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Nora D. Volkow, M.D.

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David Anderson, Editor

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SCIENCE AND PRACTICE IN ACTION

Transporting Clinical Research to Community Settings: Designing and Conducting a Multisite Trial of Brief Strategic Family Therapy
Michael S. Robbins, Ph.D., Elizabeth Alonso, Ph.D., Viviana E. Horigian, M.D., Ken Bachrach, Ph.D., Kathy Burlew, Ph.D., Ibis S. Carrión, Psy.D., Candace C. Hodgkins, Ph.D., Michael Miller, Ph.D., Eric Schindler, Ph.D., Nancy VanDeMark, Ph.D., Craig Henderson, Ph.D., and José Szapocznik, Ph.D.

DEPARTMENTS

This Issue’s Authors and Panel Respondents

Graphic Evidence. Adolescent Decisionmaking: Still a Mystery
Toward Individualized Treatment for Substance Abuse

Clinical observation and research discovery each can give rise to treatments that prove effective in clinical trials and, accordingly, are considered evidence-based. For example, motivational interviewing draws on, and addresses, clinicians’ recognition of patient ambivalence, and contingency management emerged from research on the effects of rewards on human behavior.

Whether they originate in the clinic or the research setting, evidence-based treatments provide clinicians with tools to treat patients more effectively while still treating each as a unique individual. Thus, motivational interviewing, by moving clients past ambivalence, clears the way to addressing other issues that are particular to the individual. Contingency management, similarly, can increase clinicians’ ability to address clients’ individual issues by motivating attendance in sessions and other desirable behaviors.

The future of substance abuse treatment is the development of an increasing array of evidence-based treatments that clinicians will use to address patients’ varied strengths, needs, and circumstances. We have already begun to see the emergence of evidence-based treatments for patients with certain co-dependencies and co-occurring disorders. Research reviewed in this issue of Addiction Science & Clinical Practice suggests that interventions might be developed for patients in specific stages of addiction, with different types and degrees of cognitive impairment, or with particular genotypes.

Far from reducing the role of clinicians and the importance of the therapeutic relationship, evidence-based treatments rely heavily on clinical skills and empathy. Increasingly, clinicians will need to be familiar with the variety of available evidence-based treatments, to identify the right one—or combination or sequence—for each patient and to administer a range of assessments and interventions with fidelity. For substance abuse clinicians, the tools, the challenges, and the potential for success increase in concert.

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse
Editor’s Note

From Insight to Intervention

Articles in this issue of *Addiction Science & Clinical Practice* address all three stages in the continuum of discovery, development, and implementation of evidence-based interventions. Two articles review basic research that is providing the foundation for new behavioral treatments and medications. One, by Dr. Thomas Gould, describes the two-stage process of addiction, knowledge of which can illuminate the experience of the disease for clinician and patient. In the other, Dr. Rachel Tyndale and Margaret Mroziewicz review pharmacogenetic findings that contribute to the understanding of why only some people who experiment with drugs develop dependence. This information may ultimately inform personalized addiction treatment.

Dr. Michael Robbins and colleagues provide an example of effectiveness research. They recount a test of whether multisystemic family therapy, which has been efficacious in research settings, can improve outcomes in community treatment programs. Their focus is on the ways that both the collaborating researchers and the program personnel amended business as usual to obtain results that were scientifically sound and widely applicable.

Once clinical trials confirm that a treatment is effective, its fate is in the hands of the community programs that implement or forgo it. A paper by Dr. Jody Sindelar and Dr. Samuel Ball and one by Dr. Steve Martino explore two of the issues that strongly influence this decision: cost and training. Drs. Sindelar and Ball outline a general approach to cost analysis—including cost categorizing, estimating, and tallying—while stressing that value, rather than cost, properly drives the implementation decision. Dr. Martino examines current evidence regarding which counselor training methods are best for inculcating new, high-quality clinical skills and sustaining them with fidelity.

Evidence-based treatments are currently the focus of intense investigation. This issue’s authors and panelists represent a diverse blend of experiences and viewpoints, and their combined expertise helps unravel the complexities of the latest research. I encourage readers who wish to respond to any article or panel to post comments or queries on the journal’s Reader Response Page: www.nida.nih.gov/ascp/feedback/.

David Anderson
Editor
National Institute on Drug Abuse

Drug abuse counselors can earn continuing education credits by reading *Addiction Science & Clinical Practice*. See inside back cover for details.

We invite you to join the discussion of the topics addressed in this issue. Visit our Reader Response Page at www.nida.nih.gov/ascp/feedback/ to make a comment or pose a question to an author.
Addiction and Cognition

Drug addiction manifests clinically as compulsive drug seeking, drug use, and cravings that can persist and recur even after extended periods of abstinence. From a psychological and neurological perspective, addiction is a disorder of altered cognition. The brain regions and processes that underlie addiction overlap extensively with those that are involved in essential cognitive functions, including learning, memory, attention, reasoning, and impulse control. Drugs alter normal brain structure and function in these regions, producing cognitive shifts that promote continued drug use through maladaptive learning and hinder the acquisition of adaptive behaviors that support abstinence.

In a 2005 review, Steven Hyman stated the current neurological conception of drug abuse concisely: Characterizing addiction as a disease of “pathological learning,” he wrote, “[A]ddiction represents a pathological usurpation of the neural mechanisms of learning and memory that under normal circumstances serve to shape survival behaviors related to the pursuit of rewards and the cues that predict them.”

This article reviews current knowledge on the cognitive effects of drugs and their neurological underpinnings. These effects may be particularly disruptive when individuals are exposed to drugs during brain development, which lasts from the prenatal period through adolescence, and in individuals with mental disorders. An understanding of these issues will help substance abuse clinicians identify and respond to cognitive changes that affect patients’ responses to treatment.
A MULTISTAGE PROCESS

Recent reviews characterize addiction as a two-stage process. In the first stage, the individual’s occasional drug taking becomes increasingly chronic and uncontrolled. The neurological source of these symptoms is drug-induced deregulation of the brain’s reward system (Felstenstein and See, 2008). Normally, increased dopamine signaling within this system—specifically, in the ventral striatum or nucleus accumbens (NAc)—produces pleasurable feelings that orient organisms to seek and perform life-sustaining conditions and activities, such as locating supportive environments, eating, and having sex. Drugs of abuse hyperactivate this system, triggering abrupt and large increases in NAc dopamine signaling, producing intense sensations that motivate additional drug taking, and promoting the formation of maladaptive drug-stimulus associations (Felstenstein and See, 2008).

Individuals in the second stage of the addictive process present additional clinical features, including withdrawal symptoms during early abstinence, persistent vulnerability to relapse, and alterations in decisionmaking and other cognitive processes. Although modification of the dopaminergic reward system remains important at this stage, it probably is not sufficient to maintain these complex and long-lasting changes. Kalivas and Volkow (2005) summarize evidence implicating drug-induced alterations in signals carried by the neurotransmitter glutamate from the brain area that is primarily associated with judgment—the prefrontal cortex—to the NAc. Le Moal and Koob (2007) emphasize changes in brain stress circuits and negative reinforcement (i.e., effects that motivate drug taking by causing discomfort during abstinence, such as the onset of withdrawal symptoms). Thus, whereas early drug use fosters maladaptive drug-stimulus associations that contribute to drug seeking and use, later stages disrupt cognitive and other processes that are important for successful abstinence.

The full extent of drugs’ impacts on cognition is not yet known, but research indicates that addicted individuals have alterations in brain regions including the striatum, prefrontal cortex, amygdala, and hippocampus (Jones and Bonci, 2005; Kalivas and Volkow, 2005; Kelley, 2004; Le Moal and Koob, 2007). These same regions underlie declarative memory—the memories that define an individual, without which it would be difficult to generate and maintain a concept of self (Cahill and McGaugh, 1998; Eichenbaum, 2000; Kelley, 2004; Setlow, 1997). Drugs’ capacity to act upon the substrates of declarative memory suggests that their impact on cognition is potentially extremely far-reaching.

COGNITIVE EFFECTS OF ACUTE DRUG ADMINISTRATION

Clinicians often observe that patients undergoing treatment for addiction become highly vulnerable to relapse when they return to contexts or environments where their addiction developed (Hyman, 2005; See, 2005). Clinical research confirms that cues associated with substance abuse elicit physiological responses and cravings for drugs (Franklin et al., 2007). Laboratory animals, too, develop powerful associations and cue-response behaviors in the presence of drug-related stimuli. For example, animals given a drug in one compartment of a double cage subsequently will gravitate to that compartment more than to the alternative compartment. This phenomenon, known as conditioned place preference, has been demonstrated in studies using nicotine, ethanol, amphetamine, methamphetamine, cocaine, morphine, cannabis, and caffeine (Bardo and Bevins, 2000).

The Formation of Drug-Stimulus Associations

The multistage model of addiction attributes addicted individuals’ strong responses to drug cues to a learning process that inculcates powerful drug-stimulus associations (e.g., Robinson and Berridge, 2000). In this view, the individual taking a drug perceives his or her present surroundings as highly significant (salient) and makes exceptionally strong mental connections between features of those surroundings and the intense pleasure of the drug. Subsequently, when he or she re-encounters those features, the powerful associations reassert themselves, consciously or subconsciously, and are experienced as prompts for drug seeking and drug taking. Consistent with this account, exposing addicted individuals to cues that they associate with substance abuse elicits, along with physiological responses and drug cravings, changes in the activity levels of brain regions involved in learning and memory (i.e., striatum, amygdala, orbitofrontal cortex, hippocampus, thalamus, and left insula) (Franklin et al., 2007; Volkow et al., 2006).

The acute effects of amphetamine, nicotine, and cocaine fit straightforwardly into this scenario. Each of these drugs has been shown to acutely enhance learning and/or attention (Del et al., 2007; Kenney and Gould, 2008; Matray, 1996). For example, the idea that smoking is a cognitive enhancer is well accepted by researchers and the general public. Numerous studies
have confirmed that laboratory animals’ cognitive processes improve immediately following administration of nicotine (Kenney and Gould, 2008). Similar findings in early studies with human smokers were not conclusive, because the study participants were smokers who had received nicotine following a period of abstinence. The observed enhancements might have reflected the reversal of withdrawal effects, rather than improvements over their normal cognitive powers. A subsequent review of the literature, however, suggests that acute nicotine enhances reaction time and attention in nicotine-naïve individuals (Swan and Lessov-Schlaggar, 2007). Cocaine produced similar effects in a study of rats that were treated with the drug and then exposed to a sensory stimulus; the animals exhibited enhanced neural activation when later re-exposed to the stimulus (Devonshire, Mayhew, and Overton, 2007).

Although all drugs of abuse foster the learning of strong drug-stimulus associations and cue-induced drug seeking, some appear to have mixed effects on other types of learning and cognition. For example, a clinical study of the acute effects of morphine and oxycodone concluded that these drugs have variable impacts on cognition: Both improved men’s recall of prose just slightly, but morphine slightly impaired both sexes’ performance on a test of working memory in which they were asked to repeat a set of digits in reverse order (Friswell et al., 2008). In another study, mice were given morphine or saline and trained to run away when a light signaled that a foot shock was impending; although the morphine-treated mice scored higher on the frequency and quickness with which they avoided shocks, the researchers attributed this to increased motor activity rather than enhanced learning (Aguilar, Miñarro, and Simón, 1998). In contrast to the effects of opioids on cognition, those of alcohol are clear, though bidirectional: High doses disrupt cognitive processes (Ryback, 1971), while low doses can enhance learning (Gulick and Gould, 2007; Hernández, Valentine, and Powell, 1986).

### The Persistence of Drug-Stimulus Associations
Recent research has sought to account for the strikingly long-lasting ability of maladaptive drug-stimulus associations to influence behavior and provoke relapse. Studies have shown that many abused substances can reshape the communication pathways between neurons (synaptic plasticity), which could contribute to both the formation and the persistence of maladaptive drug-stimulus associations.

Cocaine and nicotine can directly induce one form of synaptic plasticity, the strengthening of neural connections via a process known as long-term potentiation (LTP; see Learning in the Mind and Brain on page 8 and Table 1) (Argilli et al., 2008; Kenney and Gould, 2008). Amphetamine can enhance LTP (Delanoy, Tucci, and Gold, 1983). Marijuana activates the endocannabinoid system, resulting in inhibition in some instances and facilitation in others of both LTP and long-term depression (LTD), another form of synaptic plasticity in which connections between neurons become less responsive (Carlson, Wang, and Alger, 2002; Nugent and Kauer, 2008; Sullivan, 2000). Ethanol consistently disrupts LTP while enhancing LTD (Yin et al., 2007). Morphine inhibits LTP of neurons that exhibit inhibitory control of neural activity via the neurotransmitter gamma-aminobutyric acid (GABA) (Nugent and Kauer, 2008). Inhibition of GABA activity could lead to an overall increase in neural activity throughout the brain, which might lead to the formation of stronger associations than would normally occur, including maladaptive drug-context associations.

Strengthening the evidence that drugs foster long-lasting drug-stimulus associations by affecting synaptic plasticity, studies have demonstrated that the same proteins that participate in the sequential biochemical reactions (cell signaling cascades) that control synaptic plasticity (see Figure 1) come into play in drug-seeking behaviors. For example, in one experiment, researchers showed that when rats went to a cage area that they had been trained to associate with cocaine, the levels of proteins associated with learning—extracellular signal-regulated protein kinase (ERK), cyclic AMP response element-binding (CREB), Elk-1, and Fos—increased in

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**TABLE 1. Drug Effects on Synaptic Plasticity**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECTS ON PLASTICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>LTP</td>
</tr>
<tr>
<td>Cocaine</td>
<td>LTP</td>
</tr>
<tr>
<td>Ethanol</td>
<td>LTP, LTD</td>
</tr>
<tr>
<td>Marijuana</td>
<td>LTP, LTD</td>
</tr>
<tr>
<td>Morphine</td>
<td>LTP (of inhibitory synapses)</td>
</tr>
<tr>
<td>Nicotine</td>
<td>LTP</td>
</tr>
</tbody>
</table>

LTP, long-term potentiation of synaptic efficiency; LTD, long-term depression of synaptic efficiency.
their NAc (Miller and Marshall, 2005). Moreover, when the rats were treated with a compound that suppresses ERK, they stopped preferring that cage area over one in which they had received saline and showed a decrease in three biochemical participants in LTP (CREB, Elk-1, and Fos) in the NAc.

**COGNITIVE DEFICITS IN CHRONIC DRUG ABUSE**

Drug abusers who progress to the second stage of addiction are subject to withdrawal when they initiate abstinence. Many drugs produce cognition-related withdrawal symptoms that may make abstinence more difficult. These include:

- cocaine—deficits in cognitive flexibility (Kelley et al., 2005);
- amphetamine—deficits in attention and impulse control (Dalley et al., 2005);
- opioids—deficits in cognitive flexibility (Lyvers and Yakimoff, 2003);
- alcohol—deficits in working memory and attention (Moriyama et al., 2006);
- cannabis—deficits in cognitive flexibility and attention (Pope, Gruber, and Yurgelun-Todd, 2001); and
- nicotine—deficits in working memory and declarative learning (Kenney and Gould, 2008).

Nicotine provides a familiar example of cognitive changes in withdrawal. In both chronic smokers and animal models of nicotine addiction, cessation of nicotine administration is associated with deficits in working memory, attention, associative learning, and serial addition and subtraction (Bell et al., 1999; Blake and Smith, 1997; Davis et al., 2005; Hughes, Keenan, and Yellin, 1989; Jacobsen et al., 2006; Mendrek et al., 2006; Raybuck and Gould, 2009; Semenova, Stolerman, and Markou, 2007). Moreover, it has been shown that the severity of decreases in cognitive performance during periods of smoking abstinence predicts relapse (Patterson et al., 2010; Rukstalis et al., 2005). Although these deficits usually dissipate with time, a dose of nicotine will rapidly ameliorate them (Davis et al., 2005)—a situation that may contribute to some relapses. Thus, chronic substance abuse can lead to cognitive deficits that are particularly pronounced during early periods of abstinence.

While the cognitive deficits associated with withdrawal from drugs are often temporary, long-term use can also lead to lasting cognitive decline. The nature of deficits varies with the specific drug, the environment, and the user’s genetic makeup (see Genes, Drugs, and Cognition on page 11). In general, however, they impair the ability to learn new patterns of thought and behavior that are conducive to successful response to treatment and recovery.

For example, long-term cannabis users have impaired learning, retention, and retrieval of dictated words, and both long-term and short-term users show deficits in time estimation (Solowij et al., 2002), although how long these deficits persist is not yet known. As another example, chronic amphetamine and heroin users show deficits in a range of cognitive skills, including verbal fluency, pattern recognition, planning, and the ability to shift attention from one frame of reference to another (Ornstein et al., 2000). The decisionmaking deficits resembled those observed in individuals with damage to the prefrontal cortex, suggesting that both drugs alter function in that brain area (Rogers et al., 1999).

A pair of recent studies suggests that some methamphetamine-induced cognitive losses may be partially
LEARNING IN THE MIND AND BRAIN

A mind learns: It captures and stores information and impressions and discovers relationships between them. For the mind to learn, events must occur in the brain. Among the most compelling pieces of evidence for this idea are many cases of individuals who suffered drastic reductions of their ability to learn after incurring brain injuries. The most famous, perhaps, is Henry Molaison, who, after surgical removal of extensive brain tissue at age 27 to control his epilepsy, entirely lost his long-term declarative memory (Penfield and Milner, 1958) so that for the remaining 55 years of his life he could not call to mind anything that happened to him more than a few minutes earlier.

Neuroscience research has correlated learning with the elaboration of neural networks in the brain. Many experiments have established that, as learning takes place, selected neurons increase their levels of activity and form new connections, or strengthen established connections, with networks of other neurons. Moreover, experimental techniques that prevent neuronal activity and networking inhibit learning.

Neuroscience research with animals is elucidating how the brain constructs and maintains the neural networks that support learning. One process identified, long-term potentiation (LTP), has features that parallel key aspects of learning.

