscle relaxation plus standard substance abuse treatment. Patients who received the combined treatment for their OCD and substance abuse remained in treatment longer, showed greater reductions in OCD symptom severity during treatment and after treatment completion, and had higher overall abstinence rates at 12-month posttreatment follow-up. Thus, accurately identifying OCD among substance-abusing patients, along with development and implementation of treatment plans that address both disorders, is likely to result in superior treatment response and outcomes across multiple domains of functioning (e.g., reduced substance use, decreased OCD symptom severity). Later in this chapter, we describe the combined OCD-SUD treatment used in the Fals-Stewart and Schafer (1992) study.

Common Treatments for SUDs and OCD

SUD Treatments: Although medications are an important part of the treatment armamentarium of clinicians working with clients suffering from psychoactive substance use disorders (for a review, see Fals-Stewart, 2004), most treatment providers would agree that the mainstay of treatment for alcoholism and drug abuse comes in the form of peer support and psychosocial "talk" therapies. Twelve-step peer support groups (e.g., Alcoholics Anonymous [AA], Narcotics Anonymous [NA]) are the largest and most widely known self-help support groups for individuals with drinking and drug problems. Meetings consist mainly of discussions of participants' problems with alcohol and other drugs, with testimonials from those who have recovered. Participants are encouraged to work the twelve steps of AA, which include admitting powerlessness over alcohol and drugs, believing that a higher power can restore sanity, making a searching and fearless moral inventory of oneself, and so forth (Alcoholics Anonymous, 1976). The program promotes total abstinence from psychoactive substances.

Relatedly, the most commonly used formal treatment approach in the vast majority of community-based treatment programs is derived from the 12-step model; the most formalized version of this approach is referred to as Twelve-Step Facilitation (TSF) treatment. In TSF, substance dependence is viewed not as symptomatic of another illness, but as a primary problem with biological, emotional, and spiritual underpinnings and presenting features. Alcoholism and drug abuse are seen as progressive illnesses, marked largely by denial. The primary goals of treatment are: (1) to encourage clients to work

through their denial; and (2) working the twelve steps. These goals are typically accomplished in the context of individual and group therapy, with strong encouragement to attend twelve-step self-help groups on a regular basis. Along with individual and group counseling, medical services and religious services are also considered important parts of treatment because the disease of alcoholism and other drug use is viewed as affecting the biological and spiritual realms, as well as psychosocial functioning. Although there has been little research on the efficacy of treatments derived from the disease model, it is the most common form of treatment for alcoholism and drug abuse (Fals-Stewart, 2004).

One of the strongest predictors of success of treatment for alcoholism has been motivation to change. A treatment intervention that has grown out of this observation is Motivational Enhancement Therapy (MET), which attempts to get clients to assume responsibility for helping themselves and increasing their desire to change through a technique referred to as motivational interviewing (Yahne & Miller, 1999). Clients are moved through stages of change to increase motivation to change the addictive behavior, and thus, facilitate positive outcomes. Several studies have now demonstrated that MET is an effective treatment for alcoholism and other drug abuse (e.g., Miller et al., 1995).

Behavioral and cognitive behavioral treatments have been among the most widely used and investigated psychosocial treatments for substance abuse and dependence. Cognitive behavioral therapy (CBT) teaches clients coping skills to reduce or eliminate drinking or substance use. Techniques that characterize this approach include identifying high-risk situations for relapse, instruction and rehearsal strategies for coping with those situations, self-monitoring and behavioral analysis of substance use, strategies for recognizing and coping with cravings, coping with lapses, and instruction on problem-solving (Carroll, 1998).

OCD Treatments: Cognitive Behavior Therapy. Although commonly used interviewing and talk therapies often used by substance abuse therapists (of which TSF, MET, and CBT are variants) may be applied successfully to address other co-morbid psychiatric symptoms, they have proven largely ineffective in reducing OCD symptoms (Bram & Bjorgvinsson, 2004; Greist, 1990; James & Blackburn, 1995; Kringlen, 1965; Malan, 1979). Over the past three decades, numerous studies have demonstrated the effectiveness of behavior therapy as a treatment for OCD. More specifically, a behavior therapy referred to as *exposure and response prevention* (ERP), consisting of exposure to stimuli related to obsessional fears and response prevention directed towards the rituals, has been shown to be an effective mode of treatment for individuals with OCD (Fals-Stewart, Marks, & Schafer, 1993; Neel, Stevens, & Stewart, 2002). Exposure requires the patient to directly confront the feared object (e.g., dirty clothes, dogs, food), while response prevention prohibits the resulting compulsive behavior (e.g., the patient refrains from washing after being exposed to the contaminant). As part of

the treatment, patients continue their exposure to the stimulus until the associated anxiety response has diminished to a point with which they are comfortable (i.e., habituation). Cognitive behavioral therapy (CBT), which may be added to ERP, addresses such things as faulty estimation of danger or the exaggerated sense of personal responsibility often seen in OCD patients. Other techniques, such as thought stopping and distraction (which involve suppressing or "switching off" OCD symptoms) and contingency management (which emphasizes rewards and costs as incentives for ritual prevention) are generally thought to be less effective than standard CBT (March, Frances, Kahn, & Carpenter, 1997).

More than 30 open and controlled trials have shown ERP to be effective in reducing OCD symptoms (Jenike, 2004). Moreover, the positive effects of behavior therapy are fairly enduring once formal treatment has ended. A comprehensive compilation of outcome studies indicated that, of more than 300 OCD patients who were treated with ERP, an average of 76 percent still showed clinically significant relief from 3 months to 6 years after treatment (Foa & Kozak, 1996). Another study found that incorporating relapse-prevention components in the treatment program, including follow-up sessions after the intensive therapy, contributes to the maintenance of treatment gains (Hiss, Foa, & Kozak, 1994).

OCD Treatments: Pharmacotherapy. Clinical trials in recent years have shown medications that affect the neurotransmitter serotonin can significantly decrease the symptoms of OCD. The first of these serotonin reuptake inhibitors (SRIs) specifically approved for use in the treatment of OCD was the tricyclic antidepressant clomipramine (Anafranil). It was followed by other SRIs that are called "selective serotonin reuptake inhibitors" (SSRIs), which generally have a better safety and tolerability profile than does clomipramine. Those that have been approved by the US Food and Drug Administration for the treatment of OCD include flouxetine (Prozac), fluvoxamine (Luvox), and paroxetine (Paxil). Another that has been studied in controlled clinical trials is sertraline (Zoloft). All available SRIs appear effective and generally well-tolerated in randomized controlled trials with OCD sufferers who are adults (Cartwright & Hollander, 1998) and children (Grados & Riddle, 2001).

OCD Treatments: Combining Medication and Behavior Therapy. Unfortunately, few investigations have been conducted to determine how best to sequence or combine pharmacotherapy and behavior therapy for OCD. In clinical practice, however, it is very common for patients to receive both forms of treatment. In the long term, ERP or combined approaches may be more useful than medication treatment alone (Steketee, 1993). Once treatment has stopped, individuals who have been treated with a full course of ERP are less likely to experience a rapid return of symptoms than individuals who have been treated with medication alone (O'Connor, Todorov, Robillard, Borgeat, & Brault, 1999; Simpson, Gorinkle, & Liebowitz, 1999).

A Primer for Combining Treatments for OCD and SUDs

The talk therapies that are widely used to treat SUDs are very different in appearance, approach, and general form than the commonly used ERP-based behavior therapy approach commonly and successfully used with OCD, thereby making their integration (or, perhaps more accurately stated, simultaneous application) complex. As an example by way of contrast, CBT for SUDs is built on the same founding principles as CBT for other disorders, including depression; as such, the familiarity with the tenets of CBT among providers who use it to address SUDs with their patients would likely be comfortable using CBT-based interventions for patients dually diagnosed with depression. Unfortunately, the same cannot be said of commonly used talk therapies for SUDs (i.e., TSF, MET, and CBT) and the ERP-based treatments that are successful with OCD. Thus, the goal of any treatment model for patients with co-morbid OCD and SUDs is to combine these disparate interventions to address both disorders concurrently.

Thus, the following section lists the five steps we recommend be followed when treating patients diagnosed with SUDs and OCD that combines standard ERP-based OCD treatment with standard treatment for SUDs. This general approach has some preliminary support, following the procedures used in previous clinical trials with OCD-SUD patients (e.g., Fals-Stewart & Schafer, 1992). However, it is important that clinicians and treatment providers have appropriate training in administering psychological assessments, clinical interviewing, and behavioral techniques before applying any of these interventions with substance users who may have a concurrent OCD diagnosis. For the purpose of this chapter, these steps are written from the vantage of combining OCD treatment into a standard substance abuse treatment approach.

Step 1: Assessment. Typically, the initial assessment interview has a dual purpose: (1) obtaining an accurate and complete diagnosis; and (2) collecting data relevant to treatment planning. In most cases, the diagnosis of OCD becomes obvious once patients begin to describe their obsessions and rituals. Yet, interestingly, most substance abusers will not reveal information concerning their OCD-type symptoms unless directly queried, primarily out of embarrassment for what they recognize as bizarre and repulsive thoughts and behaviors. Consequently, asking questions that address behaviors often experienced by OCD patients can create an environment conducive to further exploration of these issues. Sample questions may include, "Do you have thoughts, ideas, images, or impulses that you can't stop thinking about?," and "Do you feel pressure to conduct certain behaviors again and again?"

Many clinicians have difficulty correctly diagnosing OCD; it is often confused with other psychiatric illnesses (e.g., phobic reactions, depression, schizophrenia, and obsessive-compulsive personality disorder [OCPD]). Although OCD has a number of features in common with these other disorders, the distinctions are important, as patients with these disorders respond

positively to different types of treatment. As an example, patients with phobias generally believe that harm will come to them if they come in contact with certain objects or situations; consequently, anxiety is controlled by avoiding the stimuli. In contrast, OCD patients typically reduce their anxiety by participating in specific compulsive behaviors. It is common to see obsessional thinking in patients who are depressed. However, these contemplations often have themes that vary with the depressed mood and will normally remit as the depression dissipates, whereas the obsessions associated with OCD usually remain even when a depression associated with OCD subsides. Compared to patients with schizophrenia, OCD patients are usually able to engage in effective reality testing and retain a painful awareness of the unusual nature of their thinking and behavior. Finally, OCD is commonly confused with OCPD which is characterized by meticulousness and perfectionism. However, compared to OCD, patients with OCPD perceive their meticulous behaviors as more ego-syntonic.

Accurately diagnosing OCD patients that also abuse psychoactive substances can be, in the best of circumstances, challenging. It is estimated that as many as two-thirds of patients entering treatment for substance abuse will report a variety of psychiatric symptoms, in addition to their addiction, most of which will abate as recovery progresses (Penick, Powell, Liskow, Jackson, & Nickel, 1988). As previously mentioned, some disorders (e.g., depression) can mimic OCD because there is often a contemplative quality that is associated with dysphoric mood states. Moreover, dually-diagnosed patients may also abuse substances to conceal or otherwise counteract psychiatric symptoms (Allgunder, Borg, & Vikander, 1984; Hudson & Perkins, 1984). The patient may be self-medicating in an effort to reduce anxiety and provide temporary relief of the OCD symptoms, thus masking overt symptoms that would make reaching the appropriate diagnosis difficult. In addition, the waxing and waning of psychiatric symptoms, because of intoxication and withdrawal, can further complicate the diagnostic process.

There is a well-reasoned "rule-of-thumb" that conducting the assessment interview at least two weeks after detoxification can enhance the reliability of any concurrent Axis I and Axis II diagnoses among substance-abusing patients (Kaufman, 1989). OCD typically has an early onset and studies have shown that most adults who enter treatment have grown up with a parent who exhibited signs of anxiety or depression (Steketee & Van Noppen, 2003); thus, an interview with parents or siblings, if possible, can yield information that could be quite useful in the diagnostic process. For example, information concerning the patient's idiosyncrasies (e.g., checking behavior, concerns with balance and symmetry, and excessive concerns about personal hygiene) before his or her bouts with substance abuse or during abstinent periods can also provide important clues as to the presence of OCD.

Several authors have noted that the cravings described by substance abusers seem to have an obsessive-compulsive quality (Caetano, 1985; Modell, Glaser, Mountz, Schmaltz, & Cyr, 1992). Typically, individuals diagnosed with OCD

struggle to resist or suppress disturbing thoughts that often result in maladaptive and destructive behaviors. Alcoholics and substance abusers often have strong urges to drink or use drugs, which can result in destructive substance use or drinking patterns. However, the fundamental difference is that patients with OCD tend to view their compulsive behavior as irrational, while substance abusers typically do not perceive their substance-using behavior as senseless or meaningless (Hoffman, 1991).

Step 2: Assessment of Symptom Type and Severity. After reaching a diagnosis of OCD, subsequent interviews should focus on defining the types of symptoms (i.e., intrusive thoughts, feelings, and behaviors) typically experienced by the patient, including detailed descriptions of anxiety-provoking stimuli and the subsequent ritualistic responses evoked. There are a number of excellent patient self-report measures designed to assess the kinds of obsessions and rituals that an OCD patient may experience, including the Leyton Obsessional Inventory (LOI; Cooper, 1970), the Maudsley Obsessive-Compulsive Inventory (MOCI; Hodgson & Rachman, 1977), and the Obsessive-Compulsive Checklist (Marks, 1978).

Clinicians should also investigate the degree of subjective distress caused by the OCD symptoms. Ascertaining the level of distress will allow the therapist and patient to measure reductions in symptom severity during the course of treatment. As an example, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al., 1989) asks patients to rate the severity of the symptom described in each item on a 5-point scale during the prior week up to and including the time of the interview. The Y-BOCS has separate indices that measure distress caused from obsessions and compulsions, which are combined for a cumulative score. The total score is based on 10 items (i.e., 5 items describing obsessive symptoms and 5 items describing compulsive symptoms) on a scale ranging from 0 to 40; higher scores indicate greater subjective distress from OCD symptoms. A score of greater than 20 indicates moderate to severe distress as a result of OCD symptoms. It's important to note that the Y-BOCS was designed to assess levels of symptom severity in patients with a primary diagnosis of OCD. Although rarely a problem, substance-abusing patients need to be cautioned prior to assessment that their craving and substance-seeking behavior should not be considered when answering questions from the Y-BOCS, which could artificially inflate the true score.

Step 3: Psychoeducational Therapy. Many people diagnosed with obsessive-compulsive disorder will often go to great lengths to hide or conceal their negative symptoms and other ego-dystonic behaviors, including drug or alcohol use. Reviewing basic information (e.g., prevalence rates, symptoms, etc.) can often provide relief by normalizing the condition and its associated symptoms. In addition, a discussion about the effectiveness of psychotherapeutic and pharmacological treatments should also be included in this component. With the patient's permission, family members should also be encouraged to attend the sessions. In our clinical experience, we've found patients and their families

benefit from reading Lee Baer's Getting Control: Overcoming Your Obsessions and Compulsions (2000), which offers a non-technical and accessible overview of what is known about OCD and available treatments. With regard to substance-abusing patients, it should also be noted that extensive use of alcohol and drugs may cause an increase in anxiety, and consequently, exacerbate the OCD symptoms (Fals-Stewart & Lucente, 1994).

Step 4: Creation of a Stimulus Hierarchy. As a critical initial step for eventual treatment, the patient creates a stimulus hierarchy. More specifically, the patient makes a complete list of obsessions, compulsions, and things that create anxiety, and thus, are avoided. In our experience, it is best to have patients avoid making mental edits of the items for the list; greater inclusivity is preferred to selectivity. For each item listed, the patient is then asked to rate how much anxiety is generated by the thought or behavior, rating each on the Subjective Units of Distress Scale. This scale often ranges from 1 (hardly any anxiety experienced) to 100 (extreme anxiety experienced). The patient and his or her therapist then rank order the hierarchy from lowest to highest.

Step 5: Treatment. Behavior therapy, in the form of ERP, is the gold standard treatment for OCD, achieving outcomes that equal or surpass other forms of intervention (e.g., pharmacotherapy), but are more robust in terms of relapse resilience. ERP consists of exposure to an anxiety provoking stimulus until there is habituation; ERP sessions usually take 60 to 90 minutes, but can take longer with material that elicits very high levels of anxiety. The items are taken from the stimulus hierarchy (created in Step 4), with patients moving to progressively more anxiety-provoking stimuli. Patients provide a subjective units of distress score every 10 minutes during exposure so anxiety levels can be tracked as the patient moves toward habituation. Cognitive therapy is typically combined with ERP, providing a framework for therapists to challenge patient's faulty assumptions and irrational beliefs. After behavior therapy is underway, introduction of pharmacotherapy is often beneficial; in our experience, patients tolerate the combination of therapies well and, in many cases, there are reciprocal positive effects when ERP and pharmacotherapy are used in combination. We have tended not to use or advocate pharmacotherapy without ERP with substance-abusing patients simply because of the comparatively high relapse rate associated with the cessation of medication, which has shown to be as high as 90% in some studies (e.g., Pato, Zohar-Kadouch, Zohar, & Murphy, 1988).

Because ERP-based treatments for OCD are not similar to typical treatments for substance abuse, we advocate separate sessions devoted exclusively to substance abuse treatment, while other sessions are used to address OCD symptoms. As noted earlier, 12-step model treatments are the most common for substance use disorders and often well-tolerated by OCD patients. However, we have had some patients who would obsess about their "correct" progression through the steps, but this has been rare. Additionally, because 12-step treatments tend to be group therapy oriented, some patients experience significant anxiety because of contact with other substance-abusing

participants which, in turn, can lead to premature treatment drop out. However, there are now 12-step self-help support groups for OCD in many cities in the U.S. and throughout the world, which were founded upon the principles of Alcoholics Anonymous. The familiar 12-step support group paradigm for both disorders can make participation easier on the patient.

There is little doubt that the treatments for SUDs, such as CBT and MET can also be used with OCD patients who have alcohol and other drug problems. However, the most important issue is not really the type of substance abuse treatment, as long as it is one that has shown some evidence of effectiveness. Of greater significance in the treatment for OCD and SUDs is the notion of "separate-but-equal," meaning that both disorders require attention in roughly equal parts and should be addressed concurrently.

Treating a Substance-Abusing Patient with OCD: The Case of W.L.

W.L. was a 33-year-old single, unemployed white woman with a 12-year history of alcohol, benzodiazepine, and cocaine abuse, which she reported had recently become significantly worse before seeking treatment. Prior to intake, W.L. reported she was consuming 4–6 drinks daily (mostly beer) and smoking "crack" cocaine 3–4 times weekly. In addition, W.L. also reported she had recently started experiencing blackouts and had been arrested for driving while intoxicated during the month before entering treatment. After her intake screening, during which she was given a SUD diagnoses of cocaine dependence, alcohol dependence, and benzodiazepine abuse, W.L. was admitted to a 30-day inpatient substance abuse treatment program.

During her initial evaluation when in residence, W.L. did not exhibit any manifest OCD symptoms and reported no problems with obsessions or compulsions when directly queried. However, an interview with her mother revealed W.L.'s father had experienced contamination fears (i.e., showered and washed his hands several times a day). She also reported that W.L. was always "something of a neat-nick" but this did not seem to get in the way of her functioning as she was growing up. When obtaining a detailed treatment history, W.L. revealed that she had dropped out of two substance abuse inpatient treatment programs against medical advice because she "couldn't stand living with dirty roommates." Moreover, W.L. stated that she disliked being around other drug users because she feared she might contract a disease (e.g., HIV) "just by touching them." She noted that these concerns were heightened when she was not intoxicated, adding that she had to either drink or use other drugs to leave her apartment.

As part of treatment, W.L. was asked to catalog her daily routine during the month prior to entering substance abuse treatment. W.L. reported that she washed her hands roughly 25 times daily, showered before every meal, and

spent several hours each day cleaning her apartment. In fact, W.L. revealed that her contamination fears had recently become more severe and, as a result, she could no longer make it to work in her chosen profession (i.e., waitress) because she feared getting other people's germs on her skin. Moreover, W.L. also admitted that she no longer traveled and avoided long trips because of fears around having to use public restrooms. Consequently, W.L. stated she had been using alcohol more frequently during the past few months to reduce the excessive anxiety created from her contamination fears. Interestingly, W.L. noted that this was the only instance in her lengthy treatment history (i.e., four prior inpatient admissions and several outpatient treatment engagements) in which she was specifically queried as to the nature and extent of her OCD symptoms and indicated that she would not have discussed her fears and consequent behaviors unless she had been directly asked.

In addition, W.L. admitted that her cocaine misuse began a few years ago when she began seeking help for her contamination fears. More specifically, during an initial psychiatric evaluation by a psychiatrist, W.L. was embarrassed to reveal her compulsions and instead complained of only anxiety. As a result, W.L. was prescribed diazepam (Valium), which would temporarily alleviate her symptoms, only to return a few hours after ingestion. W.L. soon began self-medicating with alcohol and cocaine, using increasing amounts of the prescribed medication, while hiding the extent of this use from her psychiatrist. Eventually, W.L.'s physician became suspicious of her drug-taking habits and ultimately discontinued the prescription. This resulted in W.L. buying different types of benzodiazepines illegally, which she had been using intermittently up to the day of intake.

In addition to the SUD, W.L. was also given an Axis I diagnosis of OCD, with no other concurrent Axis I or Axis II diagnoses. According to her score on the Y-BOCS (i.e., 26), W.L. displayed moderate to severe subjective distress caused by her OCD symptoms. As part of her treatment, W.L. was asked to create a 35-item hierarchy of anxiety-evoking stimuli, with items rated on a subjective units of distress scale; part of her hierarchy is located in Table 6.1.

Prior to the onset of an individually-tailored behavioral treatment program, W.L. attended two psychoeducational sessions devoted specifically to OCD; with W.L.'s permission, her parents and brother were also invited to attend. Interestingly, W.L. was surprised to find out that OCD was so common in the general population, which was contrary to her belief that she was the only person who experienced these symptoms. In addition, the treatment staff were able to answer a number of questions and concerns W.L. had about her typical behavior (e.g., what constituted "normal" cleaning and grooming behavior).

A treatment plan was subsequently developed to address both the OCD and substance abuse. More specifically, W.L. was to be seen by a therapist three times a week; two sessions were devoted entirely to ERP exercises, while the other session involved 12-step counseling to address her substance abuse. The primary OCD treatment was ERP, consisting of exposing W.L. to contaminants and preventing her from washing. As can be seen in Table 6.1, W.L.'s anxiety-provoking stimuli lend themselves naturally to in vivo exposure

Table 6.1 Partial Stimulus Hierarchy for W. L.

Item	Subjective Units of Distress Scale Score
Coming in contact with an IV drug user ("they might have AIDS")	100
Touching garbage or garbage can	90
Using toilets in public restroom	80
Living with dirty people	70
Touching people's plates/food	65
Using a public telephone	60
Touching door handles with bare hand	60
Touching faucets	55
Touching a pen at a bank (other people have touched it)	55
Picking up items off the ground	50
Touching anything that is moldy (e.g., bread, fruit)	50

exercises. As an example of the general ERP approach with W.L., the first ERP task required W.L. to use a telephone without using anything to cover the phone or her hand (e.g., tissue), and subsequently not washing her hands afterwards. The therapist modeled this behavior prior to asking W.L. to perform this exercise. Each session, items higher on the hierarchy were incorporated into the ERP exercises. One of the most difficult tasks for W.L. involved shaking hands with another patient, who was an intravenous (IV) drug user.

Moreover, the patient was also given a large amount of daily homework that involved engaging in such activities as touching light switches, door knobs, and the floor without washing her hands. As part of these assignments, W.L. rated her anxiety directly before, during, and 1 hour afterwards in an anxiety log; these logs were reviewed at each session by her therapist. She also was given a copy of *Getting Control: Overcoming Your Obsessions and Compulsions* (Baer, 2000) and was required to read it as part of her treatment plan. In W.L.'s case, bibliotherapy helped to further normalize her thoughts and actions.

It is also important to emphasize that being involved in an inpatient treatment program was a very significant ongoing ERP task for this patient. W.L. was allowed to take one, 15-minute shower per day, and was limited to handwashings only after using the restroom and prior to eating scheduled meals. She eventually joined an ongoing therapy group, which required interaction with other patients and forced her contamination fears about HIV infection. She was also required to attend Alcoholics' Anonymous meetings on a daily basis as part of her substance abuse treatment, which required further exposure to one of her anxiety-provoking stimuli (i.e., other substance-abusing patients). As part of the treatment plan, W.L. was monitored closely by program staff to ensure compliance with these limits on her cleaning behavior. Toward the end of her residential stay, W.L. was placed on Paxil (starting at 20 mg/day and

gradually increased to 60 mg/day) to address her OCD symptoms, which was used in conjunction with her ERP treatment.

Upon completion of her 30-day inpatient stay, W.L. scored a 14 on the Y-BOCS, which translates into a 54% reduction in symptom severity from the onset of treatment. W.L. was referred to a 12-step substance abuse outpatient treatment program for follow-up addiction treatment. In addition, as part of the follow-up program, W.L. received a referral to a behavioral therapist (who had experience working with OCD patients) for weekly therapy sessions and a psychiatrist to monitor her medications. The ERP sessions with the behavioral therapist typically focused on W.L.'s fear of germs and other contaminants, which contributed to her inability to return to work. Finally, W.L. attended a 12-step OCD support group, a format she was familiar with from her past alcoholism treatment experiences (e.g., AA).

Consequently, W.L. successfully completed the behavioral treatment and was able to address her fear of germs and other contaminants. However, W.L. continued to attend AA and OCD support groups. At the six-month post-treatment follow-up, W.L. had remained sober and had returned to work as a waitress. She reported some obsessions, but noted that they were far more manageable than they had been in the past.

Conclusions and Future Directions

From our own clinical and research experience, OCD is a surprisingly common co-occurring disorder among patients with substance abuse. However, it is a disorder that often goes undetected by those without specific background and training in OCD and its diagnosis, assessment, and treatment. With proper screening, however, OCD can be readily identified. More importantly, OCD appears to exacerbate substance abuse; thus, treating both concurrently is likely to lead to better outcomes than a sequential treatment approach. Although the behavioral treatments for OCD, particularly ERP, are quite different than those typically used for substance abuse, making their integration difficult, the good news is that there are effective treatments for both disorders. Moreover, there is evidence that a combined treatment approach for both disorders, as described herein, can effectively be used to treat substance-abusing patients with OCD. Thus, when clinicians find themselves confronted with these patients, there is good hope for a positive outcome, both in terms of OCD symptoms and substance use behavior.

The combined intervention described herein emphasized the simultaneous application of standard treatment for substance abuse with ERP, which share few practical characteristics. Because these treatments are so distinct, the approach we describe is best viewed as a *simultaneous* treatment for OCD and SUDs, versus a truly integrated invention package. With this in mind, it is important to note that several authors have argued that OCD can be

conceptualized and treated more cognitively. For example, Salkovskis (1985, 1998) has argued that since intrusive and distressing thoughts are so prominent in the symptom picture of OCD patients, targeting dysfunctional cognitions would provide a more comprehensive and general treatment than ERP; mounting evidence is providing support for this position (e.g., McLean et al., 2001). Such cognitive therapies share far more similarities with standard treatments for substance abuse, particularly CBT, than ERP; thus, their integration into addiction treatment may be more straightforward. Although the effectiveness of such an approach with patients who have SUDs and OCD has yet to be evaluated, this represents an important next step in this area of clinical research.

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Chapter 7
Treatment for Co-morbid Posttraumatic Stress Disorder and Substance Use Disorders

David S. Riggs and Edna B. Foa

Despite the widely recognized relationship between posttraumatic stress disorder (PTSD) and substance use disorders (SUD), relatively little is known about how to treat co-morbid patients. PTSD is generally under-diagnosed in treatment-seeking substance abusers (Dansky, Roitzsch, Brady, & Saladin, 1997), so most patients with co-morbid PTSD and SUD who seek treatment for substance abuse do not receive treatment for PTSD (Brown, Stout, & Gannon-Rowley, 1998). While substance abuse is often detected in PTSD patients, SUD is typically an exclusion criterion for PTSD treatment. Thus, substance abusers are often deprived of treatment for their PTSD until they are able to abstain from using substances. Only recently have clinicians and researchers attempted to study the treatment of these difficult patients. Consequently, we have few data to inform treatment of individuals who suffer with both disorders. In this chapter, we will summarize the literature on the treatment of co-morbid PTSD-SUD patients, and discuss several intervention programs that have been developed or adapted to treat this population.

Co-morbidity

Epidemiological studies consistently find a high level of co-morbidity between PTSD and SUD (Chilcoat & Menard, 2003). Substance abuse is more strongly related to PTSD than to trauma exposure *per se* (Kilpatrick, Acierno, Resnick, Saunders, & Best, 1997; Streimer, Costic, & Tennant, 1985; Warshaw et al., 1993), and the prevalence and severity of SUD are related to severity of PTSD (Breslau & Davis, 1992; Ouimette, Wolfe, & Chrestman, 1996; Saladin, Brady, Dansky, & Kilpatrick, 1995). Kessler, Sonnega, Bromet, Hughes, and Nelson (1995) found

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men with PTSD were twice as likely as those without PTSD to have alcohol abuse or dependence and almost three times more likely to have a drug use disorder. Women with PTSD were two-and-a-half times more likely than those without PTSD to have an alcohol disorder and greater than four times more likely to be diagnosed with a drug use disorder. Similarly, Chilcoat and Breslau (1998) found that, compared to individuals without PTSD, those with PTSD were three times more likely to have a substance use disorder. Adolescents with PTSD were nearly four times as likely to have an alcohol disorder diagnosis and more than eight times more likely to have a drug disorder than their non-PTSD counterparts (Kilpatrick, Acierno, Saunders, Resnick, Best, & Schnurr, 2000).

Models Relating PTSD and SUD

Several models have been put forth to explain the relationship between PTSD and SUD. For example, the self-medication model (Khantzian, 1985, 1997) posits that substances are used, and abused, to provide relief from PTSD symptoms. Another model suggests that substance use increases vulnerability to PTSD (e.g., by increasing physiological arousal, Stewart & Conrod, 2003) or interferes with the normal recovery process (Foa & Riggs, 1995). A third model suggests that substance use and abuse makes individuals more vulnerable to traumas (e.g. sexual assault, interpersonal violence) that are more likely to produce PTSD (Stewart & Israeli, 2002). Regardless of how the disorders develop, once they are established, functional relationships among the symptoms may form a vicious cycle in which PTSD symptoms and SUD serve to maintain one another (Stewart, 1996; Stewart & Conrod, 2003).

The available literature supports a model that includes a casual role for PTSD in the etiology of SUD after which a vicious cycle forms in which the two disorders serve to maintain one another (Stewart, 1996). However, this pattern does not describe all patients with co-morbid PTSD and SUD. In some cases, onset of the SUD will precede the PTSD and for some patients, the symptoms may not directly maintain one another.

Approaches to Treating Co-morbid PTSD and SUD

When dealing with a patient who has both PTSD and SUD, a clinician has three options: (1) treat the SUD first and then treat the PTSD if necessary, (2) treat the PTSD first and provide SUD treatment later if it is needed, or (3) treat the two disorders at the same time. Most clinicians when faced with this dilemma will suggest that the SUD must be treated prior to the PTSD and the PTSD treatment should begin only after a substantial period of abstinence (Ouimette, Moos, & Brown, 2003). This view reflects the belief among practitioners that treating the SUD will provide patients with additional resources (e.g., adaptive

coping skills, social support) that can help to make PTSD treatment successful. Also, this approach capitalizes on the possibility that PTSD symptoms will be alleviated once the SUD is treated (Dansky, Brady, & Saladin, 1998). Delaying PTSD treatment until a period of abstinence has been achieved also reflects the belief that PTSD treatment will lead patients to relapse to manage (or medicate) the emotional distress arising from PTSD treatment. Given the risk of SUD relapse, programs that treat PTSD subsequent to substance use treatment should continue to attend to the SUD as the PTSD symptoms are being addressed.

Unfortunately, if the substance use does help to alleviate PTSD symptoms, delaying treatment for PTSD may lead to greater relapse of the SUD (Brown, Stout, & Mueller, 1996; Dansky et al., 1998; Ouimette, Moos, & Finney, 2003). The presence of PTSD also can complicate the initial treatment of SUD by motivating continued substance use. Indeed, studies of SUD treatment programs suggest that patients with both PTSD and SUD have poorer short- and long-term outcome than do patients with SUD alone (e.g., Brown et al., 1996; Ouimette, Ahrens, Moos, & Finney, 1997, 1998; Ouimette, Finney, & Moos, 1999).

Given the difficulties treating SUD in the presence of co-morbid PTSD, it may be better to first treat the PTSD and then the SUD. However, this approach also poses potential problems. Treatments that have been shown to be efficacious for PTSD fall within the rubric of cognitive-behavioral therapies (CBT; for reviews, see Foa & Meadows, 1997; Foa & Rothbaum, 1998). These include variants of exposure therapy, stress inoculation training (SIT), cognitive therapy (CT), eye movement desensitization and reprocessing (EMDR), and combinations of these procedures. A critical element of these treatments is the activation of trauma-related memories and the associated emotions either directly or indirectly through exposure to situations that increase stress and distress. CBT interventions require patients to participate actively and to learn through the course of the therapy. The elevated emotional distress that may accompany treatment for PTSD may lead to increased substance misuse that impedes learning and the processing of new information. Therefore, clinicians will generally not attempt to treat PTSD prior to the SUD. Indeed, we are not aware of any treatment programs in which PTSD treatment is provided first followed by SUD treatment. Also, patients with SUD are commonly excluded from studies of PTSD treatments. However, van Minnen, Arntz, and Keijsers (2002) reported that alcohol or benzodiazepine use among participants who did not meet criteria for dependence predicted drop-out from PTSD treatment suggesting that treating PTSD without concurrent treatment of the substance misuse could be problematic.

In their review of treatments for co-morbid PTSD and SUD, Ouimette, Moos, & Brown (2003) note that most clinical researchers recognize the potential benefits of treating the two disorders concurrently. Importantly, the majority of co-morbid PTSD-SUD patients also preferred concurrent treatment of the two disorders (Brown et al., 1998). Recently, a number of programs designed to

address both PTSD and SUD have been developed and preliminary data are available to begin informing treatment decisions for these complicated cases. Although the specifics of these programs differ, they generally incorporate techniques to promote effective coping skills, relapse prevention, education about the links between SUD and PTSD, and treatment focused on reducing PTSD symptoms. Results from preliminary examinations of these programs suggest they hold promise for treating individuals with PTSD and SUD (e.g., Brady, Dansky, Back, Foa, & Carroll, 2001; Najavits, Weiss, Shaw, & Muenz, 1998; Riggs, Rukstalis, J. Volpicelli, Kalmanson, & Foa, 2003; Triffleman, Carroll, & Kellogg, 1999; Zlotnick, Najavits, Rohsenow, & Johnson, 2003).

In sum, co-morbid PTSD-SUD patients appear to benefit from SUD treatment, though their gains are generally smaller and less enduring than those of SUD patients without PTSD (Ouimette, Moos, & Brown 2003). Although treating SUD can result in reduced PTSD symptoms for some co-morbid patients (e.g., Dansky et al., 1998), it is thought that residual PTSD symptoms contribute to relapse in SUD symptoms when treatment for PTSD is delayed. It seems clear that an effective treatment program for co-morbid PTSD-SUD patients must address both disorders. At the very least, it is necessary to inform SUD treatment with information pertaining to PTSD and to provide PTSD treatment soon after the end of the intervention targeting the SUD (Ouimete, Moos, & Brown 2003). However, recent advances suggest that treatment of these co-morbid patients might be completed more effectively and efficiently if the treatments are provided concurrently.