- Once we learn to associate two ideas or sensations, the occurrence of one is likely to invoke remembrance of the other. Similarly, in LTP, a neuron that receives strong, or high-frequency, stimulation from another neuron responds by becoming more sensitive to future stimulation from the same source;
- Newly learned material enters our short-term memory and may or may not subsequently become established in our long-term memory. Similarly, LTP has an early phase during which short-term physiological processes support the above-mentioned increase in neuronal sensitivity and a late phase involving more long-lasting physiological processes;
- Animal studies have implicated some of the same sequences of biochemical changes (cell signaling cascades) in LTP and learning. For example, researchers showed that suppressing production of an enzyme (protein kinase A) in the hippocampi of mice prevented LTP and inhibited the animals’ ability to retain previously learned information about a maze (Abel et al., 1997).

Although LTP has not been observed in every brain region, it has been demonstrated in the nucleus accumbens, prefrontal cortex, hippocampus, and amygdala—all regions involved in both addiction and learning (Kenney and Gould, 2008; Kombian and Malenka, 1994; Maren, 2005; Otani et al., 2003).

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Recouped with extended abstinence (Volkow et al., 2001; Wang et al., 2004). Evaluated when abstinent for less than 6 months, chronic methamphetamine abusers scored lower than unexposed controls on tests of motor function, memory for spoken words, and other neuropsychological tasks. The deficits were associated with a comparative scarcity of dopamine transporters (proteins that regulate dopamine) and reduced cellular activity (metabolism) in the thalamus and NAc. When retested after 12 to 17 months of abstinence, the drug abusers’ motor function and verbal memory had risen to levels that approached those of the control group, and the gains correlated with a return toward normal transporter levels in the striatum and metabolic levels in the thalamus; however, other neuropsychological deficits remained, along with depressed metabolism in the NAc.

In another study, abusers of 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy) continued to score relatively poorly in tests of immediate and delayed recall of spoken words even after 2.5 years of abstinence (Thomasius et al., 2006). In a study of polydrug abusers who had stated a primary preference for either cocaine or heroin, deficits in executive function—defined as changes in fluency, working memory, reasoning, response inhibition, cognitive flexibility, and decisionmaking—remained after up to 5 months of abstinence (Verdejo-García, and Pérez-García, 2007).

An important question is whether nicotine’s cognitive benefit persists as smoking shifts from sporadic to chronic. In some studies with animals, chronic nicotine administration improved cognitive capacities such as attention, but other studies found that initial improvements waned with chronic treatment (Kenney and Gould, 2008). Furthermore, several recent studies have shown that smoking and a past smoking history are associated with cognitive decline. For example, in one study with middle-aged men and women, smokers’ cognitive speed declined nearly twice as much as non-smokers’ over 5 years; in addition, declines in smokers’ cognitive flexibility and global cognition occurred at 2.4 times and 1.7 times the respective rates of nonsmokers (Nooyens, van Gelder, and Verschuren, 2008). Recent quitters’ scores in these areas were similar to smokers’, and ex-smokers performed at levels intermediate between smokers and nonsmokers.

Similarly, in another study, smokers’ performance deteriorated more over 10 years than nonsmokers’ on tests of verbal memory and speed of visual searching; ex-smokers’ visual search speed slowed more than nonsmokers’ as well (Richards et al., 2003). Although some early studies suggested that smoking might retard the cognitive decline associated with Alzheimer’s disease (van Duijn and Hofman, 1991), followup studies failed
to confirm this, and others correlated smoking quantity and duration with higher risk for Alzheimer’s disease (Swan and Lessov-Slaggar, 2007).

Laboratory studies have demonstrated nicotine-related alterations in neuronal functioning that could underlie cognitive decline that persists even after prolonged abstinence. For example, rats’ self-administration of nicotine was associated with a decrease in cell adhesion molecules, a decrease in new neuron production, and an increase in cell death in the hippocampus (Abrous et al., 2002). Such changes could result in long-lasting cognitive changes that contribute to poor decision-making and addiction.

**DRUGS OF ABUSE AND THE DEVELOPING BRAIN**

The human brain continues to develop and consolidate important neural pathways from the prenatal period through adolescence. Throughout these years, the brain is highly malleable, and drug-induced alterations of neural plasticity may deflect the normal course of brain maturation.

**Prenatal Exposures**

The consequences of prenatal alcohol exposure are well-known: Fetal alcohol spectrum disorders are the leading cause of mental retardation in the United States (Centers for Disease Control and Prevention, 2009). In addition, fetal alcohol exposure increases susceptibility to later substance abuse problems (Yates et al., 1998).

Prenatal exposures to a number of other drugs have significant deleterious effects on cognition and behavior that may not rise to the level of mental retardation. In one study, 5-year-olds whose mothers had used alcohol, cocaine, and/or opiates while pregnant ranked below unexposed controls in language skills, impulse control, and visual attention. There were no significant differences between the two groups of children in intelligence, visual/manual dexterity, or sustained attention; however, both groups placed below the normative means on these measures (Pulsifer et al., 2008). Another study documented memory deficits in 10-year-old children who had been exposed prenatally to alcohol or marijuana (Richardson et al., 2002).

Clinical and laboratory research has implicated prenatal exposure to methamphetamine in both cognitive deficits and altered brain structure. For example, one study correlated shorter attention span and delayed memory with reduced volume in the putamen (-18 percent), globus pallidus (-27 to -30 percent), and hippocampus (-19 to -20 percent) among 15 children aged 3 to 16 years who were prenatally exposed to the stimulant, compared with controls (Chang et al., 2004). The drug-exposed children also exhibited poorer long-term spatial memory and visual/motor integration. Another study documented structural changes in the frontal and parietal cortex of 3- and 4-year-old children who had been exposed prenatally to methamphetamine (Cloak et al., 2009). In laboratory studies, rats that were treated with methamphetamine during pregnancy gave birth to pups that, when they reached adulthood, were slow to learn spatial relationships and exhibited spatial memory impairment (Acuff-Smith et al., 1996; Slamberová et al., 2005).

The effects of prenatal tobacco exposure are particularly concerning because so many expectant mothers smoke—by one estimate, over 10 percent in the United States (Hamilton et al., 2007). *In utero* exposure to tobacco byproducts has been linked to cognitive deficits in laboratory animals and human adolescents (Dwyer, Broide, and Leslie, 2008). Some studies suggest that such exposure can lower general intelligence; for example, one found a 12-point gap in full-scale IQ between exposed and unexposed middle-class adolescents (e.g., Fried, Watkinson, and Gray, 2003). In another study, the odds of having attention deficit hyperactivity disorder (ADHD) were more than three times as great for adolescents whose mothers smoked during pregnancy compared with children of nonsmoking mothers (Pauly and Slotkin, 2008).

Cognitive deficits following prenatal exposure to smoking may reflect structural brain changes. In one study, prenatally exposed adolescent smokers had greater visuospatial memory deficits in conjunction with changes in parahippocampal and hippocampal function compared with adolescent smokers not prenatally exposed (Jacobsen et al., 2006). Brain imaging of adolescent smokers and nonsmokers who were prenatally exposed to smoking has revealed reduced cortical thickness (Toro et al., 2008) and structural alterations in cortical white matter (Jacobsen et al., 2007). Furthermore, in rats, prenatal exposure to nicotine decreased memory-related neural activity in the hippocampus and resulted in deficits in active avoidance learning, with male and female prenatally exposed rats showing significantly fewer correct responses as young adults (Vaglenova et al., 2008). These deficits persisted into later adulthood among the male rats, but not the females.
Among the adverse consequences of prenatal drug exposure is a heightened risk of becoming a drug abuser in later life (Fergusson, Woodward, and Horwood, 1998). This is troubling, as it may lead to a downward spiral that manifests across generations and destroys family structures. Multiple factors could contribute to the increased risk of future substance abuse, including the effects of prenatal drug exposure on cognition. As already reviewed, the risk of developing ADHD is greatly increased in adolescents whose mothers smoked during pregnancy (Pauly and Slotkin, 2008). ADHD is often comorbid with substance abuse (Biederman et al., 2008; Molina and Pelham, 2003), suggesting a link between such changes in cognition and future drug abuse. Further work is needed to understand the mechanisms that underlie the increased risk of drug abuse associated with prenatal exposure.

**Adolescent Exposure**

Adolescence is a high-risk period for substance abuse. Most addicted smokers first formed the habit during adolescence (Khuder, Dayal, and Mutgi, 1999). Adolescent smoking strongly affects cognition. Adolescent smokers scored worse than age-matched nonsmokers on tests of working memory, verbal comprehension, oral arithmetic, and auditory memory (Fried, Watkinson, and Gray, 2006; Jacobsen et al., 2005). These deficits resolved upon cessation of smoking with the exceptions of working memory and arithmetic performance, which remained at comparatively low levels. In rats, nicotine exposure during adolescence was associated with visuospatial attention deficits, increased impulsivity, and increased sensitivity of medial prefrontal cortical dopamine terminals in adulthood (Counotte et al., 2009). In addition, adolescent rats treated with nicotine had long-lasting changes in the sensitivity of the adenylyl cyclase cell-signaling cascade (see Figure 1), a second messenger pathway involved in many processes, including learning and memory (Slotkin et al., 2008). These findings fit well with studies demonstrating that nicotine initially can enhance some cognitive processes, but with continued use adaptation can occur, leading to dissipation of these effects and even deficits (for review, see Kenney and Gould, 2008).

Adolescent smoking can foster cognitive decline indirectly, through the promotion of other disorders. For example, adolescent cigarette use is associated with later episodes of depression (Choi et al., 1997), a malady which in turn is associated with negative effects on cognition (Thomas and O’Brien, 2008). A laboratory investigation shed light on this relationship: Adult rats that had been exposed to nicotine during their adolescence proved less sensitive than controls to rewarding/appetitive stimuli and more responsive to stress and anxiogenic stimuli (Iñiguez et al., 2009).

Adolescent exposures to other substances of abuse, such as alcohol, cannabis, and MDMA, also cause persistent disruptions of cognition (Brown et al., 2000; O’Shea, McGregor, and Mallet, 2006; Piper and Meyer, 2004; Stiglic and Kalant, 1982). These findings indicate that the adolescent brain, which is still developing, is susceptible to insult from drug use and abuse, and such insult can result in long-lasting changes in affect and cognition.

**DRUGS OF ABUSE AND MENTAL ILLNESS**

Drug-related cognitive deficits may be particularly detrimental to the well-being of individuals whose cognitive performance is already compromised by a mental disorder. Moreover, individuals who suffer from mental disorders abuse drugs at higher rates than the general population. Substance abuse is almost twice as prevalent among adults with serious psychological distress or major depressive episodes as among age-matched controls (SAMHSA, 2007, p. 85), and it is estimated that over half of U.S. individuals with drug disorders (excluding alcohol) also have mental disorders (Regier et al., 1990). In a 1986 study, smoking rates approximated 30 percent in population-based controls, 47 percent in patients with anxiety disorder or major depressive disorder, 78 percent in patients with mania, and 88 percent in patients with schizophrenia (Hughes et al., 1986).

The case of smoking and schizophrenia provides one example of a mental disorder that features cognitive deficits in combination with abuse of a drug that causes cognitive decline. As with many comorbidities, effective treatment will likely require untangling the reasons why the two conditions so frequently co-occur:

- Some evidence suggests that patients with schizophrenia smoke to self-medicate. For example, smoking reverses schizophrenic patients’ deficits in the brain’s ability to adapt its responses to stimuli (sensory gating), which could reduce the capacity to filter information, and might account for some of the cognitive disruption seen in the mental disorder. Researchers have traced this feature of schizophrenia to a variant of the gene for the α7 nicotinic acetylcholinergic receptor subunit (Leonard et al., 2001). Consistent with this viewpoint...
is an observation that patients smoke less when given the antipsychotic clozapine, which independently alleviates this deficit, than when given haloperidol, which does not (McEvoy, Frederich, and Wilson, 1999).

- It has also been proposed that patients with schizophrenia smoke to alleviate side effects of antipsychotic medication (Goff, Henderson, and Amico, 1992). An observation that supports this idea is that patients with schizophrenia smoke more after receiving the antipsychotic haloperidol than when unmedicated (McEvoy et al., 1995).

- Another suggested explanation for the link between smoking and schizophrenia is that smoking itself may precipitate schizophrenia in people predisposed to develop the disease. Among schizophrenics, smokers have an earlier onset of illness, require hospital admissions more frequently, and receive higher doses of antipsychotic medications (Goff, Henderson, and Amico, 1992; Kelly and McCreadie, 1999; Ziedonis et al., 1994).

Another cognitive disorder that is strongly associated with smoking is ADHD. Interestingly, the cognitive symptoms associated with ADHD are similar to those displayed during nicotine withdrawal, and both have been attributed to alterations in the acetylcholinergic system (Beane and Marrocco, 2004; Kenney and Gould, 2008). The high prevalence of smoking among individuals with ADHD (Lambert and Hartsough, 1998; Pomerleau et al., 2003) may be an attempt to self-medicate, because acute nicotine use can reverse some ADHD attentional deficits (Conners et al., 1996). The desire to avoid withdrawal may be a particularly strong motivation for continued smoking in this population, as individuals with ADHD suffer more severe withdrawal symptoms than age-matched controls without the disorder (Pomerleau et al., 2003), and increases in ADHD symptoms following smoking cessation are associated with a greater risk of relapse (Rukstalis et al., 2005). As noted above, however, continued smoking in itself can lead to cognitive decline (Nooyens, van Gelder, and Verschuren, 2008; Richards et al., 2003), and hence might exacerbate ADHD-related symptoms.

Along with nicotine, ADHD is also associated with abuse of stimulants, such as amphetamine and cocaine, and psychoactive drugs, such as cannabis (Elkins, McGue, and Iacono, 2007; Galéra et al., 2008; Tang et al., 2007). Such abuse may also represent attempts at self-medication, as stimulants are used to treat ADHD symptoms following smoking cessation, and both have been attributed to alterations in the acetylcholinergic system (Beane and Marrocco, 2004; Kenney and Gould, 2008). The high prevalence of smoking among individuals with ADHD (Lambert and Hartsough, 1998; Pomerleau et al., 2003) may be an attempt to self-medicate, because acute nicotine use can reverse some ADHD attentional deficits (Conners et al., 1996). The desire to avoid withdrawal may be a particularly strong motivation for continued smoking in this population, as individuals with ADHD suffer more severe withdrawal symptoms than age-matched controls without the disorder (Pomerleau et al., 2003), and increases in ADHD symptoms following smoking cessation are associated with a greater risk of relapse (Rukstalis et al., 2005). As noted above, however, continued smoking in itself can lead to cognitive decline (Nooyens, van Gelder, and Verschuren, 2008; Richards et al., 2003), and hence might exacerbate ADHD-related symptoms.

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CLINICAL IMPLICATIONS

The literature reviewed here highlights the importance of considering past and present cognitive function when treating patients for addiction, as drug-related cognitive changes may bias patients toward responses and actions that contribute to the cycle of addiction. Clinicians face the challenge of helping patients master adaptive strategies to overcome the strong associations that contribute to relapse when patients return to environments associated with their prior substance use. In addition, cognitive deficits may hinder patients’ ability to benefit from counseling, and more sessions and/or reminders may be necessary to aid these patients in incorporating

GENES, DRUGS, AND COGNITION

An individual’s genetic makeup can influence the degree to which a drug of abuse alters his or her cognitive processes. For instance, an individual’s cognitive response to acute amphetamine depends in part on which of the alternative forms of the *catechol-O-methyltransferase* (COMT) gene he or she has inherited.

This gene encodes a protein that metabolizes dopamine and norepinephrine, among other molecules. A person inherits two copies of the gene, one from each parent, and each copy has either a valine or a methionine DNA triplet at codon 158: thus, a person may have two valine (Val/Val), two methionine (Met/Met), or a mixed pair (Val/Met or Met/Val) of codons at this location. Administration of acute amphetamine to individuals with the Val/Val pairing improved their performance on the Wisconsin Card Sorting Task (a test of cognitive flexibility that activates the dorsolateral prefrontal cortex) and increased efficiency in their prefrontal cortical function, as measured by increased regional cerebral blood flow in the inferior frontal lobe (Matty et al., 2003). However, acute amphetamine did not produce those advantages in individuals with either the Val/Met or Met/Met pairing. Interestingly, the Val/Val pairing is also associated with increased impulsivity, a trait associated with addiction (Boettiger et al., 2007).

Furthermore, smokers with the Val/Val pairing were more sensitive to the disruptive effects of nicotine withdrawal on working memory and exhibited a greater cognitive response to tobacco (Loughead et al., 2009). These results are important not only because they demonstrate a link between the effects of drugs of abuse on cognition and behavioral traits associated with addiction, but also because they provide examples of how genotype contributes to the addictive phenotype.

The cognitive symptoms associated with attention deficit hyperactivity disorder are similar to those displayed during nicotine withdrawal.
abstinence-sustaining strategies into their daily routines.

Research into the changes in cognition that accompany addiction and the neural substrates of learning and addiction is still in its infancy but has potential to reshape views on addiction. For example, a recent discovery that has generated excitement in the addiction field is that smokers who suffered damage to the insula often lost their desire to smoke (Naqvi et al., 2007). The authors of this finding proposed that the insula is involved in the conscious urge to smoke and that therapies that modulate insula function may facilitate smoking cessation. It may also be that damage to the insula will have a similar effect on the desire to use other drugs of abuse (for a review see Goldstein et al., 2009).

A better understanding of how substances of abuse change cognitive processes is needed to develop new therapeutic agents to treat addiction and ameliorate cognitive deficits. This is a complex issue, however, as different drugs of abuse appear to alter different cognitive processes and cell signaling pathways. Even among users of the same drug, cognitive impacts will vary depending on variations in environmental factors and genetics. Understanding the influence of an individual’s genetic background on the manifestation of symptoms is a critical area for future research, holding the promise of informing more effective treatments that can be tailored to the individual’s genotype. Finally, understanding how prenatal exposure to drugs of abuse changes neural development should be a high priority, as prenatal exposure increases the new generation’s susceptibility to addiction and other problems.

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**Response: Addiction, Memory, and Spirit**

*Vitka Eisen, Ed.D., M.S.W., and John Wanner, M.A., L.C.A.D.C.*

**Vitka Eisen:** The article reinforced some conversations I’ve had recently with colleagues. We were reflecting on people we’ve known who had a good 4 or 5 years of recovery under their belt and then relapsed. What appeared to connect these relapses were folks returning to places that were triggering for them.

**John Wanner:** We see this all the time. Right now, we’ve got 74 patients, and at least eight of them relapsed after between 5 and 15 years of sobriety. The article does a good job of making it clear why this happens. I’m going to send it to my colleagues. If we can explain this to patients, they will give more credence to the recommendations we make in treatment.