Specific Treatment Programs for Co-morbid PTSD-SUD

Exposure – Based Treatments. Exposure involves helping PTSD sufferers to confront distressing trauma-related memories and reminders to facilitate emotional processing of the memory and reduction of distress. Variants of exposure therapy, alone or combined with other CBT approaches, have been found effective for PTSD in survivors of rape (e.g., Foa et al., 1999, 2005; Resick, Nishith, Weaver, Astin, & Feuer, 2002); physical assault (Foa et al., 1999, 2005); domestic violence (Kubany et al., 2004); physical and sexual abuse in childhood (Cloitre, Koenen, Cohen, & Han, 2002; Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002); motor vehicle accidents (Blanchard et al., 2003; Fecteau & Nicki, 1999); as well as in refugees (Otto et al., 2003; Paunovic & Ost, 2001), and mixed trauma samples (Bryant, Moulds, Guthrie, Dang, & Nixon, 2003; Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998; Taylor et al., 2003).

Exposure therapy programs for PTSD differ somewhat in the details of the treatment, but share core components, in particular the repeated intentional recall of the traumatic memory. Prolonged exposure (PE) therapy for PTSD (Foa & Rothbaum, 1998) illustrates these key components and, as will be

described below, has been used in the treatment of individuals with PTSD and SUD. PE is delivered in an individual format and consists of 9–12 sessions, lasting 90 minutes each. The treatment includes four techniques: (1) psychoeducation about trauma, reactions to trauma, and PTSD; (2) breathing retraining; (3) *in vivo* exposure to feared but safe situations that the client avoids; and (4) imaginal exposure that instructs the client to repeatedly recount the traumatic memories orally to the therapist. *In vivo* exposure is assigned as homework beginning in the second session and imaginal exposure begins in session 3. At the end of each imaginal exposure session the client and therapists discuss thoughts and feelings that emerged during the recounting of the trauma. In addition to completing *in vivo* exercises, the client is asked to listen to tape recordings of the imaginal exposure exercise as homework between sessions. For a complete description of PE, the reader is referred to Foa and Rothbaum (1998).

The application of exposure-based treatments for PTSD to patients who have a co-morbid SUD raises potential problems. A critical element of all exposure-based treatments is the activation of the individual's fear so that corrective learning can take place (cf., Foa & Kozak, 1986). The use of substances with anxiolytic effects may interfere with recovery from trauma insofar as they impede fear activation during therapy. Substance use among PTSD patients may also promote emotional numbing or cognitive avoidance of trauma memories (Zaslav, 1994; Zweben, Clark, & Smith, 1994) and is believed to interfere with the emotional processing required for recovery (Boudewyns, Woods, Hyer, & Albrecht, 1991). It follows that the abuse of substances during treatment for PTSD may reduce treatment efficacy. Substance use may also increase in response to the arousal generated by treatment. Despite these concerns, the high efficacy of exposure-based interventions for ameliorating PTSD symptoms argues for their inclusion in comprehensive treatment programs for PTSD-SUD patients.

To date, four groups have developed and begun testing treatment programs that incorporate exposure techniques into treatments for co-morbid PTSD-SUD patients. Two programs focus on treating PTSD in the context of a particular SUD: Foa and her colleagues focus on alcohol dependence (Riggs et al., 2003); Brady and her colleagues (see Brady et al., 2001) focus on cocaine use disorders. Two other programs aim to treat co-morbid PTSD and SUD regardless of the specific substance used (Donovan, Padin-Rivera, & Kowaliw, 2001; Triffleman et al., 1999). One additional program to treat co-morbid PTSD and SUD, "Seeking Safety" (Najavits, 2003), explicitly omits exposure to traumatic memories as part of the core program (viewing trauma-focused work as an important aspect of therapy for PTSD once safety has been established in terms of abstinence, reduced self-harm, and ending dangerous relationships). However, in one study (Najavits, Schmitz, Gotthardt, & Weiss, 2005) the Seeking Safety program was combined with an exposure component adapted from Prolonged Exposure (PE) therapy (Foa & Rothbaum, 1998).

Below, we provide descriptions of each of these programs along with available data on their efficacy for co-morbid PTSD and SUD patients.

Concurrent Treatment of PTSD and Cocaine Dependence (CTPCD). Brady and colleagues (Brady et al., 2001, Coffey, Dansky, & Brady, 2003) developed Concurrent Treatment of PTSD and Cocaine Dependence (CTPCD) as a 16-session, twice weekly individual therapy. CTPCD combines Coping Skills Training (CST; Carroll, 1998; Kadden & Kranzler 1992), to reduce substance dependence with PE, to reduce PTSD symptoms. Each session includes techniques from each of the core treatments (CST and PE). On the assumption that it is important to teach skills to help maintain sobriety prior to PE, early sessions emphasize skill building and exposure is introduced in session 6. In early sessions, PTSD symptoms may be used as examples of substance use triggers or emotional distress and the link between PTSD and SUD symptoms is discussed. Once exposure is introduced, the sessions are split roughly in half with the first part devoted to PE and the second to the training of coping skills to foster abstinence. At each session patients are assigned homework (exposure and skills development) to complete prior to the next session. While abstinence is encouraged, slips and relapses do not automatically lead to treatment termination, but instead are examined to identify triggers and teach ways to cope with triggers and cravings. A more detailed description of CTPCD and a discussion of how the treatment is delivered can be found in Coffey et al. (2003) and Back, Dansky, Carroll, Foa, and Brady (2001).

Support for the efficacy of CTPCD comes from an uncontrolled study of 39 patients. Data from 15 patients who completed at least 10 of 16 protocol sessions revealed substantial reductions in both substance use and PTSD symptoms. Patients decreased cocaine use by 60% and scores on the Addiction Severity Index reduced by more than 50%. On measures of PTSD, patient-reported avoidance reduced by almost 30% and intrusive symptoms by more that 50%. Clinician ratings of PTSD showed even greater improvement with reductions of 66%, 70%, and 47% on intrusion, avoidance, and arousal respectively (Brady et al., 2001). Improvements were maintained through a 6-month follow-up. Patients who began, but did not complete, treatment showed no improvement in either disorder at the end of the 16-week treatment or at follow-up.

The high rate (61%) of drop-outs in the Brady et al. (2001) study raises the possibility that exposure is too intense for co-morbid patients. However, Coffey et al. (2003) pointed out that the drop-out rate from CTPCD is lower than the 72% rate found in the National Institute on Drug Abuse Collaborative Cocaine Treatment Study that used standard treatments for cocaine disorder (Crits-Cristoph et al., 1999). The completion rate for CTPCD also compares well to that reported by Najavits et al. (1998) using the "Seeking Safety" program without trauma memory exposure. Najavits et al. reported that 63% of patients completed 25% of sessions compared to 69% of CTPCD participants (Coffey et al., 2003). Brady et al. (2001) also report that most (75%) patients who dropped out of treatment left prior to the initiation of

exposure suggesting that leaving therapy was not due to increased distress associated with exposure.

In sum, CTPCD appears to be a viable treatment for patients with co-morbid PTSD and cocaine dependence with patients who complete CTPCD showing significant improvement in both areas. Although the drop-out rate from CTPCD is high, the program appears to be as well tolerated as other treatments for cocaine addiction (with or without a PTSD component). However, there is room for improvement with respect to adding treatment components that address treatment drop-out in co-morbid patients. Though CTPCD was designed to address the needs of cocaine dependent people, the techniques should readily transfer to other substance abusers because the CST techniques included in CTPCD were developed for use with alcohol dependent patients (Monti, Abrams, Kadden, & Cooney, 1989).

Treatment for PTSD and Alcohol Dependence. We are conducting the first controlled outcome study of concurrent treatment for PTSD and alcohol dependence (Naltrexone and CBT for Patients with Alcoholism and PTSD; PI: Foa; Grant No. RO1 AA012428). Like CTPCD, we combine effective treatments for each disorder into one program. Patients' PTSD is treated with PE while their alcohol dependence is treated with a combination of pharmacotherapy (naltrexone) and cognitive-behavioral counseling that combines motivational enhancement, coping skills, and support. The study is in progress but preliminary data have been presented (Riggs et al., 2003; Riggs, Pai, J. Volpicelli, Imms, & Foa, 2004).

Treatment is delivered individually and includes cognitive-behavioral counseling to reduce alcohol use and PE for PTSD. Sessions are initially weekly and decrease in frequency to once every two weeks after week 12 for a total of 24 weeks. Different clinicians provide PE treatment and alcohol counseling to provide control of procedures necessary for the randomized trial. The division also allows each therapist to focus sessions on one problem area rather than having to split the time in session. Thus, in contrast to the Brady et al. (2001) study in which much of the time following the imaginal exposure exercises was devoted to teaching coping skills, the PE protocol used in our study allows more time to process the imaginal exposure as is done when treating PTSD with no co-morbid alcohol disorder (Foa et al., 1999, 2005). Importantly, patients in this study begin exposure exercises soon after initiating treatment. *In vivo* exposure is introduced in the second treatment session and imaginal exposure to the traumatic memory begins in session three.

In the ongoing study participants are randomly assigned to receive naltrexone or a placebo and separately are randomized to receive PE or no PTSD treatment. All participants, regardless of other interventions receive counseling combining medication management, motivational enhancement, and cognitive-behavioral techniques to promote treatment compliance and support abstinence (J. R. Volpicelli, Pettinati, McLellan, & O'Brien, 2001). Slips and relapses are not cause for terminating treatment, but rather are treated as opportunities to learn and modify coping skills.

Preliminary analyses have been conducted on the first 70 patients entered into the study. Prior to treatment, participants drank heavily, reporting on average that they drank more than two-thirds of days and consumed about 14.5 standard drinks each day that they drank. These figures are comparable to the rates of alcohol use reported in recent studies of pharmacologic treatments for alcohol dependence (e.g., Krystal et al., 2001). PTSD symptoms in the co-morbid sample also are comparable to studies of PTSD without alcoholism (Foa et al., 2005; Resick et al., 2002). Analyses of the demographic characteristics of the co-morbid sample suggest that these individuals function less well than patient with PTSD or alcohol dependence alone. Co-morbid patients were more likely to be unemployed, with extremely low (i.e. <$10,000/year) incomes, and without a close romantic partner than samples of patients without this co-morbidity (Riggs et al., 2004).

There is a concern that combining PE with treatment for SUD will be less well tolerated than other treatments. Using rather stringent criteria to define completers (attendance of at least 12 of the 18 sessions and attendance at the final session) the drop-out rate in our study is about 38%. In comparison, a review of studies using PE, found an average drop-out rate of about 20% (Hembree et al., 2003). Similarly, our review of 22 recent studies using naltrexone to treat AD suggests an average drop-out rate of 30%. However, in most previous studies of PE or naltrexone treatment lasted no more than 12 weeks. The 12-week drop-out rate in our study was only 21%. Importantly, we found no differences in the drop-out rates among the treatments in our study.

Outcome analyses conducted on the first 44 patients to complete treatment revealed significant improvement in both PTSD and alcohol dependence symptoms. Also, patients who received PE reported a significantly greater reduction in PTSD than those who did not get PE. Importantly, there was no indication that conducting PE shortly after patients stop drinking increased alcohol use or cravings. In fact, patients treated with PE reported greater reduction in cravings than did patients who did not receive PE. Analyses of data from follow-up assessments conducted 3–6 months after treatment, though limited due to the small sample available, suggested that treatment gains were maintained. Patterns of alcohol consumption over the course of treatment and follow-up suggested that the combined treatment produced rapid and long lasting reductions in drinking. In sum, the results of our ongoing study, though tentative, suggest that concurrent treatment of alcohol dependence and PTSD holds much promise for alleviating both problems.

Substance Dependence PTSD Therapy (SDPT). Triffleman et al. (1999) developed a structured 5-month (40-session) program for substance dependent patients with PTSD. The first 24 sessions focused on attaining abstinence with the rest devoted to PTSD with some continued attention to substance use. Substance Dependence PTSD Therapy (SDPT) utilizes aspects of Coping Skills Training such as coping with drug use triggers and cravings, relaxation training, anger management, managing negative moods, assertiveness, and use of social supports. The training takes into consideration issues related to PTSD. The

second phase of treatment includes Stress Inoculation Training (SIT) for PTSD (Meichenbaum & Cameron, 1983) in which coping skills and cognitive restructuring address trauma-related distress and distortions. In addition, *in vivo* exposure exercises are used to address trauma-related avoidance. In contrast to PE, patients are instructed to remain in the *in vivo* situation only as long as they can tolerate the arousal. There is no imaginal exposure in SDPT.

One small, uncontrolled study found that SDPT reduced PTSD and substance abuse severity (Triffleman et al., unpublished cited in Triffleman, 2000). A second study randomly assigned 19 PTSD-SUD patients to SDPT or to Twelve-Step Facilitation (TSF; Nowinksi, Baker, & Carroll, 1992), a program using principals of 12-step programs to encourage abstinence. Patients were 4 dependent on cocaine, 14 on opiate-agonists and 1 opiate-dependent not on agonist treatment. Patients improved on PTSD and substance use but no difference emerged between the groups (Triffleman, 2000). Thus, while the techniques used in SDPT appear tolerable and effective with co-morbid PTSD-SUD patients, it is impossible to determine if the SDPT techniques produce any more benefit than a twelve-step program. It is possible that the lack of differences arises from the small sample included in this study. However, it is also possible that factors common to both approaches such as regular sessions with a supportive counselor led to the improvement.

Project Transcend. Project Transcend (Donovan et al., 2001) consists of a 12-week partial hospitalization program followed by outpatient groups that are encouraged, but not mandatory. The program includes techniques from psychodynamic, constructivist and cognitive-behavioral therapies as well as 12-step programs and assumes that addressing PTSD symptoms will promote faster and more lasting abstinence. Patients enter treatment in a cohort that remains together throughout the initial 12-week phase. Treatment emphasizes skills training during the first 6 weeks and trauma processing during the latter 6 weeks. Project Transcend incorporates a variety of trauma-processing techniques such as writing about the trauma, presentations to the group, and a nightmare resolution technique. Although exposure is not as structured as in the other programs described here, patients are asked to describe their trauma experiences, share them with the group and participate in discussions about their own and others' traumas.

Results for Project Transcend were reported in an uncontrolled study with 46 male Vietnam veterans with PTSD and SUD (30% alcohol, 70% poly-substance) (Donovan et al., 2001). All participants were required to abstain from substance use for 30 days prior to entry. Results revealed reductions in substance use and PTSD. However, the magnitude of PTSD reductions was rather small: overall PTSD reduced 15%, intrusions 13%, avoidance 16%, and arousal 13%. Improvements in PTSD and substance use were generally maintained over a 12-month follow-up period.

The changes in PTSD symptoms found with Project Transcend are smaller than those for the programs that used versions of PE (Brady et al., 2001; Riggs et al., 2003). It is possible that this is due to the greater exposure to one's own

trauma in the PE programs or to differences in exposure techniques (i.e., writing vs. imaginal recounting). Alternatively, the group format used in Project Transcend may be less effective in treating PTSD than is one-on-one therapy.

Seeking Safety. Seeking Safety (Najavits, 2002, 2004) is a skills training program to treat co-morbid PTSD and SUD. Seeking Safety explicitly omits exposure techniques and instead teaches patients to cope with PTSD symptoms and gain control over their current lives. Since its first formulation (Najavits, Weiss, & Liese, 1996), the program has changed from a group treatment to individual therapy and from a treatment focused on the needs of dually diagnosed women to one for men and women. The program incorporates interpersonal and case-management techniques in addition to the cognitive-behavioral approach used originally (Najavits, 2004).

Seeking Safety focuses on establishing safety throughout patients' lives including abstinence, control of PTSD, reducing suicidality and self-harm, and ending dangerous relationships (Najavits, 2004). The program addresses the two disorders simultaneously (as opposed to sequentially) and incorporates substantial discussion about the linkages between the two problems. Within the cognitive, behavioral, and interpersonal domains, the program teaches specific skills (e.g., asking for help, grounding, coping with triggers) or addresses issues pertaining to the disorders (e.g., honesty, healthy relationships, commitment, creating meaning).

As with the other programs discussed in this chapter, efficacy data on Seeking Safety are limited. In the first study, 27 PTSD-SUD women were treated in twice-weekly groups. Of these, 17 (63%) attended at least 6 of 25 meetings and were considered completers. Following treatment, completers reported significantly less substance use and a reduction in trauma-related symptoms as measured by the Trauma Symptom Questionnaire – 40 but not in core PTSD symptoms (Najavits et al., 1998). The group also improved on depression, suicidality, and social and family functioning. In a second uncontrolled study, Zlotnick et al. (2003) used Seeking Safety with 18 incarcerated women. Treatment was associated with a reduction in PTSD with half of the women no longer diagnosed with PTSD following treatment. The group also reported a reduction in drug and alcohol use following incarceration. Najavits (2004) cites two unpublished studies that incorporated control treatment groups. These studies indicated that Seeking Safety produced better outcomes that did treatment as usual (Hien, Cohen, Miele, Litt, & Capstick, 2004; Najavits, Gallop, & Weiss, under review cited in Najavits 2004). However, the Hien et al. (2004) study failed to find differences between Seeking Safety and a Relapse Prevention program. One small study examined the efficacy of Seeking Safety combined with a modified version of Foa and Rothbaum's (1998) exposure therapy to treat five men with PTSD and SUD (Najavits et al., 2005). Najavits (2003) reported that treatment satisfaction was high and treatment produced improvements on drug use and PTSD.

Case Example

To illustrate treatment of co-morbid PTSD and SUD we provide a case description of a woman treated in our PTSD and alcohol dependence program. B.C. is a 34 y/o Caucasian female with a history of physical abuse during childhood. She began drinking during adolescence and has made several attempts to stop. She is currently unemployed though she has worked as a waitress and hairdresser. She has a 7 y/o daughter, and lives with her boyfriend (not the child's father) in a small apartment. The patient has a history of homelessness during which time she would stay with friends, family, or in shelters. The patient reports a pattern of abusive relationships including one lasting 5 years during which she was severely beaten.

Although the B.C. had multiple traumas, her PTSD derived largely from an incident that occurred when she was approximately 15 years old. During the incident, her mother's boyfriend struck her repeatedly on the head and threw her down a flight of stairs. The patient suffered injuries and was rendered unconscious by the fall. As a result of the assault she was removed from her mother's home.

B.C. was diagnosed with PTSD, alcohol dependence, and major depressive disorder (MDD). Her PTSD was severe (PTSD Symptom Scale total score = 36/51) as was her depression (Beck Depression Scale total score = 42/63). She tried to stop drinking about 3.5 months before entering our program and managed to maintain her sobriety for approximately one month. At the time she entered our program, she was drinking every day with an average intake of about 15 standard drinks per day.

Under the supervision of our nurse, B.C. completed a 4-day outpatient detoxification. Treatment began immediately following and consisted of three interrelated interventions, started concurrently. She began naltrexone (50 mg/day for two days increased to 100 mg/day). Naltrexone, an opiate antagonist, helps reduce drinking in alcoholics when used with support or cognitive-behavioral interventions (Modesto-Lowe & Van Kirk, 2002; Streeton & Whelan, 2001). She was also seen for weekly outpatient appointments during which she was seen by an alcohol counselor, in this case the study nurse, who provided counseling following the BRENDA procedures (O'Brien, L. A. Volpicelli, & J. R. Volpicelli, 1996; J. R. Volpicelli, K. C. Rhines, J. S. Rhines, & L. A. Volpicelli, 1997), and a therapist who conducted treatment for PTSD using the PE protocol (Foa et al., 2005).

The BRENDA intervention promotes compliance with pharmacotherapy for substance dependence and combines medication management and motivation enhancement techniques. BRENDA is an acronym for the intervention components: (1) a **B**iopsychosocial evaluation, (2) **R**eporting the assessment results to the patient, (3) **E**mpathic understanding, (4) **N**eeds assessment, (5) **D**irect advice, and (6) **A**ssessment of the patient's response to the advice. In the case of B.C., the assessment results outlined above and the results of her

physical exam (largely normal) were discussed. Of particular concern was her social situation. Being unemployed with limited social supports and the potential to become homeless represented risk factors for treatment and later relapse. The counselor also noted her reactivity to certain drinking cues (e.g., social situations where alcohol was present) and discussed the need to avoid them if possible.

Over the course of treatment, effort was made to help B.C. move toward employment, including re-contacting former employers, filling out job applications, etc. Also, the counselor spent a portion of the sessions discussing the future of her relationship and her living arrangement. The patient was ambivalent about the relationship but felt trapped because she had no other place to live. The counselor helped her to expand her available options (e.g., applying for housing assistance). Portions of each counseling session focused on helping B.C. maintain her motivation for sobriety and identifying cues that increased her desire to drink. Discussion of the specific trauma and PTSD symptoms as drinking cues was limited due to restrictions in the research protocol; however, emotional themes related to the trauma (e.g., fear of abandonment) were discussed . The BRENDA protocol is flexible and allowed the counselor to focus each session on salient aspects of the patient's presentation. Thus, some weeks the focus was on drinking cues and emotional triggers while in other sessions the emphasis was on maintaining motivation and still other sessions centered on planning for the future and obtaining employment.

PE with B.C. followed the same protocol as PE with non-addicted patients (Foa & Rothbaum, 1998). In the first session, the therapist described the treatment program and techniques, provided a rationale for the treatment, and obtained a description of the patient's traumatic experiences. At the end of the session, the therapist instructed the patient in controlled breathing and instructed her to practice it daily. In the second session, the therapist and patient reviewed common reactions to trauma and the patient described her own reactions. The therapist provided a rationale and description of *in vivo* exposure and worked with the client to develop a hierarchy of situations and stimuli that elicited fear or avoidance. For B.C., many items related to the possibility of falling (e.g., standing on a balcony, walking down stairs) while other items cued her traumatic memory (e.g., being in the dark, taking a shower). After obtaining the hierarchy, the therapist instructed B.C. to complete two relatively easy exposure exercises in the ensuing week.

In the third session, the therapist provided a rationale for the imaginal exposure. Once it was clear that the patient understood the goals of the exposure, the therapist provided the instructions and began the exposure. The imaginal exposure exercise was tape-recorded and the patient was asked to listen to the tape each day between sessions. Additional *in vivo* exercises were also prescribed. PE continued for seven additional sessions (a total of 10 sessions completed over 12 weeks due to missed sessions).

Although initially reticent to engage in exposure exercises, B.C. was able to complete them with a little gentle encouragement from the therapist. She

completed her *in vivo* homework regularly, but typically only listened to her imaginal tapes 2–3 times per week. During treatment, B.C. remained abstinent except for one slip approximately 7 weeks into treatment when she drank four drinks in one evening. Exposure to trauma reminders often evokes craving in patients with co-morbid PTSD and SUD (Saladin et al., 2003), and B.C. reported some increase in cravings associated with the imaginal exposure exercises. However, she indicated that the increase was not so great as to cause her to drink and that the increased cravings tended to be short lived. Indeed, her scores on a measure of cravings that we administered weekly showed no substantial increase in alcohol craving when exposure exercises were initiated.

After the 10th session, B.C. was re-evaluated. She had not had a drink 37 days and had only the one slip in the preceding 91 days; she reported extremely rare and mild urges to drink. She no longer met criteria for PTSD or MDD with a PTSD Symptom Scale score of 6/51 and a Beck Depression Inventory score of 7/63. B.C. reported that she was sleeping through the night without a light (previously she was afraid of the dark) and was no longer avoiding anything on the *in vivo* hierarchy.

B.C. was maintained on her medication for an additional 12 weeks and received six more sessions of BRENDA and PE on a bi-weekly basis. It became clear that the PTSD symptoms were largely non-existent so the therapist shifted from the PE protocol to interventions focused on active problem solving and general support. The therapist did encourage B.C. to continue to engage in activities that she had previously avoided, and if difficulties related to her PTSD arose they were discussed. B.C. reported no drinking during the last 12 weeks of treatment and no urges to drink over the last month of treatment. Her PTSD and depression remained largely absent and at the final session (24 weeks after treatment began) she did not meet criteria for PTSD or MDD. Her PTSD Symptom Scale score was a 2/51 and her Beck Depression Inventory score was 2/63 at the final session. We followed-up with B.C. 3 months after her final treatment session and she reported that she had started a job, moved into her own apartment, was caring for her daughter, and continued to be alcohol-, PTSD-, and depression-free.

Summary

The high rate of co-morbidity between PTSD and SUD and the complex relationship between the disorders necessitates treatment that addresses both. Sequential treatments in which the SUD is treated first followed by PTSD treatment hold some promise, but PTSD often interferes with SUD treatment and may lead to relapse. Therefore, treatment for PTSD should be offered soon after SUD treatment rather than waiting for months as has been typical (Ouimette Moos, & Finney 2003). We could not find reports of programs that

first treat PTSD and then SUD treatment. It appears that concerns about exacerbating substance use and conducting therapy with substance abusing patients have eliminated this option from clinical consideration. Several programs address the two disorders concurrently. While these programs are in the early stages of evaluation, there is growing evidence that this approach may prove effective with this population. Results from early studies suggest that these programs are well accepted by patients and reduce symptoms of PTSD and SUD. However, conclusions about the utility of these programs are limited by the small sample sizes and absence of control groups in these preliminary studies.

In general, treatment programs for co-morbid PTSD and SUD utilize cognitive-behavioral procedures to teach patients skills to improve coping, manage urges to abuse substances, and manage trauma-related distress. Some programs also incorporate exposure-based techniques to treat PTSD. Despite concerns, available data suggest that exposure therapy helps reduce PTSD symptoms without interfering with SUD recovery (Brady et al., 2001; Riggs et al., 2003). Indeed, programs that incorporate extensive exposure techniques tended to produce greater improvement in PTSD symptoms than did programs that did not include extensive exposure. Notably, treatments for PTSD that emphasize cognitive techniques (as opposed to exposure) have not been examined in samples of substance dependent trauma survivors. Existing studies of PTSD treatment suggest that including some exposure with cognitive therapy increases treatment efficacy whereas adding cognitive techniques to *in vivo* and imaginal exposure does not appear to improve efficacy (Foa et al., 2005; Marks et al., 1998). Given that PE is effective for PTSD and that it can be effectively disseminated to community clinicians (Foa et al., 2005), including PE as part of an integrated treatment for co-morbid PTSD and SUD appears promising. Despite the hope offered by programs that address both PTSD and SUD, the data available for evaluating such programs are extremely limited. Considerable research is needed to provide clinicians with clear guidelines for how, when, and to whom these programs should be offered.

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Chapter 8
Treatment of Co-Occurring Alcoholism and Social Anxiety Disorder

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Social anxiety disorder, also called social phobia, was recognized as a distinct anxiety disorder in 1980 (American Psychiatric Association [APA], 1980). The prevalence of 13% in the general population (11% in males and 15% in females), makes it the most prevalent anxiety disorder in the United States (Kessler et al., 1994). As such, there has been a rapidly growing interest in this "neglected" anxiety disorder (Liebowitz, Gorman, Fyer, & Klein, 1985).

The cardinal feature of social anxiety disorder is extreme fear of scrutiny and negative evaluation by others in social interactions or social performance situations (American Psychiatric Association, 1994). These fears typically begin in early adolescence (Ballenger et al., 1998). In one epidemiologic survey, more than 90% of those who developed social anxiety disorder did so by the time they were 25 (Schneier, Johnson, Hornig, Liebowitz, & Weissman, 1992). If social situations are encountered and endured rather than avoided, they are done so with extreme discomfort. Social phobia is more debilitating than shyness (Chavira, Stein, & Malcarne, 2002), and it does not spontaneously remit (Bruce et al., 2005). The chronicity of the disorder results in significant underachievement and underperformance, lower levels of satisfaction with life, and a generally higher level of functional disability than individuals without social anxiety disorder (Simon et al., 2002; Quilty, Van Ameringen, Mancini, Oakman, & Farvolden, 2003).

It is well known from anecdotal reports in treatment-seeking (Chambless, Cherney, Caputo, & Rheinstein, 1987; Schneier, Martin, Liebowitz, Gorman, & Fyer, 1989) and non-treatment-seeking samples (Thomas, Randall, & Carrigan, 2003) that socially anxious individuals intentionally use alcohol to self-medicate their social fears. The self-medication hypothesis (Khantzian, 1997), the tension reduction hypothesis (Conger, 1956), and the stress-response-dampening hypothesis (Sher & Levenson, 1982) all predict that repeated use of alcohol to

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relieve social anxiety is a likely explanation for the subsequent development of alcohol problems. Alcohol might be effective in tempering anxiety symptoms initially, but as tolerance develops, the individual must drink more to receive the same relief. The alcohol use over time may, in turn, exacerbate the anxiety symptoms (Kushner, Abrams, & Borchardt, 2000). An in-depth discussion of the etiological basis of co-occurring alcoholism and social anxiety is beyond the scope of this review; the reader is referred to other expert sources (e.g., see chapter 1 and chapter 4).

The purpose of this chapter is to address the treatment of co-occurring social anxiety disorder and alcoholism, an area that has not received much scientific investigation, despite the prevalence of these co-occurring disorders. According to a recent review by Morris and colleagues, those with social anxiety disorder are two to three times more likely to develop alcohol abuse or alcohol dependence (alcohol use disorder, or AUD) as compared to those without social anxiety disorder. Similarly, those with an alcohol use disorder are up to ten times more likely to have social anxiety disorder as compared to those without an alcohol use disorder (Morris, Stewart, & Ham, 2005). It is likely that even more individuals in alcohol treatment will present with clinically significant, yet sub-threshold, levels of social anxiety (Davidson, Hughes, George, & Blazer, 1994; Stein, Torgrud, & Walker, 2000). Similarly, individuals in anxiety treatment settings may display dysfunctional drinking, while not meeting full diagnostic criteria for an alcohol use disorder. Fortunately, both social anxiety and alcoholism respond to treatment.

It should be noted that co-occurrence, co-morbidity, and dual-diagnosis are all terms used to refer to individuals with both a psychiatric and substance abuse problem, and this chapter uses these terms interchangeably. The first two sections provide an overview of current evidence-based treatments for social anxiety disorder and for alcoholism, respectively. Then, treatment options for the patient presenting with co-occurring social anxiety and alcoholism are discussed, although evidence-based treatments are still lacking. Finally, the chapter identifies research opportunities in this relatively unexplored, but fruitful area of treatment research.

Evidence-based Treatment Options for Social Anxiety Disorder

Social anxiety, like most of the mood and anxiety disorders, is a treatable condition. Psychosocial interventions that are effective for the treatment of social anxiety disorder include exposure therapy, cognitive behavioral therapy (CBT) with or without exposure, applied relaxation and social skills training, as well as interpersonal therapy and mindfulness techniques (Rowa & Antony, 2005). CBT with and without exposure has shown marked and long-lasting treatment effects (see Heimberg, 2002 for review). Given the highly cognitive nature of social anxiety disorder in terms of distorted

perception of social threat, internalized focus of attention, and self-critical thoughts, cognitive therapies also are well suited to address this form of anxiety disorder (Stangier, Heidenreich, Peitz, Lauterbach, & Clark, 2003).

Social anxiety is treated effectively with medication, and this has been an area of intense scientific investigation. For social anxiety, the most effective pharmacotherapy is the class of drugs known as the selective serotonin reuptake inhibitors (SSRI) (Stein, Ipser, & Van Balkom, 2004), such as fluoxetine, sertraline, paroxetine and citalopram. The norepinephrine/serotonin reuptake blocker, venlafaxine, has also been shown to be efficacious for this disorder, although its efficacy in social anxiety is thought to be due to its blockade of serotonin reuptake (Stein, Pollack, Bystritsky, Kelsey, & Mangano, 2005). These medications reliably reduce social fears, decrease avoidance, and improve self-reported quality of life.

Studies comparing medication to behavioral treatment have shown more rapid improvement of symptoms with medication, but a more sustained treatment gain in individuals provided behavioral therapy (Heimberg, 2001). More recent studies combining pharmacotherapy and behavioral therapy have not shown the predicted additive gains and, in fact, have shown little benefit of combining the two forms of treatments (Davidson et al., 2004).

Evidence-based Treatment Options for Alcoholism

Psychosocial Treatments. Alcoholism is also a treatable disorder. In the United States, psychosocial treatment traditionally has focused on encouraging client participation in Twelve Step support groups like Alcoholics Anonymous. In the past several years, additional therapies have been tested and shown to be effective in large-scale, multi-site trials, including Project MATCH (Project MATCH Research Group, 1997). These behavioral therapies provide clinicians with evidence-based treatment options. Motivational Enhancement Therapy (MET) involves the therapist using active listening techniques and encouraging the client to develop his/her own change plan for drinking behaviors (Miller, Zweben, DiClemente, & Rychtarik, 1995). Cognitive Behavioral Therapy (CBT) relies on the tenets of two models of human behavior—the cognitive model and the behavioral model. CBT attempts to enable clients to better understand the links between thoughts, feelings, and behaviors (i.e., drinking) and encourages clients to change self-efficacy beliefs and alcohol expectancies to help change behaviors. It also teaches specific behavioral skills, such as drink refusal skills (Kadden et al., 1992). Combined Behavioral Intervention (CBI) merges MET with a cognitive behavioral intervention that also makes use of 12-Step support groups and family involvement (Longabaugh, Zweben, Locastro, & Miller, 2005). Psychosocial therapies are the mainstay of alcoholism treatment, and treatment manuals are available (Kadden et al.,

1992; Miller, Zweben, DiClemente, & Rychtarik, 1995; Miller et al., 2004; Nowinski, Baker, & Carroll, 1994).

Adjunctive Pharmacotherapies for Alcoholism. The U.S. Food and Drug Administration (FDA) has approved three medications for the treatment of alcoholism. The first medication, disulfiram (Antabuse®), inhibits the breakdown of a toxic metabolite of alcohol, acetaldehyde, and causes unpleasant physical symptoms, including headache, nausea, facial flushing, and vomiting. The therapeutic action of disulfiram is the induction of alcohol aversion (Saitz & O'Malley, 1997). Naltrexone (ReVia®) was approved by the FDA for the treatment of alcoholism in 1994. The therapeutic effect is achieved by the antagonistic action of naltrexone on the opiate receptor; this dampens the rewarding effects of alcohol (Anton & Swift, 2003). Acamprosate (Campral®), a medication approved in 2004 to treat alcoholism, may block the release of glutamate that occurs during the days following abstinence, and thereby reduce craving and risk of relapse (De Witte, 2004). Pharmacotherapy is an important adjunctive treatment for alcoholism and one that will continue to receive research attention.

Treatments for the Patient with Co-Occurring Social Anxiety and Alcoholism

The sections above demonstrate that there are effective treatments for both social anxiety disorder and for alcoholism. Despite the epidemiological evidence showing the high co-morbidity of the two disorders, and a wealth of strong scientific evidence from controlled clinical trials that each condition responds well to treatment, few research studies have focused on the treatment of individuals with co-occurring social anxiety and alcoholism. Consequently, there are no clear, evidence-based treatment guidelines that can be recommended at this time. The available studies, however, provide some important insights and questions for future studies to address. A dilemma in the treatment of individuals with co-occurring psychiatric and substance abuse disorders, in general, is what treatment model should be used—should both disorders be treated, and if so, should they be treated sequentially or simultaneously? The treatment of the patient with co-occurring social anxiety and alcoholism is no exception. The features of the various models, along with their strengths and weaknesses, are discussed.