**Eisen:** I was left thinking about the challenges related to today’s shorter stays in treatment. When Walden House was a therapeutic community, people stayed in the program for 2 years. Now a typical stay is 6 months, with a couple months in outpatient aftercare. That gives us a lot less time to help patients rewire their brain, form new associations, change associations that formerly triggered drug use, learn some stress management skills, and titrate their exposure to the stresses outside the program. Many of our folks need to start new lives from scratch because of the communities they came from and because their friends and family members are all drug-involved.

**Wanner:** Some of the addiction literature today is pointing in the direction of longer stays. I think that Alcoholics Anonymous recognized that, without knowing the science, many years ago when they came up with the idea of 90 AA meetings in 90 days. What we try to do at Father Martin’s Ashley is to give our patients some coping skills while they are in residence and then move them on to some additional treatment, whether it’s outpatient, extended care, halfway house, or whatever, because they still need to be in an environment that’s recovery-based.

**Stages and models**

**Wanner:** We see patients in both of the stages of addiction Dr. Gould describes. Sometimes patients who are still in the earlier stages look at those in the later stages and say, “What am I doing here? I don’t belong here. I’m not that bad.” We try to tell them that even though they are not yet using every day, not waking up with the shakes, neither were these other people when they were at your stage. We also are more likely to prescribe an anti-craving medication for patients in the second stage.

**Eisen:** Walden House clients typically are indigent with lengthy histories of substance abuse, often co-occurring disorders, and often histories of incarceration. Most are in the second stage of addiction where they no longer get any pleasure from drugs. However, we used to have a residential treatment program for court-referred adolescents, most of whom were first-stage users. They tended to have lengthy histories, for such young people, of complex trauma, and many serious difficulties in their lives. Drugs often were the best thing they had going on, so it was a different challenge to try to get them to replace drugs.

Interestingly enough, some of our court-referred clients are drug dealers who are first-stage recreational drug users. With them, we try to look at drug abuse together with other behaviors, particularly criminal behaviors, that are thrill-seeking and seem to produce very similar types of rewards in the brain.

**Wanner:** Dr. Gould’s definition of addiction as “a disorder of cognition” and “a disease of pathological learning” is a neurobiologist’s view. From a treatment and patient education perspective, Father Martin’s Ashley uses the broader biopsychosocial model of the disease, which also focuses on the social, environmental, and genetic factors that influence the neurobiological processes.

**Eisen:** We assess many things when a patient arrives in our program, but we don’t make any formal assessment of cognitive status. That might be useful if we had all the time and resources in the world, but for now, it’s more useful to try to understand how our clients learn and what their life challenges are. We can use that information to identify the interventions that will be most effective for them. If we subsequently see that a client has some cognitive impairment, we can recalibrate our expectations of him or her or rework a treatment plan.

We assume that everybody comes in learning in different ways and at different paces. There are auditory learners and people who learn by talking a lot in group. There are those who need to have things written down and others for whom writing is very anxiety-producing. You can alienate clients if you don’t understand how they learn best and what they think is the most effective way for them.

**Wanner:** The neurobiological information is useful for putting to rest the idea that individuals become addicted because they are weak-willed. I use it in a lecture to families, and many of them thank me afterwards and say that they now understand why their family member makes bad decisions about drugs.

**Eisen:** Given the nature of addiction, we
have to strike a very delicate balance with our clients. We say: “You have a brain condition.” But, at the same time, we say: “You have choices and the ability to change.” The balance between personal responsibility and acknowledgment of a health condition is challenging, and it’s tricky to strike it appropriately. We want our clients to recognize that they are faced with challenges that are real, embedded in the brain. But we don’t want them to think: “It’s not my responsibility.”

Memory and spirit

**Wanner:** Many of our patients have memory problems. Many of our older patients are fighting not only years of drug and alcohol abuse, but also the normal decline in memory that happens with aging. Some of the problems are drug-specific. For example, lately we’re seeing patients come in much more cognitively impaired from marijuana, due to the increasing potency of that drug over the past 5 or 6 years.

**Eisen:** Some patients are aware that they have cognitive problems. They’ll say, “I don’t remember the way I used to be able to,” things like that. Or they may say, “What have these drugs done to my mind?” Some attribute their thinking problems to drugs, and some don’t make that connection.

**Wanner:** Patients don’t remember where they’re supposed to be, what they heard at a lecture, or what assignment they’re supposed to do. In those cases we try to have them write things down. If somebody’s having serious memory issues, we’ll try to hook them up with a buddy or ask the group members to help them. These problems do improve during treatment.

**Eisen:** We also post lots of visual cues—staff names and charts of who does what, schedules, sayings, and slogans that help reinforce the treatment environment. Memory typically may start to improve, maybe, 3, 4, or 5 months into treatment. At that point patients are starting to feel better, more capable. They’re creating relationships with friends and preparing or already in a job search. There’s a general cognitive improvement that occurs as part of a complicated interaction among drug use, withdrawal, abstinence, and mood. Many of our patients have co-occurring mood disorders, and depression of course has an impact on cognition.

**Wanner:** This is an area that could use some research. Some of the rehabilitation of patients with brain injuries already uses computer simulations, but to my knowledge, there’s not been much work applying that approach in the addictions field. Cognition-enhancing medications also seem to hold promise.

Spiritual practices can actually start to re-regulate some of the neural dysfunction that takes place as a result of addiction. We’re not talking about religion, per se, but encouraging clients to live as good people and get more connected to their lives in a positive way. In some manner, this spiritual work, which can include prayer or meditation, starts to re-regulate defective neural circuits and compensate for some of the cognitive deficits that addiction causes. Spiritual experiences can eventually replace some of the powerful negative memories associated with the drugs and give people a reason to stay abstinent.

**Eisen:** I think that we aim for the same end, which is creating other kinds of reinforcing experiences for clients so that they can practice sentient abstinence, if you will. Our focus is really on creating positive relationships among the clients as a group and with family members (if they are able to participate), staff, ex-residents, church groups, and 12-step programs. We focus on maintaining healthy relationships that are positively reinforcing for clients.

**Wanner:** Much of what you just said about positive relationships actually falls in the purview of what we would consider spiritual experiences.

**Early exposure**

**Eisen:** Dr. Gould’s section on prenatal exposure to drug and alcohol abuse is especially interesting. I’m not sure that the field has recognized how many of the people we see as adult clients were prenatally exposed to drugs and alcohol. We have to learn how to work with what may be some pretty significant deficits, impairments, or learning challenges. Historically, we thought about the social environment of being raised in a family with addiction but less about the organic impact of being prenatally exposed.

**Wanner:** I’ve probably worked with at least three or four father and son pairs over the years, and we have also had grandparents, parents, and children come through here. I can’t really say that we see cumulative increases in cognitive deficits from one generation to the next, as Dr. Gould’s text might lead you to expect. We don’t measure for that, per se. However, the addicts who come in today, especially the young ones, are different from those of 10 years ago. There is a much greater variety of drugs available, and we are seeing more cross-addictions.

**Eisen:** The clients we see today have a much higher level of acuity than 25 years ago, in terms of severity of addiction and the amount of co-occurring disorders. We speculate on the reasons. Prenatal exposures might be one, and the cumulative impact of multiple generations of addiction and alcoholism, as well as the policy of incarcerating drug abusers, may be others.
Pharmacogenetics: A Tool for Identifying Genetic Factors in Drug Dependence and Response to Treatment

Pharmacogenetics research looks at variations in the human genome and ways in which genetic factors might influence how individuals respond to drugs. The authors review basic principles of pharmacogenetics and cite findings from several gene-phenotype studies to illustrate possible associations between genetic variants, drug-related behaviors, and risk for drug dependence. Some gene variants affect responses to one drug; others, to various drugs. Pharmacogenetics can inform medication development and personalized treatment strategies; challenges lie along the pathway to its general use in clinical practice.

Substance dependence is a complex psychiatric disorder that develops in response to a combination of environmental and genetic risk factors and drug-induced effects (Ho et al., 2010). The strong genetic basis of dependence is supported by family, adoption, and twin studies, which demonstrate substantial heritability, estimated to be about 50 percent (Uhl et al., 2008). The evidence suggests that no single variant accounts for a major portion of this risk, but that variations in many genes each contribute a small amount.

Pharmacogenetics is the study of the genetic factors that influence drug response and toxicity. In this review, we briefly state the basic principles of pharmacogenetics and then provide examples of discoveries that demonstrate the impact of genetic variation on drug dependence, drug effects, and drug-induced behaviors. The primary goal of pharmacogenetic research into substance abuse is to better understand the sources of variation in the risk for dependence and the mechanisms involved. Some of the studies we discuss have identified genotypes that confer high risk for drug dependence, information that may be used to develop targeted, effective prevention programs. We also highlight how pharmacogenetics can advance the development of personalized treatments by revealing genetic variations that predict individual responses to therapeutic interventions.

PRINCIPLES OF PHARMACOGENETICS
Pharmacogenetics focuses on variation within the human genome. The human genome consists of some 30,000 genes, each composed of a sequence of hundreds to thousands of nucleotides (units of deoxyribonucleic acid, or DNA) (see Figure 1). Every person inherits two copies of most genes, one from each parent. Although any two individuals’ DNA is over 99 percent identical, the number of nucleotides...
is so large—approximately 3 billion—that millions of variant sequences still occur across the human population (Kruglyak and Nickerson, 2001). Variants that are found in more than 1 percent of the population are called polymorphisms. The most abundant type of variant is the single nucleotide polymorphism (SNP, pronounced “snip”); other common types are deletions, insertions, and tandem repeats (see Figure 2).

Genes are distributed along chromosomes, which are long sequences of DNA. This illustration shows human chromosome 15 and highlights a hypothetical gene at position 25 on the long (q) arm.

A gene is a sequence of DNA units, or nucleotides (adenine [A], cytosine [C], guanine [G], and thymine [T]). For a gene that determines a protein, the order of nucleotides precisely dictates the structure of an RNA intermediate and a subsequent protein product. In contrast to this simplified illustration, actual genes are hundreds to thousands of nucleotides long, untranslated regions (UTRs) are hundreds of nucleotides long, and promoters are typically at least 40 nucleotides long.

Each gene and its related DNA can be divided into segments:

Promoter region: The genetic machinery anchors here to begin building the RNA intermediate; sequence variation in this region may alter the machinery’s access to the gene and thereby affect its rate of RNA and protein production.

Exons: The genetic machinery transcribes these segments into an RNA intermediate, then translates the RNA intermediate (except for the RNA that came from the UTRs) into the sequence of amino acids that constitutes the protein product; sequence variation within exons can alter that product (see Figure 2).

Introns: The genetic machinery transcribes these segments into RNA but deletes them before translation into amino acids.

UTRs: These regions serve regulatory functions and contribute to the stability of the RNA intermediate; however, they are not translated into protein.

A genetic variant may alter responses to one drug or to multiple drugs.

Traditionally, pharmacogenetics has focused on the role of genetic variation in pharmacokinetics (e.g., the absorption, distribution, metabolism, and excretion of drugs) and pharmacodynamics (e.g., drug-response pro-
Gene Polymorphisms

**“Wild Type” Allele**
The most common variant; note that the sequence of each DNA triplet determines one amino acid of the protein product.

**Single Nucleotide Polymorphism (SNP)**
Substitution of one DNA unit (a nucleotide) for another at a particular site (here, a C replaces an A found in wild-type triplet); the changed sequence of the triplet results in an altered amino acid in the protein product.

**Insertion**
Insertion of an additional DNA unit or units into the gene sequence (here, a C between the T and A in wild-type triplet); this may change not only the sequence of the triplet in which it occurs, but of all subsequent triplets, producing alterations in many amino acids of the protein product.

**Deletion**
Excision of a DNA unit or units (here, an A from wild-type triplet); this may change all subsequent triplets and the corresponding amino acids of the protein product.

**Tandem Repeats**
Addition of multiple copies of a DNA triplet (here, TAT), end-to-end; each new triplet can add one more copy of the amino acid it encodes to the protein product; the resulting elongated protein product may function differently than that produced by the gene’s wild-type variant.

Polymorphism, or genetic variation in a gene’s DNA sequence, may result in alterations in the expression, regulation, and/or function of its protein product. The panels show five possible variants (alleles) of a hypothetical gene.
teins, such as receptors, channels, and transporters) (see Figure 3). However, candidate gene studies and, more recently, GWA studies have identified additional genetic influences on drug abuse and dependence. Because GWA studies cast a wide net and are without a hypothesis about which genes are involved, they are theoretically excellent tools for discovering novel common genetic variants and new genetic biomarkers that associate with particular phenotypes. For instance, GWA studies have shown that genes involved in cell adhesion, enzymatic activities, transcriptional regulation, and many other processes and functions may be associated with dependence phenotypes (e.g., Ishiguro et al., 2008; Uhl et al., 2008).

The following sampling of pharmacogenetic findings is not exhaustive but is intended to demonstrate the associations and predictive validity of some genetic variants conferring susceptibility for drug dependence or treatment response. (For further reading, see: Ho et al., 2010; Ho and Tyndale, 2007; Rutter, 2006; Uhl et al., 2008.)

**PHARMACOGENETICS OF SUBSTANCE ABUSE VULNERABILITY, ACQUISITION, AND PERSISTENCE**

Some genetic variants alter the risk for dependence on one drug; others affect responses to various drugs. A variant that alters an enzyme that metabolizes a specific drug or a receptor activated by a specific drug is likely to play a role in vulnerability to dependence upon just that drug. In contrast, vulnerability to a variety of drugs could result from a variant that affects the brain reward pathways or neuroplasticity (the brain’s formation of new neural connections in response to experience or drug exposures) (Uhl et al., 2008). Genetic variation contributing to vulnerability to, and dependence on, different drug classes has been shown for the drug-metabolizing cytochrome P450 (CYP) enzymes, receptors such as the dopamine D2 receptor (DRD2) and mu opioid receptor (OPRM1), transporters such as the serotonin transporter (5-HTT) and dopamine transporter (DAT1), and enzymes such as dopamine β-hydroxylase (DβH) and monoamine oxidase (MAO).

**CYPs and Smoking**

Variation in CYP2A6, the gene for the nicotine-metabolizing enzyme CYP2A6, influences aspects of smoking dependence by altering nicotine pharmacokinetics. CYP2A6 is primarily responsible for converting nicotine to cotinine, rendering it inactive (Benowitz and Jacob, 1994; Messina et al., 1997), and the enzyme further metabolizes cotinine to trans-3′-hydroxycotinine (Nakajima et al., 1996). Individuals with different CYP2A6 variants can be grouped according to the resulting CYP2A6 enzyme activity as normal, intermediate (approximately 75 percent of normal), or slow (less than 50 percent of normal) metabolizers (Schoedel et al., 2004).

The CYP2A6 genotype (the pair of specific variants, or alleles, in a gene that a person inherits, one from each parent) has been associated with the risk for being a smoker and with numerous smoking behaviors. For instance, studies in novice adolescent smokers have found that slow and normal metabolizers differ in their risk for conversion to dependence, as defined in the International Classification of Diseases, 10th Revision (ICD-10) (O’Loughlin et al., 2004) and in the rate at which they progress to increasingly severe dependence (Audrain-McGovern et al., 2007). Among adult smokers, slow metabolizers are less prevalent than intermediate or normal metabolizers; they smoke fewer cigarettes per day, exhibit reduced cigarette puffing, have decreased dependence, wait longer to smoke the first cigarette of the day, and have fewer nicotine withdrawal symptoms; and they make up a smaller portion of smokers as the duration of smoking increases, suggesting that they quit smoking sooner (Kubota et al., 2006; Malaiyandi et al., 2006; Schoedel et al., 2004; Strasser et al., 2007).

These findings suggest that nicotine levels remain elevated longer in smokers with slow-metabolizing CYP2A6 variants than those with fast-metabolizing variants, resulting in a decreased need to light up or puff as often to avoid withdrawal. This reduced frequency of exposure to nicotine over time may decrease nicotine-induced changes in the brain, resulting in less severe dependence and perhaps more successful quitting attempts. Although not all studies agree on these associations, variation in CYP2A6’s metabolic inactivation of nicotine appears, on balance, to be associated with variation in smoking behavior and may alter cessation rates (Munafo et al., 2004).

**CYPs and Opioid Dependence**

Several oral opioids, such as codeine, oxycodone, and hydrocodone, are metabolized by another CYP enzyme, CYP2D6, to more psychoactive metabolites, such as mor- phine, oxymorphone, and hydromorphone (Orton et al., 1993). The CYP2D6 gene is highly polymorphic, with some variants leading to a completely inactive enzyme.
Individuals who inherit such defective CYP2D6 alleles from both parents are referred to as poor metabolizers (Alvan et al., 1990). Poor CYP2D6 metabolizers are underrepresented among people dependent on oral opioids, suggesting that the CYP2D6 defective genotype is a pharmacogenetic protection factor against oral opioid dependence (Tyndale et al., 1997). Of note, CYP2D6 variation should not play a role in dependence on intravenously administered opioids (e.g., morphine) as these drugs are already psychoactive and do not depend on CYP2D6 activity for metabolic activation.

Dopamine Receptors

Drugs of abuse activate the mesolimbic dopaminergic pathway, which plays an essential role in drug reward and reinforcement (Di Chiara and Bassareo, 2007). A key mechanism in this pathway is dopamine activation of DRD2 receptors on dopaminergic neurons in the ventral tegmental area (Cohen et al., 2007; Di Chiara and Imperato, 1988; Koob, 2006). Accordingly, studies have examined the impact of genetic variation in DRD2 on responses to several drugs of abuse, and several polymorphisms have been implicated in susceptibility and dependence.

For instance, one DRD2 variant, called TaqI A, results from a SNP (32806C>T) that occurs in the DRD2-neighboring ankyrin repeat and kinase domain containing 1 (ANKK1) gene. Although this variant does not lie within the DNA region that encodes the DRD2 protein, it is nonetheless associated with a lower density of DRD2 receptors and consequently decreased dopaminergic activity (Noble et al., 1993). The TaqI A polymorphism may contribute to vulnerability to substance abuse and has been associated with polysubstance abuse (O’Hara...
et al., 1993), heroin use (Lawford et al., 2000), cocaine dependence (Noble et al., 1993), and psychostimulant polysubstance abuse (Persico et al., 1996). Some studies have suggested that TaqI A is a risk factor for smoking behaviors (Comings et al., 1996; Erblach et al., 2005; Huang et al., 2009), while other studies have not found these associations (Berlin et al., 2005; Johnstone et al., 2004; Singleton et al., 1998).

Another variant associated with the DRD2 gene, called TaqI B, located in exon 2, also results in lower density of DRD2 receptors in the striatum. Individuals with this variant are more likely than those without it to have smoked and to have started smoking at an earlier age (Spitz et al., 1998; Wu et al., 2000) to be cocaine-dependent (Noble et al., 1993), and to abuse psychostimulants (Persico et al., 1996). Additionally, a deletion variant (-141C Del) in the promoter region was associated with higher density of DRD2 receptors in the striatum (Jonsson et al., 1999) and with a higher likelihood of heroin abuse by inhalation, but not by injection (Li et al., 2002). These data suggest that, consistent with the key role of the dopamine receptor in the reward pathway, variation in DRD2 may alter multiple aspects of dependence for many drugs of abuse.

Other Dopamine Pathway Components
Genetic variation in other components of the dopamine transmission system has also been implicated in substance abuse. For instance, the gene SLC6A3 encodes the dopamine transporter (DAT1), which regulates dopamine activity by drawing the neurotransmitter back into presynaptic neurons and terminating its action. Cocaine inhibits the dopamine transporter, which contributes to the drug’s reinforcing effects.

Genetic variants consisting of variable numbers of tandem repeats (VNTR) of a 40-nucleotide unit can occur in exon 15 of SLC6A3 (Vandenbergh et al., 1992). Studies have associated these variants with cocaine-induced paranoia but not cocaine dependence (Gelernter et al., 1994) and with methamphetamine-induced psychosis (Ujike et al., 2003) but not with methamphetamine abuse or subjective responses to acute methamphetamine (Hong et al., 2003; Lott et al., 2005). These findings suggest a distinct role for this SLC6A3 genetic variation in drug-induced paranoia and psychosis, which appears to be unrelated to drug abuse and dependence. However, a different VNTR variant of SLC6A3—consisting of repeats of a unit of 30 nucleotides in intron 8—has been associated with cocaine abuse in a Brazilian population (Guindalini et al., 2006).

Variation in genes for dopamine-metabolizing enzymes has also been implicated in drug effects. The DβH gene encodes dopamine beta hydroxylase (DβH), an enzyme that metabolizes dopamine to norepinephrine (Stewart and Klinman, 1988). Two polymorphisms in DβH—an insertion-deletion variant (DβH*Ins/Del) and a SNP (444G>A)—are often inherited together and have been associated with cocaine-induced paranoia (Yamamoto et al., 2003). The enzyme MAO-A metabolizes a broad array of drugs and other molecules, including the neurotransmitters serotonin, dopamine, and norepinephrine (Shih et al., 1993). A VNTR polymorphism in the promoter region of the MAO-A gene has been associated with risk for substance use disorders (Vanyukov et al., 2004; Vanyukov et al., 2007). A variant with three repeats of a 30-nucleotide segment results in decreased expression of the MAO-A gene compared with variants having 3.5 or 4 repeats (Deckert et al., 1999; Denney et al., 1999; Sabol et al., 1998). Some studies have associated the low-activity variant with increased susceptibility to alcoholism (Contini et al., 2006; Huang et al., 2007; Saito et al., 2002) and antisocial alcoholism (Samochowiec et al., 1999; Schmidt et al., 2000), although other studies have found no such associations (Lu et al., 2002; Mokrovic et al., 2008).

The Opioid System
Genetic variation in the opioid system has been implicated in altered risk for drug dependence. For instance, the OPRM1 gene encodes the receptor for beta-endorphin (an opioid produced naturally by the body) as well as for opiate and opioid drugs and the psychoactive metabolites of heroin (morphine and 6-monoacetylmorphine) (Ho et al., 2010). The most common OPRM1 SNP (A118G) occurs in exon 1 and alters an amino acid (Asn40Asp) in the receptor (Bond et al., 1998; Zhang et al., 2005).

Studies of the effect of this variant on receptor function have yielded contradictory results. Some suggest that receptors encoded by this OPRM1 variant have an increased affinity for beta-endorphin and greater receptor activation upon binding (Bond et al., 1998), while others have found no change in receptor function, signaling, or binding affinities for various opioids (Befort et al., 2001; Beyer et al., 2004). Although variation in OPRM1 has been found to contribute to the risk for heroin addiction in some populations (Bart et al., 2004; Szeto et al., 2001), not all studies agree (Bond et al., 1998; Tan et al., 1993), heroin use (Lawford et al., 2000), cocaine dependence (Noble et al., 1993), and psychostimulant polysubstance abuse (Persico et al., 1996). Some studies have suggested that TaqI A is a risk factor for smoking behaviors (Comings et al., 1996; Erblach et al., 2005; Huang et al., 2009), while other studies have not found these associations (Berlin et al., 2005; Johnstone et al., 2004; Singleton et al., 1998).

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The Serotonin Transporter

The serotonin transporter (5-HTT) is encoded by the SLC6A4 gene and directs the reuptake of serotonin from the synapse into the presynaptic neuron. This gene’s promoter region (5-HTTLPR) occurs in short and long variants, depending on whether a 44-nucleotide sequence is deleted or not. The short variant reduces the transcriptional efficiency of the gene promoter, leading to decreased production of 5-HT and hence a dysfunctional serotonin reuptake mechanism (Heils et al., 1996; Lesch et al., 1996).

The genotype in which both copies of the gene are short (s/s) has been associated with heroin dependence, particularly in violent heroin-dependent users, among Caucasian Italians. This finding is consistent with a hypothesis linking the 5-HTTLPR s/s genotype to a general behavioral disorder characterized by aggressiveness, impulsiveness, and vulnerability to addiction (Gerra et al., 2004). However, a study in Chinese subjects did not find an association between 5-HTTLPR variation and heroin dependence (Li et al., 2002).

Studies have suggested a possible role for serotonin transmission in susceptibility to nicotine dependence with the 5-HTTLPR s/s genotype being associated with personality traits (e.g., neuroticism) typical of smoking behavior (Hu et al., 2000; 1996; Lerman et al., 2000; Lesch et al., 1996). However, not all studies agree. In adolescents, the s/s genotype frequency was significantly higher among smokers compared with nonsmokers, and among heavy smokers who started smoking early compared with moderate smokers who started smoking later (Gerra et al., 2005). Other studies found that individuals with the s/s genotype were less inclined to smoke (Ishikawa et al., 1999) or found no association between 5-HTTLPR and smoking (Lerman et al., 1998; Sieminska et al., 2008; Trummer et al., 2006).

Genome-Wide Association Studies

Whole-genome association techniques have provided some novel insights into genetic influences on drug dependence (Liu et al., 2006). For instance, GWA studies have revealed previously unrecognized influences on the development of nicotine dependence (Bierut et al., 2007). As a result of those studies, variation in nicotinic receptor genes has become a focus of pharmacogenetic research (see Figure 4).

This research has drawn attention to region 15q25 (region 25 of the long arm of chromosome 15), which includes a cluster of genes that encode subunits of the nicotinic acetylcholine receptor: CHRNA3 (encodes the α3 subunit), CHRNA5 (encodes the α5 subunit), and CHRNβ4 (encodes the β4 subunit). Some GWA studies have found a direct association between 15q25 variation and lung cancer risk that may be independent of smoking behavior or nicotine addiction (Amos et al., 2008; Hung et al., 2008), while others have associated 15q25 variation with smoking quantity, nicotine dependence, and lung cancer risk (Thorgerisson et al., 2008). This gene cluster has also been associated with risk for chronic obstructive pulmonary disease (Pillai et al., 2009).

The GWA findings are in accord with candidate gene studies that have linked variation in CHRNA3 and CHRNA5 with the number of cigarettes smoked per day (Berrettini et al., 2008) and increased absorption of nicotine and tobacco toxins (e.g., nitrosamines) per cigarette (Le Marchand et al., 2008). Candidate gene studies have also associated variation in CHRNA5 with risk of developing nicotine dependence once a person begins to smoke cigarettes (Saccone et al., 2007) and with experiencing a pleasurable rush or buzz during the initial phases of smoking (Sherva et al., 2008). These findings suggest that variation in nicotinic receptor subunit genes may be implicated in smoking behaviors, nicotine dependence, and subsequent tobacco-related illnesses, such as lung cancer and chronic obstructive pulmonary disease.

The cost-effectiveness of GWA studies has been questioned because some of the gene-phenotype relationships they reveal do not appear to be very strong, while others would be logical targets for exploration using less expensive candidate gene studies. For example, nicotinic acetylcholine receptors are the primary drug targets for nicotine in the brain, and thus their biological relevance makes them promising subjects for candidate gene studies independent of the GWA results.

However, other GWA studies have identified genetic variants that were not obvious targets for candidate gene studies and may contribute to addiction vulnerability through previously unsuspected mechanisms, including cell adhesion; protein translation, trafficking, and degradation; transcriptional regulation; transport processes; and cell structures. Once discovered by GWA, these genes become high-priority subjects for candidate studies and biochemical pathway analyses.
Nicotine initiates its effects by activating nicotinic acetylcholine receptors (nAChRs). The normal function of these receptors is to respond to the neurotransmitter acetylcholine, but the nicotine molecule binds to the same sites that acetylcholine does and also stimulates the receptors.

When nicotine attaches to an nAChR, its impact depends on the combination of subunits making up the receptor. Each nAChR consists of five subunits, drawn from a set of twelve types, designated alpha 2 to 10 and beta 2 to 4. Some types are more responsive to nicotine than others. Genetic variation in the subunits also can affect their sensitivity to nicotine and thereby alter vulnerability to smoking and many aspects of the smoking experience and behavior.

**PHARMACOGENETICS OF SUBSTANCE ABUSE TREATMENT**

The enormous personal and societal costs of substance use and abuse (Rehm et al., 2006) dictate a need for effective interventions. Two strategies for achieving improved treatment outcomes are to optimize pharmacotherapies and to personalize treatment options (Rutter, 2006). Here we review a selection of studies that have linked genetic variation to treatment response and hence may advance progress toward these two goals.

As mentioned above, CYP2A6 genetic variation has been associated with smoking dependence and behavior, suggesting that it might also affect response to nicotine replacement therapy. Researchers investigated this hypothesis in a study with Caucasian smokers who were given standard, 8-week courses of the nicotine patch or spray (Malaiyandi et al., 2006). The results confirmed that CYP2A6 genotype influences smoking behavior, but the impact on quitting could not be determined due to the small sample size. However, slow CYP2A6 activity, as measured by blood levels of nicotine metabolites, was associated with higher plasma nicotine levels and substantially greater quitting success with the nicotine patch in multiple studies (Lerman et al., 2006a; Schnoll et al., 2009). In contrast, slow metabolizers had equal quit rates relative to normal metabolizers in the group that used the nicotine spray. Nicotine spray, like cigarette smoking, allows titration for differences in nicotine need and rates of metabolism. Recently we have also shown, using either the CYP2A6 genotype or the nicotine metabolite phenotype measure, that slow metabolizers respond better to extending the duration of nicotine patch treatment (Lerman et al., 2010).

In a study comparing placebo with bupropion (Zyban), slow CYP2A6 metabolizers achieved superior quit rates during treatment with placebo compared with fast metabolizers (Patterson et al., 2008). This finding is consistent with a role for CYP2A6 in smoking behaviors—such as amount smoked and smoking duration—that can alter smoking cessation outcomes. In addition, when bupropion was compared with placebo, only fast CYP2A6 metabolizers received any additional...
benefit (Patterson et al., 2008). Together, these data suggest that CYP2A6 slow metabolizers have superior quit rates even in the absence of active drug, and this effect is enhanced by the nicotine patch. In contrast, CYP2A6 fast metabolizers do poorly in the absence of pharmacotherapy and respond relatively well to bupropion.

The cytochrome P450 enzyme CYP2B6 is responsible for metabolizing bupropion to hydroxybupropion (Faucette et al., 2000). The CYP2B6 gene sequence is variable, and some variants result in altered CYP2B6 activity (Hesse et al., 2004; Kirchheiner et al., 2003). For example, the CYP2B6*6 variant (G516T and A785G), which is found in 45 percent of Caucasians, 50 percent of African-Americans, and 25 percent of Asians, results in decreased bupropion metabolism (Hesse et al., 2004). In a clinical trial of bupropion versus placebo (Lee et al., 2007), smokers with one or two CYP2B6*6 alleles achieved significantly higher abstinence rates with bupropion than with placebo. In contrast, smokers with two copies of the more common CYP2B6*1 allele showed no difference in abstinence between bupropion and placebo treatment. This study, if replicated, would suggest that smokers with the CYP2B6*6 variant should be treated with bupropion, but smokers with the CYP2B6*1/*1 genotype are unlikely to benefit from this medication (Lee et al., 2007).

Variation in the genes that encode nicotinic receptors also alters smoking behaviors and smoking cessation rates. In one study, a SNP (rs2072661) in the 3′ untranslated region of the CHRNA2 gene, which encodes the β2 subunit of the nicotinic receptor, affected abstinence rates at the end of smoking cessation treatment; individuals with the less common allele also had substantially decreased odds of being abstinent at the 6-month followup (Conti et al., 2008). Furthermore, this SNP was associated with reduced withdrawal symptoms at the target quit date and increased the time to relapse. Overall, while these results provide strong evidence for CHRNA2 in the ability to quit smoking, they require replication in an independent sample.

The dopaminergic system has also been implicated in the response to therapeutic interventions for drug dependence. For instance, just as the TaqI A variant of the DRD2 gene has been associated with heroin dependence, it has also been associated with poor methadone treatment outcomes (Lawford et al., 2000). Additionally, smokers with the InsC genotype of the DRD2 promoter region polymorphism at -141C responded more favorably to smoking cessation treatment with bupropion, but less favorably to nicotine replacement therapy with the patch or spray (Lerman et al., 2006b). Furthermore, smokers with two copies of a DRD2 SNP (957C>T) responded better to nicotine replacement therapy than smokers with one or no copies of the variant.

Beta-endorphin is released upon acute and short-term nicotine administration and exhibits rewarding effects. The common OPRM1 A118G variant was thought to alter the receptor’s binding affinity for beta-endorphin, but it may play a larger role in altering messenger RNA (mRNA; see Figure 1) and OPRM1 receptor levels (Bond et al., 1998; Zhang et al., 2005). Smokers with this variant were more likely to be abstinent at the end of 8 weeks of nicotine replacement therapy, with more pronounced effects in those receiving the patch versus the spray, compared with smokers homozygous for the most common OPRM1 allele (Lerman et al., 2004).

The OPRM1 A118G variant may also predict naltrexone response for the treatment of alcoholism. In placebo-controlled clinical trials, individuals with this SNP were more responsive to naltrexone treatment (Anton et al., 2008; Oroszi et al., 2009), took a longer time to relapse to drinking, and relapsed at lower rates (Osline et al., 2003; Kim, et al., 2009) compared with individuals without the variant. However, the association between OPRM1 A118G and response to treatment was not replicated in other clinical trials with naltrexone (Gelernter et al., 2007; Mitchell et al., 2007) or nalmefene (Arias et al., 2008).

The progression from pharmacogenetic discovery to better substance abuse treatment may be shortened if researchers develop and use phenotype measures (e.g., amount smoked, ability to stop for a short time, motivation to stop, treatment seeking) that are informative both for pharmacogenetic studies and in the screening of human medication development (Perkins et al., 2008). Such an effort should also address the need for uniform phenotype measures that will facilitate comparison and replication of pharmacogenetic findings. Researchers’ use of broad or inconsistent phenotype definitions is a major reason why contradictory conclusions about genetic effects on phenotypes—such as many noted above—are common in the pharmacogenetic literature (Sztamari et al., 2007).

PHARMACOGENETICS IN THE CLINIC
The Food and Drug Administration (FDA) recognizes the utility of pharmacogenetics in drug development
and patient care, provides information for understanding the role of such discoveries in regulatory judgments, and has approved the inclusion of pharmacogenetic test information in the labeling of selected drugs (Food and Drug Administration, 2008; Frueh et al., 2008; Shin et al., 2009). However, challenges will need to be met before the full potential of pharmacogenetic discoveries to advance clinical practice can be realized.

Demonstrating the clinical validity and utility of pharmacogenetic testing is among the greatest hurdles facing the widespread application of pharmacogenetics in clinical practice. To be accepted, the use of pharmacogenetic testing to guide treatment must demonstrably improve clinical outcomes (Hunter et al., 2008). However, as this article has highlighted, attempts to replicate studies that have shown benefit to such testing have often failed. The question arises: What degree of clinical benefit is sufficiently robust to warrant clinical implementation?

Once the clinical benefits and risks of pharmacogenetic optimization of a treatment are clearly defined, the question of cost-effectiveness may still remain (Heitjan et al., 2008). Complicated ethical and privacy issues raised by the use of pharmacogenetic tests are the focus of other reviews (Marx-Stolting, 2007; Shields and Lerman, 2008; van Delden et al., 2004).

If pharmacogenetic testing is to become widely accepted as a clinical diagnostic tool, who should be carrying out the tests? Currently, testing is done by using FDA-approved in vitro diagnostic devices and kits sold by manufacturers or, more commonly, by clinical laboratories that are not FDA-approved (Shin et al., 2009). With such a variety of testing options, strict monitoring systems are needed to guarantee reliable results (Hunter et al., 2008).

The limited availability and cost of pharmacogenetic testing are additional challenges (Tucker, 2008). Most insurance plans will reimburse the cost of pharmacogenetic testing only if it is required by the FDA, medically necessary, or has proven clinical utility (Shin et al., 2009).

Studies have shown that pharmacogenetic variation can significantly alter susceptibility to, and response to treatment for, drug dependence. It is important that we evaluate current approaches and address concerns appropriately in order to optimize the management of drug dependence through the use of pharmacogenetics.

CONCLUSIONS
We have highlighted several pharmacogenetic findings that contribute to the understanding of substance dependence and to the variation in responses to substance abuse treatment. Clearly, environmental factors also play a role, and future studies of pharmacogenetics will be improved if they are large enough to investigate both gene-gene and gene-environment interactions. We hope that a better understanding of the role of genetic factors will contribute to the optimal use of current therapies and the development of novel and potentially more effective therapeutic strategies.