Sequential Model. In the sequential model, one disorder is treated first, to the point of remission or significant improvement, and then the second disorder is addressed. This method is useful in the treatment of co-occurring disorders where one of the disorders requires more emergent attention. For most co-occurring disorders, however, such as social anxiety disorder and alcoholism, the acuity of one disorder over the other is not obvious. In such cases, the disorder that is treated first is usually determined by whether the individual seeks treatment in a mental health facility or a specialty addiction

treatment facility. In most cases, these are separate treatment systems and are in different physical locations. As a result of the division of these treatment systems, staff are seldom cross-trained in both mental health and addiction treatment (Mojtabai, 2005). To our knowledge, no studies in the treatment of co-occurring social anxiety and alcoholism have employed the sequential treatment model.

Parallel/Simultaneous Treatment Model. In the parallel/simultaneous treatment model, both psychiatric and substance abuse problems are treated at the same time, but not necessarily by the same treatment professional, or in the same treatment facility. The benefit of this model, like the sequential model described above, is that both disorders are treated by experts. Unlike the sequential model, however, the experts would be treating the individual at the same time. The primary drawback of this model is that it is unlikely that clinical care is coordinated between treatment providers. Each provider monitors progress only of the disorder (s)he is treating, with little or no information about the progress of the co-occurring disorder. Treatment in two different treatment settings also is inconvenient for the client and will likely lead to compliance problems.

One randomized clinical trial was conducted by our research group utilizing a modification of the parallel treatment model in the treatment of socially anxious alcoholics (Randall, Thomas, & Thevos, 2001). The important modification we made was that while the treatments for social anxiety and alcohol were distinct, they were delivered within the same treatment facility and by the same treatment provider.

At the time the clinical trial was initiated, there were no medications for social anxiety treatment that could be used safely in alcoholics, and the only FDA-approved medication for alcohol treatment was disulfiram, a medication associated with high rates of non-compliance (O'Farrell, Allen, & Litten, 1995). We utilized the state-of-the-art treatments at the time for both social anxiety and alcoholism—cognitive behavioral therapy (CBT). The therapy was individual, manual-guided, and was delivered weekly over a 12-week period. Individuals were seeking outpatient treatment for their alcohol problem, not for social anxiety disorder. All individuals met DSM-III-R (American Psychiatric Association, 1987) criteria for current alcohol dependence and current, primary social anxiety disorder[1].

The subjects were randomly assigned to receive either alcohol treatment only (alcohol only group) or alcohol treatment and social anxiety treatment (dual

[1] When evaluating individuals who are actively drinking, it is important to differentiate a primary anxiety disorder from a substance-induced anxiety disorder, in which anxiety symptoms consistent with an anxiety disorder may be secondary to alcohol use or withdrawal. An individual is judged to have a primary anxiety disorder if the onset of the anxiety symptoms preceded the onset of the alcohol use disorder. Social anxiety disorder precedes alcohol dependence in most individuals when the two diagnoses co-occur (Sareen, Chartier, Kjernisted, & Stein, 2001), making substance-induced social anxiety disorder less of a differential diagnostic issue than for other types of anxiety disorders.

treatment group). Topics covered in the alcohol treatment included coping with urges to drink, managing thoughts about alcohol, problem solving, drink refusal skills, and planning for emergencies (Kadden et al., 1992). Subjects in the dual group also received social anxiety treatment. Both types of treatment were administered by a licensed counselor (experienced in the treatment of both alcoholism and social anxiety) within the same treatment session. The social anxiety treatment (Butler, 1989) began with an introductory session and training in relaxation techniques. Then, triggers for social anxiety were discussed and each client constructed a hierarchy of feared social situations, from the least to the most feared, to be targeted over the course of treatment. Homework assignments included progressive and systematic exposure to feared situations to maximize the likelihood of positive social interactions as well as expectations for future success (see Randall, Thomas, & Thevos, 2001 for list of content areas covered in each session).

The intent-to-treat analysis showed that both groups improved from baseline on both alcohol and social anxiety measures. Critical to interpreting these findings is the fact that there was no differential improvement in social anxiety indices in the two groups over the 12-week trial and three months after the end of treatment, which was counter to our hypothesis. In addition, the dual-treated group had somewhat worse outcomes than the alcohol-only group on three of the four standard alcohol indices (percent days abstinent, percent days heavy drinking, total number of drinks consumed, but not drinks/drinking day). In trying to account for these results and in processing some anecdotal information gained during the trial and more recently in the context of additional research in this area, we propose some possible explanations for the failure to find a decrease in drinking behaviors.

The alcohol outcome measures typically used in clinical trials with alcoholics—quantity and frequency of drinking—may not have been sensitive indicators of success with this unique population. We did not realize at the time of the trial that as social fears decreased, individuals avoided social situations less often, and therefore had more opportunities to drink in social settings. This might explain why the dual group had fewer abstinent days and more total drinking days than the group that received the alcohol-only treatment. An index of dysfunctional drinking (i.e., drinking specifically to cope with social fears) may have been a more relevant outcome measure. The increase in percent days heavy drinking in the dual-treated group might be explained by the fact that individuals in this group were encouraged, as a part of their CBT for social anxiety, to expose themselves to feared social situations. Therefore, this group encountered more situations where they would typically consume alcohol to cope with their fears and, in alcoholics who likely have built up a high tolerance for alcohol, the amount consumed would likely be sufficient to meet criteria for a heavy drinking day (i.e., five drinks/day for men and four drinks/day for women). This is speculative, however, since drinking during exposure situations was not specifically assessed or recorded in the progress notes by the therapist in the trial.

We expected that the dual treatment group would show significant improvement in their social anxiety severity over the 12-week trial, as compared to the alcohol-only treatment group. This was not the case; both groups improved similarly (albeit modestly) in their social anxiety. In attempting to explain the lack of difference in social anxiety level between the dual-group and the alcohol-only group, there are several possible explanations. First, it is possible that the treatment we used for social anxiety was ineffective. CBT was delivered individually, not in groups, but individual CBT has been shown to have the same effect size as group therapy (Taylor, 1996). However, CBT in general may have been ineffective for our participants due to their alcohol dependence. Studies supporting the efficacy of CBT for social anxiety either excluded alcoholic subjects or did not assess alcohol use to determine if individuals met criteria for alcohol dependence (Gelernter et al., 1991; Heimberg et al., 1990). In cases of simple phobia, the presence of alcohol in the blood at the time of exposure to a feared situation (or a feared stimulus) interferes with the benefit of exposure therapy by not allowing the subject to experience the fear in a natural state (Himle et al., 1999). It is possible that some participants may have used alcohol during exposure to social situations, although this was not explicitly monitored. To avoid a possible reduction in treatment efficacy, total abstinence during exposure to social situations is recommended.

Another possibility is that the cognitive demands placed on the dual-treated group were overwhelming and complicated an otherwise effective treatment (Conrod & Stewart, 2005), possibly through a reduction of self-efficacy (Brownell, Marlatt, Lichtenstein, & Wilson, 1986). The need to consider the modality of treatment(s) so that there are not negative interactions is something that recently has been observed in clinical trials of psychiatric disorders (Davidson et al., 2004).

It is also possible that the "dose" of social anxiety therapy was insufficient for alcoholics accustomed to coping with their social fears by drinking. In our project, exposure therapy began at week 4 of treatment. The average number of sessions attended in the 12-week period was eight, which was similar for both the alcohol-only group and the dual treatment group, but perhaps too few exposure opportunities to realize any differential impact of CBT specific to social anxiety. A longer follow-up might have shown a differential slope of improvement in the two groups, especially if the results of CBT for social anxiety, with the new skills and cognitive set developed during therapy sessions, emerged following treatment. It also might be important to include additional sessions or focus addressing avoidance and safety behaviors to address any maladaptive coping styles that might be present in this group (Ouimette, Ahrens, Moos, & Finney, 1998).

The results of this study, showing poorer alcohol outcomes on quantity and frequency measures, should not be misinterpreted to indicate that social anxiety should not be treated in the course of alcoholism treatment. Rather, this study was not a true test of the hypothesis since, as noted above, both groups improved similarly and modestly in social anxiety severity. Additional research

must be conducted before any conclusions regarding treatment of social anxiety in alcoholics can be made.

Though it did not provide support for an evidence-based intervention, this pioneering study highlighted some important issues for consideration in future studies related to the treatment of social anxiety and alcohol use disorders. For example, what is the best sequence of staging treatments? What treatment modality for alcohol or social anxiety is most appropriate to the question being addressed? Will the treatment or treatment modalities interact negatively? In terms of study design, it will be important to assess drinking motives or stress relief from alcohol at baseline to define a population who is drinking deliberately to cope with social fears, to include as a primary outcome variable, a measure specifically related to drinking to cope in situations where drinking occurs to determine criteria to indicate improvement in social anxiety (i.e., self-rated scales or clinician-rated scales), and to conduct data analyses using an intent-to-treat approach, but also include a completers/compliers analysis. This is especially true for behavioral studies in which skill development or shifts in cognitive factors are necessary for the gains to be realized. More studies taking into account the lessons learned from this initial clinical trial using the parallel/simultaneous model of treatment are needed.

Integrated Model. In a completely integrated model, social anxiety and alcoholism are addressed, or at least monitored, simultaneously by a single individual qualified to treat both disorders. Clients respond to this model because it attempts to show them how problems are interrelated, rather than approaching the dual-diagnosis as two separate problems that need to be treated individually. It helps clients become more aware of their drinking for mood management, and it allows them to incorporate other coping strategies learned in the course of treatment.

A completely integrated approach is not always feasible, however. In community treatment clinics, expertise is typically divided between mental health facilities and addiction treatment facilities, which are not often co-located. In this case, both problems can be addressed simultaneously only when the treatment providers communicate with each other and attempt to treat the disorders within a unified treatment plan. In the treatment of the seriously mentally ill with an alcohol problem, this divided yet integrated treatment model has shown great success as long as the treatment is coordinated (see Mueser, Noordsy, Drake, & Fox, 2003; Weiss & Najavits, 1998 for reviews). The lack of adequately trained professionals who are able to recognize and treat both addiction and anxiety hinders more widespread use of this model in real-world treatment settings.

Integrated treatments specifically for co-morbid alcoholism and social anxiety disorder have not yet been tested, although one such trial with socially anxious college students who drink heavily is in progress (Tran, personal communication). While it remains to be determined what type of intervention(s) will produce the best outcomes in integrated treatment models, CBT is well suited for integrated treatments. Therapists can demonstrate the link

between anxiety triggers and drinking, identify symptoms of social anxiety and help the individual break the cycle of drinking to cope by teaching alternative coping behaviors, challenge distorted thinking associated with negative evaluation, encourage exposure therapy to help with avoidant behavior, and use similar techniques to enforce relapse prevention once drinking has stopped. Once social anxiety is managed, group therapy and/or 12-step group meetings might actually be beneficial to individuals with social phobia and alcoholism because it allows practice of social interactions in a safe setting.

With appropriately trained specialists, the integrated model has promise in the area of co-occurring social anxiety and alcoholism regardless of the type of intervention, be it behavioral or pharmacological. In fact, the integrated model has shown great success in treatment of other co-morbid disorders such as PTSD and addiction (Ouimette, Brown, & Najavits, 1998) and bipolar disorder and addiction (Weiss et al., 2000). The important ingredients are (1) the recognition of the need for treatment of both disorders in a client, and (2) a therapeutic approach that is aimed at targeting both disorders, such that the complex interrelation between them is recognized and influences treatment planning. For example, the idea that anxiety often influences the desire to drink should be discussed, in addition to the fact that alcohol use may actually increase anxiety (or at least interfere with extinction) in the longer term. It also is critical in the integrated approach to monitor improvement in both social anxiety and alcohol on a regular basis. Such monitoring will allow the client and therapist(s) to review treatment gains and also to recognize time-lagged gains. Discussion of these results may help uncover the relationship between the two disorders, facilitating greater awareness in both the therapist and the client.

The following is a case report illustrating an example of integrated pharmacological intervention. The client, who was seeking treatment in our clinical program, met DSM-IV criteria for alcohol dependence and social anxiety disorder. The psychiatrist (co-author SWB, who has expertise in the treatment of anxiety and addiction) chose to use two medications, sertraline and acamprosate, each shown to effectively treat social anxiety and alcoholism, respectively. Importantly, the physician discussed the connection between social anxiety and alcohol use, including the client's use of alcohol to cope and how continued alcohol use could hamper treatment for social anxiety.

Case Illustration

A is a 34-year-old woman who initially presented for treatment at the urging of her parents after crashing her car into a telephone pole while under the influence of alcohol. Fortunately, no one was injured and there was no police involvement, though the incident was very frightening to the client. Ms. A endorsed drinking vodka drinks, typically 3–5 per occasion, as often as 4 times weekly. She admitted that her alcohol use had been out of control for the past two years, coinciding with a divorce that left her with sole parenting responsibilities for

two small children and forced her back into the workplace. Ms. A reported that she felt that alcohol had initially helped to embolden her to face her new responsibilities in the workplace, but now she feared her alcohol use had become a problem. She reported that she wanted to drink less and on several occasions had tried to cut back or quit but had been unsuccessful.

Elaborating her reasons for drinking, she reported she experienced marked anxiety in any situation that required her to meet new people, make "small talk", or speak to people in authority. These feelings began when she was a teenager, and she reported that alcohol relieved this anxiety. Her new position as a server in a restaurant presented several challenges regarding social interactions. For example, she struggled with speaking to customers; she feared that they were sizing her up unfavorably, assuming she was "stupid." Ms. A stated that she often avoided extra contact with customers, which adversely affected her work performance. Following her separation from her husband, she struggled with developing a new social circle. She frequently drank after work to ease her anxiety when socializing with coworkers. The car accident that served as the impetus for treatment occurred on one such evening.

Although her parents were very concerned about her alcohol use, Ms. A actually requested treatment for social anxiety, as this was her primary concern. The psychiatrist discussed the benefits of treating both disorders and highlighted their interrelatedness to the patient. Ms. A eventually consented to an integrated approach, agreeing that her alcohol use was worsening her anxiety symptoms.

She was started on sertraline, a selective serotonin reuptake inhibitor, titrating up to 150 mg daily, as well as acamprosate (666 mg three times daily). In the next several months, her life changed dramatically. After two weeks she reported that she had cut back on her alcohol use and was thinking about attending a meeting of Alcoholics Anonymous, something that had been daunting to her in the past due to her social anxiety. By six months, she reported that she was no longer uncomfortable in social situations and no longer felt the need to drink. She took a new part time job as a customer service representative at a local hospital and was making more friends and feeling more hopeful. At the end of one year, she had a full time job with benefits and an active social life that did not involve alcohol.

Etiologic Model. The specific co-morbidity of social anxiety disorder and alcoholism is unique in that for the vast majority of cases, alcohol problems follow social anxiety onset (Sareen, Chartier, Kjernisted, & Stein, 2001). There is likely a substantial subset of co-morbid individuals for whom the relationship between social anxiety and alcoholism is causal: drinking to medicate anxiety symptoms resulted in the development of alcohol problems (Kushner, Abrams, & Borchardt, 2000). For such individuals, particularly those who are early in their alcohol problems (who have not yet developed severe alcohol dependence), treating the social anxiety may translate into improved alcohol outcomes even if the alcohol problem is only minimally addressed. This theory has not yet been thoroughly tested, though preliminary evidence from a pilot study

conducted by our group suggests that treating the social anxiety disorder with an SSRI may improve drinking outcomes (Randall et al., 2001).

Our pilot study was an 8-week, double-blind, placebo-controlled clinical trial. Individuals were recruited from community advertisements. All participants (N = 15) met DSM-IV criteria for both social anxiety disorder and an alcohol use disorder (abuse or dependence). At baseline, participants were moderately to markedly severe in their anxiety symptoms according to Clinical Global Index (CGI) ratings (Guy, 1976); alcohol problems were in the mild to moderate range (according the CGI and the Alcohol Dependence Scale, Skinner & Allen, 1982). Nine participants were randomized to the paroxetine treatment group (target dose, 60 mg/day); six participants received placebo. Results showed that, as expected, the paroxetine-treated group significantly improved social anxiety (vs. the placebo-treated group) after approximately six weeks of treatment, as measured by both patient and clinician ratings. Clinician ratings also showed that alcohol problems improved at week 7 and 8. The study was short in duration and did not include a follow-up, so it is not known if treatment gains were maintained and/or if alcohol use continued to decline.

Our group is currently conducting a randomized clinical trial to more fully address these issues. The study includes a longer treatment period (16 weeks), a larger sample size, a 6- and 12-month follow-up evaluation, and specifically includes individuals who are seeking treatment for social anxiety and who endorse drinking to cope with their social fears. It also includes a measure of quantity and frequency of drinking to cope (in addition to general alcohol quantity/frequency measures) as an important outcome. All participants have a co-morbid alcohol use disorder, but none are seeking treatment for their alcohol problem, and no participants require medical detoxification, nor have any participants ever had medical alcohol detoxification. The primary purpose of this study is to determine if the successful treatment of social anxiety can reduce drinking in individuals who use alcohol as a primary coping strategy.

Additional (though indirect) support for the value of the etiologic model that social anxiety precedes alcohol use disorder comes from studies conducted in children. For example, Caspi and colleagues found that behavioral differences in the first three years of life were associated with alcohol problems as adults (Caspi, Moffitt, Newman, & Silva, 1996). Specifically, male children who were identified as inhibited at age 3 (children who were shy, fearful, or easily upset) had significantly more alcohol-related problems at age 21 than children who were classified as well-adjusted at age 3. Given that age 21 is still young in terms of the development of alcoholism, it is likely that a follow-up of these same groups as they age will reveal even higher prevalence of alcohol-related problems, and perhaps females, who typically begin drinking later than males, will show alcohol-related problems as well (Johnson, Richter, Kleber, McLellan, & Carise, 2005; Randall et al., 1999). A recent longitudinal study in children treated with CBT for an anxiety disorder and assessed seven years later indicated that children whose primary anxiety disorder was still primary at follow-up drank more frequently than individuals whose primary anxiety was no

longer primary at follow-up (Kendall, Safford, Flannery-Schroeder, & Webb, 2004). Because children were still relatively young at follow-up, it is not possible to determine how many actually would go on to develop an alcohol use disorder as adults. These studies in children and adolescents did not specifically focus on social anxiety. However, the results of the studies have implications for the etiologic relationship between social anxiety and drinking that should be addressed in future studies. That is, does early treatment of social anxiety prevent the development of future alcohol-related problems?

The adolescent years are a critical period for peer acceptance and the development of complex social skills. Without treatment, the socially anxious adolescent might turn to alternative ways to cope, and alcohol is likely to be one of them. It is important to postpone alcohol use as long as possible because for every year that drinking is delayed in adolescents, the likelihood of developing alcoholism as an adult decreases (Grant, Stinson, & Harford, 2001). Recent studies in animals indicate that the adolescent period is uniquely sensitive to alcohol-induced social facilitation (Spear & Varlinskaya, 2005). It is tempting to speculate that if these findings are also shown to be true in humans, shy adolescents would find alcohol even more reinforcing than non-socially anxious teens. If they learned that drinking, through its action of stimulating social facilitation, helped them overcome their social fears, they would be more likely to continue to use alcohol for self-medication purposes. Continued negative reinforcement through symptom relief would put the socially anxious adolescent at risk for the development of an alcohol use disorder. Thus, as suggested in chapter 11, early intervention may be a good strategy for preventing the development of co-morbidity.

Future Studies and Conclusions

Individuals with social anxiety disorder and alcoholism comprise a unique subgroup of alcoholics. The risk of not treating co-occurring social anxiety disorder and alcoholism has inherent clinical implications—it will keep the individual functionally and socially disabled, will reduce the benefit of treatment, and in the case of alcohol treatment, overlooks the presence of stress, a known precipitant to relapse.

Treatment of individuals who have significant levels of social anxiety and use alcohol as a primary coping strategy is a relatively unexplored research area. Opportunities are ripe for treatment studies aimed at all stages of disease severity. Regarding prevention, studies are needed to determine whether interventions provided shortly after the onset of social anxiety help reduce the risk of later alcohol problems. In adults seeking treatment for social anxiety who use alcohol to cope with their social fears and who are drinking at abusive levels, the impact of social anxiety treatment on drinking behavior remains to be shown.

In socially anxious individuals who meet diagnostic criteria for alcoholism and are seeking alcohol treatment, the ideal staging of treatment, the most efficacious and cost-effective treatment modalities, and the best treatment combinations are unexplored areas. Should anxiety treatment be initiated after successful alcohol treatment and conceptualized as "relapse prevention," given the high recidivism rate in this population? Alternatively, should social anxiety be addressed directly in alcohol treatment settings? This may be true especially for those alcohol treatments that rely on 12-step philosophies since engaging in this treatment may be hindered by untreated social anxiety. Using the Project MATCH dataset, our group showed that socially anxious female alcoholics had better outcomes if treated with CBT than with Twelve-Step Facilitation therapy, while socially anxious men fared equally well in both CBT and Twelve-Step Facilitation (Thevos, Roberts, Thomas, & Randall, 2000). It is not known, for example, if pharmacotherapy for social anxiety provides relief enough to enable the client to engage in treatment, stay in treatment longer, and benefit from self-help groups—all process measures that are associated with improved treatment outcomes.

Human laboratory-based studies can be utilized to better understand the relationship between social stress, drinking, and relief from anxiety. They can also be used to evaluate potential therapeutic interventions, both behavioral and pharmacological, on social anxiety relief as well as voluntary alcohol consumption. Social interaction animal models can also be utilized to identify the underlying biological relationship between social stress and drinking and for medication evaluation and medication development. Genetic studies in humans and animals are needed for prevention efforts as well as to improve treatment through the potential of targeted pharmacotherapy based upon genotype.

The relationship between social anxiety and alcoholism is a complex one, and one possibly different from other co-morbidities because of the selective use of alcohol to cope (Thomas, Carrigan, & Randall, 2006; Thomas, Randall, & Carrigan, 2003). Future studies should include other anxiety groups as comparison populations (e.g., generalized anxiety disorder, PTSD, OCD) to determine if the high endorsement of drinking to cope and the deliberate use of alcohol in certain situations for symptom reduction is unique to social anxiety.

In summary, despite the high co-morbidity of alcohol use disorders and social anxiety disorder in treatment settings, there has been a paucity of systematic research specifically aimed at identifying optimal treatment for this unique subgroup. Such studies are clearly warranted.

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Chapter 9
Treating Co-Morbid Panic Disorder and Substance Use Disorder

Tony Toneatto and Neil A. Rector

Introduction

Despite the marked co-morbidity between substance use disorders (SUD) and panic disorder with or without agoraphobia (PDA) in both clinical and community samples (e.g., Grant et al., 2004; Kushner, Abrams, & Borchardt, 2000; Toneatto, Negrete, & Calderwood, 2000), and the generally negative prognostic impact of such co-morbidity (e.g., Burns, Teesson, & O'Neill, 2005; Willinger, et al., 2002), the development of effective treatments has been slow. Due to conflicting treatment philosophies, non-integrated health-care systems, limitations in treatment providers' clinical training and skill, lack of validated conceptual models of co-morbidity, absence of valid assessment and diagnostic tools for co-morbid populations, and lack of resources (cf. Weiss, Najavits, & Hennessy, 2004), treatments for individuals presenting with concurrent PDA and SUDs continue to generally focus on either the anxiety disorder or the addictive disorder (i.e., sequential or parallel treatment) rather than targeting the concurrent disorders in an integrated approach. This chapter will briefly review the treatment literature specific to PDA and SUD, describe common methods of assessing these disorders, and outline a functional analytic approach to the assessment and treatment of the PDA–SUD relationship.

Models of Concurrent PDA and SUD

Several conceptual models have been posited to explain the relationship between SUD and PDA (Kranzler & Tinsley, 2004). The observation that the anxiety syndromes seen in alcoholics (and other substance abusers) may often

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be organic sequelae of chronic alcohol (or drug) use or withdrawal symptoms suggests that the cessation or reduction of alcohol may effectively treat the anxiety symptoms as well (Anthenelli & Schuckit, 1995; Schuckit & Hesselbrock, 1994). However, others (e.g., Clark & Sayette, 1993; Kushner, Abrams, & Borchardt 2000) have argued that anxiety disorders often precede and contribute to the development/maintenance of the SUD and thus require explicit treatment. Often referred to as the 'self-medication' hypothesis, this model posits that people turn to substance use to deal with the distress associated with the anxiety they experience. In addition to these two dominant conceptual models of concurrent disorder, the risk or common factor model posits that both the PDA and SUD are expressions of an underlying, more basic, factor (e.g., anxiety sensitivity; DeHaas, Calamari, Bair, & Martin, 2001; genetic risk; Merikangas, Stevens, & Fenton, 1996; trait anxiety and other personality traits, Kushner, Abrams, & Borchardt 2000; childhood sexual and physical abuse, Mancini, van Ameringen, & MacMillan, 1995). A fourth 'chance overlap' model considers the possibility that PDA and a SUD may co-exist but may be completely unrelated to each other (e.g., a cannabis-dependent individual who develops PDA in response to a severe psychosocial stressor). Of course, some of these models may not be mutually exclusive, especially when SUD is chronic, unremitting, or treatment resistant. For example, even if initially psychoactive substances were used to manage panic anxiety, with chronic use, a substance-induced panic disorder could also emerge.

Treatment of Concurrent PDA and SUD[1]

It is often difficult to establish the nature of the relationship between PDA and a SUD during the baseline assessment. For example, neither the client nor the clinician may be able to disentangle true anxiety symptoms from those that are produced by a psychoactive substance. Traditional advice has suggested that initial treatment interventions focus on the SUD to alleviate substance-induced anxiety symptoms that may have developed and reduce the need for unnecessary or inappropriate anxiety-specific treatment (e.g., Oei & Loveday, 1997; Raskin & Miller, 1993). Of course, this may be easier to accomplish if the individual is admitted to a residential program where the direct effects of withdrawal from a psychoactive substance on anxiety symptoms can be observed.

A recent review of the psychological treatment literature by Schade et al. (2003) identified only one study (i.e., Bowen, D'Arcy, Keegan, & Senthiselvan, 2000) that specifically targeted PDA in substance abusing clients. In this study,

[1] The focus in this chapter will only be on the psychological treatment of concurrent substance use dependence and panic disorder. A cursory survey of the pharmacotherapy for this form of co-morbidity revealed no existing literature (Weiss et al., 2004). An examination of the issues in the development of effective pharmacotherapies is beyond the scope of this chapter.

Bowen et al. (2000) randomly assigned 231 individuals diagnosed with panic disorder admitted to a 4-week residential alcohol program to either treatment as usual or 12 hours of cognitive-behavioral treatment (CBT) for panic disorder. There were no group differences on measures of abstinence, depression and anxiety at end-of-treatment or at the 12-month follow-up. Since the publication of the Schade et al. (2003) review, there have been three treatment outcome studies of co-morbid PDA–SUD. In a recent pilot study of 14 subjects, Toneatto (2005) compared two treatments for concurrent alcohol dependence and PDA. A 10-session behavioral treatment, consisting of 5 sessions each for alcohol dependence and PDA was compared to a 10-session CBT which treated dysfunctional cognitions mediating the alcohol problem and anxiety symptoms throughout the 10 sessions. There were no group differences in frequency or quantity of alcohol consumption or in anxiety symptoms post-treatment or at a one-year follow-up. Both groups showed within group improvements on measures of both alcohol and anxiety symptoms suggesting both were promising treatments for this form of co-morbidity. Even more recently, Toneatto, Shirley, Calderwood, and Tsanos (2006) randomly assigned 81 alcohol-dependent individuals with a concurrent anxiety disorder diagnosis (about 50% of whom had a primary diagnosis of PDA) to one of two CBT treatments. Half of the sample received an alcohol-only treatment consisting of 6 sessions of alcohol-specific outpatient treatment. The other half of the sample also received 6 sessions of alcohol- specific treatment plus an additional 4 anxiety-specific sessions (i.e., 10 sequential sessions in total). Similar to the results of Toneatto (2005), no significant between-group differences on measures of alcohol consumption or psychiatric (including anxiety) symptoms were found at post-treatment; however there were significant reductions on both classes of symptoms in both groups. Kushner et al. (2006) compared 31 patients with a diagnosis of panic disorder admitted to an alcohol addiction program who received 12-session (over two weeks) integrated 'hybrid' treatment consisting of psychoeducation, cognitive restructuring and cue exposure adapted for those with concurrent panic disorder to 17 patients, from a different sample, who received treatment as usual (i.e., alcohol-focused). Significant improvements for the enhanced treatment over the treatment as usual were found at the 4-month follow-up on several measures including the diagnosis of panic disorder and alcohol dependence, number of panic attacks, number and days of drinking, and drinking binges. Kushner et al. (2006) suggested that comprehensively assessing and treating cognitions and behaviors related to the anxiety-alcohol association in the hybrid treatment may explain the benefits of the integrated treatment.

Treatment studies for co-morbid PDA–SUDs, apart from those involving alcohol disorders, are sparse. One exception is the work of Otto, Safren, and Pollack (2004) on benzodiazepine discontinuation in patients with PDA. These researchers have extrapolated to the treatment of benzodiazepine dependence the interoceptive exposure-based approaches to panic disorder. In this approach, the patient is encouraged to experience internal cues associated

with panic (e.g., dizziness, tachycardia) without behavioral or cognitive defensive responses (e.g., Otto et al., 2004). Noting that tapering benzodiazepine produces many of the internal sensations that are feared by PDA patients, Otto et al. (1993) developed a treatment package outlining the application of the strategies effective in panic treatment to the discomfort associated with benzodiazepine withdrawal in patients with co-morbid panic disorder and benzodiazepine dependence. Another exception is a recently-developed treatment for co-morbid tobacco dependence and PDA. Recently, Zvolensky, Feldner, Leen-Feldner, and McLeish (2005) have reviewed considerable evidence demonstrating the interrelationship between smoking behavior and panic-spectrum disorders. They have developed a conceptual model to explain the high rates of co-morbidity between tobacco dependence and panic-related anxiety disorders (see also Zvolensky, Schmidt, & Stewart, 2003) and have developed and pilot tested an integrated treatment based on many of the same principles as Otto and colleagues' integrated treatment for panic disorder and benzodiazepine dependence (see chapter 10).

Issues in Diagnosing Concurrent PDA and SUD

Establishing the diagnostic status of the anxiety disorder as a valid independent disorder or a substance-induced disorder is important for making treatment-related decisions (e.g., pharmacotherapy, psychotherapy, case management). However, there are many obstacles to arriving at a valid clinical diagnosis beyond the practical issues of time to conduct interviews and the need for specially trained staff. As mentioned earlier, many psychoactive substances may produce symptoms, during intoxication and/or withdrawal, which mimic panic symptoms and phobic behavior. In addition, many symptoms that may appear to indicate a SUD may also be related to the concurrent anxiety disorders but mistakenly attributed to the substance misuse by the client (e.g., neglect of obligations and responsibilities, interpersonal difficulties, social withdrawal).

While there are no validated psychometric measures to determine which model of concurrent disorder may best explain the concurrent PDA–SUD, skillful clinical interviewing as formalized in the Structured Clinical Interview for DSM-IV Structured Clinical Interview for DSM-IV (SCID; First, Gibbon, Spitzer, & Williams, 1996) or the Composite International Diagnostic Interview (CIDI; Wittchen, 1994) can yield the necessary data to make a valid, even if initially provisional, diagnosis. This approach to diagnosis will generally cover the following main areas:

1. *Order of onset of major symptoms.* When the PDA symptoms have consistently followed substance misuse, substance-induced panic symptoms may be considered and confirming evidence sought (e.g., amelioration of anxiety symptoms during periods of reduced substance use or anxiety

symptoms exacerbated during substance misuse). However, if intensification of substance misuse reliably follows the occurrence of PDA symptoms, a self-medication model may best explain the observed co-morbidity. Individuals with chronic substance use histories, multiple substance misuse, and substance-related cognitive impairments may make the accurate determination of symptom chronology more difficult and require multiple assessments over time. A review of concurrent disorder assessment and treatment conducted by Health Canada (2001) advised multiple assessments as an important way of deriving valid diagnoses. Any provisional diagnosis can be evaluated longitudinally through the collection of additional information at repeated time points.

2. *Clinical Observation*. If the clinician has the opportunity to evaluate the client on several occasions (e.g., residential treatment, multiple appointments, telephone contact), the relationship between anxiety and substance misuse may be ascertained directly in a prospective fashion.
3. *Periods of abstinence from substance misuse*. The diminution of PDA symptoms during extended periods of abstinence from substance use (or their exacerbation during heavy substance use) would support the hypothesis that the anxiety symptoms were substance-induced. Should the PDA symptoms persist during periods of substance abstinence, this might serve as evidence for the independent status of the PDA. If the individual reports very recent substance misuse, the effect on anxiety symptoms can be compared to previous assessment points. Conversely, amelioration of substance misuse during periods when panic and agoraphobic symptoms are less frequent might support the hypothesis that the PDA is an independent anxiety disorder.
4. *History of treatment*. Examination of treatment history for the PDA or SUD may provide some indication of the independence of the disorders. Repeated, unsuccessful treatment of either class of disorder and repeated relapses may be indicative of important risk factors that underlie the PDA and SUD and may require a more comprehensive assessment (e.g., Kushner, Abrams, Thuras, & Hanson, 2000).

Identification of Concurrent SUD in PDA Samples

Screening is frequently the first step in determining the most appropriate treatment response to individuals who present with concurrent SUD and PDA. Screening for either class of disorders may include informal and very brief inquiries as well as more objective, structured approaches. Since the client may not always present at a treatment location where expertise in concurrent disorders is readily available, the ability to evaluate the presence of a concurrent disorder in both addiction and mental health settings is crucial in providing optimal care. An overview of the issues involved in screening for addictive

disorders in individuals who present for treatment of PDA can be found in Negrete (2005), Brady (2004), and Health Canada (2001). A few of the recommended assessment approaches are summarized briefly below.

- Brief self-report screening measures for addictive behavior such as the *C-A-G-E* (Mayfield, McLeod, & Hall, 1974), *Michigan Alcoholism Screening Test* (MAST; Selzer, 1971), *Drug Abuse Screening Test* (DAST; Skinner, 1982), and *Alcohol Use Disorders Identification Test* (AUDIT; Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) can help determine the likelihood of a co-morbid SUD;
- Brief objective screening measures such as the *Substance Abuse Subtle Screening Inventory* (SASSI-3; Miller, Roberts, Brooks, & Lazowksi, 1997) can be used to bypass resistance to acknowledging substance use problems;
- Assessment of quantity-frequency of substance use such as the *Time-Line Follow-Back* procedure (TLFB; Sobell & Sobell, 1995);
- Previous treatment for substance abuse;
- Abnormal liver function;
- Toxicology screening such as urinanalysis;
- Collateral reports (e.g., spouse, health care worker).

Identification of Concurrent PDA in SUD Samples

While structured interviews may be time-consuming and require specially trained staff to validly administer, there are several screening measures that can rapidly evaluate suspected PDA symptoms (i.e., self-report or observation of intense symptoms of anxiety or avoidance behavior) in an SUD population. A recent publication by Antony, Orsillo, and Roemer (2001) is an excellent resource for the assessment of PDA and other anxiety disorders. Only a few of the more common measures are briefly described below.

The *Beck Anxiety Inventory* (BAI; Beck, Epstein, Brown, & Steer, 1988) consists of 21 self-reported items (four-point scale) used to assess the intensity of physical and cognitive anxiety symptoms during the past week. Scores may range from 0 to 63 and total scores can be used to classify anxiety severity as follows: minimal anxiety (0–7), mild anxiety (8–15), moderate anxiety (16–25), and severe anxiety (26–63). The *Panic Disorder Severity Scale* (PDSS; Shear et al., 1997) consists of 7 clinician-administered items (5-point scale) and is used to assess different dimensions of panic disorder (PD) severity in patients already diagnosed with PD. The dimensions include panic attack frequency, distress during panic attack, severity of anticipatory anxiety, fear and avoidance of agoraphobic situations, fear and avoidance of panic-related sensations, and impairment in work and social functioning.

Mobility Inventory for Agoraphobia (MIA; Chambless, Caputo, Jasin, Gracely, & Williams, 1985) is a self-report questionnaire consisting of 26 situations

commonly avoided by patients with agoraphobia. It measures severity of agoraphobic avoidance (rated on 5-point scale and scored by calculating means for all items) and frequency of panic attacks (rated on 5-point scale and scored by using frequency count) during the past week. The *Panic Disorder and Agoraphobia Scale* (PAS; Bandelow, 1999) is a 13-item scale that assesses severity of illness in patients with PDA. This measure has five subscales that represent the main factors that reduce quality of life in PDA patients: panic attacks, avoidance, anticipatory anxiety, disability, and worries about health. This questionnaire can be administered both as a self-report scale and as a structured clinical interview.

The *Agoraphobic Cognitions Questionnaire* (ACQ) and the *Body Sensations Questionnaire* (BSQ; Chambless, Caputo, Bright, & Gallagher, 1984). The ACQ consists of 14 self-administered items measuring specific thoughts that may occur when feeling anxious and that are associated with PDA. The ACQ may be scored as a total scale, or according to its two subscales: loss of control and physical concerns. Each of these subscales consists of 7 items. Loss of control items address cognitions such as fear of acting foolish, fear of going crazy, or fear of hurting someone. Physical concerns items refer to cognitions such as fears of throwing up, choking, or having a heart attack. The BSQ consist of 18-items in which specific body sensations associated with fear and anxiety are rated on a 5-point scale ranging from 1 (not at all) to 5 (extremely).

Functional Analysis of Concurrent SUD and PDA

Despite over two decades of epidemiological research demonstrating the reliable relationship between anxiety and substance misuse (e.g. Grant et al., 2004), empirically validated treatments for PDA and SUD are still early in their development. The available research does not yet strongly support the inclusion of anxiety-specific treatments (e.g., Bowen, D'Arcy, Keegan, & Senthiselvan, 2000; Toneatto et al., 2006) although the recent research on an integrated treatment program presented by Kushner et al. (2006) is an exception. Methodological limitations of the studies to date in this nascent area of research (e.g., small sample size, power, lack of randomization, short-follow-ups) preclude any firm conclusion about treatment for concurrent PDA–SUD at this stage. Clearly, much more research is needed to evaluate this important issue.

The remainder of this article is devoted to the description of a phenomenology of PDA and SUD that may have clinical implications. Advancement in the development of effective interventions for co-morbid PDA and SUD may benefit from a more descriptive phenomenology specifying the functional relationship between PDA symptoms and psychoactive effects of substances. The functional approach dates back to the earliest decades of scientific psychology and remains one of the core elements of a behavioral analytic approach to understanding, predicting, and modifying behavior (Bellack &

Hersen, 1978; Skinner, 1959). In its most basic formulation, it is expressed as a probabilistic statement linking the occurrence of the dependent variable as a function of an independent variable (Karen, 1974). Operant approaches to behavior change are typically based on the identification of reliable functional associations between stimuli and responses. Of course, most cognitive-behavioral treatments for SUD and PDA include a functional analysis and functional assessment during the assessment/case conceptualization phase of treatment. Work by Zack, Toneatto, and McLeod (1999, 2002) has experimentally demonstrated the functional associations between anxiety and alcohol use disorders at a cognitive-perceptual level. Their work has shown that, in problem drinkers, state anxiety significantly predicted recall of alcohol-related concepts when exposed to negative affective cues (compared to neutral cues) and suggest that anxiety is a proximal activator of explicit alcohol-related memory networks. However, a clinically-relevant functional analysis may need to consider a more elaborated model of PDA and SUD than has generally been available (e.g., Hanley, Iwata, & McCord, 2003; Haynes & O'Brien, 1990; Kushner, Abrams, & Borchardt, 2000).[2]

A functional analysis of PDA and SUD encompasses a diversity of direct somatic, behavioral, cognitive, and affective events that define the experience of anxiety, substance use, and their unique (and variable) interactions. While diagnostic systems such as the DSM-IV (American Psychiatric Association [APA], 1994) summarize these experiences in the description of psychiatric syndromes (e.g., panic disorder, alcohol dependence) they tend to be limited and, in the case of the substance dependencies, emphasize the consequences of addictive behavior. A much broader description of the subjective experiences that define both PDA and SUD and their functional associations will be elaborated.

There is significant overlap and congruence between the concept of functional analysis of co-morbidity and other research literatures related to the development of expectancy, beliefs, attributions, intentions, motivations, reasons, homeostasis, purposes, or desires. All of these constructs reflect the learning process (e.g., experiential, observational, cultural) that establishes associations between an individual and their environment. The functional analytic approach emphasizes the discovery of the causal relationship between the symptoms of substance misuse and panic anxiety based on the individuals' direct experience rather than through vicarious or social influences. This approach also generally avoids any extensive theorizing about such relationships, preferring a more empirical approach.

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[2] For the purposes of this discussion, the definition of functional analysis suggested by Haynes and O'Brien (1990) will be adopted: 'The identification of important, controllable, causal functional relationships applicable to a specified set of target behaviors for an individual' (p. 654).

Functional Analysis of PDA

For the purposes of this discussion, PDA will be conceptualized multidimensionally rather than syndromally or symptomatically. This is consistent with the work of Lang (1985) and Izard (1977) who have analyzed the dimensions that are shared by all emotions. Barlow (1988), in his seminal work on anxiety, has elaborated a conceptualization of anxiety as a behavioral-cognitive-affective structure with a corresponding physiology and his work has also influenced the present model. A multidimensional approach is less focused on determining a diagnosis or elaborating a conceptual construct but in describing the experiences of PDA across different levels of human functioning as might be expressed within a biopsychosocial perspective. Although not exhaustive, six primary dimensions (see Table 9.1) meaningfully capture the most important levels of analysis relevant to PDA and include: *behavioral* (e.g., avoidance, agitation, impulsivity), *somatic* (e.g., shallow breathing rapid heart beat, sweating), *cognitive* (e.g., beliefs of probability of dying or fainting), *imaginal* (e.g., images of social judgment or loss of control), *affective* (e.g., fear, despair, embarrassment), and *interpersonal* (e.g., isolation, awkwardness, loneliness) dimensions. Within these 6 categories, all of the symptoms for PDA as currently defined within DSM-IV (APA, 1994) can easily be slotted.

Functional Analysis of Psychoactive Substance Use

Interacting with the PDA symptom dimensions described in Table 9.1 are the effects of psychoactive substances on biopsychosocial functioning. As with PDA, drug and alcohol use can be understood at multiple levels of analysis ranging from the molecular to the spiritual, each with a corresponding therapeutic approach. Within a functional analytic model, the aspect of psychoactive substance use that is of greatest clinical relevance is its capacity for rapidly and effortlessly modifying behavior, cognition, and awareness. Without a rapid psychopharmacological effect, a substance would unlikely become a target of abuse (e.g., consider the abuse liability of a substance that required days to deliver its effect). A cocaine or alcohol misuser expects salient effects to occur very quickly, within seconds or minutes. In contrast, non-pharmacological coping responses (e.g., behavioral) may require considerable amount of time to regulate anxiety and may only do so unreliably, if at all. The incentive to rely on the rapid and reliable impact of psychoactive substances on PDA symptoms as a coping response can thus be strong and compelling. For example, responding to an urge to drink with alcohol consumption may be easier, quicker, and more effective than drawing on cognitive, affective, and behavioral coping responses.

In addition to speed, the optimal effect of a psychoactive substance on cognition and behavior may also be influenced by type of substance

Table 9.1 Effects of SUD on dimensions of PDA symptoms

	Dimension of PDA symptoms					
Effect of SUD	Somatic	Behavioral	Cognitive	Affective	Imaginal	Inter-personal
Increase	heart rate; arousal	likelihood to enter phobic situations	frequency of self-mastery thoughts	anger	mastery images	social behaviors
Decrease	insomnia; physiologic reactivity to stress	Agitation	negative thoughts	Fear	Threat imagery	social inhibitions
Transform	tension to relaxation	avoidance to approach behavior	pessimistic thoughts to optimistic ones	fear into depression	Despair imagery into angry imagery	avoidance into approach
Detach	reduced concern	reduced concern	reduced concern	reduced concern	reduced concern	reduced concern

(e.g., depressant vs. stimulant vs. hallucinogen), rate of consumption (e.g., quickly vs. slowly), the individual's history with the substance (e.g., novice vs. experienced), and the biopsychosocial context within which consumption occurs (e.g., social environment, emotional state). The latency to experiencing the impact of substance misuse on PDA symptoms is another variable to consider in the functional relationship. Generally, the most desirable effects of substance use will occur earlier (immediately or soon after ingestion) while undesirable effects of substance use may be experienced later (i.e., when overly intoxicated, or during withdrawal). These delayed effects, although negative, may not diminish the immediate reinforcement that substance ingestion may produce. Consequently, an individual with PDA may choose to ingest a specific substance (e.g., alcohol, rather than a stimulant such as cocaine) at a rate (e.g., 2 drinks per hour) when feeling panicky (e.g., heightened somatic arousal), intending to maximize the benefits of using the psychoactive substance (e.g., to diminish the somatic sensations). Depending on the specific PDA symptoms and their intensity, modifications in the rate, frequency, and dose of the substance may be necessary to achieve the desired effects.

Four major ways (there may be additional ones) that psychoactive substances may impact on PDA-related symptoms will be discussed: increase, decrease, transform, and detach. Toneatto (1999b) has shown, in a sample of psychiatrically co-morbid (mainly anxiety and depression) substance abusers, a preference for detachment from, and transformation of, unpleasant mental states. Moreover, the co-morbid sample evidenced strong beliefs that failure to regulate unpleasant mental states would produce discomfort, sleep disturbance, and persistence/intensification of the anxiety or depression. Sbrana et al. (2005) reported that their sample of concurrent panic disorder-SUD subjects reported the following effects of substance use: improvement of mood, maintenance of euphoria, relief of tension, and increase in energy. The report of positive effects associated with substance use suggests that drugs and alcohol may not only relieve aversive symptoms but may also indeed enhance positive states of mind which may diminish the impact or salience of aversive symptoms. For example, feeling euphoric while under the influence of alcohol may reduce the frequency of, or attention paid to, thoughts of dying or fainting.

Another factor to consider is that not all symptoms of PDA may be equally aversive. Although the DSM-IV (APA, 1994) description of panic assigns equal weighting to each symptom, they may be perceived very differently between individuals. For some individuals, the social consequences may be most disturbing; for others the cognitive symptoms may be particularly unpleasant; for another, the somatic aspects of anxiety may be the most difficult to tolerate. With experience, in addition to the intended consequences of substance use (e.g., interrupting aversive ruminations), unintended consequences of dependence will also be encountered (e.g., withdrawal, tolerance, substance-induced dysphoria, interpersonal consequences). Of course, it is these negative consequences that form the core of the substance dependence syndrome as

Table 9.2 Intended and unintended effects of psychoactive substances on PDA symptom dimensions

Dimension of PDA	Example of symptoms	Example of intended effect	Example of unintended effect
Somatic	shallow breath; rapid heart beat	Relax	increased heart rate
Behavioral	avoidance; agitation	overcome avoidance	substance-induced avoidance
Cognitive	fears of death; fears of fainting	eliminate thoughts	fear of loss control
Affective	fear; despair; embarrassment	comfort	exacerbate fear
Imaginal	social judgment; rejection	relief from fear imagery	self-critical imagery
Interpersonal	social isolation; feeling misunderstood	social facilitation	social conflict

defined within the DSM-IV (APA, 1994). Table 9.2 shows an example of intended and unintended effects of drug and alcohol use on PDA symptoms.

Functional Assessment of Concurrent PDA and SUD

The implications of the model briefly outlined above suggests that a much more comprehensive assessment of the functional relationship linking PDA and substance misuse may be required to fully understand the complex relationship between PDA symptoms and substance misuse. The utility of standard tests and questionnaires typically used to assess PDA (e.g., Agoraphobic Cognitions Questionnaire) and SUD (e.g., AUDIT) may provide important syndrome-specific or level of severity information but will neither provide a clinician with useful information regarding the unique associations between PDA and SUD symptoms nor rationally guide treatment interventions for co-morbid individuals. A functional analysis, based on the multidimensional assessment of PDA, is an approach that can quickly yield treatment-relevant data. Table 9.3 illustrates a simple approach to a functional assessment through the systematic exploration of the effects of psychoactive substances on PDA symptoms and the effect of PDA symptoms on the use of drugs and alcohol. Each of the questions illustrated in Table 9.3 can be further qualified by assessing the rapidity of the association, the temporal contiguity (proximal or distal), and their salience. Thus, the exact analysis of PDA symptoms will reflect the unique experience of the individual. For example, if there is polysubstance abuse, the functional assessment may need to be conducted for each substance separately. Similarly, if the individual is suffering from other anxiety or mood disorders in addition to the PDA, these can also be included within the functional analysis.

In situations in which the functional relationship between substance misuse and PDA is either minimized or denied by the individual, there are many

Table 9.3 Example of a functional analysis of PDA symptoms and their associations with Substance Use/Abuse

PDA symptom	Functional analytic assessment	Examples	Example of intervention
Somatic	Are there sensations and perceptions that are modified by substance use? Are there sensations and perceptions that are more likely to be associated with substance use?	arousal may decrease; sensations of well-being may increase; better sleep initially when using a substance	relaxation exercises; mindfulness training; breathing retraining
Behavioral	Are there behaviors that are more likely to be associated with substance use? Are there behaviors that are less likely to occur when using substances?	less phobic when drinking initially but more phobic when fully intoxicated; more sedated when drinking but more agitated when intoxicated	graded exposure
Cognitive	Are there thoughts that are more likely to be associated with substance use? Are there thoughts that modified when using substances?	catastrophic thinking diminish; thoughts of increased self-efficacy increase; reduced likelihood of believing heart attack will occur	cognitive restructuring
Affective	Are there feelings that are more likely to be associated with substance use? Is the intensity of feeling modified when using substances?	fear reduced, embarrassment diminished, anger increased, depression increased	cognitive restructuring; distraction; breathing retraining
Imaginal	Are there images that are more likely to be associated with substance use? Are images modified when using substances?	Images of confidence and overcoming increased; imaginal scenarios more likely to end with successful resolutions	cognitive restructuring; imaginal restructuring
Interpersonal	Are there situations that are more likely to be associated with substance use? Are there situations less likely to occur when using substances?	Less social withdrawal, more interaction; more tense interactions due to intoxication; inappropriate verbal and non-verbal interpersonal behavior	improved communication skills; lifestyle intervention

strategies that can be used by the clinician to educate the client about the functional relationship. These include the use of self-monitoring of substance use and anxiety symptoms, negotiating an alcohol-/drug-free period to observe the effects on anxiety, examining the development of urges and cravings and the subjective mental and physical states with which they are correlated (Toneatto, 1999a).

Clinical Case Example of a Functional Analysis

The following clinical example illustrates the functional association between PDA and alcohol abuse that could be determined using the framework outlined in Table 9.3 and that could form the basis of therapeutic intervention.

Jim, a 34-year old male with concurrent PDA and alcohol dependence, found it impossible to leave his home and complete chores and tasks without first consuming several beers. When sober, he was home-bound and thus unable to work regularly. He was occasionally successful at obtaining some casual work but would always consume some alcohol in order to attend work. Not surprisingly, this behavior would eventually be exposed and Jim would lose his job. His partner, Mike, preferred to support Jim financially rather than to tolerate Jim's aggressive and obnoxious behavior when he consumed alcohol during times when he was employed. A functional analysis of Jim's alcohol consumption revealed that acute doses of alcohol (consumed approximately a half hour before leaving his apartment) initially relaxed him physically, allowed him to leave his apartment, completely eliminated thoughts about fainting in public, allowed him to tolerate standing in lineups in stores, enhanced feelings of personal power and confidence, and flooded his mind with soothing images that he was indeed normal. Since he would carry a mickey with him while he completed his work chores, he would become increasingly intoxicated and the initially reinforcing effects of alcohol would produce unintended effects. Specifically, he would stumble as he walked home and attract the unwanted attention of others, he often had vivid memories and images of others observing him with fear and disgust, he experienced symptoms of dizziness and nausea (which Jim found highly aversive), and he would become easily irritable and agitated by Mike's comments and behavior leading to frequent arguments. As a result, Jim and Mike would not speak to each for days following such interactions. Jim would subsequently experience strong anxiety in the days after drinking characterized by fear (including thoughts and images) that Mike would leave him, that he would never be 'normal', and that he was inherently defective. When these mental states became too intense, he would become highly aroused physically (i.e., racing heart, shallow breathing, paresthesias, and trembling) – symptoms which were only relieved by excessive drinking (while Mike was at work) and which inevitably left Jim emotionally numb and sedated. Mike would often return home to find Jim asleep.

Addressing Poor Clinical Progress and Relapse Through Functional Analysis

The likelihood of a relapse following SUD treatment is high and may be even further elevated in the case of a concurrent anxiety disorder such as PDA (Kushner et al., 2005). In addition, progress may be slower than expected if resistance is met from the client in implementing the strategies to modify both the anxiety and substance use behaviors. It is therefore important to apply a functional analytic approach to lapses, relapses, or slow clinical progress. The assessment of urges and cravings is one approach to determining the functional association between PDA and substance misuse when treatment is not progressing satisfactorily (Toneatto, 1995, 1999a). A cognitive analysis of urges and cravings can provide important clinical information about intra- and interpersonal situations with which the individual is having difficulty coping without the consumption of drugs or alcohol. For example, the simple expression, 'I have an urge to drink' could be expanded and elaborated to reveal the following important clinical information: 'I have an urge / craving / strong desire / need to drink / use drugs because if I do not, I will not be able to stop/decrease/change/transform these frightening thoughts/feelings/sensations that lead me to believe that I am going to faint/die/be embarrassed.' Urges and cravings are most likely to occur among individuals who do not possess effective coping responses in the presence of high-risk interpersonal or intrapersonal situations that trigger PDA symptoms and thus are an important source of clinical data that may predict therapeutic regression.

By conducting a functional analysis on a regular basis (and by instructing the client in conducting their own functional analysis), the clinician will be able to identify PDA symptoms that are particularly difficult to treat and which remain highly correlated with substance misuse. These dimensions, and the symptoms they include, may represent serious threats to recovery and can become the focus of clinical intervention. For example, a post-treatment functional analysis may demonstrate that certain affective symptoms associated with PDA (e.g., feelings of embarrassment about panic attacks in public) may remain highly associated with substance use post-treatment and may require ongoing intervention.

The persistence of lapses and relapse or poor clinical progress may also reflect an incomplete or inaccurate functional analysis. The clinician, in collaboration with the client, may find it beneficial to review the conditions that maintain the addictive or anxiety behavior and detect deficiencies in the case conceptualization that may have either been overlooked or which may even emerged since the beginning of treatment. By viewing functional assessment as an ongoing clinical activity, the client may become increasingly more self-aware of threats to their recovery and the potential relapse situations they may encounter. Thus, training clients in functional assessment may help them learn to respond proactively and effectively.

Conclusion

This chapter has briefly reviewed the evidence for the well-established relationship between substance misuse and PDA. As with other concurrent disorders, several models have been postulated to explain this relationship and were briefly described. Issues in assessment and diagnosis were also raised and some common assessment measures described. Unfortunately, very little research has been published on the most effective treatment for concurrent panic disorder and the substance dependencies; the few such studies that have been conducted were surveyed. There exists no empirically-validated standard for treating co-morbid PDA–SUD although a recent integrated approach developed by Kushner et al. (2006) appears promising. A limitation of the existing models of co-morbidity is the lack of a description of how anxiety symptoms and substance use actually interact at a phenomenological or experiential level. That is, how do individuals with concurrent PDA–SUD experience the impact of drugs and alcohol on the specific symptoms of panic anxiety? What is the nature of their interaction? In response to these queries, a functional analytic model of panic-substance use was outlined, emphasizing the potency of psychoactive substances to rapidly transform subjective experiences in ways that are highly reinforcing, especially to those who display symptoms of panic anxiety. When the symptoms of panic anxiety are considered from a multidimensional perspective (i.e., behavioral, somatic, interpersonal, affective, cognitive, imaginal), at a level of analysis that reflects the individuals' phenomenological experience, the powerful impact of psychoactive substances is readily apparent. By eliciting a detailed description of the functional relationships between the effects of drugs and alcohol and the symptoms of anxiety, a comprehensive description of the panic-substance interaction can be elicited which may assist not only in the explanation of the development of this common class of co-morbidity but may also help to account for the difficulties some individuals experience in treatment and the high rates of relapse.

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Chapter 10
Cognitive-Behavioral Treatment of Co-morbid Panic Psychopathology and Tobacco Use and Dependence

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Although individuals with anxiety disorders have high rates of substance use, abuse, and dependence compared to persons without such conditions (Breslau, 1995; Merikangas et al., 1998; Regier, Burke, & Burke, 1990), research and practice on the nature of such co-morbidity has thus far been limited. This neglect is apparent for a wide variety of anxiety and substance use problems, but it is particularly well-illustrated in the case of co-morbidity between tobacco use and dependence and panic psychopathology (Zvolensky, Baker, et al., 2005). This is unfortunate, as cigarette smoking remains the leading preventable cause of death and disability in the United States (Centers for Disease Control and Prevention [CDC], 1994a, 1994b; USDHHS, 1989). Aside from well-known negative physical effects, emerging findings suggest that (1) smoking and panic problems often co-occur, (2) smoking is a risk factor for, and may serve to maintain, panic attacks and panic disorder (PD), and (3) pre-morbid panic-specific vulnerability variables and full-blown panic problems are related to coping-oriented smoking motives and perhaps the maintenance of smoking behavior (Zvolensky, Feldner, Leen-Feldner, & McLeish, 2005). As described in recent integrative models, smoking and panic processes may therefore interplay in a variety of clinically-significant ways (Zvolensky & Bernstein, 2005). The overarching purpose of the current chapter is to summarize research on smoking and panic psychopathology and present a therapeutic model for concurrently targeting these commonly co-morbid problems.

Co-occurrence of Smoking among those with Panic Problems

The majority of studies examining the co-occurrence of smoking and panic have focused on the prevalence of smoking among persons with panic-related problems, including panic attacks, PD, or agoraphobia. These studies include

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community, treatment clinic, and epidemiologically-defined samples, although the largest percentage has focused on individuals seeking treatment for anxiety problems. Across investigations, rates of current daily smoking among those with PD are greater than those found among individuals without psychiatric problems and certain types of other mental health problems (Zvolensky, Feldner, Leen-Feldner, & McLeish 2005). For instance, Lasser et al. (2000) recently found in an analysis of over 4,000 respondents from the National Comorbidity Survey (NCS) that current smoking rates were highest among persons with panic attacks, PD, and agoraphobia, as well as other anxiety disorders where panic attacks are common (i.e., posttraumatic stress disorder and generalized anxiety disorder). These same studies suggest that the association between smoking and anxiety psychopathology is not due to sociodemographic characteristics, other psychiatric conditions, or symptom overlap in diagnostic criteria (Zvolensky, Schmidt, & Stewart, 2003).

Relation of Smoking to Panic Problems and Vulnerabilities

In regard to smoking contributing to panic problems, it is first important to highlight that the onset of daily smoking typically occurs between ages 15 and 20 and rarely after age 25 (Breslau, Johnson, Hiripi, & Kessler, 2001). The median age of onset for PD is approximately 24 years of age (Burke, Burke, Regier, & Rae, 1990), suggesting that smoking initiation typically precedes the onset of PD.

Prospective studies. With this background, researchers have evaluated the association between smoking and risk of panic-related problems in a number of studies. Breslau and Klein (1999) tested the association between daily smoking and risk for panic attacks and PD. Participants were drawn from two separate epidemiologically-defined data sets. Results indicated that there was a significant lifetime association between daily smoking and onset of panic attacks and PD; daily smokers were almost 4 times more likely to experience panic attacks and 13 times more likely to develop PD after controlling for major depression and gender. Additionally, among individuals who continued to smoke, compared to those who had quit, there was a significantly increased risk for experiencing a panic attack and PD. This also was true of the NCS data, which indicate that daily smoking is associated with increased risk of panic attacks, after controlling for major depression and gender (Breslau & Klein, 1999; see also Johnson et al., 2000).

In another prospective study completed in Germany, 2,500 participants (ages 14–24 years at baseline) were evaluated over 4-years (Isensee, Wittchen, Stein, Hofler, & Lieb, 2003). Compared with all other levels of smoking, dependent regular smokers at baseline were significantly more likely to develop panic attacks and PD, and a similar pattern was observed for agoraphobia. Similarly, Breslau, Novak, and Kessler (2004) evaluated daily smoking and

subsequent onset of psychiatric disorders. Results indicated that the onset of PD (odds ratio = 2.6) and agoraphobia (odds ratio 4.4) were associated with pre-existing daily smoking after controlling for age, gender, ethnicity, and educational level. Additionally, after controlling for pre-existing psychiatric disorders and sociodemographic characteristics, current nicotine dependent smokers were more likely to have PD compared to current non-dependent smokers and former smokers. Importantly, the likelihood of PD and agoraphobia was significantly reduced as time since quitting increased; these effects were specific to these conditions and not other psychiatric disorders (e.g., major depressive disorder), suggesting quitting smoking may decrease risk of panic problems.

Cross-sectional studies. Smoking among those with panic attacks or PD also is cross-sectionally associated with more severe panic problems. For example, Zvolensky and Forsyth (2002) found that smokers with panic attacks reported greater bodily vigilance and anxiety sensitivity compared to persons with either panic attacks or smoking histories alone. In a follow-up investigation, Zvolensky, Schmidt, and McCreary (2003) found that smokers with PD compared to those who were not smokers reported more severe and intense anxiety symptoms, greater interview-based overall severity ratings of panic symptoms, and more social impairment. Finally, Zvolensky, Leen-Feldner, et al. and colleagues (2004) employed a voluntary hyperventilation paradigm to examine associations between smoking and panic-relevant fearful responding to bodily sensations. Results indicated smokers with PD reported greater levels of anxiety than smokers without PD at baseline and showed greater increases in anxiety during the post-challenge assessment and recovery periods. Although smokers with, versus without, PD did not differ on baseline or post-challenge anxiety, smokers with, compared to without, PD, recovered more slowly in terms of affective responding to the challenge.

Relation of Panic Vulnerabilities to Smoking Behavior and Processes

Panic vulnerability characteristics also appear to relate to smoking behavior in a variety of ways, including (1) smoking cessation outcome, (2) the experience of nicotine withdrawal symptoms, and (3) smoking motives. In our earlier work, we proposed an integrated model of the smoking-panic relation, which predicted smokers with PD (and even smokers at risk for developing PD) are more likely to have difficulty quitting smoking by virtue of their cognitive vulnerabilities and associated emotional sensitivity to anxiety-related states and bodily perturbation (Zvolensky, Schmidt, & Stewart, 2003). Specifically, panic-vulnerable persons are fearful of anxiety-related states, tend to react with anxiety and fear when confronted with personally-relevant stressors, and often cope with such emotionally distressing events by trying to escape or avoid such

experiences. These affect-relevant characteristics may increase the likelihood that panic-vulnerable regular smokers will be sensitive and emotionally reactive to aversive interoceptive cues (e.g., bodily tension, anxiety) that routinely occur during smoking abstinence (Hughes, Higgins, & Hatsukami, 1990). Moreover, these panic-vulnerable smokers may be particularly apt to smoke as a way of avoiding or regulating negative affect, and in doing so, are at higher risk for relapse.

Smoking cessation and panic. In regard to smoking cessation, there have been two epidemiologic studies that have evaluated quit rates as a function of panic spectrum problems (Covey, Hughes, Glassman, Blazer, & George, 1994; Lasser et al., 2000). Using the NCS data, Lasser et al. (2000) reported quit rates (i.e., proportion of lifetime smokers who were not current smokers) in relation to psychiatric diagnosis. Findings indicated that quit rates among individuals with a lifetime diagnosis of panic attacks, PD, and agoraphobia were 36.9%, 41.4%, and 34.5%, respectively. Covey and colleagues (1994) reported similar results. When 1-month rather than lifetime diagnostic status was used, the quit rate was 29.8% for persons with panic attacks, 32.9% for those with PD, and 23.2% for persons with agoraphobia. Individuals with panic problems in the past month were significantly less successful in quitting smoking compared to individuals with no mental illness (42.5%). Using a community sampling approach, Zvolensky, Lejuez, Kahler, and Brown (2004) evaluated the association of nonclinical panic attacks among regular smokers with the duration of the longest quit attempt (lifetime). Smokers with panic had a significantly shorter average quit attempt compared to smokers without panic. An alternative approach to this work has been the use of laboratory methodologies to correlate smoking history characteristics with panic-relevant processes in "real time." Using this approach, Zvolensky, Feldner, Eifert, and Stewart (2001) evaluated emotional reactivity to bodily sensations in heavy smokers using a biological challenge paradigm. Participants were young adult heavy smokers ($>$ 20 cigarettes per day) without psychopathology. Individuals were partitioned into those who were able to quit for at least seven days and those who were not able to quit for this long. Participants were exposed to a panic-relevant 20% carbon dioxide-enriched air (CO_2) challenge. Here, heavy smokers who were unable to remain abstinent from smoking for at least one week demonstrated significantly greater cognitive-affective reactivity to the challenge relative to their counterparts, suggesting anxious responding to bodily sensations is related to duration of quit attempts.

Nicotine withdrawal and panic. Studies also have found associations between panic problems, nicotine withdrawal symptoms experienced during quit attempts, and motivation to smoke to avoid negative affect. In an early study in this domain, Breslau, Kilbey, and Andreski (1991) found tobacco withdrawal symptoms in a sample of young adults were significantly elevated among smokers with "any anxiety disorder" compared to individuals without a history of these disorders. Since this study, investigations have more closely examined panic-related factors and the nature of tobacco withdrawal. For example,

Zvolensky, Baker, and colleagues (2004) found that daily smokers with a history of panic attacks reported significantly more intense anxiety-related withdrawal symptoms (e.g., anxiety, restlessness) compared to smokers without such a history; no differences were evident for other tobacco withdrawal symptoms. More recently, Zvolensky, Feldner, et al. (2005) evaluated the incremental validity of acute nicotine withdrawal symptoms (elicited via two hours of nicotine deprivation) relative to negative affectivity and nicotine dependence in predicting anxious responding to a panic-relevant three-minute voluntary hyperventilation challenge. Among a general community sample screened for axis I psychopathology, these investigators found that greater levels of pre-challenge nicotine withdrawal symptoms uniquely predicted post-challenge intensity of panic symptoms and anxiety relative to other established factors. These data suggest even *acute* nicotine withdrawal offers unique explanatory value in regard to the perceived intensity of panic-relevant physical symptoms and anxiety reactions.

Smoking-based motivational processes and panic. In a recently completed multinational investigation, Zvolensky, Schmidt et al. (2005) examined whether PD was associated with specific motivations to smoke and confidence in remaining abstinent. Among a sample screened for a lifetime history of alcohol dependence or substance use disorder, current or past schizophrenia, or an organic mental disorder (determined via structured clinical interviews by trained researchers), investigators found that smokers with PD reported higher levels of smoking to reduce negative affect than their counterparts without such a history; this effect was significant above and beyond variance accounted for by nicotine dependence, negative affectivity, and gender. Additionally, individuals with PD, relative to those without a psychiatric history, reported significantly less confidence in remaining abstinent from smoking when emotionally distressed. These findings are consistent with other investigations demonstrating a correlation between anxiety sensitivity (fear of anxiety) and smoking to reduce negative affect among daily smokers (Comeau, Stewart, & Loba, 2001; Novak, Burgess, Clark, Zvolensky, & Brown, 2003; Stewart, Karp, Pihl, & Peterson, 1997; Zvolensky, Bonn-Miller, Feldner, et al., 2006) as well as the expectation that smoking will relieve negative affect (Zvolensky, Feldner, et al., 2004).

Summary

Extant work suggests (1) smoking rates are particularly high among those with panic attacks and PD (Lasser et al., 2000), (2) smoking typically precedes the onset of PD, (3) smoking increases the risk for panic problems (Johnson et al., 2000), and (4) smoking is associated with more severe panic symptoms among those with PD (Zvolensky, Leen-Feldner, et al., 2004). Additional research suggests individuals with panic problems have more problems quitting smoking (Covey et al., 1994) and report more intense anxiety-relevant withdrawal

symptoms during quit attempts (Zvolensky, Lejuez, et al., 2004). Also, acute nicotine withdrawal increases the risk of anxious responding to bodily sensations (Zvolensky, Feldner, Leen-Feldner, et al., 2005) and smokers with PD compared to those without the disorder report higher levels of smoking for the explicit purpose of reducing negative affect (Zvolensky, Schmidt, et al., 2005).

Integrative Model for Understanding the Interplay Between Co-occurring Panic and Smoking Problems

Integrative theoretical models addressing the nature of smoking-panic co-morbidity posit that these behavioral problems interplay with one another in a clinically significant manner (Zvolensky & Bernstein, 2005; Zvolensky, Schmidt, & Stewart, 2003). These models begin with the recognition that smoking often precedes the development of panic attacks and PD (Johnson et al., 2000). Among daily smokers with panic attacks or PD, smoking also serves important affect regulatory functions (Zvolensky, Schmidt, et al., 2005). Specifically, these individuals expect tobacco use to help alleviate aversive anxiety states (Zvolensky, Feldner, et al., 2004) and often principally smoke to regulate affect (Zvolensky, Bonn-Miller, Bernstein, et al., 2006). As the objective mood-dampening qualities of smoking are complex and not fully explicated (Kassel, Stroud, & Paronis, 2003; Parrott, 1999), it may well be useful to conceptualize these processes at the cognitive level of analysis. Thus, in the absence of more adaptive coping strategies, smokers with panic attacks or PD may learn to rely on smoking to manage anxiety states and fears of bodily sensations in the relatively short-term. Over long periods of time, however, smoking itself may lead to increased risk of bodily sensations and aversive internal states via a number of routes, including nicotine-related withdrawal symptoms, health impairment, and perhaps diagnosable physical illness. Exposure to these types of aversive stimuli may facilitate learning that internal cues can be personally harmful, dangerous, and anxiety-evoking (Bouton, Mineka, & Barlow, 2001). Although smokers with panic problems or even pre-morbid vulnerability factors like high levels of anxiety sensitivity (fear of anxiety) are often especially motivated to quit smoking (Zvolensky, Baker, et al., 2004), they also are at higher risk for problems quitting (Lasser et al., 2000; Zvolensky, Lejuez, et al., 2004). Specifically, these persons are apt to be particularly fearful of, and emotionally reactive to, internal states that occur during smoking discontinuation; they may therefore experience more distressing emotional experiences in general (Zvolensky, Kotov, Antipova, & Schmidt, 2003), but particularly during cessation attempts (Zvolensky, Lejuez, Kahler, & Brown, 2003). Thus, a vicious cycle may develop, whereby smoking is used to cope with aversive states in the short term, yet paradoxically smoking confers longer-term risk for the maintenance of panic problems. See Fig. 10.1 for a graphical depiction of these interactive processes.