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Strategies for Training Counselors in Evidence-Based Treatments

Evidence-based treatments (EBTs) for substance abuse and dependence have demonstrated superiority over treatment as usual when applied with strict fidelity in controlled clinical trials. Effective counselor training is critical if substance abuse programs are to realize these interventions’ full potential to enhance client outcomes in community practice. Although few empirical evaluations of training in EBTs have been conducted to date, the existing data warrant tentative conclusions concerning the appropriate roles and effectiveness of workshops, clinical supervision, distance learning, and blended learning. Among several outstanding research issues are questions of benchmarks for counselors’ performance in training and the relationships between such performance and clients’ substance abuse outcomes.

More than a decade ago, the Institute of Medicine (1998) challenged addiction professionals to implement evidence-based treatments (EBTs) in community programs. Although EBTs have been defined in various ways (Miller, Zweben, and Johnsen, 2005), in general they are treatments that have been shown to improve client outcomes in more than one randomized clinical trial (Chambless and Ollendick, 2001). In practice, counselors use their clinical expertise to apply these treatments in a manner that addresses their clients’ unique characteristics, cultures, and preferences (American Psychological Association Presidential Task Force on Evidence-Based Practices, 2006). EBTs may be pharmacological (i.e., methadone, buprenorphine, naltrexone, and disulfiram) or psychosocial (i.e., cognitive-behavioral therapy, contingency management, motivational interviewing, and 12-step facilitation) and typically are the best treatments counselors have to offer clients.

As addiction counselors’ awareness of EBTs has grown, their attitudes toward these treatment strategies, particularly psychosocial ones, have become increasingly positive (Garner, 2009), and they have increasingly begun to seek training (Miller et al., 2005). This demand has raised questions about how best to train addiction counselors in EBTs; how to evaluate their performance of the interventions; and how counselor, client, and organizational factors influence their learning and performance. This article describes current empirical knowledge on these issues and critical areas for research.
TRAINING STRATEGIES

Workshops are the most frequently used format for training counselors in EBTs. Clinical supervision is an important tool for helping counselors apply what they have learned in a workshop, or by other means, in practice with clients (Carroll and Rounsaville, 2007; Center for Substance Abuse Treatment, 2007; Miller et al., 2005, 2006). Distance learning and blended learning methods are relatively new training options that expand the possibilities for EBT dissemination. Each approach is described below, along with the evidence for its effectiveness.

Workshops
In a typical workshop, an expert or experts provide instruction via lecture and slide presentation, reinforced with reviews of treatment manuals and handouts. The workshop usually lasts hours or 1-2 days and often involves opportunities for participants to practice applying the EBT principles and skills in experiential and role-play activities. Most workshops include participants from different programs and regions; programs that provide their own workshops may tailor the training to their own specific context and issues (Baer et al., 2009).

Research indicates that workshop training improves counselors’ attitudes, knowledge, and confidence but does not adequately equip them to deliver EBTs to patients (Walters et al., 2005). For example, counselors consistently exhibit small increases in motivational interviewing (MI) skills after a workshop but revert quickly to pre-workshop levels, sometimes after only 2 months (Baer et al., 2004; Miller et al., 2004; Mitcheson, Bhavsar, and McCambridge, 2009). Although workshops are insufficient EBT training mechanisms in themselves, they are useful, and may be necessary, to inculcate basic skills and principles that counselors can further develop and hone in supervised practice experiences.

Clinical Supervision
Traditionally, substance abuse programs providing clinical supervision have relied on generic supervision principles such as those described by Powell and Brodsky (2004) or in the publication Competencies for Substance Abuse Treatment Clinical Supervisors (Center for Substance Abuse Treatment, 2007). These include establishing a supervisory alliance, recognizing supervisee stage of professional development, setting supervisory goals, and understanding organizational context and administrative functions.

Recent supervisory practice has emphasized competency-based approaches that (1) explicitly identify the knowledge, skills, and values that form the basis of competency in a particular EBT and (2) use specific learning strategies and evaluation procedures to sequentially build the counselors’ skills appropriate to their clinical settings (Falender and Shafranske, 2007). The core elements of high-quality competency-based supervision are the same activities that have been used to train counselors in the clinical trials that established treatments as evidence-based: direct observation of counselors’ sessions and the use of performance feedback and individualized coaching (Baer et al., 2007). Supervisors listen to audiotapes of counselors’ client sessions and rate the frequency with which the counselors use specific treatment strategies, their skill when implementing the strategies, and any intrusion of counseling strategies that are incompatible with the EBT (Waltz et al., 1993). The supervisors review their observations with counselors,
give advice for improvement, and sometimes suggest practice scenarios or exercises (e.g., role-play during supervision) or model or demonstrate skills. A typical clinical supervision schedule calls for biweekly discussions, some with individual counselors and some with groups of counselors, extending over several months.

Several studies have shown that competency-based clinical supervision improves counselors’ ability to deliver EBTs. Miller and colleagues (2004) found that counselors who received mailed feedback, phone-based coaching, or both after attending a workshop on MI gained more proficiency than others who attended a workshop with no supervisory followup. Notably, only when counselors received the most intensive level of supervisory input—both feedback and coaching—did their clients exhibit significant improvements in motivation for change within their sessions. Sholomskas and colleagues (2005) similarly found that counselors who attended a cognitive-behavioral therapy (CBT) training workshop with 3 months of followup supervision showed greater improvements in skill and received more “adequate” ratings for their delivery of the intervention than counselors who trained themselves in the therapy using a manual. Smith and colleagues (2007) described successful use of an innovative approach to MI training in which supervisors listen to client sessions over a phone and provide performance feedback and coaching via a modified telephone headset worn by the counselor (“bug-in-the-ear”). In another study, counselors’ performance of contingency management improved when supervisors offered drawings for cash prizes to those who met criteria for adherence to the protocol (Andrzejewski et al., 2001).

Despite these promising findings, it can be difficult to engage counselors in intensive supervision. Many trainers have noted that counselors are reluctant to provide their supervisors with recordings of their client sessions or to participate in session reviews, even when they are offered at no cost (Baer et al., 2004; Miller et al., 2004; Mitcheson, Bhavsar, and McCambridge, 2009). Moreover, many substance abuse programs, pressed by time constraints, omit supervisory reviews or focus them solely on administrative issues and case review (Center for Substance Abuse Treatment, 2007). Hence, the addiction treatment community needs additional feasible EBT training options. Distance learning methods may answer this need.

**Distance Learning**

Distance learning methods include computer-assisted and Web-based training and simulation programs (see Weingardt, 2004, for review of this literature). They typically use a variety of media (e.g., text, video, audio instruction, animation, and interactive exercises); tailor content to meet specific training needs (e.g., by allowing learners to select from a menu of learning modules); put learners in control of the order and speed of presentation; repeat material as needed; and feature built-in opportunities to practice newly learned skills, sometimes with performance feedback. Overall, distance learning modules offer individualized training with few geographic or temporal constraints, standardized quality, and low cost.

In the field of education, distance learning has been shown to produce equivalent gains in knowledge and skill relative to traditional workshop trainings (Weingardt, 2004). However, few data are available on its effectiveness for training addiction counselors. One randomized trial investigated the efficacy of supplementing training that used the Twelve-Step Facilitation Therapy Manual (Norwinski, Baker, and Carroll, 1992) with a computer-assisted CD-ROM that was keyed to the manual (Sholomskas and Carroll, 2006). Two groups of counselors spent a minimum of 10 hours over 3 weeks reviewing the manual; at the end of this period, the group that also used the CD-ROM demonstrated significantly improved twelve-step facilitation (TSF) Therapy performance and greater gains in knowledge than the group that relied on the manual alone. The same research center reported that supplementing manual-based training with
a Web-based training module produced superior CBT skills improvements throughout a 12-week followup period (Sholomskas et al., 2005). In this study, however, a workshop followed by clinical supervision yielded the best results (Figure 1).

Weingardt and colleagues (2009) developed an online eight-module CBT course (www.nidatoolbox.org) based on the Therapy Manual for Drug Addiction, Manual 1 (Carroll, 1998). They tested the course with two groups of counselors, one of which took it in a prescribed progression of two modules per week, while the other completed the modules in their own chosen order. Both groups also received weekly Web counseling supervision, the former on the material in their assigned modules, the latter largely unstructured. Both groups showed improvements in CBT knowledge and self-efficacy, suggesting that a flexible training model might be as effective as a more structured approach. Skills improvement was not measured in this study.

A new strategy for training uses computer programs to provide instruction via a virtual coach, who then provides feedback during an on-screen simulated practice session, praising good performance and offering corrective advice as needed. Hayes-Roth and colleagues (2004) developed and pilot-tested a program of this type to teach medical and nursing students a brief intervention for individuals who screen positive for having a substance abuse problem. Students who trained on the program performed the intervention significantly better in a test with standardized patients than did others who studied the intervention with a self-paced e-book.

These studies suggest that technology-based distance learning strategies can effectively teach counselors EBTs. However, none of them tested how well the strategies may affect counselors’ abilities to deliver EBTs with real clients in community program practice settings, nor did they examine effects on client treatment outcomes. Pending further studies, it may be prudent to consider distance learning methods as promising adjuncts to traditional counselor training strategies, rather than replacements for them (Weingardt, 2004).

**Blended Learning**

Blended learning involves combinations of training techniques and strategies to help counselors learn EBTs (Cucciare, Weingardt, and Villafranca, 2008). These may include traditional approaches (reading manuals, workshops, face-to-face supervision) and distance learning approaches (computer- and Internet-based courses and seminars, audio podcasts, online or telephone-based supervisory support). The most appropriate mix for a particular program will depend upon its counselors’ needs and interests and its trainers’ familiarity with multiple methods and skill in blending them. Blended learning typically sequences its component strategies over time, scheduled at the discretion of the trainer or according to the counselors’ preferences. This approach goes beyond one- or two-session trainings and usually

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**FIGURE 1. In Training, Method Matters**

Community-based substance abuse counselors who attended a seminar and received clinical supervision achieved greater gains in cognitive-behavioral therapy (CBT) adherence and skill than counselors who only studied a CBT manual. Counselors who worked with a Web-based CBT training program achieved adherence and skill ratings in between these two groups. Performance scores were assigned by independent raters based on observing the clinicians in a role-play exercise. The solid horizontal line indicates the level of performance that typically receives certification in clinical efficacy trials.

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Technology-based distance learning strategies can effectively teach counselors EBTs.
One of the best methods for assessing counselors’ performance is for an observer to rate it with a reliable and valid scale.

The experimental interventions that were compared in three above-cited training studies are examples of blended learning, combining a workshop with mailed or telephone feedback (Miller et al., 2004); a workshop with clinical supervision (Sholomskas et al., 2005); and Web-based CBT instruction with weekly teleconference supervision (Weingardt et al., 2009). Liddle and colleagues (2006) described a comprehensive blended approach to teach day-program counselors and other staff to perform multidimensional family therapy for adolescent substance abuse. Training was divided into two phases. An initial 6-month formal phase included group didactic sessions about adolescent development, families, and drug abuse treatment; skill-building workshops; and completion of daily diaries about key principles and skills. A 14-month implementation phase followed and involved regular supervision with feedback and coaching, co-therapy sessions with experts, and booster skill-building sessions. The researchers documented significant improvement in the use of the family therapy strategies, client satisfaction ratings, and self-reported drug abstinence from baseline to followup. The study did not have a control condition.

Blended learning is appealing because combining multiple learning methods with guided practice to teach complex psychosocial EBTs makes intuitive sense. However, research has not yet determined which combinations and sequences of training strategies over what periods of time are best for which types of EBTs, counselors, and organizational contexts. Also, the cost-effectiveness of these ambitious programs has not been determined. Counselor training and client outcome improvements might need to be large to justify the substantial investment required to develop and deliver these systems (Cucciare, Weingardt, and Villafranca, 2008).

EVALUATING PERFORMANCE

Studies have shown that counselors often overestimate their ability to deliver EBTs in the early stages of learning (Carroll, Nich, and Rounsaville, 1998; Martino et al., 2009; Miller et al., 2004). As self-evaluation is misleading, training efforts need to adequately prepare supervisors to properly judge counselors’ ability to use EBTs and provide them with teaching resources to further develop their skills. Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency (Martino et al., 2006) is an example of a supervision tool designed for this purpose. One of the best methods for assessing counselors’ performance is for an observer to rate it with a reliable and valid scale that researchers developed to certify counselors in clinical trials. Some of these scales are specific to one EBT; others may be adapted to evaluate counselors’ performance of several EBTs. An example of the latter is the Yale Adherence and Competence Scale (YACS) (Carroll et al., 2000), which is designed to rate counselors’ delivery of CBT, contingency management, TSF, MI, and interpersonal therapy. The YACS identifies the key strategies and techniques that define each treatment and interventions inconsistent with them. Typically, supervisors use the ratings to give counselors feedback on their performance and help them improve. The YACS also features parallel self-report versions that counselors can use to make self-assessments of their own performance that they can compare with their supervisors’ assessments. Counselors who do this may be more accepting of supervisory feedback and likely to provide suggestions for their own skill development (Sobell et al., 2008).

The reliability and validity of EBT counselor performance rating scales have been well established in clinical trials. However, the scales take time to learn, and the degree to which community supervisors or consultants can apply them accurately in real world treatment settings has not been well established. In one study that yielded promising results, Martino and colleagues (2009) found that community program-based supervisors who were trained to use a YACS-based scale to evaluate counselors’ use of MI could accurately identify the presence or absence of many strategies consistent with this treatment. The supervisors gave the counselors slightly higher marks than independent observers did, but lower marks than the counselors gave themselves, on the frequency of use of MI strategies.

Another method for evaluating counselors’ delivery of EBTs is to examine evidence of clients’ responses to treatment, such as changes in symptoms or outcome data. Although competent and faithful EBT delivery does not guarantee client improvement—for example, sudden and severe psychosocial stressors may cause setbacks—this trend should be generally present in counselors’ caseloads. Monitoring clients’ progress with standardized measures on an ongoing basis may be a valuable way to evaluate how counselors’ implementation of EBTs relates to positive behavior change. Lambert and colleagues (2001) provide an example of this method: Supervisors administered the Outcome Questionnaire 45
to obtain weekly self-reports of psychotherapy patients’ symptom distress, interpersonal relationships, and social role performance. Based on the results, the supervisors classified each patient’s status in one of four color categories: green (adequate functioning with no change in treatment strategy needed), yellow (less than adequate functioning with need for treatment adjustments), red (poor functioning with need for substantial treatment adjustments), or white (normal functioning and possible treatment completion). The supervisors disclosed these assessments to the patients’ therapists and, where indicated, helped the therapists review and find ways to improve their methods and interactions with their patients. In several studies, patients whose therapists received this feedback and input had more positive treatment responses (Lambert et al., 2005), although the specific impact on therapists’ actions within sessions was not studied.

This same methodology with appropriate standardized measures might be adopted for evaluating and improving addiction counselors’ implementation of EBTs. For example, cocaine abusers’ performance of homework assignments might be an informative indicator of how well their counselors are implementing CBT, inasmuch as the extent of homework completion corresponds to coping skills and cocaine use outcomes, even after controlling for treatment retention and baseline client motivation (Carroll, Nich, and Ball, 2005). As another example, the tenor and pattern of clients’ talk about change may be a good measure of counselors’ performance of MI, an intervention in which developing and supporting change talk is an essential counselor skill (Miller and Rose, 2009).

FACTORS INFLUENCING LEARNING AND PERFORMANCE OF EBTs
To learn an EBT well, counselors likely must be receptive and have beliefs, orientations, and core counseling skills that are consistent with the treatment (Ball et al., 2002). For example, McGovern and colleagues (2004) found that counselors who endorsed a 12-step model as their primary orientation were more likely than counselors who did not have this allegiance to use TSF and less likely to use MI, CBT, or behavioral couples counseling. Similarly, Sholomskas and colleagues (2005) and Baer and colleagues (2009) found that counselors who endorsed a 12-step model showed fewer gains in CBT and MI skills, respectively, although Miller and colleagues (2004) did not find that counselor characteristics affected MI training outcomes. A relatively unexplored area has been examination of counselors’ personal characteristics and predispositions that might affect their ability to learn EBTs. For example, Miller and colleagues (2005) speculated that counselors might require a minimum level of empathic ability to learn MI and later suggested that programs wishing to implement a particular EBT might screen counselors to identify those whose personal qualities are best suited to learning and delivering it (Miller et al., 2006).

With EBTs, as with other interventions, counselors may find a particular treatment model easier to apply with some clients than with others. Gaume and colleagues (2009) found that counselors’ skill in delivering MI depended on the clients’ stated ability to change their drinking. While all counselors demonstrated effective use of MI when clients expressed high levels of ability to change, some showed markedly poorer overall MI performance with clients who said they found it difficult to not drink. Thyrian and colleagues (2007) found that counselors who were treating postpartum women for smoking demonstrated greater adherence to MI with those women who had stopped smoking than those who were daily smokers. These studies show that counselors’ EBT skills may waver when the clinical going gets tough and suggest the need to provide ongoing training support as counselors apply EBTs in real-world practice.

Organizational factors can help or hinder counselors’ efforts to learn, implement, and sustain an EBT over time. Fuller and colleagues (2007) found that counselors were more likely to support EBTs when they felt that
their programs had a greater need for improvement and when their programs had more Internet access, better opportunities for professional growth, a clearer sense of organizational mission, and higher organizational stress. Baer and colleagues (2009) found that training improved counselors’ MI skills most when they felt their programs were open to change and not supportive of counselors functioning completely independently. Other studies have demonstrated that the influence of peer opinion leaders who advocate for EBTs is essential for successful implementation, and loss of these key individuals may derail training efforts (Squires, Gumbley, and Storti, 2008). Careful consideration of these and other critical organizational issues—e.g., staffing stability, policies and procedures, financial resources, administrative support—should be part of the planning process when preparing EBT training for counselors (Center for Substance Abuse Treatment, 2009; Simpson and Flynn, 2007).

QUESTIONS FOR RESEARCHERS
As the foregoing suggests, the empirical basis for training counselors in EBTs is developing but still far from complete. We have partial answers to some of the questions that follow and no answers to others.

Which Training Strategies Are Optimal to Teach Counselors EBTs?
Given the limited evidence about training strategy effectiveness, it is premature to specify guidelines for how to best train counselors in EBTs. Nonetheless, the research findings to date warrant provisional conclusions that:
- distance learning methods appear to develop counselors’ knowledge;
- workshops may serve as a platform for establishing basic skills;
- counselors likely require clinical supervision that includes observation, feedback, and coaching to become proficient in using EBTs with real patients;
- blending some or all of these strategies is probably the best way to approach counselor training.

On this basis, programs might consider sequential training that begins with the least resource-intensive methods. Thus, counselors who are new to an EBT might first complete a Web- or computer-based training to understand the basic concepts, then attend a workshop to obtain initial hands-on experience using multiple practice exercises, then implement the treatment under clinical supervision.

As noted earlier, some counselors may “take to” an
EBT quickly, while others may struggle to learn it. Some researchers have accordingly proposed adaptable training approaches that can provide each counselor with the intensity of training that he or she needs (Collins, Murphy, and Bierman, 2004). Such approaches will require performance criteria or benchmarks for identifying counselors who need additional training.

**What Should the Criteria Be for Evaluating Counselor Learning?**

No empirically derived training criteria or benchmarks linked to client outcomes exist in the literature for any EBT. With the exception of Liddle and colleagues’ (2006) descriptive training trial, none of the studies noted above examined whether training counselors to use EBTs actually improved clients’ substance use outcomes. However, Sholomskas and colleagues (2005) and Sholomskas and Carroll (2006), in their above-mentioned studies of CBT and TSF training, reported the percentage of counselors who reached the same YACS-based standards of performance used to certify counselors in studies in which those interventions were efficacious. Miller and colleagues (2004) used the Motivational Interviewing Skills Code (MISC)—a validated instrument for measuring fidelity to MI, although not one linked to outcomes—to establish standards for counselor proficiency in MI. More research with outcomes-linked performance measures is needed to establish empirically derived training goals.

**How Does Training Affect Counselors’ Interactions With Clients?**

To date, most studies that have evaluated counselors’ ability to implement EBTs have done so by assessing their performance in demonstration sessions with actors portraying clients. It is not clear that such assessments accurately predict how counselors will use EBTs with real clients. Real clients will likely vary more in clinical presentation and responsiveness to interventions than client actors (Miller et al., 2004). Resolution of this issue will require randomized controlled trials that evaluate how well counselors use EBTs with real clients and that collect practice samples with more than one client at each assessment point to gain a more valid measure of the counselors’ skills in using EBTs.

**How Will Training Strategies Sustain Counselors’ Skills?**

Most training studies to date have tested the effectiveness of interventions that were relatively brief (1-4 months) with posttraining followup periods of only a few months. Evidence that training strategies produce initial skill increases does not mean that these effects are durable, nor is it likely that the counselors’ skills will improve further without subsequent training and guided practice. While extended blended training interventions have promise for teaching counselors complex psychosocial EBTs, many questions remain unanswered, such as:

- What mixture of blended strategies should be used?
- How intensive should each strategy be, and how long should the intervals be between strategies?
- How long does it take for performance standards to be met?

In addition, the order of training targets might also be important. Miller and Moyers (2006) proposed eight ordered stages for learning MI; for example, becoming familiar with the underlying philosophy of the intervention precedes recognizing and reinforcing client statements that support change. While they acknowledge that their exact ordering may not be desirable in all cases, their stages do suggest a possible progression for extended blended training programs. Further development and testing may advance EBT training.

**What Qualifications Should Trainers Have?**

Quality assurance standards need to be developed for trainers to ensure high-quality counselor training. These standards should include competence in performing the EBT and other skills necessary to be an effective trainer—for example, facilitating discussions, organizing materials, and adapting content and methods to meet trainee needs. Direct observation is necessary for establishing counselors’ competence in delivering EBTs, and the same holds true for trainers. Martino and colleagues (2007) found that one-third of the applicants for a training-of-trainers workshop in the use of an MI supervision product were unable to demonstrate modest standards of MI proficiency based on an independent review of recorded client sessions. The specification of competencies for EBT trainers and methods to train them to these standards requires future development.

**How Well Does Formal Coursework Prepare Students to Implement EBTs?**

Most professionals first learn how to provide substance abuse treatment through formal coursework in graduate or certification programs. Coursework usually is coupled with clinical experiences to help students learn how to
apply the material. Unfortunately, this training often does not emphasize EBTs, and most new substance abuse professionals enter practice unprepared to implement these interventions (Weissman et al., 2006). Work is needed to develop and evaluate curricula for substance abuse EBTs, possibly incorporating some of the counselor training strategies described above. Given that graduate and certification courses typically are designed to conceptually build upon one another, the progression of coursework might offer a unique opportunity to study the developmental process or stages by which counselors learn EBT skills.

How Cost-Effective Are the Different Training Strategies?

Many have noted that the cost of counselor training must be weighed against the benefits expected from using EBTs (Cucciare, Weingardt, and Villafranca, 2008; Miller et al., 2005). This is particularly true for technology-based approaches and comprehensive blended learning approaches that require a substantial investment of resources. Studies to date have not estimated the costs involved with training or how much benefit consumers of training programs are likely to get for their money. Cost-effectiveness analyses need to be part of future counselor training trials.

What Studies Are Under Way That Might Advance Our Understanding of How to Train Counselors in EBTs?

Two NIDA-funded trials are currently testing counselor training strategies. Moyers is conducting a randomized clinical trial to determine if workshop and supervision training in MI can be streamlined by emphasizing the elements that presumably make the intervention work. The study will examine whether training counselors to recognize, reinforce, and elicit change language increases clients’ use of such language in counseling sessions. Martino is currently conducting a randomized clinical trial to test the effectiveness of supervising counselors in MI using the Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency. This study aims to determine the impact of clinical supervision on client outcomes and the extent to which the counselors’ adherence and competence in using MI mediates these outcomes.

CONCLUSIONS

While evidence-based practices are now established and widespread in substance abuse treatment, the knowledge base regarding counselor training methods has just begun to form. Although the evidence is far from complete, it indicates that ongoing training with supervisory support and rating-based feedback and coaching—spaced over time and individualized to the counselors’ training needs—is effective. New distance learning approaches have potential to extend training to more counselors and may be particularly useful when blended with traditional approaches to help learners master the complexities of psychosocial substance abuse treatments. Research has shown that counselors vary in their capacity to learn EBTs, depending on their treatment orientations, the types of clients they treat, and the nature of the organizations within which they work. More effort is needed to better understand these relationships. Finally, while training increases EBT skills and fidelity, the impact on client outcomes and cost-effectiveness are unknown.

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CLINICAL PERSPECTIVE—TRAINING COUNSELORS IN EVIDENCE-BASED TREATMENTS • 39
Response: Fidelity and Flexibility

Michael Shopshire, Ph.D.; Michael Levy, Ph.D.; and Carrie Dodrill, Ph.D.

Michael Shopshire: Programs and counselors are clearly interested in and even excited by motivational interviewing (MI) and other evidence-based practices. They attend trainings and say they implement evidence-based practices, but we don’t know what they’re actually doing in their sessions. They may not really be implementing the practices in the way that the creators intended or in a way that is supported by evidence.

I try not to be rigid about following treatment manuals. Speaking as one who has developed a manual-based treatment, I really believe that it’s useful for a clinician to make a treatment his or her own. However, you still need to be sure that you maintain the basic mechanism of change that makes the treatment work. As I’ve trained people in my cognitive-behavioral anger management treatment, some clinicians have said, “Well, I do your anger management treatment, but I only do the parts of it that I like.” There really is a bottom line: Either you are teaching a client a cognitive-behavioral anger management strategy, or you’re doing something that isn’t evidence-based at all. I’ve had people say, “Oh, I just let my clients have a temper tantrum, so they get their anger out in a cathartic way.” Well, wait a minute, that’s something the manual says you’re not supposed to do. If you do that, you’re no longer doing what researchers consider an effective approach.

So the question becomes, how do we make sure that people do what is prescribed in the treatment manual and don’t introduce contradictory practices or water down the treatment? Part of the formula is training, so front-line clinicians know how to do the treatment in the first place, but the other part is adherence, so that clinicians apply it correctly and consistently in practice. That’s where supervision is critical.

Dr. Martino’s product, Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency (MIA:STEP), is a good example of how one can take an evidence-based treatment and come up with procedures for supervising clinicians’ performance. It’s very innovative in that it’s one of a few examples of researchers making a concerted effort to come up with a training course for supervisors.

To date, the California–Arizona Node of the NIDA Clinical Trials Network (which is now part of the Western States Node) has conducted about three trainings in MIA:STEP. We took a two-step approach. First, we found out that a lot of clinicians said they’d taken classes on MI but weren’t comfortable enough to actually implement it. So, we hired an advanced trainer from the Motivational Interviewing Network of Trainers who gave some preparation to front-line clinical staff. Then, in our second step, we tried to attract the clinicians’ supervisors to complete the supervisor training. Unfortunately, that didn’t go as well as we had hoped. Only a few supervisors attended. We will follow up with those programs to see whether the supervisors were actually able to implement the MIA:STEP procedures and to identify the reasons they did not.

The low response from supervisors is very understandable. Programs these days are very busy treating their clients and dealing with various challenges. They may be coping with funding constraints and just trying to get by. Implementing something new and complicated may not be seen as a top priority compared with giving their clients the basic services they need. So even though programs are interested in learning about MI, they may not follow through and implement it in the precise manner that’s prescribed by the treatment manual. Some programs appear interested in MI because of mandates, rather than because they’re convinced it can improve their outcomes. As long as they feel that way, they may not see that it’s worth the effort that’s required to implement it with the fullest possible fidelity.

The supervision model that’s embodied in MIA:STEP is something that’s very familiar to researchers. The supervisor sits in on a session or listens to a tape, decides whether each transaction between the counselor and client is consistent with the treatment manual, and rates the transaction on adherence and competence. As researchers, we’re very aware of how to come up with competency and adherence measures and do this kind of rating. It’s a very microlevel critique. Rating portions of two session tapes might...
take 2 to 3 hours, and then it takes more time to give the clinicians their feedback. As researchers we’re used to it. However, it’s different from the kind of supervision that most programs do, and programs may find it too complicated and time-consuming to implement. The supervisor has to become almost an expert on the intervention to be able to recognize which interactions follow the manual and which don’t. It’s very difficult to get front-line clinicians engaged to this extent, especially because there’s usually no one they can directly bill for it.

There may be ways to ease the burden on supervisors’ time. They might listen to only parts of sessions, or they might collect tapes from all sessions and randomly select a few to evaluate. Clinicians might be motivated to adhere consistently if they knew that any one of their sessions might be evaluated. It may also be possible to use an outside agency to provide expert review of sessions. In multisite clinical trials, session tapes are often sent to a central location for review and feedback by experts in the research protocol. Still, programs might be wary of such an arrangement. Some criticize the evidence-based approach on the grounds that these treatments always seem to come out of elite universities, and it appears to them that businesses are built around the treatment manuals must be purchased, the trainers must be paid—and if it were then suggested to them that they now should pay a company to do the rating, too, they may feel that the effort is more motivated by financial profits than by a genuine interest in improving treatment outcomes.

Dr. Martino’s article points in the right direction and gives hope that we can come up with innovative ways to overcome these obstacles. Maybe we can develop self-paced online training alternatives for clinicians. Maybe we can make supervision easier by training clinicians to a higher level of skill, which will in turn increase adherence and fidelity before supervisor ratings are implemented. Ultimately, we need to convince programs of the importance of this kind of supervision and look for a cultural shift so that there’s a spirit of trying to adhere.

**Michael Levy:** Dr. Martino’s article lays out very well the different approaches to training and the incredible challenges to implementing evidence-based practices in real-world settings. CAB’s programs have experience with a number of evidence-based treatments, including methadone and buprenorphine, contingency management, Seeking Safety, the Adolescent Community Reinforcement Approach coupled with Assertive Continuing Care (ACRA/ACC), and Motivational Enhancement Therapy/Cognitive Behavioral Therapy 5 (MET/CBT 5). Our training approaches for these treatments have differed. For contingency management, I attended some trainings, and we gave a couple of in-house trainings using materials provided by the Addiction Technology Transfer Center. For the ACRA/ACC, one supervisor attended a workshop and became certified, then trained our staff. He used digital recorders to review their work and gave them feedback. His reviews were monitored, in turn, by the outside agency that developed ACRA/ACC.

We’re currently using the MIA:STEP model to train supervisors to work with their clinicians in MI. The clinicians have taken workshop training, but without ongoing supervisor monitoring, you don’t really know how well they sustain what they’ve learned; it’s kind of a black box. Supervisor support is critical to look very closely at what people do, code the work, and give them feedback—like, “here’s something you could do a little better.”

Clinical supervisors are busy people. When you’re rolling out something like this, it’s much more manageable for each supervisor to review tapes of a couple of clinicians at first, rather than his or her whole group, and to listen to maybe 15 minutes of each tape. When the first clinicians are doing well, supervisors can move on to a couple of others, and so on. Otherwise, the clinical supervisors will be overwhelmed.

Recording patient sessions has not been the norm in our organization. It represents a cultural shift. Many people were and are scared about it. However, we haven’t had much resistance. A key for successfully introducing any new practice is that the counselors have to really want to do it. For example, we started Seeking Safety at a time when our counselors were looking for ways to help a woman who struggled with trauma and substance use disorders, so the staff really were invested and eager to do it. Many of our clients grapple with ambivalence about change, so when I was ready to introduce MI and said, “Hey, do people want to get trained in this really cool process to assist people who are ambivalent about changing?” I got a lot of buy-in. If I hadn’t presented it in terms of how it can help counselors with a challenge that they all face, but instead had just said, “This is what we’re going to do,” I think we’d be doomed to fail.

Dr. Martino talks about organizational culture in his paper. I think this is another reason we haven’t had much resistance to session monitoring. CAB is known for not doing business just one way, but for trying to do cutting-edge, state-of-the-art things. When we hire people, they’re aware that we embrace a lot of different treatment modalities, and we aim for them to be skilled in a lot of different things to best serve our clients. Although recording patient sessions is now scary for some staff, it will eventually become an established part of this culture, and new clinicians coming on will see it as just a feature of the way we do things here.

Some counselors have spoken about feeling, at times, inhibited by the supervisory oversight. They feel self-conscious knowing that they will be rated, and that hinders their work a little bit. But, once they reach a level of proficiency and adherence, the frequency of reviews drops, they can make the intervention more their own, and it starts to feel more comfortable.

How much flexibility needs to be built into an evidence-based treatment to make
it as good as possible? I think there should be a fair amount, because, for example, it’s important to meet patients where they are. I could be following a manual and thinking, “This is what I’m going to do,” but when that client comes in, he or she is in a totally different place. If I don’t adjust and work a little differently, I might not engage the client, or the client might not be happy with that day’s session. I sometimes tell counselors to regard a new evidence-based practice as something new to put into their tool kit, one more thing they can use along with the other things they do. In practice, they draw from this, they draw from that, and they eventually make the intervention their own.

I was struck by Dr. Martino’s comment that counselors’ performance of MI may waver when the clinical going gets tough. He cites a study in which counselors demonstrated effective use of MI when clients expressed high levels of ability to change, but the counselors performed the intervention poorly when clients said they found it difficult not to drink. That is a point worth thinking about. It suggests that counselors who are going to deliver a treatment in community programs may require a higher level of training than those who administer it in clinical trials in research settings. The reason for this would be that the people who volunteer to participate in clinical trials may be more ready to change than those in the community programs, many of whom are there because a spouse or parole officer has given them an ultimatum.

Dr. Martino gives a good account of what we know about training for evidence-based practices, but it’s worth pointing out that evidence-based practices are only a part of the puzzle of how to help people recover. Many things go into a quality treatment program. Our staff get training in our treatment philosophy, quality management, Addictions 101, and the importance of customer service. We view and discuss a tape of the Stanford prison experiment (Haney, Banks, and Zimbardo, 1973) to increase awareness of the power we have over patients and the need to take care not to misuse it, even with the best intentions. There’s a lot of research that supports the importance of nonspecific variables, such as the quality of the therapeutic alliance, in patient outcomes. We could use more research that looks at what clinicians are actually doing moment to moment in therapy, because I think a lot of people are doing pretty good work. They’ve never written it up in a manual, but I think some treatment as usual is pretty good stuff.

Carrie Dodrill: I think the best clinical skill set is to be able to draw from an armamentarium of evidence-supported procedures and adapt to individual situations and things that are observed in sessions. It’s better to be flexible and apply a variety of evidence-based processes than to just do the same workbook with every person in the same way all the time.

I’m always fascinated by the many people who come to MI training believing that they’re already using the technique. They think MI is so basic that sometimes they don’t pay attention in the beginning. However, if you record and listen to exactly what they say in their sessions, it’s not MI. After they’ve gotten some feedback, they realize, “Oh, that’s what you mean, ” and that it’s not so easy. For example, they’re doing reflective listening, which does become basic when you practice it. But they’re not doing it in a two-to-one ratio to questions on a sustained basis, and that’s hard without sounding robotic.

So I agree with Dr. Martino that workshops are necessary for MI training, but not sufficient. You get the most behavior change with the blended approach, with ongoing supervision. The supervision can be singly or in a group, by phone or in person, by recording or directly observing counseling sessions, but one way or another, it’s indispensable to review actual sessions.

Counselors will be pretty nervous unless they are confident that their supervisors will score their tapes without bias. Anxiety about their scores and keeping their jobs might disrupt their learning. To alleviate that fear, in the Screening, Brief Intervention, and Referral to Treatment (SBIRT) project in Houston, a separate team of trainers and coaches reviewed tapes and provided skill scores for the providers every quarter. I and the others on the team were not the providers’ direct supervisors and had no say over whether they kept their jobs. Some providers still felt concerned that the scores would affect their job security, but overall I think they were comfortable and glad to have a chance to make mistakes and develop their skills in a somewhat protected setup. If you’re going to use an in-house rater, it will help to have someone who is highly trained and expert in the approach that he or she rates. That removes some of the subjectivity from the scoring.

As far as I know, no one in the Houston SBIRT program has been fired only for not meeting MI performance criteria—there were other performance criteria not being met for the one or two who lost their jobs. A couple of counselors were put on probation when they couldn’t use the skills after taking training that seemed to be sufficient for everyone else. These counselors got some extra training and feedback. I recall that they came up to par, and perhaps one of them dropped below par again, you know, and sort of hung around right on the edge.