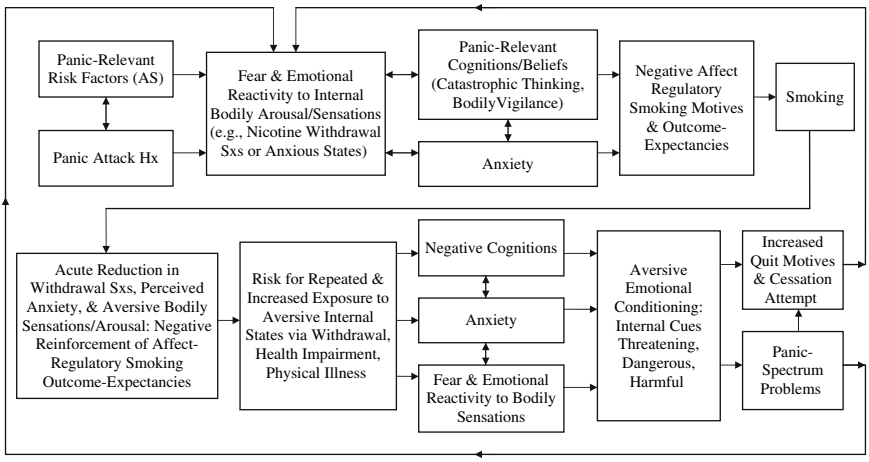

Fig. 10.1 A model to understand the relationships among smoking and panic spectrum problems

From an intervention standpoint, empirical and theoretical work on smoking and panic problems suggests it may be fruitful to *simultaneously and concurrently* target these risk factors in one overarching model to reduce panic problems while also stimulating cessation-oriented behavior. Because panic factors and smoking interact in clinically meaningful ways, addressing one of these factors without addressing the other in this same context may not result in optimal efficacy regarding intervention goals. For example, simply targeting the cognitive-based fear of anxiety without a recognition of smoking among those who often manage affect by smoking neglects clinically-relevant self-regulation processes. Alternatively, because anxiety sensitivity is related to poorer success in quitting smoking (Brown, Kahler, Zvolensky, Lejuez, & Ramsey, 2001), a failure to target this cognitive-based affective vulnerability may yield lower rates of success in cessation. Thus, smoking should theoretically be directly targeted within the context of clinical intervention for preventing panic attacks and PD. It is noteworthy that there is still debate about using sequenced or combined programs for smoking cessation when addressing another health behavior (e.g., diet). For example, Spring et al. (2004) found support for a sequenced approach for smoking and diet behavior, whereas Hall, Tunstall, Vila, and Duffy (1992) have found support for integrative (combined programs) for these same behaviors. In terms of addressing smoking and psychological factors, however, combined integrative programs are more predominant (Brown et al., 2001). This integrative focus for treatment planning is consistent with the larger literature on systems of integrated, concurrent care for individuals with co-occurring addictive and mental disorders (Mueser & Kavanagh, 2001; Pechter & Miller, 1997). As described below, our program, specifically,

is integrative in nature in the sense that it combines evidence-based elements of two separate intervention programs which are adapted for one another in novel ways.

Therapeutic Model: Anxiety Sensitivity-based Program for Targeting Panic and Smoking Problems

We have developed an integrated treatment protocol for targeting these behavioral problems in an overarching model. This intervention program integrates therapeutic strategies from the cognitive-behavioral treatment of PD with evidence-based smoking cessation counseling strategies adapted for panic vulnerable persons. This program, termed the Vulnerability-Targeted Cognitive-Behavioral Treatment for Smoking-Panic Co-morbidity (VT-SPC), is structured around the theoretically-relevant cognitive risk factor of anxiety sensitivity. This vulnerability factor is targeted for two key reasons: (1) anxiety sensitivity is known to be a critical cognitive process relevant to panic attacks and PD, and (2) anxiety sensitivity is related to the maintenance of smoking and decreased success in quitting. By structuring the intervention around anxiety sensitivity, the program is expected to simultaneously alter both panic problems and smoking behavior. A brief summary of the evidence supporting this conceptualization is presented as a basis for better understanding the core treatment elements.

Theory. Contemporary accounts of PD posit that the fear of anxiety (anxiety sensitivity) is critical in the development and maintenance of this disorder (Barlow, 2002; Clark, 1986; McNally, 1990). Anxiety sensitivity is a traitlike cognitive characteristic that predisposes individuals to the development of panic problems via heightened fear of anxiety-related symptoms and their perceived consequences or meaning (Taylor, 1999). It encompasses fears of physical, mental, and publicly observable experiences (Zinbarg, Barlow, & Brown, 1997), all of which can theoretically serve to amplify preexisting anxiety (Reiss, 1991). Please see chapter 11 for further details regarding anxiety sensitivity.

Risk factor for panic vulnerability. Aside from the theoretical relevance, empirical evidence suggests anxiety sensitivity is an optimal candidate for a PD treatment program. Research has found that anxiety sensitivity levels are elevated among individuals with PD compared to those without the disorder (Kearney, Albano, Eisen, Allan, & Barlow, 1997; Rabian, Peterson, Richters, & Jensen, 1993; Taylor, Koch, & McNally, 1992). Moreover, prospective studies with healthy adults (Schmidt, Lerew, & Jackson, 1997, 1999) and adolescents (Hayward, Killen, Kraemer, & Taylor, 2000) indicate anxiety sensitivity predicts the future occurrence of anxiety symptoms and panic attacks. Other work suggests anxiety sensitivity significantly predicts affect regulation processes

characterized by avoidance-based response styles for coping with aversive events (Zvolensky & Forsyth, 2002).

Risk factor for maintenance of smoking. There also is evidence that anxiety sensitivity is associated with poor cessation outcome and problems during quit attempts (Brown et al., 2001). Another investigation has found anxiety sensitivity to predict the intensity of affect-relevant withdrawal symptoms during quit attempts even after controlling for theoretically-relevant smoking and affect factors (Zvolensky, Baker, et al., 2004). Further investigations have shown that anxiety sensitivity is correlated with smoking motives to reduce negative affect among smokers (Comeau et al., 2001; Novak et al., 2003; Stewart et al., 1997) as well as the expectation that smoking will relieve negative affect (Zvolensky, Feldner, et al., 2004). These findings are clinically important given evidence that the expectation of negative affect reduction from smoking has been found to predict end-of-treatment smoking cessation outcome (Wetter et al., 1994) and the maintenance of smoking behavior (Cohen, McCarthy, Brown, & Myers, 2002). Collectively, such studies suggest that anxiety sensitivity, a panic-specific vulnerability factor, is associated with problems during cessation and that such effects cannot be accounted for by other smoking and affect variables. This same body of work also indicates that anxiety sensitivity is correlated with smoking and other types of drug/alcohol use to reduce negative affect (Brown et al., 2001). Moreover, anxiety sensitivity moderates the risk of smoking in terms of the development of panic attacks (Zvolensky, Kotor, Antipova, & Schmidt, 2003), suggesting regular smokers with higher anxiety sensitivity are at increased risk for experiencing panic-related problems.

Malleability. Numerous investigations have provided evidence of the malleability of anxiety sensitivity in response to exposure-based cognitive-behavioral interventions for PD (see chapter 11). Therefore, unlike many other panic risk factors (e.g., family history of PD), it can be specifically targeted for therapeutic *change* in clinical work. Indeed, changes in anxiety sensitivity appear to be largely responsible for PD treatment response (Smits, Powers, Cho, & Telch, 2004). That is, anxiety sensitivity mediates the relation between treatment and recovery. Of particular importance to the present therapeutic model, Otto and colleagues have provided empirical evidence for both the role of anxiety sensitivity in drug relapse problems (e.g., benzodiazepines) and the clinical utility of panic-derived exposure interventions for targeting anxiety sensitivity in treating benzodiazepine dependence (see Otto & Reilly-Harrington, 1999, for a review). Such data provide empirical precedent for the underlying rationale of the present model: that cognitive-behavioral strategies for panic-related problems can be used to decrease anxiety sensitivity in a clinically meaningful way among panic vulnerable individuals and thereby facilitate drug discontinuation. Please see chapter 9 for further details regarding Otto and colleagues' work.

Core Treatment Elements

The present therapy employs a cognitive-behavioral approach to treating PD while simultaneously facilitating smoking cessation among daily smokers with PD. The VT-SPC program utilizes cognitive restructuring and interoceptive exposure strategies with a specific focus on reducing AS and related anxiety processes in order to (1) decrease panic attacks and worry about having such episodes in the future and (2) facilitate successful smoking cessation, thereby reducing the risk of panic reoccurrence. The protocol incorporates key elements of cognitive-behavioral treatment for AS and panic, as well as elements of evidence-based behavioral counseling for smoking cessation; these are in-line with the most recent clinical practice guideline from the U.S. Department of Health and Human Services, *Treating Tobacco Use and Dependence* (Fiore et al., 2000). This treatment is designed to be conducted in either a twelve or sixteen 60–90 minute per session format. It has been conceived with the recognition that it can be adapted for utilization in either individual or group-based formats.

Within this context, there are three key elements that are offered in the program: (1) psychoeducational provision of an integrated therapeutic rationale, (2) decreasing emotional sensitivity and reactivity to anxiety, bodily cues, and nicotine withdrawal via cognitive-behavioral methods, and (3) specialized smoking-oriented psychoeducation and relapse prevention.

Element one: Integrated therapeutic rationale. Although many persons with PD are more likely to be daily smokers (Lasser et al., 2000), it is likely that many do not understand that smoking may promote or exacerbate panic problems. Indeed, such individuals are likely to believe that smoking actually helps them manage or cope with negative affectivity associated with panic psychopathology or pre-morbid panic vulnerability factors. This issue is perhaps not surprising given that many professionals who specialize in the treatment of anxiety and its disorders do not understand or address the role of smoking in terms of improved mental health functioning. For example, among practitioners who specialize in anxiety, only 30% assess smoking behavior in clients seeking treatment for anxiety disorders, most perceive themselves as "unprepared" to deliver smoking cessation therapy, and very few (17%) have received training in empirically-based smoking cessation practices (Zvolensky, Baker, et al., 2005).

Due to this limited knowledge of the interaction between smoking and anxiety problems, we first provide clients with a thorough psychoeducational rationale for targeting smoking within the context of their anxiety treatment. Thus, we emphasize that due to the negative associations with one another, it is important to target these behaviors together; that is, to effectively treat and prevent relapse to PD, it is important to quit smoking. This rationale focuses on the idea that in addition to proven strategies for smoking cessation, the current treatment focuses on helping the individual learn and practice strategies that will help them better manage interpreting, coping, and tolerating emergent

withdrawal symptoms and anxiety symptoms. Specifically, we introduce the concepts of fear of anxiety (i.e., anxiety sensitivity), catastrophic thinking (e.g., "I'm losing control"), and smoking (and other negative affect-based negative-reinforcement behaviors) as a maladaptive way of coping with anxiety-related distress. In this context, we pay particular attention to highlighting the process of the forward-feeding anxiety cycle, whereby catastrophic thinking and fears of anxiety sensations (anxiety sensitivity) can lead to both subjective threat evaluations and heightened attention to threatening stimuli, resulting in a greater risk for panic attacks as well as the exacerbation of interoceptive states like withdrawal symptoms. We also indicate such reactions may sensitize a person to the interoceptive and environmental cues that signal such distress in the future, leading to smoking as a way of coping. Finally, we articulate that targeting the fear of anxiety and modifying it via thinking and behavioral exercises is important in enhancing *both* panic and smoking outcomes. In this context, we emphasize that practicing cognitive-behavioral exercises both in and out of session is an important element of the intervention that directly contributes to each individual's ultimate success. Overall, targeting emotional sensitivity and reactivity to internal cues typically takes two–three sessions, but an "integrative" focus (on smoking and panic) is embedded throughout the treatment.

Element two: Decreasing emotional sensitivity and reactivity to anxiety, bodily cues, and nicotine withdrawal via cognitive-behavioral methods. The second core element involves using empirically-derived cognitive-behavioral strategies developed for anxiety and panic programs to decrease emotional sensitivity and reactivity to interoceptive stimuli. One important distinction between this and other anxiety programs is that the exposure exercises are adapted to target interoceptive cues across varying intensity levels of nicotine withdrawal (elicited via deprivation from smoking for various time periods). The central task of such an intervention component is to help panic-prone smokers learn (or relearn) a sense of tolerance, control, and safety in the presence of anxiety-related sensations: a task presumably hastened by helping individuals experience the sensations directly and in a controlled fashion, where emotionally corrective outcomes are facilitated, rather than in the naturally-occurring context where catastrophic misinterpretation of these symptoms is likely to occur (e.g., during cessation or smoking abstinence).

Accordingly, we integrate (1) interoceptive exposure with (2) corrective information about anxiety and cognitive interventions designed to teach patients alternatives to catastrophic misinterpretations of the sensations and their feared consequences ("I will lose control"), as well as (3) continued use of situational exposure. Specifically, we use cognitive-restructuring aimed at targeting the elimination of catastrophic beliefs about the meaning and consequences of anxiety sensations and symptoms of withdrawal. In addition to cognitive restructuring strategies, acceptance-based strategies are employed to foster increased tolerance for anxiety and related sensations. Furthermore, we systematically employ interoceptive exposure to extinguish fears of aversive

internal sensations (regardless of their source), with specific preparation for sensations that would be experienced as part of smoking discontinuation (withdrawal). Patients are explicitly taught that the goal of such therapeutic work is not to attempt the impossible task of eliminating anxiety or emotion-laden withdrawal sensations, but rather to ensure that these internal cues are not interpreted fearfully, escalating bothersome sensations into debilitating anxiety and perhaps panic. Exposure to somatic and other interoceptive symptoms *in advance of cessation* theoretically should help ensure that participants have practice with an alternative model of symptom management well before the characteristic symptoms of smoking discontinuation are encountered (or systematically induced). We believe this "pre-training" is important for providing patients with a new way of interpreting and managing internal distress and emergent withdrawal symptoms.

Interoceptive exposure is described, demonstrated, and practiced in session and individuals are encouraged to practice the exercises outside of session (as part of assigned homework). The importance of varying practice contexts to facilitate the "unlearning" of fear responses across settings is emphasized as a rationale for frequently practicing exercises out of session. Three interoceptive exposure exercises (e.g., head rolling, voluntary hyperventilation, and chair spinning) are typically completed each session, which is generally feasible within the given time constraints. For example, dizziness is induced by a head-rolling exercise in which patients gently swing their heads around in circles with their eyes closed for one minute. The repeated use of such exercises provides adaptation to the sensations (habituation) and reduces the probability that such sensations will trigger anxiety and panic in future circumstances. While performing these exercises, we pay particular attention to drawing a clear connection between aversive anxiety-related states and somatic changes and discuss such experiences in the context of changing smoking behavior (e.g., during a cessation attempt). Once participants can identify and isolate bodily sensations, they are coached to change their cognitive reactions to these sensations by reframing them in more adaptive ways and accepting them as "normal" rather than "dysfunctional" reactions.

An important element to this treatment is that, as the patient progresses through the interoceptive exposure exercises, we increase exposure intensity by incorporating periods of smoking deprivation into the interoceptive exposure exercises. By adapting existing exposure-based interventions for PD to target negative emotional processes related to smoking withdrawal symptoms, it may be possible to decrease negative emotional responding to smoking-related withdrawal symptoms, a primary factor in poor cessation outcomes (Kenford et al., 2002), and thereby facilitate smoking cessation within the context of treatment for PD.

In all cases, participants are asked to practice at least one self-exposure per day out of session and to monitor their performance using an exposure monitoring data recording card. The targeting of emotional sensitivity and reactivity to internal cues typically requires four–nine sessions. It also is emphasized to

individuals that such exercises are useful in terms of maintaining treatment goals and relapse prevention.

Element three: Specialized smoking-oriented psychoeducation and relapse prevention. The final element of the treatment program provides evidenced-based information for altering smoking behavior that is specifically designed for an anxiety vulnerable population. In regard to the smoking information, we base our discussion generally on the most recent clinical practice guideline from the U.S. Department of Health and Human Services, *Treating Tobacco Use and Dependence* (Fiore et al., 2000).

This component includes a variety of information, representing nine separate aspects. First, we provide positive reinforcement and social support for quitting. For example, therapists are instructed to congratulate participants for deciding to quit smoking in the context of PD treatment, review the positive health consequences of quitting, and express their willingness to help the participant succeed. Second, we discuss past quit experiences. Within a functional analytic assessment context, these past quit attempts are reviewed to identify what strategies contributed to success and what factors hindered previous attempts. Third, we work with the patient to set a quit date. This quit date occurs only *after* the patient has demonstrated progress in interoceptive exposure exercises in and outside of session (i.e., successfully and regularly completing homework). Here, it is important to have observed progress both for the exposure exercises in withdrawal and non-withdrawal states. Fourth, we initiate a formal self-monitoring program for smoking and other (alternative) coping behaviors (e.g., physical exercise). Specifically, participants track each cigarette they smoke through quit date and note situational cues for smoking as well as alternative strategies that they could have used instead of smoking.

Fifth, we work with the patient to identify idiographic high-risk situations for smoking. The focus of these discussions is in *anticipating* situations that likely will place them at risk for relapse and planning how to handle such situations ahead of time (without smoking). Sixth, we present and discuss the abstinence violation effect (Marlatt & Gordon, 1985). Namely, patients are prepared for the possibility of lapsing and given strategies for coping with the potential negative emotional reactions to lapsing. For example, patients are encouraged to identify and alter maladaptive thinking patterns both about lapsing (e.g., altering thoughts such as "I might as well give up because I just had a cigarette" to "I just smoked, but this is not an excuse to alter my longer-term effort to changing my smoking behavior. I can learn from this situation and adapt in the future to prevent it from happening again"). Seventh, we help patients identify and develop skills to support adaptive coping strategies. Due to the unique psychological concerns of individuals with PD, these coping strategies often reflect three key aspects of self- and emotion-regulation. The first pertains to coping behaviors that would alter negative emotional experiences in the short-term, particularly anxiety and worry. The second pertains to longer-term health-oriented lifestyle behaviors such as physical exercise. For

each individual, therapists assist the patient in developing behavioral and cognitive strategies for coping with emotionally salient events in the short-term and help develop plans for evoking longer-term health-oriented change. Third, therapists help each patient identify specific high-risk situations for smoking and provide support to avoid them altogether. For example, therapists often advise patients to avoid or reduce the use of alcohol or other recreational substances (e.g., cannabis) to assist in smoking quit attempts or management of affect.

Eighth, we attempt to help patients enlist social support for quitting. Therapists advise patients to tell their friends and family about their quit date and discuss ways to increase social support during the quit attempt. For example, patients often are encouraged to share with friends and family that their "weak moments" tend to be related to dysregulated affect (e.g., worry, anxiety) and that they are trying to quit smoking by responding differently to such affective events. We believe this approach enhances the psychological environment for, and explicitly recognizes the role of anxiety-specific processes in, behavior change. Patients also are encouraged, when applicable, to ask smokers in their household to avoid smoking in their presence. Finally, patients are encouraged to prepare for quitting by removing all tobacco products from their environment. This strategy helps remove unnecessary risks for tobacco use prior to vulnerable time periods and acts as a "behavioral index" of commitment to change lifestyle patterns.

Related issues often arise outside of the above mentioned aspects of this treatment element. While space limitations do not allow for a review all of these issues, one in particular is considered. Beginning with the session of the quit date and continuing thereafter, therapists encourage participants to describe their quitting experiences – including degree of withdrawal symptoms, general emotional distress, and strategies used to avoid smoking – and then help problem-solve difficult situations that have arisen. Referring back to interoceptive exposure exercises, it is emphasized to clients that anxiety and withdrawal symptoms are *opportunities* to practice skill development. Thus, unlike traditional approaches that highlight avoidance and reduction of withdrawal-eliciting stimuli, this approach embraces these as opportunities to increase resilience. Here, therapists explicitly reinforce success and provide support and encouragement for participants who lapse and smoke. Therapists convey, specifically, that one lapse does not constitute a complete relapse (e.g., returning to regular smoking behavior).

Targeting specialized smoking-oriented psychoeducation and relapse prevention typically takes four–seven sessions. As before, the importance of conceptualizing such exercises as positive mental health tactics (i.e., a positive lifestyle change) is emphasized. Moreover, throughout the treatment, we prompt and support participants to not only think differently about anxiety-related experiences, but also to behave differently (i.e., by facing fears rather than rigidly attempting to escape or avoid them).

Status of Efficacy

The VT-SPC program has been developed in a theoretically-driven manner and is supported indirectly by a relatively large body of empirical literature, albeit non-treatment oriented. These studies, as reviewed earlier in the chapter, suggest that there is an important bi-directional cycle between smoking and panic problems (Zvolensky & Bernstein, 2005). This "ground-up" approach to constructing the VT-SPC program has both strengths and challenges. On the one hand, because the program is based upon numerous studies and integrative theoretical models that explicate interplay between smoking and panic processes, there is a relatively logical extension of this work to the therapeutic approach. At the same time, due to the focus on theoretical development and marshalling support from non-treatment studies, direct tests of the efficacy of the approach are only now being conducted. For this reason, there is not yet data that speak to either the efficacy or effectiveness of this intervention. Nonetheless, there is precedent for implementing this approach among individual clients and variants of the program in the context of a controlled prevention trial for high anxiety sensitive daily smokers. To begin to better contextualize the clinical issues that may be related to the implementation of the program, or key aspects of the program, we now summarize the status of these findings.

Case study. We have completed single-participant evaluations of this type of integrated program. We do not review case reports in detail, as they already have been published (see Zvolensky, Lejuez, Kahler, & Brown, 2003). These initial single-case test trials helped shape the nature of the VT-SPC program described above. Yet, because they were an earlier version of the program, they do not exactly match the described VT-SPC protocol here, as we have refined the program based upon these early case studies. Specifically, one important distinction is that the earlier versions were less focused on the integration of the smoking and panic-relevant material. We now review one of these cases to more fully illustrate the clinical issues that often arise when implementing this type of program.

A single patient with a primary diagnosis of PD attended weekly outpatient therapy for 16 sessions over the course of 5 months. Sessions typically lasted 60 minutes. Treatment consisted of two main components: (a) cognitive-behavior therapy using select modules of the *Master of Your Anxiety and Panic* treatment manual (MAP; Craske & Barlow, 2000) and (b) smoking cessation treatment based on select segments of the most recent clinical practice guidelines from the U.S. Department of Health and Human Services, *Treating Tobacco Use and Dependence* (Fiore et al., 2000), as well as interoceptive exposure-based exercises for smoking withdrawal symptoms. The nicotine patch or other nicotine replacement therapies were not employed in the treatment because (1) the patient preferred not to include such agents and (2) we theorized that they would dampen emotional responsiveness, and hence, interfere with the exposure process.

The MAP treatment involved five main modules dealing with psychoeducation about PD, the nature of anxiety and fear, self-monitoring, exposure exercises, and preparing for the future (Chapters 1, 2, 3, 9, and 14, respectively). Other MAP components were not included because of limited time due to the inclusion of a modified smoking cessation program. Smoking cessation was integrated into the MAP protocol by adding: (a) psychoeducation regarding the role of smoking in terms of panic psychopathology; (b) instruction in basic smoking cessation skills; and (c) exposure exercises that directly targeted affect processes both while he continued to smoke and while voluntarily abstaining from smoking.

During the initial stage of treatment (sessions 1–2), we targeted panic-related processes via psychoeducation regarding the nature of anxiety/fear, PD, and how such emotional processes can be affected, in part, by smoking. Explicit attention was devoted to the smoking-stress relation, which suggests emotionally vulnerable persons may tend to rely on smoking as a coping strategy for dealing with negative emotional states (Parrott, 1999). Moreover, we discussed that although the potential anxiolytic effects of smoking are complex (Kassel & Unrod, 2000), smokers generally *expect* tobacco smoking to relieve (temporarily) anxiety-related states (Juliano & Brandon, 2002), which may actually be brought on by nicotine withdrawal. Thus, a self-perpetuating cycle may ensue, whereby smoking is used to cope with anxiety states, yet such behavior will be ineffective in reducing the overall levels of anxiety about bodily sensations and indeed lead to a nicotine dependence that may paradoxically heighten risk for anxiety-related symptoms and disorders. This conceptualization of the putative relation between smoking and panic appeared to resonate with the patient, as his motivation to quit smoke increased from a 50 (pre-treatment) to a 70 (on a 0–100 scale) following this segment of psychoeducation.

In sessions three–five, basic instruction in smoking cessation was provided. This included receiving a standard, individual smoking cessation treatment based on the most recent clinical practice guidelines (Fiore et al., 2000). A number of key domains were targeted, including: (1) providing reinforcement for quitting (e.g., congratulate patient for deciding to quit, review positive health consequences of quitting, and express willingness to help); (2) discussion of past quit attempts (e.g., his past quit attempts were reviewed to identify what strategies contributed to success and what factors hindered previous attempts); (3) setting a specific quit date (designated session 14); (4) stressing the importance of total abstinence (not even a single puff) from smoking; (5) help to identify high-risk situations (e.g., anticipate situations that will place him at risk for relapse, remove tobacco products from home); (6) develop coping strategies (e.g., for each high-risk situation identified, assistance was provided in terms of developing behavioral and cognitive strategies for coping with them); and (7) enlistment of social support (e.g., advised to tell his friends and family about his quit date and discussed ways to increase social support during the quit attempt). Additionally, the patient was given a copy of the National Cancer Institute publication, *Clearing the Air*, which discusses these types of cessation

strategies for smokers who are trying to quit. Throughout this instructional phase, the importance of quitting smoking in terms of helping reduce panic problems was emphasized, as a way to maintain cessation motivation.

In sessions 6–13, exposure exercises were implemented. Initially, exposure was conducted consistent with the MAP treatment (i.e., with no change in smoking behavior). Various interoceptive exposure techniques were practiced in session and the patient practiced these same strategies at home at the rate of one self-guided exposure per day. The patient's overall post-exposure anxiety ratings decreased from an average of 95 prior to treatment to an average of 55 on a 0–100 scale by session 8.

In sessions 9–13, we modified this exposure program so that it occurred during voluntary smoking abstinence; duration of abstinence was incrementally increased for in-session practice from 2 hours in session 9 to 12 hours in sessions 12 and 13. Additionally, the patient practiced at least one self-guided daily exposure at home; however, there was no change in smoking withdrawal for such practice sessions. Overall, this modified exposure strategy was included because the patient reported that his major reason for failing in past quit attempts was due to feeling "hyperaroused," "extremely hypervigilant," and "emotionally stressed" when in smoking withdrawal. Thus, by exposing him to bodily sensations when in active periods of withdrawal, we theoretically could reduce negative emotional responsivity to such withdrawal. Here, mean in-session post-exposure anxiety ratings decreased from 70 during session 9 to 35 on session 13. This change is noteworthy given that duration of nicotine withdrawal *increased* during the same time period. Moreover, the patient reported that his self-confidence in quitting smoking increased during this exposure period, presumably because he became less distressed about emotional arousal and/or possibly because by preparing for the exposure exercises he demonstrated to himself that he could stop smoking for longer periods. In fact, his ratings of confidence in terms of quitting increased from 25 at baseline to 75 by session 13 on a 0 (*no confidence*) to 100 (*complete confidence*) scale.

After session 13, there was a two week break before session 14 (quit date). The purpose of this break was for the patient to begin a relatively short nicotine fade, cutting down one to two cigarettes every other day. The nicotine fading program was not implemented earlier in the treatment program because we were attempting to maximize the effect of smoking withdrawal during exposure exercises. By session 14, the patient was successful in cutting-down 14 cigarettes from his average of 25 per day (thus, averaging approximately 11 cigarettes per day at the time of the quit date). On session 14, the patient began his smoking cessation attempt. Follow-up assessment of cessation on sessions 15 and 16 revealed that the patient remained abstinent, as indexed by his self report and CO analysis; additionally, abstinence was independently verified by his wife and son. Follow-up assessment of panic symptoms indicated that he had no panic attacks in the past two weeks and demonstrated a decrease in anxiety-related symptoms relative to pre-treatment. For instance, his anticipatory anxiety level decreased from 6.2 pre-treatment to a mean of 2.5 post-treatment. He also

reported less anxiety sensitivity and indicated his panic symptoms caused him substantially less impairment, relative to the baseline assessment, across occupational, social, and home domains. His exposure SUDS ratings post-treatment remained low following the start of his cessation attempt (i.e., post-treatment). The 12-month follow-up assessment revealed that the patient had maintained all of his treatment gains, including remaining abstinent from smoking. Since session 16, he reported no panic attacks, did not seek medical care for panic-related concerns, and showed global improvements in psychological functioning across various life domains. These effects were supported by the continued low SUDS in response to the 6-month follow-up session exposure challenge.

Prevention. We also recently completed a randomized controlled prevention trial of an intervention that utilizes the same key principles of that used in the VT-SPC. Specifically, this study sought to develop and empirically evaluate a theoretically-driven prevention protocol for high anxiety sensitive daily smokers. The Psychosocial Intervention targeting Anxiety Sensitivity (PIAS; Feldner, Zvolensky, Babson, Leen-Feldner, & Schmidt, 2005) consisted of a single two-hour session focused on (1) psychoeducation regarding anxiety, PD, and associations between PD and smoking, (2) instruction in basic smoking cessation skills, (3) practice in various panic and smoking-relevant interoceptive exposure techniques, and (4) homework assignments consisting of practicing self-guided exposure. Program effects were compared to a health information control group, which was based on previous control conditions utilized in anxiety prevention research (Schmidt & Vasey, 2000, 2002). The overarching aim was to apply theory and research in the panic-smoking domain to the development of an integrative prevention program that seeks to proximally alter anxiety sensitivity and smoking behavior (e.g., enhance motivation to quit). It was hypothesized that the PIAS would reduce anxiety sensitivity and increase cognitive-affective aspects of smoking cessation "readiness" (e.g., greater motivation to quit, greater smoking cessation self-efficacy) compared to the control group; at the present stage of intervention development, no explicit attempt was made to alter actual quit behavior (e.g., cessation attempt). Overall, these hypothesized effects were expected to maintain throughout the six-month follow-up period.

In regards to the effects of the PIAS on proximally targeted risk factors, consistent with prediction, the PIAS reduced anxiety sensitivity compared to the control group by the post-group assessment and this effect maintained through the three-month follow-up assessment. Although trends in mean differences consistent with these findings remained at the six-month follow-up, groups did not significantly differ. In terms of smoking behaviors, results indicated the PIAS increased overall motivation to quit smoking. Specifically, the intervention increased motivation to quit during the follow-up period, whereas such motivation decreased among persons in the control group. Trends ($p = .06$) suggested participants in the intervention, compared to the control group, reduced the number of cigarettes they were smoking per day by the

3-month follow-up assessment. Overall, this study suggests that conducting such an intervention in a group format is feasible and warranted. Although studies are needed prior to testing this approach in large scale trials, this study lays the groundwork for such programs of research. It also adds to the theoretical and empirical basis of smoking-panic processes and underscores the utility of developing integrated intervention programs for them.

Conclusions and Future Directions

We summarized multiple lines of research that illustrate the clinically-meaningful co-occurrence of smoking behavior and panic problems, as well as their dynamic, bidirectional impact on one another. Next, we made an effort to synthesize this empirical body of knowledge about smoking-panic relations into an integrative theoretical model (see also, Zvolensky & Bernstein, 2005). This model was presented with the intention of explicating how these smoking behaviors may be related to the etiology, maintenance, and relapse of anxiety problems via an interactive, dynamic, and forward-feeding cycle. A key, multi-faceted point advanced by this model is that (a) smoking is used as a coping strategy to regulate and reduce negative affective states such as anxiety and fears of bodily sensations among individuals with panic problems and panic vulnerability in the short-term. Yet, paradoxically for the smoker with panic problems or panic vulnerability who relies on smoking as a coping strategy, research suggests that, in the long-term; (b) smoking confers increased risk for the maintenance and severity of panic-spectrum problems and (c) that panic-specific vulnerability variables and full-blown panic psychopathology are related to the maintenance of smoking behavior.

In addition to promoting understanding of smoking-panic relations, the theoretical model was intended to facilitate the "translation" of the empirical body of knowledge to an efficacious treatment program targeting smoking-panic co-morbidity. Specifically, the empirically-based and theoretically-driven treatment program is intended to simultaneously and concurrently target a key panic-specific cognitive vulnerability factor and smoking cessation inhibitor: anxiety sensitivity. This is achieved via empirically-supported cognitive behavioral treatment strategies targeting panic problems paired with evidence-based smoking cessation strategies tailored for panic-vulnerable individuals.

A number of important future directions for clinical research are critical to further advance understanding of smoking-panic co-morbidity and for "translating" clinical research to efficacious clinical practice. First, although cross-sectional and prospective studies point to systematically meaningful associations between smoking and panic problems, there has been little experimental psychopathology work evaluating causal-oriented hypotheses of the role of smoking (e.g., quit behavior and nicotine withdrawal) in the onset and maintenance of panic problems. For example, using randomized controlled designs, experimental

manipulations of nicotine withdrawal in the context of laboratory-based fear-inducing biological challenge tests could help to isolate the role of withdrawal in triggering panic attacks.

Second, for some individuals, smoking and panic psychopathology also co-occurs with other forms of drug use, abuse, and dependence (Zvolensky, Bernstein, et al., 2006; Zvolensky, Bonn-Miller, Bernstein, et al., 2006). Isolating the unique variance accounted for by smoking in regard to panic problems above and beyond other drug behavior on the one hand and better understanding the relations between polydrug problems, smoking, and panic on the other, may be of particular importance. If, based on such research, a need is identified, future clinically-oriented scientific efforts may extend the current tobacco smoking-panic treatment model and program by integrating polydrug use, abuse, and dependence as additional targets.

Finally, we describe an empirically-based and theoretically-driven treatment program targeting smoking-panic co-morbidity. There is a clear need to evaluate the program rigorously in terms of its efficacy within a controlled clinical trial. These investigations are ongoing, but data are not currently available to document such effects. This type of research would be even more useful if in addition to measuring smoking cessation and panic outcome efficacy, process-level evaluation was conducted.

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Chapter 11
Personality-based Approaches to Treatment of Co-morbid Anxiety and Substance Use Disorder

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Co-morbidity Between Anxiety Disorders and Substance Use Disorders

Co-morbidity is defined as the presence of any co-occurring condition in a patient with an index disease (Kranzler & Rosenthal, 2003). Epidemiologic surveys of psychopathology in the United States have found that while approximately half of the general population will experience a major psychiatric illness at some point over their lifetime, the majority of affected individuals will simultaneously meet diagnostic criteria for two or more disorders (Kessler et al., 1994). Co-morbidity has important clinical implications including: more severe symptoms, more functional disability, longer illness duration, and higher treatment service utilization (see de Graaf, Bijl, ten Have, Beekman, & Vollebergh, 2004).