Dr. Martino mentions the idea of giving clinicians cash prizes for learning treatments. We talked about doing this in the SBIRT project, but finally couldn’t see any way within the county rules about pay and promotions. But, for private organizations, I think it’s a great idea. Incentives can never hurt.

When we talk about training examples in the addiction field, we’re usually talking about MI training. That’s because MI developers have said from the outset that anyone can learn to do the technique, and they’ve created an extensive set of resources for training both supervisors and front-line providers. That’s not the case with some other evidence-based approaches that seem
to presume that only a subset of people with
certain types of training really can do them.
For those treatments to have the best chance
to be utilized to full advantage, it’s important
that providers be exposed to them in their
graduate training.

One type of training Dr. Martino
doesn’t mention is team-based learning. I
had a very good experience training teams of
medical residents in what to do with patients
who misuse alcohol. There was an initial
lecture or workshop for a few hours, and
then three annual booster sessions, each
with a refresher lecture and case example.
The residents formed teams to go over the
examples and answer questions about it
based on what they had learned. Teams
that got all the questions right won a prize
of candy or a healthy snack. We also gave
prizes to the resident who had done the
most screenings for alcohol misuse and for
other achievements. The residents found
the training very engaging, and we felt it
was successful.

Implementing a new practice puts
considerable demands on an organiza-
tion. Leadership has to believe that doing
so will improve its operation or outcomes.
They have to build time for training into
clinicians’ schedules and into their budget.
They absolutely must obtain buy-in from
the people who are going to be trained in
the new practice. I’ve seen cases where all
these things didn’t happen for programs
that have strong evidence supporting their
efficacy, and that’s unfortunate and sad.

REFERENCES
Cost Evaluation of Evidence-Based Treatments

Many treatment programs have adopted or are considering adopting evidence-based treatments (EBTs). When a program evaluates whether to adopt a new intervention, it must consider program objectives, operational goals, and costs. This article examines cost concepts, cost estimation, and use of cost information to make the final decision on whether to adopt an EBT. Cost categories, including variable and fixed, accounting and opportunity, and costs borne by patients and others, are defined and illustrated using the example of expenditures for contingency management. Ultimately, cost is one consideration in the overall determination of whether implementing an EBT is the best use of a program’s resources.

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Substance abuse treatment programs continually pursue the operational goals of providing effective treatments to clients and maintaining a stable business. Many programs have adopted or are considering evidence-based treatments (EBTs) as a way to advance both objectives. These are interventions that have demonstrated their ability to enhance patient retention, abstinence, and/or other desirable outcomes when compared with clinics’ established treatments. Programs that adopt EBTs may improve revenue flows by attracting new clients and by drawing referrals and funding from sources that require the use of interventions with proven efficacy.

This article aims to help programs considering whether to adopt an EBT. We briefly discuss criteria for identifying suitable EBTs and then focus primarily on costs: basic cost concepts, cost estimation, and the use of cost information in the final adoption decision. Ultimately, a program’s assessment of its organizational goals and traits, together with an analysis of costs, prepares it to determine whether implementing an EBT will produce adequate value. We illustrate concepts using the example of contingency management (CM), an EBT that has been shown to enhance outcomes in a variety of treatment settings.

FIRST STEPS: DEFINING GOALS, IDENTIFYING CONSTRAINTS

Programs have many EBTs to choose from, both psychotherapeutic (e.g., motivational interviewing [MI], cognitive-behavioral therapies [CBTs], CM, and family-based models such as multisystemic therapy) and pharmacological (e.g., buprenorphine/naloxone, naltrexone, disulfiram, acamprosate, and medications for co-occurring medical or psychiatric disorders). For a comprehensive list, see www.nrepp.samhsa.gov.
Not all EBTs are equally suitable for every program. Before focusing on any specific EBT, a program should clarify what it hopes to accomplish by implementing a new intervention. One primary goal will almost always be to provide more effective treatment; another is likely to be to ensure financial stability or make a profit; and a third might be to attract more clients from new demographic groups, users of other types of drugs, or individuals referred from new sources (e.g., criminal justice, child protection, or employee assistance systems). Programs may implement EBTs to attract, develop, and retain staff members who are highly skilled, knowledgeable about advances in the field, and engaged in quality improvement. A program may see EBT adoption as an effective strategy to improve its ability to compete successfully with other programs and maintain a reputation as an innovative and effective provider of addiction treatment. Clinics that receive public funding, and hence have a responsibility to society at large, may utilize EBTs to improve secondary outcomes of drug abuse treatment such as reducing the spread of disease (tuberculosis, HIV/AIDS), crime, and unemployment.

Whatever the reasons for a program’s interest in EBTs, its client, organizational, and funder characteristics delimit the set of potentially suitable interventions (see Table 1). In general, a clinic will want to consider only EBTs that have demonstrated efficacy, in several studies, among patients who are similar to those it intends to treat—for example, in terms of primary drugs of abuse, age (e.g., adolescent or adult), gender, co-occurring disorders, and other problems (Harwood and Myers, 2004). Before moving ahead with an EBT, a program should be confident that clinic staff either possess the skills to administer the intervention effectively or can be trained to do so. Otherwise, inadequate skill levels or negative attitudes may hinder or preclude effective delivery, no matter how well the intervention performed in controlled clinical trials. For example, a program whose staff objects to paying patients for abstinence may not attain the same outcomes from CM as one whose staff accepts the intervention’s underlying rationale of tangible positive reinforcement for achieving treatment goals. Similarly, with regard to funders, a model that provides incentives, or one that emphasizes harm reduction and client choice rather than abstinence and treatment compliance, might not obtain buy-in from the criminal justice or child protection systems.

Once a program has defined its goals and constraints, it can match them to available EBTs by consulting a growing reservoir of published materials. These include EBT psychotherapy manuals, pharmacotherapy protocols, computer programs, and other guidelines that have been made available by the National Institute on Drug Abuse (NIDA), the Center for Substance Abuse Treatment (CSAT), the Substance Abuse and Mental Health Services Administration (SAMHSA), and other sources (see Resources for EBT Decisionmaking on page 48).

COST AND VALUE
Before committing to an EBT, a program should answer three key questions regarding costs:

TABLE 1. Questions to Ask Prior to Adopting an EBT

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What evidence-based treatments (EBTs) are available? Which would be</td>
<td>most suitable, be most likely to be effective, and give the greatest value to</td>
</tr>
<tr>
<td>the clinic?</td>
<td>the clinic?</td>
</tr>
<tr>
<td>How strong and generalizable are the effectiveness findings? Do the</td>
<td>findings apply to the clinic characteristics and clinic’s clients (e.g.,</td>
</tr>
<tr>
<td>findings apply to the clinic characteristics and clinic’s clients (e.g.,</td>
<td>primary drug use, women, adolescents, criminal justice clients)?</td>
</tr>
<tr>
<td>primary drug use, women, adolescents, criminal justice clients)?</td>
<td></td>
</tr>
<tr>
<td>Does the treatment improve the outcomes that the clinic, client, and</td>
<td>staff care most about (e.g., abstinence, reduced drug use, reduced crime,</td>
</tr>
<tr>
<td>staff care most about (e.g., abstinence, reduced drug use, reduced</td>
<td>better family functioning, increased employment, harm reduction)?</td>
</tr>
<tr>
<td>crime, better family functioning, increased employment, harm reduction)?</td>
<td></td>
</tr>
<tr>
<td>Is the EBT a good match to the clinic in terms of staff, clients,</td>
<td>payers, etc.?</td>
</tr>
<tr>
<td>Will adopting one treatment prevent, or facilitate, the adoption of</td>
<td>the adoption of others now or later?</td>
</tr>
<tr>
<td>Will clients and those referring clients (e.g., criminal justice system)</td>
<td>interested in and satisfied with this treatment?</td>
</tr>
<tr>
<td>will be the extra costs of adoption, staff training, new staff,</td>
<td>management time, etc.?</td>
</tr>
<tr>
<td>Will payers be willing to pay for any extra costs? Which payers and</td>
<td>much?</td>
</tr>
<tr>
<td>Will staff be eager to adopt? Will adopting the EBT affect morale?</td>
<td>Will adopting the EBT affect satisfaction and turnover? Is there a</td>
</tr>
<tr>
<td>How difficult and expensive will it be to provide high-quality, effective</td>
<td>staff champion of the EBT?</td>
</tr>
<tr>
<td>care (e.g., fidelity to psychotherapies)?</td>
<td></td>
</tr>
<tr>
<td>How available, user-friendly, and costly are the methods available to</td>
<td>learn and adopt the new EBT and/or obtain technical assistance?</td>
</tr>
<tr>
<td>Should the EBT be phased in slowly or fully adopted immediately?</td>
<td></td>
</tr>
<tr>
<td>Can the adoption decision be reversed without large costs to the clinic if</td>
<td>it proves to be a poor decision?</td>
</tr>
<tr>
<td>Should all the patients get this treatment?</td>
<td></td>
</tr>
<tr>
<td>What are the benefits to adopting? The costs? Do the incremental costs</td>
<td>outweigh the benefits gained?</td>
</tr>
<tr>
<td>To what extent does the clinic want to follow up and evaluate costs and</td>
<td>profits as well as staff satisfaction?</td>
</tr>
</tbody>
</table>

Resources for EBT Decisionmaking on page 48.
• What will be the fixed and variable costs of implementing and maintaining the EBT?
• Will the intervention increase, decrease, or have no impact upon the financial bottom line?
• Will the intervention be the best use of the resources that it will require?

The first and second questions are strictly financial: their answers indicate whether the program will have sufficient resources to implement and maintain the new intervention and the potential impact on profitability. The third question is about value. To answer it, the program must weigh all the advantages expected from the EBT—e.g., monetary benefits, improved client outcomes, public health improvements—against what might be obtained by dedicating the same amount of resources to the next best available use (see Table 2). Whatever the outcome of the cost inquiries, adoption of the EBT is only suitable if the answer to the value question is affirmative.

**COST CATEGORIES**
EBTs vary widely in what they require in terms of training, equipment, counselor time, and other inputs and in the cost of the inputs. For example, pharmacotherapies involve outlays for medication, associated tests, physician and nursing time, storage, and inventory control; psychosocial treatments entail expenditures for initial training as well as ongoing supervision and retraining. Costs may also vary with the scale of operation, the type of clinic, and even the geographic location. The impact of each specific cost on the desirability of implementing an EBT depends upon whether it is (1) variable or fixed, (2) accounting or opportunity, (3) paid by the clinic, patients, and payers, or society at large.

**Variable and Fixed Costs**
Most EBT costs are variable. This category includes any expenditure that is tied directly to the number of patients or service units provided. Counselor time and medications are core variable costs. Depending on the specific procedures used, a program’s outlays for training activities and clinical supervision to maintain fidelity to an EBT may also count as variable costs.

A program can tally variable costs to predict the cost consequences of a new policy, such as increasing its census or implementing an EBT. For example, suppose a program contemplates expanding the number of patient slots for buprenorphine maintenance therapy. As long as the cost of buprenorphine remains unchanged, the program can project additional variable costs based on the number of new patients and the average cost of the medication per current patient. However, suppose a program adopts an EBT that requires patients to attend more frequent counseling sessions than the program’s prior standard. In this case, the program’s new outlays for counseling time will reflect both the number of new patients and a higher per-patient outlay for counseling time.

The fixed costs of a treatment include overhead such as rent, mortgage, insurance, and other contracts and expenses that remain stable over a long period of time, typically a year or more. As an illustration, a program that to date has provided only psychosocial services but now plans to implement a pharmaceutical EBT will anticipate new variable costs (cost of the medication), and also new fixed costs to maintain a pharmacy—e.g., rent (if a new space is needed), upkeep, and costs related to stocking the medication and fulfilling regulatory requirements. As another example, a program that adds prize-based CM to its service offerings will project new variable expenditures for prizes and new fixed costs to acquire and store prizes and manage the prize system.

A program may consider a new EBT a financial success if it produces sufficient income simply to allay its own variable or total costs, or the program may require that the intervention help allay preexisting overhead as well. As with variable costs, there is an interplay between the fixed and per-patient costs of an EBT. For example, if the rental cost for pharmacy space is the same whether 20 or 100 patients receive medications, the per-patient cost will be smaller if 100 patients are served. Because of this interplay, an EBT may be fiscally unfeasible at a small scale yet profitable at a larger scale.

**Accounting and Opportunity Costs**
Variable and fixed EBT-related outlays are often also opportunity costs, defined as disbursements that might alternatively be used for other ends. For example, an EBT-related outlay that is paid from a program’s operating surplus represents an opportunity cost, since the program has the option to use that money to pursue its aims in any way it chooses—such as to expand its present services or lower patient fees. In contrast, an EBT-related outlay that is paid entirely from a grant that is made specifically to support that particular intervention is not an opportunity cost, because the program must either use that money for the EBT or return it to the granting agency. The opportunity cost of adopting one...
The importance of CM rewards declines as patients become motivated by improvements in their quality of life.

EBT may be that another one cannot be adopted. The concept of opportunity costs reflects the reality that most clinics have limited monetary and other resources, and implementing a new EBT usually means forgoing other opportunities. Opportunity costs indicate the real value of resources and should be used in cost and cost-benefit considerations.

Costs to Patients and Others
Programs, especially public programs, must also consider EBT-related costs that will be borne by their patients, patients’ families, and communities. For patients, these costs typically can include fuel or fares for transportation to clinic visits, costs for child care, and time that is spent in the clinic but might otherwise be used to earn wages or for other positive activities. A patient’s family may have parallel expenditures if members accompany the patient to the clinic, participate in family therapy, or provide other support, such as child care.

An EBT that imposes unacceptably high costs upon patients or other stakeholders may attract fewer clients or experience lower adherence to treatment. For example, an intervention that requires fewer clinic visits may appeal to patients more than one that requires more clinic visits, even though the latter might yield superior benefits for those who stick with it.

Additional Costs
Along with the costs to deliver a particular EBT, clinics may incur indirect costs as a result of changes related incidentally to implementing the intervention. For example, if patients increase adherence and attend the clinic longer with the new EBT, they will generate more treatment costs. In such a case, the additional treatment costs might or might not be offset by the increased revenue from the patients’ additional clinic sessions.

PUTTING NUMBERS TO CONCEPTS: COSTING OUT CM
CM is a robust psychosocial EBT that has improved outcomes in clinical trials with abusers of a wide range of substances in a variety of treatment settings. At the core of CM is the use of tangible rewards to reinforce abstinence, attendance, and/or the achievement of prosocial or recovery-oriented goals. Patients typically earn cash, a prize, or a voucher for goods or services each time they present objective evidence of commitment or progress in treatment. CM interventions most commonly reward drug-free urine or breathalyzer tests, and some give prizes for attendance and participation in counseling sessions. CM has been shown to improve abstinence, length of stay in treatment, clinic attendance, and medication compliance (Lussier et al., 2006).

Early CM incentive programs were relatively expensive, but more recent CM designs have reduced costs while maintaining effectiveness. The three most significant CM outlays, discussed below, are the reward payments to patients, drug test kits, and labor to administer the incentive intervention. Each rises and falls in close correlation with the number of patients and so is a variable cost. Fixed costs of CM include establishing a reward and tracking system. An indirect effect may be that patients in CM stay longer; this could result in greater costs as well as greater reimbursement.

Reward Payments
The cost of reward payments in CM depends on the structure and generosity of the prize schedule, the clientele and their successes, the frequency of testing, and the effectiveness of the underlying usual care. The first tested version of CM gave cash rewards that totaled as much as $1,000 to each patient who remained abstinent throughout a 12-week treatment period (Higgins et al., 2000). Subsequent CM models have reduced costs by using a lottery system to award prizes (so that only a portion of patients meeting reward criteria receive rewards with monetary value), de-escalating payments in the later stages of treatment, and/or using nonmonetary rewards such as the right to take home medications. Petry and colleagues (2004) developed an incentive program in which patients who provide drug-free tests earn the right to draw for a set of prizes; the number of draws increases as the number of days of continuous abstinence increases. In a clinical trial, this design improved abstinence with total average payouts ranging from $36 to $68 (Petry et al., 2004).

Test Kits
CM protocols test frequently for drug use to provide patients with ample opportunities to earn the rewards that enhance motivation for abstinence. The frequency of testing in CM is more than that of most standard care protocols, and the added tests constitute a substantial variable cost of the EBT. For example, if a CM protocol schedules patients for two additional tests per week, and patients attend all their appointments, the clinic may incur costs of $8.40 per patient per week ($4.20 per urinalysis test cup). In a more realistic sce-
to the steps involved in putting the intervention into practice. The Iowa Consortium for Substance Abuse Research and Evaluation developed *Evidence-Based Practices: An Implementation Guide for Community-Based Substance Abuse Treatment* (2003), which provides EBT definitions, literature reviews, adoption and implementation challenges and barriers, assessments of readiness to change, and evaluation guidelines (www.uiowa.edu/~iowapic/files/EBP%20Guide%20%20%20Revised%2005-03.pdf).

The National Implementation Resource Network (NIRN) operated at the University of North Carolina, Chapel Hill, provides a wide array of resources related to best practices and the integration of science and service within several areas of behavioral health. The NIRN Web site (www.fpg.unc.edu/~nirn/) provides information on training institutes, conferences, other Web sites focused on dissemination, implementation research, and technical assistance as well as access to relevant articles, reports, and newsletters related to the stages and processes of implementation. In collaboration with NIDA and CSAT, the Institute for Research, Education and Training in Addictions (IRETA; www.ireta.org/ireta_main/nida_initiative.htm) provides a range of resources related to the implementation of best practices. The Web site contains or provides links to information on intervention implementation, technical assistance, fidelity measurement, staff training, and other EBT references.

**Labor Costs of Operating the Reward System**

The labor cost to operate a CM reward system will depend on the simplicity or complexity of the specific protocol, the efficiency with which it is implemented and run, and the wage rate of the personnel involved. In surveys of clinics in 2002, the total labor cost, including shopping for prizes, was estimated to be about $11 per client per week. However, clinics should be able to provide CM less expensively than this because: (1) the surveyed clinics employed trained counselors (at about $20 to $22 per hour, including fringe benefits) rather than technicians to administer the intervention, and (2) for purposes of the trial, the clinics did not implement CM on an efficient scale.