One of the most common co-morbid conditions is anxiety disorder co-occurring with substance use disorder. Studies that have examined rates of alcohol dependence in anxiety disorder outpatient samples suggest ranges from 15% to 30% depending on the particular anxiety disorders (see Barlow, 1997). Other epidemiologic studies cite lifetime prevalence rates of clinically significant anxiety disorders in patients with alcohol dependence as ranging from 25% to 45% (Kushner et al., 2005). These rates of alcohol dependence in anxiety disorder patients, and of anxiety disorders in alcoholism patients, are markedly elevated relative to base-rates in the general population. Nonetheless, co-morbidity studies with patient populations can lead to overestimates of co-morbidity due to the issue of "Berkson's bias" – the fact that individuals with more than one disorder may be more likely to seek treatment than those with only one disorder (Galbaud du Fort, Newman, & Bland, 1993). Thus, population-based studies are important to examine "true" rates of co-morbidity of anxiety and substance use disorders.

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In the Epidemiological Catchment Area Survey (ECA), which included more than 20,000 respondents from five communities in the United States, alcoholics were significantly more apt to have a co-morbid anxiety disorder than non-alcoholics (19.4% vs. 13.1%) (Regier et al., 1990). Moreover, the ECA survey found that individuals with any anxiety disorder had a 50% increase in the odds of being diagnosed with a lifetime alcohol use disorder (alcohol abuse or dependence). Co-morbid psychiatric symptoms, such as anxiety, can make accurate assessment of substance use more difficult and is associated with a poorer substance use outcome following treatment (Kranzler & Rosenthal, 2003). Indeed, anxiety disorders may especially complicate the treatment of substance use disorders in that they have been found to take significantly longer to remit as compared to mood disorders (Wagner, Krampe, & Stawicki, 2004).

Another issue relates to whether the anxiety disorder is seen as being "independent" of the substance use disorder or "substance-induced". The former views onset of an anxiety disorder occurring before that of an alcohol disorder and/or persisting after the substance abuse is resolved and in need of specific treatment. The latter views onset of an anxiety disorder occurring after that of an alcohol disorder due to substance intoxication and/or withdrawal and not in need of specific treatment; rather, substance-induced anxiety disorders will resolve as the substance abuse is brought under control. Using the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [DSM-IV]; American Psychiatric Association [APA], 1994) in a large epidemiologic survey, Grant et al. (2004) concluded that the vast majority of the anxiety disorders found in the general population and in alcoholism treatment settings are independent of substance abuse (see chapter 1).

Approaches to Treatment of Co-morbidity

Traditionally, two approaches have been used in the treatment of individuals with co-morbid disorders: serial treatment (where either one or the other disorder is addressed first and the other is addressed next, if necessary) and parallel treatment (where both disorders are addressed concurrently but typically without formal interaction of clinicians or programs involved) (Kranzler & Rosenthal, 2003). Current research suggests the greater effectiveness of a more integrated approach to the treatment of co-morbidity. For example, there is some evidence that the addition of cognitive-behavioral therapy (CBT) focused on the concurrent disorder to traditional treatment programs for substance abuse/dependence enhances efficacy of treatment for substance use disorder co-morbid with both unipolar and bipolar depression (Brown, Evans, Miller, Burgess, & Mueller, 1997; Weiss et al., 2000); personality disorders (Fisher & Bentley, 1996); schizophrenia (see Drake, Mercer-McFadden, Mueser, McHugo, & Bond, 1998); and anxiety disorders, such as posttraumatic

stress disorder (Najavits, Weiss, Shaw, & Muenz, 1998; Ouimette, Brown, & Najavits, 1998; see also chapter 7).

It should be noted that integrated treatment requires an understanding of both disorders, as well as strategies for assimilating and modifying traditional approaches to the treatment of each disorder so that they work well together. Integrated treatments for co-morbidity, however, go beyond simply adding therapeutic techniques established in the treatment of the co-morbid disorder to existing treatments known to be helpful in the treatment of the index disorder. Truly integrated treatments involve addressing the functional interrelations between the symptoms of the two disorders. While research indicates that integrative approaches work better, they only do so in individuals who can engage with, and complete, treatment. Many substance dependent individuals do not manage periods of abstinence that are adequate or sustained long enough to facilitate engagement in treatment. For these reasons, it is important that co-morbid individuals be identified early enough in their substance use careers so as to be better able to benefit from treatment.

Approaches to the treatment of co-morbid anxiety and substance use disorder are impelled by theoretical models of the relationship between the two disorders. For example, one model postulates that anxiety problems precede and contribute to the development of substance abuse, which suggests that a more strategic focus on the anxiety (vs. substance use) disorder might yield the best results. Alternatively, substance abuse may precede and contribute to the development of anxiety disorders; in which case, targeting the substance use via traditional substance use disorder treatments may be sufficient for the amelioration of both concurrent disorders. A third model proposes that anxiety and substance use disorders serve to exacerbate or maintain each other, which suggests that the best approach would be concurrent integrated treatment of both disorders. Finally, a fourth model proposes that anxiety and substance use disorders could be linked through a common third variable, such as an underlying personality-based predisposition to both anxiety and substance use disorder development. In this case, the most effective treatment approach would be to target the common etiologic mechanism (Conrod & Stewart, 2005; Stewart & Conrod, 2003).

Personality-based models of co-morbidity, a form of the fourth model discussed above, fit with motivational theories of substance abuse. Such motivational theories postulate that specific personality characteristics are associated with differential activation of brain motivational systems and differential susceptibility to specific drug-reinforcement effects (Cloninger, 1987; Conrod, Pihl, Stewart, & Dongier, 2000). For example, Cloninger et al. (1988) have proposed a distinction between two types of alcoholism: one, characterized by anxious personality traits and rapid development of tolerance and dependence on the anti-anxiety effects of alcohol; and a second type characterized by antisocial personality traits and persistent seeking of alcohol for its euphoriant effects. The former subtype would presumably have implications for the understanding of the common co-morbidity of anxiety and substance use disorders.

Recently, Gunnarsdottir et al. (2000) differentiated two broad subtypes of cocaine abusers on the basis of personality characteristics. Male veterans undergoing treatment for drug abuse were divided into two groups based on their harm avoidance and novelty-seeking traits. Gunnarsdottir et al. found that individuals who scored high on harm avoidance and low on novelty seeking (i.e., the "self-medicators"), reported markedly higher levels of trait anxiety than did those who scored high on novelty seeking and low on harm avoidance (i.e., the "sensation seekers"). Again, the former subtype would presumably be most relevant for the understanding of the anxiety disorders and substance use disorders relationship. Brain imaging added further support for the findings by revealing decreased brain perfusion, specifically in the left frontal lobes, only in the "self-medicators" (Gunnarsdottir et al., 2000). Finding evidence of the existence of two distinct personality styles compatible with different motivations for cocaine abuse, prompted Gunnarsdottir et al. (2000) to suggest that treatment efficacy might be improved by matching different types of cocaine abusers to different treatment strategies based on personality styles.

Even more recently, Hooten et al. (2005) reported finding specific personality correlates associated with poorer outcome following treatment for tobacco dependence. Hooten et al. (2005) found that high scores on neuroticism (tendency to experience negative affect, including anxiety) were associated with poorer outcomes from the tobacco treatment (i.e., lower rates of abstinence). Similarly, Stewart et al. (2006) examined the relationship between anxiety sensitivity (fear of anxiety-related sensations), an important personality risk factor for anxiety disorders (Stewart, Knize, & Pihl, 1992), and smoking cessation outcome in a group of smokers who took part in a structured, 4-week tobacco intervention program. Results showed that anxiety sensitivity levels were associated with more state anxiety during the first week of smoking cessation and poorer short-term outcome, with high anxiety sensitive smokers being at greater risk for relapse to smoking at one month follow-up.

These studies provide support for the motivational hypothesis that one's vulnerability to substance abuse development and maintenance is linked to individual differences in personality that produce different susceptibilities to the reinforcing properties of drugs of abuse. It would seem that personality profiling could be a valuable tool for guiding treatment approaches to substance abuse, particularly if the substance abuse is co-morbid with other disorders, such as anxiety disorders, for which there are known personality risk factors (e.g., anxiety sensitivity).

Personality-based Approaches to Treatment of Co-morbidity

To date, personality-based approaches to the treatment of co-morbidity have not been tested with treatment-seeking individuals, although results with non-treatment-seeking samples provide much promise. Conrod, Pihl, et al. (2000)

tested the motivational hypothesis by investigating the validity of classifying a community-based sample of non-treatment-seeking, substance abusing women according to four personality factors known to increase risk for substance abuse: anxiety sensitivity, introversion-hopelessness, impulsivity, and sensation seeking. Anxiety sensitivity is a dispositional variable or personality style that involves a fear of arousal-related sensations (e.g., increased respiration and palpitations) based on the belief that these sensations portend dire consequences (e.g., physical illness, loss of mental control, or social embarrassment) (Reiss, Peterson, Gursky, & McNally, 1986). Elevated levels of anxiety sensitivity are associated with increased risk for anxiety-related disorders (Maller & Reiss, 1992) and substance abuse (Stewart, Peterson, & Pihl, 1995). As a personality style, anxiety sensitivity has been found to be associated with sensitivity to the anxiety-reducing effects of alcohol (MacDonald, Baker, Stewart, & Skinner, 2000; Stewart & Pihl, 1994), as well as to higher levels of coping and conformity motives for drinking (Stewart, Zvolensky, & Eifert, 2001).

Introversion is a personality factor that has been found to distinguish between primarily depressed alcoholics, and nondepressed and secondarily depressed alcoholics, with highest rates of introversion observed in those where the depression emerged prior to the alcoholism (Epstein, Ginsburg, Hesselbrock, & Schwarz, 1994; Martin & Sher, 1994). Introversion is believed to reflect sensitivity to punishment and introversion-hopelessness may be motivationally linked to substance abuse through these individuals' sensitivity to drug-induced analgesia (see Conrod, Pihl, et al., 2000). Impulsivity has been linked to an elevated risk for early-onset alcohol and drug problems (Pulkkinen & Pitkanen, 1994). An individual with an impulsive personality style may be motivated to use substances that are immediately reinforcing due to their inability to inhibit their behavior in the face of negative consequences. Finally sensation seeking, in particular the intensity- versus novelty-seeking component of sensation seeking, is associated with a tendency to drink to experience the euphoric and intoxicating effects of alcohol in the absence of other forms of co-morbid psychopathology (Comeau, Stewart, & Loba, 2001; Conrod, Pihl, et al., 2000).

Participants in Conrod, Pihl, et al.'s (2000) study included 293 non-treatment-seeking women who responded to recruitment advertisements. Participants were eligible if they scored above 10 on the brief version of the Michigan Alcoholism Screening Test (Brief MAST; Pokorney, Miller, & Kaplan, 1972) and/or 12 on the Drug Abuse Screening Test (DAST; Skinner, 1982) and/or met three or more of the seven criteria indicating substance dependence as defined by the DSM-IV (APA, 1994) indicating the likely presence of a substance use disorder. Motivational profiles were compiled based on participants' performance on a battery of personality inventories.

Consistent with predictions based on the motivational hypothesis, results showed that different personality profiles revealed specific patterns of drug dependency and distinct patterns of co-morbid psychopathology. For example, a profile characterized by elevated anxiety sensitivity was associated with higher

rates of anxiolytic substance dependence, certain anxiety-related disorders (e.g., simple phobia and somatization disorder); introversion-hopelessness was associated with elevated rates of opioid substance dependence, depressive disorders and social phobia; impulsivity was associated with a higher incidence of stimulant substance dependence and antisocial personality disorder; sensation-seeking was associated with alcohol dependence exclusively but no other distinct concurrent psychopathology. A fifth profile, characterized by low scores on all four personality dimensions, was associated with less severe substance abuse problems and lower rates of co-morbid psychopathology relative to the other four profiles.

Conrod, Pihl, et al.'s (2000) findings suggested the potential value of developing intervention strategies that differentially target specific personality profiles. In a subsequent study, Conrod, Stewart, et al. (2000) investigated the effect of matching motivation-specific cognitive-behavioral interventions to different personality and motivational profiles for substance abuse. Interventions were designed to target the four personality profiles that had emerged as being associated with high-risk for substance abuse and co-morbid psychopathology in the previous study. In this study, 243 substance-abusing women were randomly assigned to one of three brief 90-minute interventions that differentially targeted their personality profile and their distinct reasons for drug use.

One group of women in Conrod, Stewart, et al.'s (2000) study was assigned to a motivation-matched intervention which involved the administration of a brief intervention specifically targeting participants' particular motivational profile (i.e., anxiety sensitivity, introversion-hopelessness, impulsivity, or sensation seeking). The intervention included personalized feedback on results from the extensive personality and motivational assessment, and discussion of the short-term reinforcing as well as the long-term negative consequences of their preferred substance of abuse. The intervention also included motivation-specific cognitive-behavioral skills training aimed at maladaptive coping strategies including substance misuse specifically relevant to each personality profile. For example, an individual high in anxiety sensitivity would be informed of the role this personality factor plays in the development and maintenance of psychopathology (e.g., anxiety disorders) as well as substance use (e.g., alcohol and anxiolytic drug use). She would be encouraged to consider the short-term reinforcing properties of her preferred drug (e.g., tension reduction) so as to understand better the reasons for her excessive drug use, followed by a discussion of the long-term aversive consequences of excessive drug use (e.g., anxiety enhancement). Clients would learn how to identify the automatic thoughts associated with high anxiety sensitivity (e.g., catastrophizing about arousal-related sensations) that increase risk for substance abuse. Training in cognitive restructuring and rehearsal of coping self-statements would provide the client with techniques to employ in challenging these anxiety-inducing thoughts when they arise. Finally, women would engage in activities designed to induce these automatic thoughts while being encouraged by the therapist to use their new skills to counter such thoughts.

A second group of women was assigned to a motivational control intervention which involved clients watching and then discussing a film designed to enhance their motivation for changing their substance abuse. A third group of participants was assigned to a motivation-mismatched intervention that involved motivational and coping skills training identical to that provided in the matched intervention but which targeted a personality profile that did not match the client's actual profile. For example, a client with an anxiety sensitive profile would be administered an intervention more befitting a client with an introverted-hopeless profile. The interventions in Conrod, Stewart, et al.'s (2000) study were delivered in a structured one-on-one format that involved close adherence to a treatment manual. Participants were given the manual at the end of treatment and encouraged to practice the recommended strategies at home. Assessment of outcome at six months indicated that, as compared to the motivation-matched control, participants in the motivation-matched intervention showed a significant reduction in reported frequency and severity of problematic substance use, and reduced use of mental health services. Moreover, participants in the motivation-matched intervention showed marginally better substance-related outcomes relative to the mismatched intervention groups.

Conrod, Stewart, Comeau, and Maclean (2006) conducted another study in which they examined the extent to which the personality-based approach to substance abuse treatment could be adapted for at-risk youth in intervening early with alcohol misuse. Interventions were developed based on those used in the previous study, as well as qualitative interviews and quantitative survey data with high risk youth. The efficacy of this novel early intervention approach was tested using a randomised control trial in Canadian high schools. Two-hundred-and-ninety-seven students between 14 and 18 years of age (mean age = 15.67 years) who showed personality risk (one standard deviation above the mean on measures of anxiety sensitivity, hopelessness, and sensation seeking) and who indicated drinking in the past four months were randomly assigned to the appropriate personality intervention (group format; 2 sessions) or to a no-treatment control group at each site. The Rutgers Alcohol Problem Index (RAPI; White & Labouvie, 1989), a well-validated, 23-item self-report measure of drinking problems commonly experienced by both clinical and community samples of adolescents and young adults, was used to assess drinking problems. The average score on the RAPI at pre-treatment was 15.22 (SD = 18.07; range = 0–82). This is just above the recommended clinical cutpoint of 15 showing that selecting adolescents for elevations on the personality factors and any drinking in the past four months (study inclusion criteria) pulled for a sample with moderately high levels of drinking problems. Participants were then re-assessed four months later. Results indicated intervention effects on drinking quantity, binge drinking and problem drinking symptoms. Furthermore, interactions between personality type and intervention condition indicated that the interventions were most effective in changing drinking behaviours that were

specific to each personality dimension. For example, students with high levels of anxiety sensitivity who participated in the personality-matched intervention had significantly lower baseline-adjusted mean scores on the RAPI at follow-up relative to the anxiety sensitivity control group.

With the aim of replicating these findings and demonstrating a preventative effect on the onset of substance-related behaviours, Conrod and Castellanos (2006) recently conducted a similar study in London, England that targeted younger students aged 13–16 (mean age = 14) who had not yet begun drinking at the outset of the study (n = 396). Conrod and Castellanos also expanded the intervention program to include interventions targeting impulsive personality traits in addition to anxiety sensitivity, hopelessness, and sensation seeking. Whereas there was no indication that the personality-targeted approach was associated with prevention of the onset of drinking behaviour, robust intervention effects were observed on binge drinking and quantity/frequency measures of alcohol consumption. Furthermore, the researchers replicated the results of the Canadian study by demonstrating personality-specific effects on various alcohol outcome measures. They also extended the results of the Canadian study by examining the effects of the interventions on mental health outcomes (Castellanos & Conrod, 2006). They found personality-specific effects of the various interventions on theoretically-relevant mental health outcomes. For example, students with high levels of anxiety sensitivity who participated in the personality-matched intervention had significantly lower rates of panic attacks at follow-up relative to the anxiety sensitivity control group (Castellanos & Conrod, 2006).

In a similar vein, Mushquash, Comeau, and Stewart (2007) conducted an open-trial pilot test of the efficacy of the personality-matched, motive-specific early interventions with Canadian Aboriginal youth with high levels of anxiety sensitivity, sensation seeking, or introversion-hopelessness. The youth ranged in age from 14 to 18 years (mean age = 16.56 years). In contrast to the Conrod and Castellanos (2006) study and similar to the original design of the Conrod et al. (2006) study, these youth were required to be drinkers at study outset and the interventions were adapted to be culturally appropriate for use in this group. The average RAPI score at pre-treatment was 25.20 (SD = 17.69; range = 0–70), which is well above the recommended clinical cut-point of 15 and suggestive of more severe problem drinking in this sample of young people than in the original Conrod et al. (2006) sample which had been drawn from the majority culture. Findings from this preliminary pilot study indicated that the interventions were associated with significant reductions in drinking rates and drinking-related problems relative to the normal developmental course of drinking behavior in a comparison group (i.e., adolescents who met inclusion criteria but who, for various reasons, did not participate in the interventions). The authors concluded that the personality-based approach to early intervention could be a promising method for reducing drinking behavior and early signs of drinking problems among this high risk population (Mushquash et al., 2007).

The findings of these studies highlight the importance of designing treatments for substance use disorder that take into account particular personality attributes of individuals at risk for substance abuse and co-morbid psychopathology, such as anxiety sensitivity. Following from Conrod's initiative, Watt, Stewart, Birch, and Bernier (2006) designed a brief group-based CBT to specifically target elevated levels of anxiety sensitivity in young adults at risk for both anxiety disorders and substance abuse. Because anxiety sensitivity is known to be associated with reports of heavy drinking and frequent alcohol problems (Stewart, Samoluk, & MacDonald, 1999), young adults with high levels of anxiety sensitivity are considered to be at risk for the development of alcohol disorders. Moreover, research has reliably found anxiety sensitivity to be related to coping motives for drinking (i.e., drinking for emotional relief) and coping motives are associated with heavy drinking, drinking problems, and a preoccupation with drinking (Stewart et al., 1999). Thus, it follows that interventions specifically designed to target anxiety sensitivity should improve drinking outcomes and prevent alcohol disorders for this subgroup of at-risk individuals by targeting their underlying motivation for drinking.

Watt, Stewart, Birch, et al. (2006) conducted a randomized controlled trial to evaluate the efficacy of a small group format, brief CBT in reducing anxiety sensitivity levels among female undergraduates. Only female participants were included in the Watt et al. study so as to control for effects of gender. Female students were recruited for participation in the study based on their ASI scores collected during in-class mass screening. In contrast to the intervention studies by Conrod, Stewart, et al. (2000) and Conrod et al. (2006), participants in the present intervention were selected based on their personality characteristics only rather than on a combination of personality and substance misuse behavior. Individuals scoring high and low on a measure of anxiety sensitivity (operationalized as one standard deviation above and below the gender-specific normative mean) were randomly assigned to either a CBT or control condition. The control condition consisted of group discussion about ethics in psychology and it was intended to control for non-specific effects of the intervention that could influence results (e.g., therapist or group exposure). All participants attended three one-hour sessions in one of four groups: high anxiety sensitive-CBT, high anxiety sensitive-control, low anxiety sensitive-CBT, or low anxiety sensitive-control. Each small group (6–10 people) attended intervention sessions conducted over three consecutive days, which were facilitated by two clinical psychology graduate students with experience in the application of CBT techniques.

The brief CBT followed a treatment manual which had been adapted from previous interventions (Conrod, Stewart, et al., 2000; Harrington & Telch, 1994) and consisted of three components: psychoeducation, cognitive restructuring, and a novel interoceptive exposure activity (i.e., running). Interoceptive exposure involves the repeated, intentional elicitation of physical sensations that produce anxiety (e.g., via running) with the goal being to break the connection between physical sensations and fear by providing the individual with

concrete experiences indicating that the physical sensations do not lead to the feared consequences, and by permitting habituation to occur (Carter & Barlow, 1993). On the first day, participants completed a series of pre-treatment baseline questionnaires including the Anxiety Sensitivity Index (ASI; Peterson & Reiss, 1992), Drinking Motives Questionnaire-Revised (DMQ-R; Cooper, 1994), Rutgers Alcohol Problem Index (RAPI; White & Labouvie, 1989), and the Alcohol Craving Questionnaire (ACQ; Love, James, & Willner, 1998). Then, those assigned to the CBT condition were introduced to the psychoeducation component of the program.

The psychoeducation component of the brief CBT consisted of informing participants about the anxiety cycle whereby exposure to anxiety-related sensations (stressful situations) can trigger negative cognitions (e.g., catastrophizing) about potentially hazardous outcomes (panic) in high anxiety sensitive individuals. On the second day, participants learned about two types of thinking errors that can occur in processing information related to anxiety sensitivity. They learned how to identify these dysfunctional automatic thoughts (i.e., probability overestimation and catastrophic thinking) and how to challenge them by examining the evidence ["what are the chances" that a harmful consequence (e.g., fainting) will ensue?], decatastrophizing ("what if" you did faint?), and substituting anxiety-provoking cognitions with more reasonable thoughts ("what else" could you think? – what is another way of looking at it?).

On the third day, participants met in a venue conducive to physical activity and engaged in ten minutes of running, following which they completed the Hyperventilation Questionnaire (HVQ; Rapee & Medoro, 1994). In order to ensure safe participation in the running exercise, participants with illnesses like asthma, allergies and cardio-vascular problems were screened out during telephone recruitment for the study. The rationale for using running as an interoceptive technique was that highly anxious individuals have been reported to avoid activities (e.g., sex, exercise) that can induce the anxiety-related bodily sensations which they so fear (McWilliams & Asmundson, 2001). It has also been theorized that reduced aerobic fitness might contribute to the pathophysiology of panic disorder and evidence exists of reduced aerobic fitness in patients suffering from anxiety disorders (see Broocks et al., 1997). All data was collected pre-intervention (baseline) and approximately ten weeks post-participation. It was hypothesized that drinking outcomes would improve only among participants with high (vs. low) anxiety sensitivity who were assigned to the CBT (vs. control) group. At the end of the third session, participants were given a homework assignment: they were asked to complete 30 minutes of running on at least 10 additional occasions prior to the three-month follow-up session, and to complete the Hyperventilation Questionnaire after each running exercise. The follow-up session involved completion of outcome measures, explanation of the study, and feedback from participants. Each participant in the CBT condition was given the manual to keep and was encouraged to continue to use it after the study was completed.

To date, 221 students have participated in the Brief CBT study. Consistent with predictions, results indicate a significant reduction in anxiety sensitivity levels only among participants with high (vs. low) premorbid levels who had been assigned to the CBT (vs. control) condition (Watt, Stewart, Lefaivre, & Uman, 2006). Moreover, as reported in Watt, Stewart, Birch, et al. (2006), a reduction in the proportion of "high consequence" drinkers (i.e., those scoring above the clinical cut-off of 15 on the RAPI; Winters, 1999) from pre-intervention to follow-up has been found for high anxiety sensitive participants in the CBT condition only, with no similar reduction found for the other three groups. High (vs. low) anxiety sensitive participants in the CBT (vs. control) condition show a reduction in relief alcohol outcome expectancies (i.e., *Drinking would make me feel less jittery*), and in conformity motives for drinking alcohol (i.e., drinking to fit in with a group you like). The finding that the intervention influenced conformity but not coping motives was contrary to hypothesis, as we had expected the intervention to reduce both of these negative reinforcement motives among high anxiety sensitive individuals. However, it is possible that conformity motives are more tightly linked than coping motives to anxiety sensitivity in young drinkers (Comeau et al., 2001).

Schmidt et al. (2007) also targeted anxiety sensitivity in an "at risk" sample (i.e., high average levels of anxiety sensitivity) defined by a relatively young (mean age = 18), predominantly female group. Participants were recruited from local schools, the community, and the university undergraduate population. Exclusionary criteria included a history of anxiety disorders or other current Axis I disorder, including alcohol abuse or dependence. Eligible participants were randomly assigned to a risk reduction (n = 200) or control condition (n = 200) and followed for approximately 24 months. Both conditions involved information delivered via an audiovisual computer presentation lasting 30 minutes. This 30-minute presentation was followed by 10 minutes spent with an experimenter when participants in the risk reduction condition reviewed presented information and interoceptive exposure exercises were explained; control condition participants only had questions about the presentation addressed.

The risk reduction condition was modeled after educational and behavioral procedures commonly used with patients with anxiety disorders (Telch et al., 1993). This presentation emphasized the benign nature of stress in regard to its immediate effects on the body by describing (1) the nature of stress, (2) effects of stress on the body, (3) the relation between stress and physiological arousal, and (4) the relation between stress and medical conditions. Participants also were taught that they may have developed a conditioned fear to certain bodily cues. Interoceptive conditioning processes were explained along with a description of behavioral exercises that are designed to recondition interoceptive cues. The video used in the control condition did not discuss anxiety-related issues, but focused on general health and nutrition not specific to anxiety.

The average overall ASI score at the outset of the intervention was approximately 26, which is about 1 SD above the mean for a community

sample (Schmidt & Joiner, 2002). Data on the intervention immediately post-treatment suggests that it produced statistically significant changes (30% reduction) in AS. Moreover, evaluation of change in the cognitive measures suggests good specificity since the intervention did not produce differential changes in other relevant domains [i.e., injury sensitivity or negative evaluation sensitivity (see Reiss, 1991)]. Data collected during follow-up are consistent in indicating that the intervention is having a positive effect. During follow-up, there was maintenance of the AS reduction in the intervention group with no reduction of AS over time in the control group. Also, based on structured diagnostic interviews conducted by assessors blind to condition and using the *Structured Clinical Interview for DSM* (SCID; First, Spitzer, Gibbon, & Williams, 1994), the intervention group showed a significantly lower incidence of anxiety disorder diagnoses during the follow-up. More specific to substance misuse, there appeared to be encouraging trends suggesting a reduction in the incidence of alcohol use disorders in the active treatment condition.

Recently, Feldner, Zvolensky, Babson, Leen-Feldner, and Schmidt (2006) evaluated the feasibility and short-term efficacy of a preventative intervention for anxiety sensitivity and smoking – two malleable risk factors for anxiety disorders (see chapter 10, for additional information). Members of a high risk cohort, defined by high levels of anxiety sensitivity and current daily smoking ($n = 96$), were randomly assigned to either a one session intervention focused on reducing smoking and anxiety sensitivity or a health information control condition of comparable length. Participants were followed for six months. Consistent with hypotheses, those in the treatment condition showed reduced anxiety sensitivity and this effect was maintained across the follow-up period. Some evidence emerged suggesting the program also increased motivation to quit smoking. Unfortunately, this study was underpowered to evaluate incidence of substance use diagnoses but there were some promising preliminary data suggesting that reductions in anxiety sensitivity may have a positive effect on successful smoking quit attempts.

The findings of all these studies provide support for the efficacy of targeting the personality vulnerability of anxiety sensitivity in the prevention and treatment of substance use disorder. Of course, further research is needed to determine the most efficient method of preventing and treating substance abuse among high personality risk individuals. For example, is group (vs. individual) therapy more beneficial, is computer presentation of material as effective as in-person, and is it best to target only the substance abuse directly, only the underlying motivation for the substance misuse, or some combination of both interventions? Further research is also needed to identify the active component(s) of the present type of intervention, and their mechanisms of action. For example, in addition to psychoeducation and cognitive restructuring, participants in the Watt et al. study were asked to engage in several sessions of physical exercise as an interoceptive exposure homework activity during the follow-up interval. Exercise could yield benefits via the mechanism of exposure or

conditioning effects. It is also possible that exercise could provide a prophylactic effect given that previous research suggests that increasing regular exercise may help to prevent, as well as treat, substance abuse in young people (Collingwood, Sunderlin, & Reynolds, 2000). Limitations of all the studies to date include relatively short follow-up intervals, as well as a limited ability to generalize results to males, non-Caucasians, and non-university students.

Case Study

To illustrate the applicability of the personality-based approach to the treatment of co-morbid anxiety and substance use disorders, a sample case study follows.

The client was a middle-aged, recently divorced woman with benzodiazepine dependence as well as alcohol abuse who was treated in the course of the personality-matched intervention study for adult substance abusing women (Conrod, Stewart, et al., 2000). This participant was diagnosed with co-morbid panic disorder and agoraphobia. Her personality assessment indicated elevations relative to norms on a variety of trait risk factors including introversion-hopelessness, but her most extreme elevation was on anxiety sensitivity. Her anxiety tended to escalate to the level of panic when she engaged in catastrophic thoughts about her anxiety symptoms and her inability to tolerate anxiety.

The client accessed her benzodiazepines through a friend who was a physician. She showed a strong interpersonally dependent relationship with this friend which she recognized was related to her desire to allow her access to a benzodiazepine prescription. She was quite vigilant about always having a bottle of alcohol readily available and described how she would become quite anxious if she could not easily access a drink. A timeline follow-back (TLFB; L. C. Sobell, Maisto, M. B. Sobell, & Cooper, 1979) assessment revealed that her benzodiazepine dependence was quite long-standing with an increase in use since her divorce. Her alcohol abuse had a more recent onset and appeared to be related to an attempt to control further her reported escalating anxiety symptoms. At the outset of treatment, she did not recognize her benzodiazepine use pattern as a substance addiction. Rather she saw her escalating use as an indicator that her medical treatment was failing and that she needed to find another medication to control her anxiety; this was her primary reason for referring herself to the study.

On being introduced to the idea of a personality-based model of managing her anxiety and reducing her substance misuse, she was initially quite resistant to the idea that her anxiety could be managed in ways other than through medical means (i.e., drug management). But she did recognize that she had some kind of constitutional susceptibility to anxiety that was long-standing and far beyond that of others – a feature of the model that resonated for her and provided a starting point for the intervention. During the course of our brief

intervention she was guided through a cognitive exercise which required her to identify the contextual, physiological, and cognitive antecedents to a situation where she had experienced extreme anxiety and substance misuse. While actively engaged in this exercise, she acknowledged realizing that her thoughts had a catastrophic nature and were contributing to her elevated anxiety and panic attacks and to her tendency to engage in avoidance behaviors including benzodiazepine use and alcohol abuse. She was then taught techniques for managing her anxiety-prone thinking, such as decatastrophizing and evaluating the probability of negative outcomes, and she practiced these techniques in other exercises with examples drawn from her own experience. By increasing her motivation to learn to manage her anxiety and reduce her avoidance (through providing her with a reasonable model of the interplay between her two sets of symptoms), and by training her in more appropriate cognitive and behavioral skills, the intervention proved immensely beneficial for this anxiety-sensitive client. By six-months following the intervention, this client showed an outcome of significant reduction in both her alcohol and benzodiazepine use.

Summary and Conclusions

The above case study nicely illustrates the key components of an effective treatment approach for co-morbid anxiety and substance use disorder matched to an individual's particular personality profile. To begin, a careful assessment is required in order to determine the magnitude and key diagnostic features of the presenting problem(s). The case study client revealed high levels of anxiety sensitivity which predisposed her to catastrophic thinking when confronted with arousal-related sensations. A chronological assessment revealed that the pathway to co-morbidity was from anxiety to benzodiazepines to alcohol, the latter of which seemed to have evolved from increasingly futile efforts to manage an escalating anxiety problem. The format of the intervention provided the client a useful structure for separating out and examining the various components of her anxiety – contextual (stressful situations and events, like divorce), physiological (arousal-related sensations), and cognitive (catastrophizing tendencies). Cognitive skills helped the client to gain control over anxiety-exacerbating thoughts, and behavioral techniques reduced her efforts at avoidance. Follow-up evaluation confirmed that the gains made in treatment were maintained.

The case study also raises the question of the role of adjunctive pharmacotherapy in the treatment of co-morbid anxiety and substance use disorder. It is possible that the efficacy of adjunctive pharmacotherapy in some clients could be enhanced by due consideration to personality profiling in treatment matching (see Gunnarsdottir et al., 2000). However, it has been suggested that some classes of medications may be incompatible with CBT treatments. For example, there is some evidence that patients with co-morbid anxiety and

substance use disorder treated with CBT-type approaches do less well over the long term if they are undergoing concurrent benzodiazepine therapy (see Barlow, 1997; Westra & Stewart, 1998).

In summary, personality-based approaches to the treatment of co-morbid anxiety and substance use disorder appear to hold promise for enhanced treatment outcomes. Finding evidence of positive effects on drinking behavior for even brief (3-hour) CBT interventions focused on underlying personality risk factors is particularly encouraging. Such a treatment approach offers a number of advantages for clients. By targeting shared antecedents of anxiety and substance use disorders, this approach could reduce the number of treatment goals for clients, which may reduce drop out relative to more demanding integrated treatments (Conrod & Stewart, 2005). Skills learned in the personality-based approach may generalize more readily to other maladaptive coping strategies (e.g., avoidance behavior including but not limited to substance misuse among anxiety sensitive individuals). Finally and perhaps most importantly, these interventions carry considerable potential for the prevention of onset and relapse of both disorders.

The process by which such changes occur is a worthy line of investigation. While there is some evidence that personality-targeted interventions reduce AS levels, it seems ambitious to expect that brief interventions can change personality. It will be important to investigate whether these interventions have a direct impact on personality vulnerability, or if their impact on AS happens indirectly via their effects on problematic coping behaviours (e.g., drinking and avoidance) that may increase AS levels above and beyond an individual's personal vulnerability. If the former hypothesis is supported with further investigation, it will have implications for current theories on the stable nature of AS and neurotic traits, more generally (e.g., Taylor, 1999).

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Chapter 12
Medical Management of Co-Morbid Anxiety and Substance Use Disorder

E. Jane Marshall

Treatment Studies

Pharmacotherapies for people with anxiety and substance use disorders (SUDs) are primarily adjunctive treatments and should be used in the context of a comprehensive treatment plan incorporating a range of interventions, including tailored psychosocial support, cognitive behavior therapy, coping skills training, and educational strategies (Kranzler, 2000). Used appropriately they can provide a window of opportunity to engage in treatment, and may help to reduce morbidity and mortality. Most controlled studies of pharmacotherapies in addictive disorders have focused on treatment of the addictive disorder alone, specifically excluding subjects with co-morbidity. Clearly the feasibility of carrying out such studies is restricted by methodological, clinical and economic factors (Babor & Del Boca, 2003). Although treatment facilities for patients with co-morbidity are increasing, they still find it difficult to access traditional addiction treatment programs. Their complex needs are more labour-intensive and difficult to manage (Cornelius, Rukstein, Salloum, & Clark, 2003), and they require close supervision and clinical input from well-trained and experienced staff. These factors combine to make treatment more expensive. As a result very few randomized controlled trials of pharmacotherapy for co-morbid anxiety disorder and SUDs have been carried out (Litten & Allen, 1999).

This chapter will focus on the pharmacological treatments that have been used to treat anxiety in individuals with SUDs. These treatments include a number of drug classes such as benzodiazepines, tricyclic antidepressants (TCAs) and related drugs, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), buspirone, dopamine D_2 antagonists, anticonvulsants, and beta-blockers. The selection of a particular drug class, and of a specific drug

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within that class, should be determined by the evidence base supporting its use and by whether the patient has had any experience of treatment with that compound (Baldwin et al., 2005). Treating doctors must be aware of the major adverse effects and problems associated with the prescription of these psychotropic drugs. The chapter opens with a section on general guidelines for treatment. The above drugs will then be discussed in the context of anxiety and a range of SUDs including alcohol, opioid, stimulant, cannabis, and benzodiazepine use disorders. Finally the pharmacological treatment options for the specific anxiety disorders that commonly co-exist with SUDs will be considered.

General Guidelines for Medical Management

Assessment and Diagnosis. A clear drug and alcohol history is essential. This should include a history of caffeine and nicotine use, self-medication, and use of herbal products. It is important to distinguish between drug-/alcohol-induced and independent anxiety disorders. This can be facilitated by obtaining the age of onset of each disorder, the sequence of onset, and whether on not the anxiety disorder persists during abstinence. A family history of anxiety disorders, and a history of previous treatment and response should also be obtained, as should a history of self-harm and overdose, either intentional or accidental. A collateral history is always helpful. Ideally a 4-week period of abstinence from alcohol should be allowed before a diagnosis is made (DSM-IV-TR; American Psychiatric Association [APA], 2000).

An assessment of anxiety (with or without depression) should be carried out, using validated scales such as the Beck Depression and Anxiety Inventories (BDI; BAI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Beck, Epstein, Brown, & Steer, 1988) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Assessment of suicidal ideation is also important because severe anxiety is a possible predictor of suicidal ideation and panic disorder is linked with suicidal attempts (Fawcett, 1992). Mental state and physical examination should be followed by laboratory investigations to rule out medical disorders associated with anxiety, such as hyperthyroidism, Cushing's Disease, and phaeochromocytoma. A urinary drug screen is necessary to exclude use of other drugs.

Initial Intervention. Treatment must address both disorders and should be carried out in partnership with the patient, and where appropriate with their family or significant other(s). Withdrawal from alcohol/drugs should be supervised. The setting will depend on the severity of the alcohol/drug dependence, and the psychiatric and medical problems. Substance-specific pharmacotherapy, for instance naltrexone or acamprosate for alcohol dependence or methadone substitution for opioid dependence, should be considered. Cessation of alcohol/drugs is likely to exacerbate mood/anxiety disorder, so patients may be distressed and at risk of withdrawing prematurely from treatment at this point.

Psychological therapy (CBT) and self-help (bibliotherapy) should be instigated. Benzodiazepines should be avoided, or used in the short-term only. A risk/benefit analysis should be carried out to decide whether to prescribe an SSRI (see section below). These are effective and suitable as first-line treatment in panic disorder, generalized anxiety disorder (GAD), social anxiety disorder (social phobia), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) (see section below). If it is decided to commence an SSRI, the patient should be informed of its potential side-effects, and of potential discontinuation or withdrawal symptoms. Patients started on an SSRI should be seen at regular weekly intervals to monitor symptoms of anxiety and agitation, to assess for suicidal ideation (especially in the early stages of SSRI treatment), to monitor side-effects, and to ensure compliance with medication. An easy-to read handout on the nature and course of treatment can help patients, as well as their family members and carers. Information about self-help groups is also beneficial.

Consolidation and Long-term Treatment. Consolidation usually involves a combination of psychosocial treatment for both disorders (CBT, coping skills therapy, individual and/or group support, Alcoholics Anonymous [AA]) and pharmacological treatment. The long-term use of benzodiazepines is controversial. Short self-report questionnaires can be used to monitor improvements in anxiety and substance use. Long-term treatment should target maintenance of abstinence, and remission from anxiety disorders. Psychological treatment may need to continue for a longer period than would be usual for anxiety disorder alone. Patients should be encouraged to attend self-help groups. In some situations a written, individualized treatment contract may be necessary. Only one doctor should write the prescriptions, as patients often seek benzodiazepines from other doctors. Screening for alcohol and drugs may be necessary.

The various pharmacological treatments will now be discussed, according to drug class, starting with benzodiazepines and SSRIs, and moving on to consideration of other appropriate drugs. The evidence base for the use of each drug will be presented, together with information on indications for use and important side-effects.

Pharmacological Treatments

Benzodiazepines. Benzodiazepines, despite their relative safety and efficacy in the short-term management of anxiety disorders in the general population, should not routinely be prescribed to individuals with alcohol or drug dependence, because of their established abuse potential, and high risk of tolerance and dependence. As a general rule the prescribing of benzodiazepines to individuals with SUDs is contra-indicated, except for very specific purposes and on a time-limited basis. One instance in which benzodiazepines are routinely used with SUD clients is in the treatment of alcohol withdrawal, where symptoms of anxiety are prominent. Several meta-analyses and reviews have concluded

that benzodiazepines are the treatment of choice for alcohol withdrawal (Mayo-Smith, 1997; see Lingford-Hughes, Welch, & Nutt, 2004 for further references). It should be noted, however, that the methodological quality of many of these trials is questionable. Benzodiazepines are typically prescribed in tapering doses over a 7-day period. Longer acting benzodiazepines, such as diazepam and chlordiazepoxide, are more effective at preventing withdrawal seizures and delirium, but are poorly tolerated by people with severe liver disease and among the elderly. Some clinicians advocate "front-loading", that is, giving a loading dose of diazepam or another benzodiazepine and further doses every 90 minutes until light sedation is achieved (Sellers et al., 1983). This regimen can only be carried out on an in-patient basis and requires skilled medical supervision. Symptom-triggered therapy, where patients are given benzodiazepines only when they manifest overt alcohol withdrawal symptoms, also has its advocates (Saitz et al., 1994). This form of withdrawal also requires supervision, and may not be as effective as other regimes in preventing withdrawal seizures.

Diazepam and chlordiazepoxide are the main benzodiazepines used to treat alcohol withdrawal symptoms, although oxazepam, which has a shorter half-life, is preferred in the elderly and in individuals with alcohol-related liver disease. In patients with a known anxiety disorder and alcohol dependence it may be sensible to slow down the withdrawal regime, perhaps reducing the benzodiazepine dose over a 10–14 day period, while monitoring the symptoms with an alcohol withdrawal scale and an anxiety questionnaire (Edwards, Marshall, & Cook, 2003).

It is important to defer a full anxiety assessment in the alcohol dependent patient until after the withdrawal period. State anxiety scores typically return to the normal range by the second week of a medically-managed withdrawal from alcohol (Brown, Irwin, & Schuckit, 1991). However the DSM-IV-TR recommends that individuals be abstinent for a full four-week period before diagnosis of an independent anxiety disorder (APA, 2000).

Side-effects of benzodiazepines include behavioural disinhibition and respiratory depression, the latter a risk when benzodiazepines are used in combination with alcohol. Abstinent alcohol dependent patients may be at greater risk of benzodiazepine abuse and dependence than the general population because they experience the rewarding effects to a greater extent (Ciraulo et al., 1997). Severity of dependence may be an index of abuse potential. Patients with severe alcohol dependence, antisocial personality disorder, and multiple substance use appear to be at greatest risk of abusing benzodiazepines, while less severely alcohol dependent patients are at lesser risk (Ciraulo, Sands, & Shader, 1988; Ciraulo & Nace, 2000; Posternak & Mueller, 2001). Benzodiazepines such as temazepam and lorazepam have the highest abuse potential because of their short half-life, high potency, and rapid absorption. Alprazolam, diazepam, and lorazepam, as well as being rapidly absorbed, also have a positive effect on mood in alcoholics, that is not seen in non-alcoholics (Ciraulo, Barnhill, et al., 1988; Ciraulo et al., 1997) and

this mood enhancing effect may facilitate abuse potential (see chapter 2). Alcoholics with a positive family history may be at particular risk as the mood-enhancing effects of alprazolam have been shown to be greater in sons and daughters of alcoholics than in people without a history of parental alcohol dependence (Ciraulo et al., 1996). Any prescribing of benzodiazepines for alcohol dependent individuals should therefore be carried out with caution and incorporate a risk assessment.

Most guidance warns against the use of benzodiazepines in patients with co-morbid anxiety and drug use disorders (Scott, Gilvarry, & Farrell, 1998). In North America, alprazolam and diazepam are the two benzodiazepines most abused by individuals in methadone maintenance treatment programs (Sellers et al., 1993). Caution is therefore needed when prescribing alprazolam to treat anxiety in these clients. Some benzodiazepines have proven efficacy in the treatment of panic disorder, GAD, and social anxiety (APA, 1998; Baldwin et al., 2005; Nutt, 2005a). However, they can cause sedation when used in acute treatment, and dependence is a problem with long-term use. In general their use should be restricted to patients who have not responded to at least two treatments (e.g., non-response to both an SSRI and a psychological treatment). Concerns about their abuse potential should not prevent their use in patients with severe, persistent, and distressing symptoms (Baldwin et al., 2005; Muller, Goldenberg, Gordon, Keller, & Warshaw, 1996).

Stimulant use exacerbates symptoms of anxiety disorders and chronic amphetamine and cocaine use can precipitate anxiety states and panic attacks (Gossop, 2003; see chapte 5). Some stimulant using individuals self-medicate anxiety and panic symptoms with alcohol and sedatives, but heavy alcohol use, in turn, can contribute to continuing anxiety. Any attempt to improve symptoms of anxiety in such a situation is contingent upon abstinence from stimulants (and alcohol, where implicated). Benzodiazepines may be helpful in the acute stages of stimulant withdrawal.

Selective Serotonin Reuptake Inhibitors (SSRIs) and Venlafaxine. SSRIs have a broad spectrum anxiolytic effect and are more effective than benzodiazepines at improving the psychic symptoms of anxiety, including worry, tension, irritability, and concentration difficulties (Synderman, Rynn, Bellew, & Rickels, 2004). Although they are as effective as TCAs in the treatment of panic disorder, agoraphobia, and generalized anxiety disorder, they have a safer side-effect profile, are better tolerated, non-addictive, and do not react with alcohol in the brain to cause respiratory depression (Bakker, Van Balkom, & Spinhoven, 2002). They are usually, therefore, the first-line pharmacological treatment for anxiety disorders. However they have the potential to cause unpleasant side-effects such as increased nervousness, insomnia and nausea, and sexual dysfunction (Baldwin et al., 2005). Furthermore, if stopped abruptly, most SSRIs and venlafaxine (an SNRI) can cause a discontinuation syndrome characterized by dizziness, insomnia, and flu-like symptoms (Haddad, 2001). SSRIs are also associated with an increased risk of the serotonin syndrome. This is a pharmacodynamic interaction which has been reported with a variety of antidepressants,

buspirone, and other drugs, usually in combination, but sometimes taken alone or in overdose. Symptoms (in increasing severity) include restlessness, sweating, tremor, shivering, myoclonus, confusion, seizures, and death (Sternbach, 1999).

As the SSRIs are less dangerous than TCAs if taken with cocaine or in overdose, they may be more suitable for the treatment of anxiety in cocaine users, despite the potential risk of the serotonin syndrome. However caution is needed when prescribing SSRIs (or TCAs) to stimulant users with co-morbid anxiety. Both groups of anti-depressants have a delayed onset of action, taking from between 10 days to 2 weeks to show the required effect. This delay can put the patient at increased risk of substance relapse. Some patients may experience an initial activation leading to a worsening of anxiety, and this can also predispose to relapse to substance misuse (Gossop, 2003).

Although clinical trials have demonstrated the efficacy of SSRIs in the treatment of anxiety disorders in individuals without SUDs, very few studies have been carried out in individuals with anxiety disorders and co-morbid SUDs. Sertraline has been shown to reduce alcohol consumption in non-anxious individuals with late onset alcohol dependence (Pettinati et al., 2000). A pilot double-blind, placebo-controlled 8-week study of paroxetine in alcohol dependent patients with social anxiety found that paroxetine was more effective at improving anxiety than placebo (Randall et al., 2001). Paroxetine was also associated with reduced alcohol consumption, but this effect was not as marked as the anxiolytic effect. The use of paroxetine in the treatment of social anxiety disorder and co-morbid alcohol dependence is considered in greater detail (see chapter 8). The efficacy of sertraline has been investigated in two placebo-controlled trials of PTSD in individuals with alcohol dependence. In one study sertraline improved symptoms of PTSD but decreased alcohol use in a subset of the population (Brady, Sonne, & Roberts, 1995). In the other study, 93 patients were divided into 4 groups according to the presence or absence of additional anxiety and affective disorders (Labbate, Sonne, Randall, Anton, & Brady, 2004). Patients in all 4 groups showed moderate improvement in depression and PTSD scores.

No treatment trials investigating the management of anxiety disorders in stimulant use have been carried out, although some evidence may be extrapolated from treatment trials of depression in alcohol and drug-dependent patients (Nunes & Levin, 2004). Both paroxetine and fluoxetine are potent inhibitors of the isozyme CYP 2D6 which metabolises cocaine and MDMA. SSRIs are also metabolized by CYP 2D6, so paroxetine and fluoxetine effectively inhibit their own metabolism, thus leading to elevated levels of these antidepressants in the blood. Elevated levels of SSRIs, together with raised serotonin levels caused by cocaine and MDMA, increase the risk of the serotonin syndrome.

Acute use of cannabis and other hallucinogens can be associated with the onset of panic attacks and disorder in susceptible people and this usually occurs when high doses have been used (see review in chapter 5). A small study recently showed that paroxetine, in doses up to 40 mg daily, was

effective in reducing symptoms of panic disorder associated with cannabis use (Dannon et al., 2004).

Bupropion (Noradrenaline and Dopamine Reuptake Inhibitor). Cigarette smoking may be causally related to the onset and severity of panic disorder (Amering et al., 1999; Kushner, Sher, & Erikson, 1999; see also chapters 5 and 10) and this lessens with smoking cessation. The treatment of nicotine dependence has been investigated in a large number of randomized controlled trials (RCTs) and the evidence summarized in systematic reviews and guidelines (Lingford-Hughes et al., 2004; National Institute for Clinical Excellence [NICE], 2002; Silagy, Lancaster, Stead, Mant, & Fowler, 2003). Nicotine replacement therapy and bupropion are effective interventions (see Lingford-Hughes et al., 2004). However evidence is lacking for pregnant women, adolescents, and individuals with co-morbid anxiety and SUD. Bupropion sustained release may be effective in the treatment of panic disorder and merits further investigation (Simon et al., 2003).

Tricyclic and Related Antidepressant Drugs (TCAs). Tricyclic and related antidepressant drugs are well established, effective treatments for some anxiety disorders. They have a greater side-effect profile than SSRIs or venlafaxine, and should be reserved for use in non-response to, or poor tolerance of SSRIs or venlafaxine (Baldwin et al., 2005). Abrupt cessation can also cause a discontinuation syndrome. Controlled studies have shown that both imipramine and trazodone are as effective as diazepam in relieving anxiety symptoms in non-alcohol dependent patients with GAD without major depression (Rickels, Downing, Schweizer, & Hassman, 1993). TCAs should be avoided in patients at risk of suicide (Nutt, 2005b). A meta-analysis of randomized controlled trials investigating the treatment of depression in patients with opioid dependence concluded that TCAs may improve mood but not necessarily the drug-related behaviour (Nunes & Levin, 2004). These data further show that TCAs, especially doxepin, also decreased symptoms of anxiety in this group (Kleber et al., 1983; Titievsky, Seco, Barranco, & Kyle, 1982; Woody, O'Brien, & Rickels, 1975; Woody, O'Brien, McLellan, Marcovici, & Evans, 1982). Some stimulants inhibit the metabolism of TCAs, which in turn have a high risk of death when used in overdose. It could therefore be argued that the use of TCAs in cocaine misusers carries unacceptable risks and they should probably be avoided.

Monoamine Oxidase Inhibitors (MAOIs). The monoamine oxidase inhibitor (MAOI), phenelzine, is of proven efficacy in the treatment of panic disorder (Baldwin et al., 2005), but its use is not widely advocated, because of the dangers of dietary and drug interactions and of interactions with alcoholic and low alcohol drinks. Moclobemide, a reversible MAOI, has some efficacy in treating panic disorder and social anxiety. No trials of MAOIs have been carried out for the specific indication of treating anxiety in alcohol use disorders. The use of MAOIs with stimulant drugs may precipitate a hypertensive crisis (Hersh & Modesto-Lowe, 1998), so are best avoided in these patients.

Buspirone. Buspirone, a $5HT_{1A}$ partial agonist, is an effective anxiolytic agent, with a relatively delayed onset of action and a high safety profile, which

is licensed for the treatment of anxiety in several countries. Buspirone and the benzodiazepines are the most commonly prescribed drugs for anxiety in the United States (Rickels, Pollack, Sheehan, & Haskins, 2000). The rationale for using buspirone is based on the hypothesis that alteration in serotonin function can predispose to relapse (low serotonin turnover rate is associated with increase alcohol consumption) (George et al., 1999). The efficacy of buspirone has been assessed in three randomized controlled trials of alcohol dependent individuals with generalized anxiety disorder (GAD). Buspirone showed some effect on both alcohol and anxiety outcomes in two of the studies (Kranzler et al., 1994; G. Tollefson, Montague-Clouse, & S. Tollefson, 1992), but no effect was observed in the third (Malcolm et al., 1992).

The Tollefson et al. (1992) study included 51 out-patients (37 men and 14 women) with DSM-III (APA, 1980) alcohol dependence and concurrent GAD, randomised to placebo or buspirone, and treated/followed up for 6 months. All patients had recently been discharged from in-patient units. Only those with a Hamilton Rating Scale for Anxiety (HAM-A) score > 18 and a Hamilton Rating Scale for Depression (HAM-D) score < 18 were included in the trial (Hamilton, 1959). Forty two patients (42/51) completed at least 4 weeks of treatment. The buspirone group showed greater reductions in anxiety and craving, and more overall clinical improvement.

The Kranzler et al. (1994) study was a 12-week randomized placebo-controlled trial of buspirone in 61 alcoholics with GAD (80.9% men) who met criteria for DSM-III-R (APA, 1987) alcohol dependence. All were recruited through advertisements, and had to agree to have weekly cognitive-behavioural therapy. They were required to remain abstinent for 7 days before the initiation of treatment, and only those with HAM-A scores of 15 or over were included. Buspirone was associated with greater retention, reduced anxiety, a slower return to heavy drinking, and fewer drinking days during the 6-month follow-up period.

The Malcolm et al. (1992) study investigated 77 inpatients (all male veterans) with DSM-III-R (APA, 1987) alcohol dependence and GAD (buspirone $n = 33$; placebo $n = 34$). Patients were treated and followed up over a 6 month period. All patients were involved in the analysis. Median number of weeks in the study was 9.1 weeks for the buspirone group and 12.8 weeks for the placebo groups. Buspirone showed no benefit over placebo on anxiety and drinking outcome measures. Two further RCTs showed that buspirone did not improve drinking outcomes in non-anxious patients (Fawcett et al., 2000; E. Malec, T. Malec, Gagne, & Dongier 1996). Buspirone may help to retain alcohol dependent people with GAD in treatment, and to reduce anxiety symptoms, and heavy drinking (Kranzler et al., 1994).

Dopamine D2 Receptor Antagonists. A six-month study in patients with alcohol dependence and co-morbid anxiety and/or depressive disorders found that tiapride, an anti-psychotic drug with selective antagonist properties at the dopamine D_2 receptor resulted in a 43% reduction in daily alcohol intake and abstinence rates approaching 79% (Shaw, Majumdar, Waller, MacGarvie, &

Dunn, 1987). The findings revealed an overall decrease in anxiety and depressive symptoms as well. However, these effects may have been secondary to the reduced alcohol consumption. Tiapride is not widely available and its routine use is limited by extra-pyramidal side-effects typical of anti-psychotic drugs such as Parkinsonian symptoms, dystonia (abnormal face and body movements), akathisia (restlessness), and tardive dyskinesia (involuntary movements of the tongue, face, and jaw).

Other Agents. Although some anti-convulsants have been shown to be effective in the treatment of anxiety disorders, few RCTs have been carried out. Carbamazepine is known to enhance the metabolism of methadone, so patients on the two drugs are at risk of developing end-of day withdrawal symptoms and/or the re-emergence of craving. These drugs should therefore be reserved for patients who do not respond to, or who are intolerant of treatments with an evidence base (Baldwin et al., 2005).

Specific Patient Groups. Evidence is lacking for specific patient groups with co-morbidity including pregnant substance users, adolescents, the elderly, and individuals with physical illness co-morbidity.

Studies in pregnant substance users suggest that TCAs and fluoxetine are safe in the first trimester, but their potential for teratogenicity and effects on the development after birth is unknown (Baldwin et al., 2005). Fluoxetine and citalopram should be avoided in breast-feeding mothers as their secretion into breast milk is higher than for other SSRIs.

The onset of symptoms of social anxiety and OCD typically occur in adolescence and many young people are extremely disabled by these distressing and persistent symptoms. Some find that alcohol helps them to cope. Those who present to services are more likely to be drinking in a hazardous or harmful manner rather than displaying symptoms of alcohol dependence. Most trials testing the efficacy of pharmacological treatments in people with anxiety and SUDs have been carried out in adults; thus, there is no evidence base for those under age 18 years (Dawes & Johnson, 2004). No anti-depressant currently has United States Food and Drug Administration (FDA) approval for treatment of adolescent panic disorder (Campbell-Sills & Stein, 2006). Careful monitoring is essential when prescribing for those under 18 years of age, and it may be wiser to reserve SSRIs for those who do not respond to evidence-based psychological interventions. Adolescents with co-morbid anxiety disorders and SUDs should therefore be referred for cognitive behavioral therapy (CBT) in the first instance and followed carefully (see chapter 11).

Many elderly people are troubled with symptoms of anxiety, a proportion of whom have a co-morbid alcohol or other SUD. Very few controlled investigations have been carried out. Venlafaxine has been shown to be effective among elderly patients with GAD (Katz, Reynolds, Alexopoulos, & Hackett, 2002), and citalopram has been shown to be effective in elderly patients with a variety of anxiety disorders (Lenze et al., 2005).

Physical Illness Co-morbidity. Patients who have suffered traumatic brain injury (TBI) may learn to use alcohol to treat the subsequent affective and anxiety

lability, and are thus at risk of developing alcohol dependence. A proportion of these individuals will already have been alcohol dependent at the time of injury. Anti-convulsants may have a role in attenuating co-morbid emotional lability in this group (Beresford, Arciniegas, Clapp, Martin, & Alfers, 2005).

Individuals with SUDs and Hepatitis C have high levels of co-morbid anxiety and depression (De Bie, Robaeys, & Buntinx, 2005) which largely goes undiagnosed and untreated (Golden, O'Dwyer, & Conroy, 2005). SSRIs should be used, where possible, to treat the anxiety and depression before and during Hepatitis C treatment with Interferon. Interferon itself is associated with a higher risk of depression.

Pharmacological Treatment of Co-morbid Anxiety and SUDs

The following section sets out the pharmacological treatment options for the anxiety disorders which commonly co-occur with SUDs: panic disorder, GAD, social anxiety disorder, OCD and PTSD. Where there is no specific evidence available on the treatment of co-morbid anxiety and SUDs, suggested treatment options are based on studies of anxiety disorders without SUDs. Over the past ten years, a number of consensus documents and evidence-based practice guidelines have been issued by influential bodies including the American Psychiatric Association (APA, 1998, 2004), the International Consensus Group on Depression and Anxiety (Ballenger et al., 2001), the British Association for Psychopharmacology (BAP) (Baldwin et al., 2005; Lingford-Hughes et al., 2004) and the National Institute of Clinical Excellence (National Institute for Clinical Excellence [NICE], 2004, 2005a, 2005b). These guidelines have been used here to indicate the best pharmacological treatment options for patients with co-morbid anxiety and SUDs.

Panic disorder. In general, all SSRIs are recommended as first-line pharmacological treatment for panic disorder (APA, 1998; Baldwin et al., 2005; Campbell-Sills & Stein, 2006; NICE, 2004). The initial dose should be relatively low, in order to avoid activation (e.g., fluoxetine 10 mg/day or less; paroxetine 10 mg/day or less; sertraline 25 mg/day or less) (Campbell-Sills & Stein, 2006). In general, therapeutic doses are in the range of fluoxetine 20 mg/day, paroxetine 40 mg/day, sertraline 50 mg/day, and citalopram 20–30 mg/day, although some patients will respond to lower doses (Campbell-Sills & Stein, 2006). Side-effects can be minimized by increasing the dose slowly. Patients should be closely monitored and supported during the first six weeks of treatment, and treatment should continue for up to 12 weeks to assess effectiveness. For those who respond at 12 weeks, SSRI treatment should continue for 6–12 months. If there is no improvement, or an SSRI is not tolerated or suitable, a TCA (imipramine, clomipramine), or an SNRI (venlafaxine: 75–225 mg/day) can also be considered for acute treatment. In fact, venlafaxine recently received FDA approval for this indication. Some benzodiazepines have proven efficacy

in acute treatment (i.e., alprazolam, clonazepam, diazepam, lorazepam), but should not be used in the long-term. Information on treatment goals and efficacy are outlined in the APA Practice Guidelines for the Treatment of Patients with Panic Disorder (APA, 1998), the BAP Evidence-based Guidelines (Baldwin et al., 2005), and the NICE guidelines (NICE, 2004).

Generalized anxiety disorder (GAD). Some SSRIs (escitalopram, paroxetine, and sertraline), the SNRI venlafaxine, the TCA imipramine, some benzodiazepines (i.e., alprazolam and diazepam) and buspirone, are all of proven efficacy in acute treatment of GAD. SSRIs should be considered for first-line pharmacological treatment. As for panic disorder, treatment should continue for 12 weeks to assess effectiveness, and for another 6 months in patients who are responding at 12 weeks. If there is no improvement at 12 weeks, the prescriber might consider switching to venlafaxine or imipramine (Baldwin et al., 2005). Benzodiazepines may be considered if there is no response to SSRI and SNRI treatment.

Social anxiety disorder (social phobia). A number of pharmacological treatment approaches are of proven efficacy in the treatment of social anxiety disorder including most SSRIs (i.e., escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, phenelzine and moclobemide (Baldwin et al., 2005). Some benzodiazepines (i.e., bromazepam and clonazepam) and anti-convulsants are also effective. Buspirone has been shown to have an effect in co-morbid social anxiety disorder and SUDs. An SSRI should perhaps be considered as first-line pharmacological treatment and should be continued for 12 weeks to assess efficacy. Drug treatment should be continued for another 6 months in patients who are responding at 12 weeks. If initial treatment with an SSRI fails, the prescriber might consider switching to venlafaxine. If there is partial response to an SSRI, the prescriber can consider adding buspirone. Benzodiazepines such as clonazepam should only be considered for patients who have not responded to other treatments.

Obsessive-compulsive disorder (OCD). There is high-level evidence for efficacy of the TCA clomipramine and the SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) in acute pharmacological treatment of OCD (Baldwin et al., 2005; NICE, 2005b). Higher doses of SSRIs have been associated with greater efficacy in some trials (see Baldwin et al., 2005, for references). Treatment periods of at least 12 weeks are necessary to assess efficacy, and drug treatment should be continued for 12 months in patients who are responding at 12 weeks.

Post-traumatic stress disorder (PTSD). Evidence from several RCTs indicates that some SSRIs (i.e., fluoxetine, paroxetine, sertraline) should be first-line pharmacological treatment for individuals with PTSD. RCTs have also shown efficacy for some TCAs (amitriptyline, imipramine), phenelzine, venlafaxine, mirtazapine (a pre-synaptic alpha-2 antagonist), and lamotrigine (an anti-convulsant) (APA, 2004; Baldwin et al., 2005). Initial treatment should be continued to up to 12 weeks to assess efficacy, and this should be continued for another 12 months in patients who are responding. If initial treatments fail, the prescriber might consider switching to another evidence-based treatment, or combining evidence-based treatments provided there are no contraindications.

Augmentation of anti-depressants with an anti-psychotic treatment may be necessary.

Clinical Vignette

Mary was a 46 year-old full-time mother with three children. She had developed symptoms of OCD at the age of 8 years but this problem was unrecognized and untreated until she presented with to her family doctor with alcohol dependence at the age of 35 years. In her teens she started using alcohol in the context of her OCD symptoms, as a form of affect-avoidance, and began to drink heavily. Mary married at the age of 25 years and had her children over the next 4 years. She began to drink more heavily when she was a full-time mother, and was clearly alcohol dependent by the age of 35 years. She tried to become abstinent on a number of occasions, but periods of abstinence were always associated with a resurgence of her OCD symptoms. Her family doctor referred her to the local psychiatric services but she was unresponsive to the treatment on offer, so they gave up on her. A friend suggested a specialist alcohol unit and she accordingly arranged a referral. In-patient treatment at this alcohol unit, however, was not a success. Mary was twice discharged because she could not "comply with the program". She then embarked on individual treatment with an addiction psychiatrist, who facilitated a network of support including the family doctor and the local community alcohol team, and also referred her for CBT. During the 18-month period that she was on the waiting list for CBT, she continued to see her psychiatrist monthly. Medication initially included fluoxetine 60 mg daily, together with naltrexone 50 mg daily. The first three years of treatment were a roller-coaster, with frequent relapses and multiple admissions to her local general hospital following accidents sustained during heavy drinking occasions, some of them life-threatening. As she was unable to maintain abstinence, supervised disulfiram 200 mg daily was added to her regimen. This proved helpful so the naltrexone was discontinued. She was able to engage with CBT and this treatment was carried out over a 2-year period, during which time her 14-year old son was also diagnosed as having OCD and was referred for specialist treatment. Seven years after referral she remains on fluoxetine and disulfiram, is largely abstinent, and is beginning to engage in AA. She is still somewhat troubled with OCD symptoms, but feels in control of her life. She has been discharged from CBT.

Conclusions

Further RCTs of pharmacological treatments for anxiety and SUD co-morbidity are needed to identify which medications, the optimal doses, the optimal combination of pharmacological treatment and CBT, duration and sequence of treatment that gives the best outcomes (Cornelius et al., 2003; Litten & Allen, 1999).

The role of other factors such as gender, age, ethnicity, and pregnancy status in predicting treatment outcomes needs to be clarified (Cornelius et al., 2003). Exclusion of co-morbid patients from efficacy trials acts as a barrier to extending the current knowledge base. Effectiveness trials in "real world" settings should be carried out, using a variety of outcome measures including patient compliance, level of functioning/quality of life, treatment utilization, and patient expectations (Cornelius et al., 2003). Longer term treatment studies are also needed to test the efficacy of various drug combinations.

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Part IV
Integration and Conclusions

Chapter 13
Anxiety Disorder and Substance Use Disorder Co-Morbidity: Common Themes and Future Directions

Sherry H. Stewart and Patricia J. Conrod

In this concluding chapter to the volume, we first provide a theoretical integration of the material contained in the initial two sections of the book. We review models, theories, and mechanisms to account for the high co-morbidity of anxiety and substance use disorders including notions involving self-medication, substance-induced anxiety, and third variable (e.g., anxiety sensitivity) explanations. Which particular pathway is most likely to be at play in explaining co-morbidity onset appears to vary as a function of the precise anxiety disorder involved as well as the specific substance being abused. We then move on to a consideration of processes involved in the maintenance of co-morbidity, as this knowledge may prove most useful in treatment. We consider recent evidence as to whether the presence of a co-morbid anxiety disorder impacts recovery from a substance use disorder. Regardless of the specific pathway to the onset of co-morbidity, once both disorders are present, they may serve to maintain one another or even exacerbate one another to create a vicious cycle such that the presence of one disorder can impede recovery from the other. In this chapter, we present an adaptation of Marlatt and Gordon's (1985) cognitive behavioral model to understand the factors and processes involved in the maintenance of anxiety disorder – substance use disorder co-morbidity. We conclude with a review of promising new approaches to the treatment and prevention of co-morbid anxiety and substance use disorders. We contrast sequential, parallel, and integrated approaches and present a theoretical argument for the superiority of integrated interventions, setting an agenda for future clinical trials in this area. Finally, various practical issues around the provision of treatment for co-morbid anxiety disorder – substance use disorder patients are considered.

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S. H. Stewart, P. J. Conrod (eds), *Anxiety and Substance Use Disorders.*

Causal Pathways

As noted in chapter 1, there are a variety of models, theories, and mechanisms that might explain the high degree of co-morbidity of anxiety disorders and substance use disorders observed in clinical and community samples alike. Three potential models of the onset of co-morbid anxiety and substance use disorder are illustrated in Fig. 13.1. The first two of these (top two panels in Fig. 13.1) posit a direct causal relation between the two disorders. For example, the model indicated in the top panel of Fig. 13.1 posits that anxiety disorder promotes the development of a substance use disorder. Theories that have been proposed to support this model include the self-medication (Khantzian, 1985), tension reduction (Greeley & Oei, 1999), and stress-response-dampening (Sher & Levenson, 1982) theories which hold in common the idea that anxiety disordered patients learn to use substances for the reinforcing effects that result from substance use (see review in Morris, Stewart, & Ham, 2005). A variety of mechanisms could be operative to explain this potential causal pathway (see chapte 2 and 3 for reviews of possible neurobiological, neuroendocrine, and psychophysiological mechanisms). For example, some drugs have negatively reinforcing anxiolytic, stress-response dampening, or depressant properties (e.g., alcohol) which could be particularly rewarding to an individual suffering from an anxiety disorder. Drugs might also exert their reinforcing effects via cognitive means (e.g., alcohol's dampening of the tendency to catastrophize the meaning of arousal-related bodily sensations among panic-prone individuals; see MacDonald, Baker, Stewart, & Skinner, 2000). A less obvious example of self-medication is through a process of enhancement of a sense of well-being induced by some drugs like cocaine and ecstasy, which may also be reinforcing for those with anxiety-related disorders.

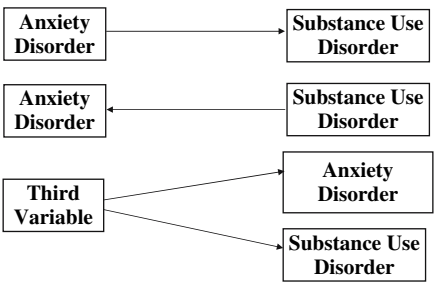

Fig. 13.1 *Illustration of three possible models of the onset of anxiety – substance use disorder co-morbidity*. The top panel is consistent with a self-medication theory of co-morbidity; the middle panel is consistent with a substance-induced induction of anxiety theory; and the bottom panel is consistent with a common third variable explanation (e.g., common personality or genetic predisposition causes both anxiety and substance use disorder, while there is no causal relation between anxiety and substance use disorder, *per se*)

A second potential model indicated in the middle panel of Fig. 13.1 posits that substance use disorder promotes the development of an anxiety disorder. Both psychological and neurobiological theories have been developed to explain this substance-induced anxiety enhancement model (see review in Sabourin & Stewart, in press). Suggested neurobiological mechanisms have included a 'kindling' process induced via multiple substance withdrawal experiences (see Kushner, Sher, & Beitman, 1990), or substance-induced disruptions in the stress-response system (see chapter 2). Chapter 10, for example, provides a solid theoretical articulation of the ways in which a history of smoking and nicotine dependence can contribute to the development of panic-related psychopathology – a theory which is consistent with this second model in Fig. 13.1 (see also Zvolensky, Schmidt, & Stewart, 2003). Chapter 5 provides a similarly useful review of why use of various other drugs might be panicogenic.

In terms of the support for these two direct causal models, one approach has been to examine relative order of onset of the two disorders in co-morbid cases. Although this approach alone does not establish causality, temporal order of onset consistent with the proposed direction of causality is a necessary (but not sufficient) condition for determining causation (Chilcoat & Breslau, 1998). Chapter's 13 review of the epidemiologic literature suggests that in at least 75% of cases of co-morbidity involving substance dependence, the anxiety disorder developed first. This means that substance-induced anxiety is a viable explanation for the onset of co-morbidity in only 25% of cases. Another method has been to use the methods outlined in the DSM-IV (American Psychiatric Association [APA], 1994) to distinguish between 'independent' and 'substance-induced' anxiety disorders not only by examining relative order of onset, but by examining whether the anxiety persists for at least four weeks after cessation of substance abuse and withdrawal. An epidemiologic study by Grant et al. (2004) strictly applied these criteria and showed that substance-induced anxiety was actually quite rare (see review in chapter 1). Taken together, these findings suggest that the self-medication theory (top panel of Fig. 13.1) is more consistent with the epidemiologic data on co-morbidity than the substance-induced anxiety theory (middle panel of Fig. 13.1).

However, which of the two causal hypotheses is best supported appears to vary as a function of the specific anxiety disorder in question as well as by the specific substance involved. For example, the fact that generalized anxiety disorder has been shown to be likely to resolve following substance use disorder treatment (Kushner et al., 2005) suggests that this particular anxiety disorder is likely to be substance-induced (middle panel of Figure 13.1) among co-morbid cases. In contrast, Kushner et al. (2005) have shown that co-morbid social phobia and post-traumatic stress disorder are unlikely to resolve with substance use disorder treatment, a pattern that is inconsistent with a substance-induced anxiety pathway to co-morbidity. Another approach has been to examine individuals' own perceptions of whether they are self-medicating their anxiety; this tendency has been shown to vary across anxiety disorders. For example, a

recent study by Bolton, Cox, Clara, and Sareen (2006) used data from the National Co-morbidity Survey (NCS) to examine self-reports of self-medication with alcohol/drugs among those with an anxiety disorder in a representative American sample. Consistent with theoretical speculation that self-medication is unlikely for certain anxiety disorders where substance use is not a socially acceptable coping response (e.g., Kushner, Abrams, & Borchardt, 2000), the lowest rates of self-medication were observed in those with the public speaking fear subtype of social phobia (i.e., where only 7.9% reported self-medicating). But, interestingly, the highest rates of self-medication were observed among those with generalized anxiety disorder (GAD) where a full 35.6% endorsed self-medicating with alcohol/drugs. Given the inconsistencies across methodological approaches regarding the direction of causality in GAD – substance abuse co-morbidity (e.g., Kushner et al., 2005 vs. Bolton et al., 2006), the nature of the relationship between GAD and substance abuse is clearly a topic deserving of further research attention. This dearth of knowledge is also evidenced by the absence of a specific chapter devoted to this topic in the current volume.

In terms of variable support of the self-medication vs. substance-induced anxiety models across specific drugs, the review in chapter 5 points out that studies examining order of onset of panic attacks and substance use have generally shown that, with the exception of alcohol use, the substance use generally precedes the development of panic attacks. This is inconsistent with a self-medication model of the development of co-morbidity. Unfortunately, most epidemiologic surveys comparing alcohol use disorders to 'other drug use disorders' as a group fail to provide more precise information about the types of drugs that are most likely fit to the self-medication pathway to co-morbidity development. We recommend that in the future, statistics be provided separately by drug class as was done in the Epidemiologic Catchment Area (ECA) survey (Regier et al., 1990) to allow for evaluation of important hypotheses such as that drugs with depressant or tranquillizing effects are most likely to fit the self-medication pathway to co-morbidity, while drugs with stimulant effects are most likely to fit the substance-induced anxiety pathway to co-morbidity.

A third possible model of the high co-morbidity of anxiety and substance use disorders is the 'third variable' model, illustrated in the bottom panel of Fig. 13.1. This model posits that a common underlying vulnerability (the third variable) contributes to the development of both disorders, while there is no direct causal relation between the two disorders themselves. Possible candidates for such third variables include a common personality predisposition (e.g., anxiety sensitivity; see reviews by Stewart & Kushner, 2001; Stewart, Samoluk, & MacDonald, 1999) or a common genetic basis to the two disorders. For example, family and twin studies have provided some evidence of possible common genetic contributions to the correlation between anxiety symptoms and alcohol consumption (e.g., Tambs, Harris, & Magnus, 1997). It should be noted that the genetic and personality vulnerability theories are not mutually exclusive in that a genetic predisposition could result in a specific personality vulnerability profile (e.g., demonstrated genetic contribution to anxiety

sensitivity; Stein, Jang, & Livesley, 1999), which in turn could predispose to the development of both anxiety and substance use disorders. Further research is needed on various third variable candidates before firm conclusions can be reached regarding the relative utility of the model at the bottom of Fig. 13.1 compared to the direct causal models presented in the upper portions of Fig. 13.1. If common third variables can be identified, this has important prevention implications as programs targeting the common risk factor (see chapter 11) can have a 'double impact' in preventing both anxiety and substance use disorders.

Maintenance

The factors involved in the maintenance of anxiety – substance use disorder co-morbidity need not be the same as those involved in co-morbidity onset. In fact, as suggested in the review above, there are likely multiple pathways to the development of a co-morbid anxiety disorder. But once the two disorders are present in a given individual, each may serve to maintain or even exacerbate the other. This 'vicious cycle' involved in the maintenance of anxiety disorder – substance use disorder co-morbidity is illustrated in Fig. 13.2. The figure makes clear how both the self-medication and substance-induced intensification of anxiety processes described earlier contribute to the maintenance of co-morbidity. For example, in chapter 5, Norton applies this mutual maintenance model to the understanding of panic disorder – alcohol dependence co-morbidity. In a patient with this form of co-morbidity, regardless of whether the panic attacks or alcohol abuse began first, once the two problems are established, the co-morbid patient may continue to use alcohol to manage his panic symptoms in the short term, with frequent experiences of alcohol withdrawal actually exacerbating panic symptoms in the longer term to ultimately create a vicious cycle between the symptoms of the two disorders.

The mutual maintenance model makes certain predictions. Most importantly for treatment, this model predicts that if one were to attempt to treat one of the two disorders without simultaneously treating the co-morbid problem, the individual would be at high risk of relapse to the treated disorder. For instance, in the case example above of the patient with co-morbid panic disorder and alcohol dependence, if we treated the patient's alcoholism without attending simultaneously to the panic disorder, the patient would be at high risk of relapsing to alcohol misuse, particularly during the withdrawal phase, since he would have no other means of coping with his untreated panic anxiety and his fear of interoceptive cues. We now turn our attention to data which has examined this prediction of the mutual maintenance model.

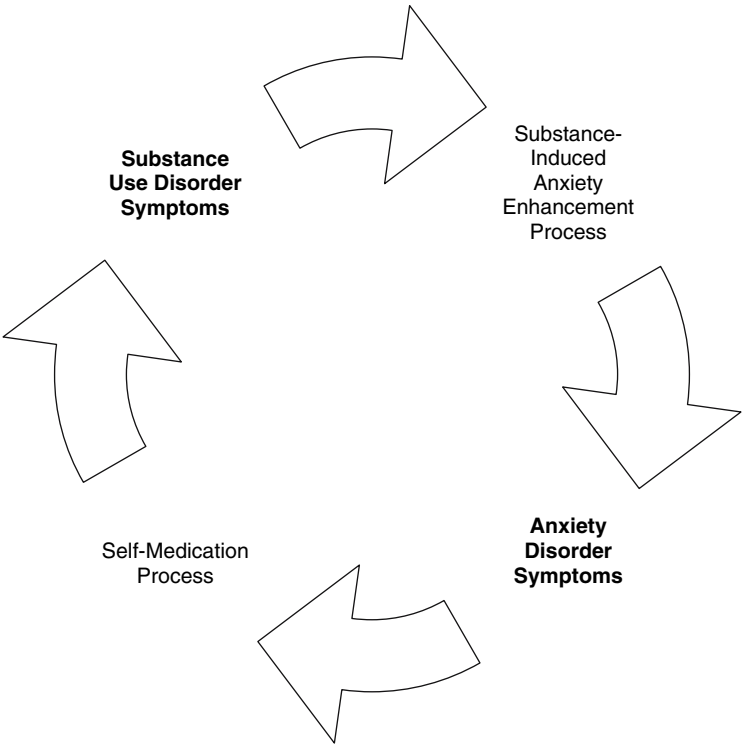

Fig. 13.2 *Illustration of the vicious cycle at play between anxiety disorder and substance use disorder symptoms in co-morbid individuals*. Note: This model is also referred to as the 'mutual maintenance' model

Impact of Co-morbid Anxiety on Recovery from a Substance Use Disorder

When individuals who suffer from co-morbid anxiety – substance use disorders enter treatment for either disorder alone, their treatment outcome is often affected negatively by the presence of the co-morbid disorder. For example, alcohol use disorders have been found to predict poorer anxiety disorder treatment outcomes for patients with panic disorder/agoraphobia, generalized anxiety disorder, social phobia (Bruce et al., 2005), and PTSD (Forbes, Creamer, Hawthorne, Allen, & McHugh, 2003).

Co-morbid anxiety disorders have also been shown to increase the likelihood of relapse to substance misuse in treated or abstinent substance abusers (e.g. Driessen et al. 2001; Kushner et al., 2005; Willinger et al., 2002) as would be predicted by the mutual maintenance model. But not all studies have shown this relationship, however. For example, Marquenie et al. (2006) compared relapse rates for alcoholics with co-morbid panic disorder/agoraphobia or

social phobia to relapse rates for alcoholics with no co-morbid anxiety disorder, following standard alcoholism treatment. Inconsistent with predictions of the mutual maintenance model, the co-morbid anxiety disorders did not have a significant impact on either relapse rates or number of days to relapse. Nonetheless, Sabourin and Stewart (in press) have pointed out some methodological problems that may account for this long-term retrospective study's failure to support higher substance abuse relapse among treated alcoholics with co-morbid anxiety disorders.

In contrast to the results of Marquenie et al. (2006), several studies have reported higher substance use relapse rates in co-morbid anxiety disorder patients. For example, a study that examined the effects of trait anxiety on alcohol abuse relapse in among treated alcoholic patients showed that higher trait anxiety levels significantly predicted relapse to uncontrolled drinking (Willinger et al., 2002). Similarly, Driessen et al. (2001) showed that treated alcoholic patients with co-morbid anxiety had about 30% higher alcoholism relapse rates than did treated alcoholics without co-morbid anxiety. Most recently, Kushner et al. (2005) found that alcoholic patients with a co-morbid anxiety disorder (especially those with co-morbid panic disorder or social phobia) were significantly more likely to relapse to problem drinking than alcoholic patients with no co-morbid anxiety disorder. These findings are particularly convincing given the methodological soundness of the study (e.g., use of multiple criteria for drinking relapse; see review in Sabourin & Stewart, in press). Thus, it appears fairly safe to conclude that the presence of a co-morbid disorder impacts treatment outcome and relapse rates for the treated disorder, in a pattern consistent with mutual maintenance model predictions. This pattern strongly suggests that both disorders need to be addressed simultaneously to improve treatment outcome for co-morbid anxiety – substance use disorder patients.

Review of Promising New Approaches to Co-morbid Anxiety and Substance Use Disorder Treatment

Those who suffer from anxiety disorder – substance use disorder co-morbidity present a challenging population with respect to treatment. As we reviewed above, this population often suffers worse anxiety and substance use disorder treatment outcomes and appears at increased risk for relapse to substance misuse relative to those suffering from only one of these two disorders. Although the study of specific treatments for anxiety – substance use disorder co-morbidity is still in its infancy, this area is growing rapidly. There are now several promising approaches to treating co-morbid anxiety and substance use disorder as illustrated through each of the chapters in the treatment portion of this book. In this section, we briefly review the state of knowledge regarding effective treatments for anxiety – substance use

disorder co-morbidity in an attempt to integrate the material presented in the third section of this book.

The self-medication theory proposes that treatment of the 'underlying' anxiety disorder should have effects not only on the anxiety disorder, but also on symptoms of the substance use disorder. There have been mixed findings regarding the effects of pharmacological treatment for anxiety on substance use outcomes. Some studies have demonstrated improvements in substance use outcomes while other studies have found more mixed results (for more information, see review by Kushner et al., 2000). For example, Randall, Johnson, et al. (2001) attempted treatment of individuals with co-morbid social phobia and alcohol use disorder via paroxetine (a selective serotonin reuptake inhibitor [SSRI] that is established in the treatment of social phobia; see review by Marshall, this volume). As noted in the social phobia – SUD co-morbidity treatment chapter in the present book (see chapter 8), Randall, Johnson, et al. (2001) found that treating these co-morbid individuals with paroxetine did lead to improvements in anxiety and in the Clinical Global Index for alcohol, consistent with predictions of the self-medication theory. However, contrary to predictions of the self-medication theory, treatment with paroxetine did not result in significant decreases in drinking quantity and frequency. Two other similarly-designed studies by Kranzler et al. (1994) and Tollefson, Montague-Clouse, and Tollefson (1992) demonstrated that, consistent with self-medication theory predictions, successful treatment of anxiety with buspirone also led to a reduction in alcohol use. These findings are partially consistent with predictions of the self-medication hypothesis. Nonetheless, the paroxetine study (Randall, Johnson, et al., 2001) appears to suggest that there is more to the maintenance of problematic drinking behavior in socially phobic individuals than just the self-medication process.

More consistent with a mutual maintenance model, recent studies have examined the idea that treating both disorders may be the best approach to intervention in anxiety disorder – SUD co-morbid individuals. One way of classifying the various combined approaches is whether they are sequential (treating one problem and then the other), parallel (both treatments provided simultaneously but not necessarily in an integrated fashion), or integrated (Sabourin & Stewart, in press). Integrated treatments recognize the complex relationship between anxiety disorders and substance use disorders in co-morbid individuals (Zahradnik & Stewart, in press). The aim of integrated treatments is to create a hybrid of the treatments that are already known to work best for each disorder individually. Furthermore, truly integrated approaches explicitly include in the treatment strategy, an understanding of the reciprocal influences each disorder has on the other (Zahradnik & Stewart, in press). While sequential treatments continue to be the norm in clinical practice (e.g., the common practice of having an individual address their substance use disorder before they are accepted into anxiety disorder treatment), research has begun to address the utility of parallel and integrated approaches. Most studies to date

have focused on parallel approaches. The findings for parallel approaches thus far appear quite mixed with results varying from significant positive effects, to no group differences, to significant negative effects of combined treatments relative to control treatments.

For example, Randall, Thomas, and Thevos (2001) examined whether conducting two parallel cognitive behavioral therapy (CBT) treatments aimed at decreasing social phobia symptoms and at addressing problematic alcohol use would have additional benefits for social phobia – alcohol use disorder co-morbid individuals compared to co-morbid individuals treated for the alcohol use disorder alone. For the parallel treatment, the sessions consisted of CBT treatment for alcohol followed immediately by CBT for social phobia (i.e., the two treatments were offered simultaneously by the same therapist, but independently of each other). In direct contrast to predictions of the mutual maintenance model, Randall, Thomas, et al. (2001) found that patients who participated in the parallel treatment had *worse* drinking outcomes, as assessed by drinking quantity and frequency measures, than did those who participated in the alcohol only treatment. There are several possible explanations for these unexpected findings. Clients in the parallel treatment group may have participated in more social activities following their social phobia treatment, resulting in more opportunities to drink. Additional research needs to be conducted that would include other types of outcome measures that are not specifically linked to frequency or quantity of drinking. As suggested by Stewart, Morris, Mellings, and Komar (2006), coping drinking motives and problematic consequences of drinking are useful therapy targets for co-morbid social phobic – alcohol abuse patients. It is also possible that the lack of integration of the two treatments or the excessive demands of combining two already intensive treatments may have affected results in the Randall, Thomas, et al. (2001) study. The parallel treatment did in fact lead to somewhat higher drop out rates than the alcohol treatment alone, suggesting that the parallel treatment may have been too demanding for co-morbid patients to handle (Conrod & Stewart, 2005).

A similarly-designed study by Bowen, D'Arcy, Keegan, and Senthilselvan (2000) found *no* group differences in alcohol outcomes among panic disorder – alcohol use disorder co-morbid patients when patients were offered parallel CBT for panic disorder and standard alcohol treatment vs. alcohol treatment alone. Interestingly, though, both treatments resulted in significant reductions in anxiety. There are at least two possible interpretations of these findings. One explanation is consistent with the alcohol-induced anxiety theory of co-morbidity. Specifically, some might argue that additional panic-focused treatment is not necessary since anxiety will resolve once drinking levels are reduced. Another explanation, suggested by the authors, is that the relaxation training and stress management components of the standard alcohol treatment might have limited the ability to distinguish between treatments as these components may have been useful in targeting the co-morbid anxiety even in the alcohol alone treatment (i.e., control) condition. If so, then this study begs the question of what specific anxiety-management strategies are necessary and

sufficient for co-morbid anxiety disorder – SUD clients in combined treatment approaches.

A recent randomized, controlled trial conducted by Schade et al. (2005) compared standard alcohol treatment alone to standard alcohol treatment with anxiety treatment consisting of CBT plus optional fluvoxamine (an SSRI; see review in chapter 12) treatment (again, a parallel approach) in patients with a primary diagnosis of alcohol dependence and a co-morbid diagnosis of panic disorder, agoraphobia, or social phobia. There were no differences in alcohol outcome measures between the two groups of patients. The additional anxiety treatment did, on the other hand, improve anxiety symptoms. It can be speculated that improved anxiety scores are significant for this population, as decreased anxiety may serve as a protective factor for decreased risk for alcoholism relapse. The study examined outcome results 32 weeks after initial assessment, but did not look at longer-term outcomes in these patients. Future studies should examine longer-term treatment outcomes in co-morbid anxiety and substance use disorder patients to test the hypothesis that effective treatment of the co-morbid anxiety disorder serves a protective function in terms of risk for relapse to the substance use disorder in the longer-term.

Integrated Treatment Approaches. As briefly mentioned above, integrated treatment models recognize the complex relationship between anxiety disorders and alcohol use disorders and their possible mutual maintenance (Zahradnik & Stewart, in press). Furthermore, their aim is to create a hybrid of the treatments that work best for each disorder separately, and to also include in the treatment strategy an understanding of the reciprocal influences each disorder has on the other (Zahradnik & Stewart, in press). A sample integrated treatment was developed and tested for co-morbid panic disorder and alcohol use disorder by Kushner et al. (2006) (see also review in chapter 9). The treatment integrated CBT for panic disorder with content focusing on the interaction between alcohol use and panic symptoms. The integrated treatment was provided on top of treatment as usual (TAU) for the alcohol use disorder and compared to a group who received only the TAU. The trial showed promising results. The group receiving the integrated treatment showed better anxiety and alcohol outcomes than the TAU alcohol only treatment group. Furthermore, chapter 11 describes how personality-targeted treatments are promising as an early intervention model. Such interventions possess features of integrated treatments because they are designed and have been shown to indirectly impact both anxiety and substance-related symptoms by directly targeting a third variable, the underlying personality vulnerability.

It is hoped that integrated treatments will provide a more effective strategy in treating co-morbid anxiety disorder – substance use disorder patients. Integrated treatments appear to be the most recommended by 'expert opinion' and have been shown to be effective in the treatment of other patterns of co-morbidity (see review by Conrod & Stewart, 2005). However there have been relatively few randomized controlled trials, or even quasi-experimental designs,

testing the efficacy of truly integrated treatments in the anxiety – substance use disorder co-morbidity field (Watkins, Hunter, Burnam, Pincus, & Nicholson, 2005). This may be because there are some conceptual difficulties in fully integrating certain key aspects of each set of treatments (Conrod & Stewart, 2005). For example, one conceptual problem when integrating exposure-based treatment models for anxiety disorders with relapse prevention treatment for substance use disorder is that messages around exposure to high risk situations may be contradictory. This may not be a problem when CBT treatments for depression or bipolar disorders are integrated with relapse prevention models, due to greater theoretical overlap between CBT models for mood disorders and substance use disorders. Furthermore, even if a treatment could get around such conceptual incongruity, co-morbid clients may actually lack necessary coping skills required to tolerate or navigate through specific treatment components, such as exposure. More research is clearly needed to refine models of anxiety – substance use disorder co-morbidity in order to develop and test newer integrated treatment strategies. To conclude this section, we provide an example of how a classic cognitive behavioral model of substance use disorders (Marlatt & Gordon, 1985) could be adapted for treatment of substance use disorder clients with a co-morbid anxiety disorder, to facilitate further theoretical and empirical work in this area.

Adaptation of Marlatt and Gordon's (1985) Cognitive Behavioral Model to Understanding Co-Morbidity

Over two decades ago, Marlatt and Gordon (1985) developed a cognitive behavioral model to help explain the relapse process in substance abusers. This model has proven extremely useful in the prevention of relapse among treated substance abusers (see also Marlatt & Donovan, 2005). We present an adaptation of this model (Fig. 13.3) to highlight the how the presence of a co-morbid anxiety disorder can impact on each of the components of the relapse pathway in the original model.

The presence of a co-morbid anxiety disorder can impact the types of situations that are high risk situations for relapse. For those with co-morbid anxiety disorders, these are situations that are perceived as threatening in some way, although the precise situational triggers to heavy drinking/drug misuse may vary across the specific anxiety disorders. A patient with co-morbid panic disorder/agoraphobia is theoretically at high risk for relapse to heavy drinking/drug misuse in situations where he or she experiences feared bodily arousal sensations and situations where escape might be difficult or embarrassing if he or she were to have a panic attack. In contrast, a patient with social phobia is theoretically at high risk for relapse to substance misuse in social interaction or performance situations.

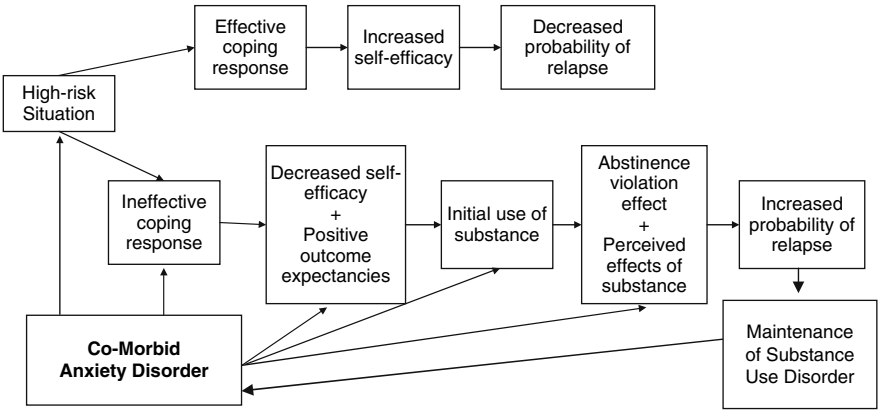

Fig. 13.3 Adaptation of Marlatt and Gordon's (1985) cognitive behavioral model of substance use disorder for explaining maintenance of anxiety disorder – substance use disorder co-morbidity [Adapted with permission from Marlatt, G.A., & Gordon, J.R. (1985). *Relapse prevention: Maintenance Strategies in the Treatment of Addictive Behaviors*. New York, Guilford Press (p.38)]. Reprinted with Permission of the Guilford Press

Those with co-morbid anxiety disorders are theoretically more likely than substance abusers without co-morbid anxiety disorders to choose ineffective coping responses to deal with the high risk (i.e., threatening) situations for relapse. This is particularly the case given the established tendency of anxious individuals to use avoidant coping strategies (Barlow, 2002). Substance misuse may simply be part of a more general pattern of avoidance of feared internal or external situations, among those substance abusers with co-morbid anxiety.

Co-morbid anxiety disorders can also impact the next step in the CBT model of relapse. Specifically, co-morbid anxiety can impact both self-efficacy (see review in chapter 4, this volume for the case of social phobia) and the particular positive outcome expectancies the substance abuser holds about the likely consequences of ingesting a given substance in this high risk situation. Across a variety of co-morbid anxiety disorders, general tension reduction expectancies may be particularly important predictors of substance use. But specific positive outcome expectancies may hold in the case of particular co-morbid anxiety disorders (e.g., social facilitation expectancies may be particularly important predictors of substance use for those with social phobia; see review in chapter 4). Recent data suggest that positive socially-related alcohol expectancies and low self-efficacy to avoid heavy drinking interact in predicting increased problematic drinking among socially anxious individuals (Burke & Stephens, 1997; Gilles, Turk, & Fresco, 2006).

Together their sensitivities to high risk situations involving threat, their tendency to engage in avoidant coping, their tendency to hold certain problematic positive outcome expectancies (e.g., tension-reduction expectancies), and their low self-efficacy to refrain from problematic substance use in high risk situations, make substance abusers with co-morbid anxiety much more likely

than other substance abusers to engage in an initial lapse to substance misuse when in a situation they find threatening. At this point, the individual crosses over the border from abstinence (or controlled use) to lapse (uncontrolled use episode) (Marlatt & Gordon, 1985). According to the original model, whether or not this initial lapse is followed by a total relapse depends largely on the patient's perceptions of the cause of the lapse and the patient's reactions to its occurrence. And again, it can be argued that substance use disorder patients with co-morbid anxiety are a highly vulnerable population for having an initial lapse turn into a full-blown relapse to their substance use disorder. This is because anxiety disorder patients have a cognitive tendency to catastrophize (Barlow, 2002) and they might thus be hypothesized to be likely to perceive the lapse as indicating a personal loss of control and a failure experience and thus to suffer guilt about the lapse incident. They are also theoretically more likely to notice and appreciate the desired negative reinforcing effects of the substance (at least with substances like alcohol or depressant/anxiolytic drugs). These factors would place a recovering substance abuser with a co-morbid anxiety disorder at heightened risk for continuing down the road toward relapse to a full-blown substance use disorder. Finally, we have added other components to the model (see Fig. 13.3), which accommodate the literature supporting the mutual-maintenance hypothesis, whereby anxiety symptoms can be further exacerbated by the substance use (see chapter 5).

The various predictions of this model could be tested in future research. If this adapted model is well supported though research, it can help explain why those substance abusers with co-morbid anxiety disorder seem to be at such elevated risk for relapse to substance abuse following treatment of their substance use disorder. This model would also have treatment implications in terms of providing several highly specific targets for therapy for co-morbid individuals in order to prevent substance abuse relapse. These targets would include not only each of the components in Marlatt and Gordon's (1985) original model, but also the co-morbid anxiety disorder which is seen to be driving the susceptibility to relapse at each level of the model.

Practical Issues in Treatment

There are several practical issues that need to be considered in the development and delivery of treatment approaches for co-morbid anxiety and substance use disorders. First and foremost are the challenges to integrated treatments presented by the continued tendency to separate addiction from mental health services in most health care delivery programs worldwide. This practice presents obstacles to the delivery of integrated treatments for co-morbid clients because practitioners in either service are typically not trained to assess and/or treat the other problem (i.e., addictions counselors rarely trained to identify and treat co-morbid anxiety disorders; mental health practitioners not usually trained to treat substance use

disorders). Parallel and sequential approaches require only that practitioners in each service be able to appropriately assess for the presence of a co-morbid substance use or anxiety disorder and then refer the co-morbid client to an expert for the treatment of the co-morbid disorder; in contrast, integrated approaches require that the practitioner also be appropriately trained in treatment of both disorders. It should be noted that it is theoretically possible that parallel approaches to treatment could accomplish many of the same goals as integrated treatments (e.g., simultaneously addressing the two inter-connected problems; decreasing the likelihood that the presence of the co-morbid disorder at the end of treatment of the 'index' disorder would serve as a risk factor for relapse of the 'index' disorder) provided that there is good communication between the two service providers (i.e., the 'case management' approach).

Nonetheless, even with excellent communication between service providers and outstanding coordination of services, there are still, theoretically, some limitations of the parallel approach relative to the integrated approach. For example, as we have noted elsewhere (Conrod & Stewart, 2005), parallel treatment requires the simultaneous provision of two empirically validated treatments and can be quite demanding of patients with complex problems, relative to a single integrated treatment. This factor may contribute to the high drop out rates observed in parallel approaches to treatment. As another example, relative to an integrated treatment delivered by a single well-trained therapist, parallel treatments create an artificial separation of the two disorders and fail to explicitly recognize and contend with the functional relations between the two disorders. This can be confusing to patients who perceive the symptoms of their anxiety disorder and substance use disorder to be functionally inter-related (e.g., Brown, Stout, & Gannon-Rowley, 1998; see also review by Stewart, 1996). Moreover, directly addressing the functional inter-relations between the two co-morbid disorders is a key ingredient in the treatment of co-morbid disorders from a theoretical perspective (Zahradnik & Stewart, in press). Finally, from an economic point-of-view, integrated treatments can be accomplished more efficiently than parallel treatments. Theoretically, then, integrated treatments should prove superior to parallel treatments which should prove superior to sequential treatments in terms of treatment outcome indices for both disorders and in terms of reducing risk for relapse of either disorder in the longer term. This hypothesis still requires empirical validation, however.

Another practical issue in treatment of co-morbidity concerns the increasing specialization required for the provision of empirically validated treatments for co-morbid patients. In general, the integrated treatments that are being developed and tested target very specific subtypes of co-morbidity (e.g., Kushner et al. [2006] integrated treatment for co-morbid panic disorder and alcoholism; Otto's et al. [1993] integrated treatment for benzodiazepine dependence in panic disorder's patients; Brady, Dansky, Back, Foa, and Carroll's [2001] integrated treatment of co-morbid PTSD and cocaine dependence). Although the establishment of clinics specializing in the integrated treatment of such very specific forms of co-morbidity are realistic in larger centers with an adequate population base,

such specialized services are not realistic in smaller centers where a smaller number of service providers must be prepared to deal with multiple forms of anxiety and substance use disorder co-morbidity. As more and more highly specific integrated programs are developed and validated, it becomes increasingly unrealistic to expect that service providers will be able to develop sufficient expertise in each new protocol to allow for efficient and effective service delivery (for an excellent discussion of this issue, see Kushner et al., 2006).

The personality-based approach described in chapter 11 provides a possible solution to this dilemma in that only two protocols would have to be mastered by clinicians (i.e., the anxiety sensitivity intervention which is relevant to many anxiety-related disorders and the introversion-hopelessness intervention which is relevant to certain anxiety disorders such as social phobia) in order to effectively treat the common factors contributing to various forms of co-morbid anxiety and substance use disorder. Nonetheless, as outlined in chapter 11, although this approach has been repeatedly been shown to reduce harmful substance use in both adults and adolescents (e.g. Conrod, Stewart, Comeau, & Maclean, 2006; Conrod et al., 2000; Watt, Stewart, Birch, & Bernier, 2006), more work is needed on establishing the efficacy of this approach in treating symptoms of the co-morbid anxiety disorder. An exception is a recent study by Castellanos and Conrod (2006) where it was shown that the anxiety sensitivity intervention was also effective in reducing panic attacks in youth.

There is also a movement afoot in the anxiety disorders field toward the development of more global 'broad-band' types of interventions that are effective in the treatment of anxiety disorders in general rather than focusing narrowly on protocols designed to treat only one anxiety disorder in particular (see Barlow, Allen, & Choate, 2004). For example, Westra and her colleagues have developed, manualized, and evaluated such a broad-band approach for the treatment of panic disorder with or without agoraphobia, social phobia, and generalized anxiety disorder patients. This treatment approach is 10 sessions in duration, is delivered in a group context, and includes psychoeducation, cognitive restructuring, and exposure components (see Westra, Dozois, & Marcus, 2007; Westra, Stewart, & Conrad, 2002, for program description and efficacy data). For practical reasons, it would be useful for future research to focus on the development and evaluation of a 'broad-band' integrated intervention designed to treat a variety of forms of anxiety disorder – substance use disorder co-morbidity. For example, the anxiety management protocol developed by Westra et al. (2002, 2007) could be adapted for suitability to the co-morbidity context in the same manner that Kushner et al. (2006) adapted Barlow and Craske's (2000) 'narrow-band' CBT for panic disorder for suitability as an integrated treatment for panic disorder – alcohol abuse co-morbidity. In fact, in their attempt to develop and test an integrated CBT for panic and alcohol dependence, Kushner et al. (2006) identified that an additional obstacle to implementing such a program was the presence of multiple co-occurring anxiety disorders within this co-morbid population. They, too, suggested that perhaps a broad-band integrated approach may be more suitable

for the treatment of co-morbid anxiety and substance use disorders. Future research would be needed to determine how much is sacrificed in terms of efficacy when moving to a more broad-band approach to co-morbidity treatment relative to the narrower protocols being investigated to date. And this would need to be weighed against the increased reach and efficiency of services that could be achieved with the broad-band approach.

A final practical issue pertains to applications of Prochaska and DiClemente's (1992) stages of change model to the treatment of anxiety disorder – substance use disorder co-morbidity. If a given co-morbid patient presenting for treatment is at an advanced stage of readiness for change for one disorder (e.g., in the action stage for the anxiety disorder) but at a very early stage of readiness for change for the (e.g., precontemplative for the substance use disorder), it would be tempting to take this as support for a sequential approach to treatment. Should therapy not simply focus first on the disorder where the patient is evidencing the greatest readiness to change? One must still consider the mutual maintenance model depicted in Fig. 13.2 and the revision of Marlatt and Gordon's (1985) model depicted in Fig. 13.3. Failure to simultaneously address the two disorders can leave the patient vulnerable to relapse of the treated disorder. But from a practical perspective, a therapist can engage the client in initially beginning to address the disorder where readiness to change is greatest, while providing psycho-education around the functional relations between the two disorders. Use of a motivational interviewing approach (Miller & Rollnick, 1991) can be helpful to work toward enhancing readiness to simultaneously address the co-morbid disorder through a more integrated approach to treatment. Indeed, this type of approach has been applied effectively to the treatment of co-morbid substance use and psychotic disorders (Barrowclough et al., 2001), but awaits formal evaluation in terms of its applicability to treatment of co-morbid anxiety and substance use disorders.

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Author index

Subject Index

C

D

E

F

G

H

I

L

M

N

O

P

R

S

T

W