Note that CM labor costs do not include outlays to counselors for administering the standard counseling, even though CM patients also receive such counseling. This is because CM is implemented as a discrete supplement to standard therapy.

**TALLYING AND TOTALING COSTS**

The most appropriate method for estimating the complete costs of an EBT is usually to itemize and price all service units that are allocated to the intervention. Service units are the specific inputs utilized in the intervention, such as an hour of counselors’ time, a dose of medication, a drug test kit, recordkeeping, and use of facilities and equipment. The quantity of each unit will be estimated prior to implementation of the EBT, and then tracked following implementation.

The advantage of the service unit approach is that it isolates the incremental costs of an EBT—that is, the extra expenses that the intervention adds to overall operating costs. In a demonstration of this approach, Anderson and colleagues (1998) asked program personnel to keep a diary for 1 week and record each time they provided any of 94 different service inputs. The researchers used the diaries on unit use plus information on the unit price for each input—for example, the number of counselor hours and the counselor’s hourly wage rate, the price of a drug test kit and the number of kits used, use of clinic space and fair market real estate values—to calculate the total expenditures related to each scenario, patients may keep only 50 to 75 percent of their appointments and the incremental costs for CM test cups decline accordingly. The labor cost for administering each urine test has been estimated to average less than $2.50. To reduce these costs, some clinics have tried reducing the number of drug tests later in treatment, on the supposition that the importance of the CM rewards declines as patients achieve sufficient recovery to become motivated by improvements in their quality of life. Note that these cost estimates will, of course, vary over time and across geographic areas.
Yates (1999) provides a step-by-step description of the use of daily time sheets to estimate service unit costs. A few published studies have estimated the costs of particular EBTs. Programs may use these as benchmarks in EBT decisionmaking, but with the caveat that protocol, organizational, and contextual differences may result in significant cost variance from program to program. Jones and colleagues (2009) examined the costs of providing buprenorphine for opioid dependence. The study compared the costs of clinic-based methadone (MC), office-based methadone (MO), and office-based buprenorphine (BO). Treatment costs were calculated over 6 months of maintenance for patients who had previously been stabilized for at least 1 year. The total monthly cost of treatment per patient was estimated to be $147 (MC), $220 (MO), and $336 (BO). Much of the cost advantage of methadone was due to its lower price, which was $93 (MC) or $86 (MO) per month, compared with $257 for buprenorphine. The patients’ treatment-related costs (e.g., time taken to attend clinic, transportation costs, babysitting costs, etc.) were $92 (MC), $63 (MO), and $38 (BO).

NIDA’s Clinical Trials Network analyzed the effectiveness and cost-effectiveness of prize-based CM in a set of large, multisite trials. In one study, patients remained in treatment longer and achieved longer periods of abstinence after CM was added to the psychosocial services offered by eight outpatient programs (Olmstead, Sindelar, and Petry, 2007a). The incremental cost for CM was estimated to be $448 (range $306 to $582) per treatment episode, with an average patient stay of slightly more than 8 weeks. Of this amount, $213 was for prize payments, $146 for operating the prize system, $50 for testing costs, and $39 for extra counseling costs incurred due to clients’ longer stays in treatment. In a second study, the incremental cost to add CM to methadone maintenance was $225 overall, of which $130 was dispensed as prizes (Sindelar, Olmstead, and Peirce, 2007). Comparison of the results of the two studies suggested that adding CM to methadone maintenance was more cost-effective than adding the EBT to the psychosocial

<table>
<thead>
<tr>
<th>TABLE 2. Common Costs and Benefits of Introducing New EBTs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERSPECTIVE</strong></td>
</tr>
</tbody>
</table>
| Clinic | **Staff** | • Training and retraining  
• Ongoing supervision to ensure fidelity  
• Time providing treatment  
• Administration such as treatment notes | • More effective treatments  
• More satisfied clients  
• Reputation for cutting-edge, quality care  
• Ability to attract new clients, new and more referrals  
• Greater revenue  
• More satisfied staff, lower turnover, easier to attract staff |
| | **Management** | • Startup and ongoing oversight | |
| | **Medications** | | |
| | **Other Resources** | • Space, tests, materials, technical assistance, medical services, etc. | |
| | **Longer length of stay due to satisfaction** | | |
| Patients and Their Families | **Extra time and travel for additional visits, additional tests, etc.** | • More effective and durable treatment, resulting in  
– Better mental and physical health  
– Greater employment and income  
– Greater family functioning  
– Reduced expenditures for drugs  
– Fewer legal problems | |
| Payers and Society | **Higher outlays for treatment** | • Reduced crime and fear of crime  
• Reduced spread of HIV/AIDS, STDs, hepatitis C, and other contagious diseases | |
programs. The likely reason was that the patients in the psychosocial programs tended to do fairly well without the addition of the EBT.

Zarkin and colleagues used their Substance Abuse Services Cost Analysis Program (SASCAP) to estimate the costs of providing methadone (Zarkin, Dunlap, and Homsi, 2004). In a sample of 70 programs, they estimated the annual per patient cost to be $4,176, including initial assessment, group counseling, medication purchase and dispensing, and other cost components. They indicated that other similar estimates ranged from $2,800 to $6,300 (in 2000 dollars) (Zarkin, Dunlap, and Homsi, 2004). Roebuck and colleagues (2003), using data from a large number of studies fielded over 10 years, estimated that the mean cost per patient for methadone maintenance was $91 per week, or $7,358 per treatment episode. The Drug Abuse Treatment Cost Analysis Program instrument that was used to make this estimate is available online (datcap.com).

Perhaps over time NIDA, CSAT, or other professional groups could develop a set of template cost calculations, cost-effectiveness studies, or cost-benefit studies that would guide clinics in EBT adoption decisions. The information would be most useful with adjustment factors to reflect variable clinic characteristics: for example, type (e.g., residential, outpatient, methadone maintenance), client population (e.g., mixed gender or women only, primary drugs of abuse), funding sources, and geographic area. Such efforts would simplify EBT decisionmaking and by doing so encourage more widespread adoption of EBTs.

TO ADOPT OR NOT?
Substance abuse treatment programs should consider implementing EBTs, which have demonstrated their ability to improve client outcomes and potential to support other strategic and financial objectives. By consulting the literature, most programs will be able to identify a selection of EBTs that are well suited to their goals, organizational traits and strengths, and client and funder needs and expectations. Cost estimation and analysis provide critical information toward the question that ultimately should determine the course of action: Among all the options we have for using our resources, is this the one that will do the most to advance the totality of our organizational objectives?

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REFERENCES
Janet Wood: I found the article timely. In Colorado, we are trying to institute unit costing statewide to get folks to be able to define what it is they do, pair costs and outcomes, and paint a better picture of what they’re delivering. Some organizations are very skilled in this, but not all.

Greg Brigham: I enjoyed the article. I think that, in general, people don’t focus enough on how to decide when to implement an evidence-based practice. I especially appreciated the authors’ table of questions to ask prior to adopting an intervention. They are good questions, and they exemplify the sort of thoughtfulness that’s required to make good decisions.

Ron Jackson: They’re the meat of the article.

Interventions small and large
Greg Brigham: The authors’ choice of contingency management (CM) as a main example to illustrate cost concepts is a good one, in the sense that its elements are relatively tangible and easily counted, almost like a medication. You can just tally up the costs of the gifts and the costs of administering the program, and that’s basically what the intervention is going to cost.

Jackson: Another advantage of CM is that it’s relatively easy to monitor fidelity. Did you follow the reinforcement schedule or not? Did people get their reinforcers in a timely fashion? Yes or no?

Brigham: Cost assessment can be considerably more challenging, however, for some other evidence-based practices. For example, motivational interviewing (MI), which is very popular, requires more training and supervision than CM. Fidelity evaluation for MI is more complex than simply counting the number of gifts being given out. Cognitive-behavioral therapy is another intervention that’s more complex than CM; it takes more training and supervision and may require special staff.

Wood: CM is also simple to cost out compared with many other practices, because you usually add it to your treatment as usual instead of using it to replace something else you do. For the same reason, the cost-benefit question—how much improvement am I getting for my investment?—is often easier to answer with CM.

Brigham: Yes, programs will find it difficult to separate out the impact of some of the bigger, more involved evidence-based interventions from the effects of all of the associated inputs and changes. For those interventions, in general, I think programs have to rely on the research findings for estimates of effect sizes to use in their cost–benefit calculations.

Jackson: Research has fallen short, however, in articulating what kind of bang for the buck community programs can expect and how to measure against some benchmark. For example, what percentage of increase in positive patient outcomes can a program expect to get from adopting CM versus the cost of its treatment as usual? If I’m going to get a 10 percent bump in outcomes, but it’s going to cost me 25 percent more, I may not be as interested.

Brigham: Finding useful research can be a
challenge. Ideally, what a program wants are estimates from studies done with treatment-seeking people and community settings and providers as close as possible to its own. Unfortunately, many practices have been validated mainly in efficacy studies that were conducted in special settings with specialized counselors, narrow inclusion criteria, and specific control conditions, which may or may not resemble real care in the community. Nevertheless, even though the estimates from efficacy studies may not be ideal, they may provide some sense of what to expect in the way of results, if applied thoughtfully.

Wood: The article’s references include a number of studies and resources that can help programs with cost and cost-benefit calculations. If you aren’t already doing cost accounting, you don’t have to start from the beginning. You can go to one of these, put in the specifics for your organization, and get the estimates you need.

A new intervention or a new receptionist?

Brigham: The concept of opportunity cost is important. If resources are limited, as they often are in substance abuse treatment settings, using a resource for one thing means sacrificing the opportunity to do something else.

There is a push now for people to adopt evidence-based practices, and I am a big supporter of this. I think it’s a really good idea for providers to look at these practices. However, programs may have other needs that are higher priorities for spending their resources. These would include, for example, having clean and safe facilities and making sure that all staff, starting with the receptionist who answers the phone, treat people with dignity and respect. One could argue that having sufficient staff and adequate hours of operation to offer treatment on demand trumps the value of any intervention—since failing to offer treatment in a timely fashion can undo what you’re trying to do, and offering it quickly can really improve engagement and outcomes. If a program has a long waiting list, its lobby is not clean, and there aren’t enough friendly staff to greet people at the door, then adopting an evidence-based practice would be like putting an expensive GPS system into a car with bald tires.

Jackson: Don’t forget about the care and feeding of the treatment staff themselves.

Brigham: Good point. For any intervention to work well, your program needs to have adequate salaries, benefits, and training and an environment that keeps people at your center, so that you aren’t having constant staff turnover.

Wood: Your basic elements of leadership, staff makeup, and the strength of your business are prerequisites for putting you into a position to adopt evidence-based practices. The culture of your organization is also critical so that there is administrative support and an environment of acceptance of new ideas. I always recommend that providers who are just starting to explore evidence-based practices begin with the Network for the Improvement of Addiction Treatment (www.niats.net/Home/Home.aspx) to help them get used to the changes.

Jackson: One thing we haven’t talked about is the degree to which community treatment programs routinely monitor their own outcomes. Those who don’t may not even have a baseline to compare the effect of the adoption of an evidence-based practice.

Wood: True. That’s step one.

Jackson: One source of the pressure on community programs to adopt evidence-based practices is external mandates. A county contractor, a State director, a State overseer will say, “We want you to do more evidence-based practice.” But you’ve only got a finite amount of money. They don’t tell you what you’re supposed to do less of.

Wood: Well, now, I’m a State director, so hold on here.

Jackson: I know, Janet. But that’s the real world, and you know that’s true.

Wood: In Colorado we allow programs a lot of flexibility in what evidence-based practices they adopt. There is a wide continuum of interventions, with some that are easier and less costly to implement and others that require more resources and effort. At one end there is CM, and at the other are family therapies, such as multisystemic therapy, where you need master’s level therapists and 2 weeks of intensive training often delivered out of State by the developers. In addition, our State uses services from the Addiction Technology Transfer Center (ATTC), provides some funds for training costs, and facilitates other cost-saving activities. For example, we sponsor semiannual research forums that attract about 300 people for raising awareness of evidence-based practices, and then we pair those events with actual skill-building training for a smaller number of people.

That said, we are now considering whether we might want to choose one or two practices to focus on, make sure they’re disseminated widely, and build from there. The issue is the extent to which the cost of offering training for many different interventions diffuses our resources. We are constantly in touch with our ATTC, and we’ve got a pretty active group of people in recovery and other stakeholders who work together to help us make these decisions.

Costs to patients

Wood: The cost to patients is a real issue in Colorado. Our providers are not reimbursed for nearly the full cost of care, and the patients make up the difference in fees. The patients are bearing a high cost now, and new evidence-based interventions may push it even higher—for example, if the intervention requires more intensive visits or supplemental medications.
Brigham: I’m glad the authors included this concept in their paper. To me, the question for patients is similar to what the question should be for providers: What value do I get back for this investment?

In my experience, patients who are serious about dealing with their problems don’t mind incurring a lot of personal cost, even if they have to come to the clinic several times a week for several hours. What they don’t like to do, and shouldn’t have to do, is participate in things that don’t provide any value to them. That would include making extra visits just to get assessed without getting treatment or having to travel to multiple locations. Some substance abuse treatments have a very high cost in time, inconvenience, and invasiveness, even aside from the fees.

Jackson: I completely agree. Treatment Center X, why are you charging me $10 more a session now? What am I getting for that additional $10? Medicaid, legislatures, and funders ask the same questions, and you have to find plausible answers if you expect to get reimbursed.
Transporting Clinical Research to Community Settings: Designing and Conducting a Multisite Trial of Brief Strategic Family Therapy

This paper describes the development and implementation of a trial of Brief Strategic Family Therapy (BSFT), an evidence-based drug intervention for adolescents, in eight community substance abuse treatment programs. Researchers and treatment programs collaborated closely to identify and overcome challenges, many of them related to achieving results that were both scientifically rigorous and applicable to the widest possible variety of adolescent substance abuse treatment programs. To meet these challenges, the collaborative team drew on lessons and practices from efficacy, effectiveness, and implementation research.

Brief Strategic Family Therapy (BSFT) is an evidence-based treatment (EBT) that addresses family relationships associated with adolescent drug use (Szapocznik, Hervis, and Schwartz, 2003). BSFT has been shown to be efficacious in reducing adolescent drug use and conduct problems and in improving family functioning overall (Santisteban et al., 2003; Szapocznik et al., 1983; Szapocznik et al., 1986; Szapocznik et al., 1988). Here we describe the implementation of a multisite trial to determine whether BSFT can be effective in the community-based programs where adolescent drug abusers typically receive treatment.

We focus on the study design and protocol adjustments that we devised to meet two challenges that are common to all attempts to evaluate EBTs in community settings:

• to produce results that combine scientific rigor with validity for the range of community programs that treat the types of patients that the intervention is designed to help;

• to address the complex interplay between therapists, the interventions they deliver, and the service-delivery contexts into which interventions are to be implemented (Aarons and Sawitzky, 2006; Backer, 2000; Ducharme et al., 2007; Henderson, MacKay, and Peterson-Badali, 2006; Simpson, 2002).

The requirement to achieve both rigor and broad validity has led to the development of hybrid research designs. Such designs combine features typically associated with efficacy studies, which measure benefits in a research setting, with criteria of effectiveness research, which assesses the impact of interventions in community
settings. As is typical of such designs, our study sought to preserve the integrity of treatment comparisons by including intensive therapist training and supervision and well-developed procedures for assessing fidelity to interventions, while enhancing the generalizability of findings by enrolling a heterogeneous patient sample that reflects those typically seen in community programs (Carroll and Rounsaville, 2003; Clarke, 1995; Schoenwald and Hoagwood, 2001).

The need to consider the service-delivery environment has given rise to implementation research, which focuses on the modifications to interventions and adjustments to service-delivery systems that affect success in community settings. The community programs in our study made a number of such adjustments, including, for example, altering their normal procedures for training therapists and for billing.

We hope that this account of our experience will help researchers and community programs prepare for collaborative effectiveness studies by providing examples of issues that may arise and one group's solutions. Some of the strategies we describe are relevant to implementation research in general. Others are particularly suitable for studies of family-based treatments of adolescent drug abuse (Dennis et al., 2004; Henggeler, 2004; Liddle et al., 2006; Schoenwald, Brown, and Henggeler, 2000).

**STUDY OVERVIEW**

The BSFT effectiveness study was a collaboration between the clinical research faculty at the University of Miami Center for Family Studies, where BSFT was developed and its efficacy established, and the Clinical Trials Network (CTN) of the National Institute on Drug Abuse. The CTN is a consortium of a Federal funding agency, treatment researchers, and community-based treatment agencies that was formed to implement and test EBTs in community settings (Ducharme et al., 2007; Marinelli-Casey, Domier, and Rawson, 2002; Reback et al., 2002). Our trial compared BSFT to adolescent outpatient treatment as usual at eight community-based treatment agencies belonging to the CTN: Arapahoe House (Thornton, Colorado); Crossroads Center (Cincinnati, Ohio); Daymark (Salisbury, North Carolina); Gateway Community Services, Inc. (Jacksonville, Florida); La Frontera Center (Tucson, Arizona); Universidad Central del Caribe (Bayamón, Puerto Rico); Tarzana Treatment Centers (Tarzana, California); and The Village South (Miami, Florida).

The BSFT trial is one of the largest and most complex evaluations of a family-based intervention for drug abuse to date. Participants included 480 adolescents, their families, and other significant individuals in their lives—1,894 individuals altogether. Seventy-five therapists took part. Of these, 30 were assigned to deliver BSFT, and 23 of those received the full BSFT clinical training.

Treatment as usual varied considerably from agency to agency. It might include individual, group, and family therapy, as well as case management and psychiatric consultation. At one agency, it consisted of intensive outpatient services with several hours daily of individual and group therapy sessions. Because we anticipated variability in treatment as usual, we planned to analyze differences in the effects of BSFT and treatment as usual at each site as well as across all sites.

The primary study hypothesis was that BSFT would reduce adolescent drug use more than treatment as usual would. Secondary hypotheses were that BSFT would be more effective in engaging families in treatment; in reducing teens’ risky sexual behaviors, delinquency, and externalizing disorders; and in improving family functioning and positive social activities. Patients’ primary and secondary outcomes were measured for 1 year after they were randomly assigned to one or the other treatment. All BSFT-related treatment and assessments have been completed, and analysis of the data is currently under way. The study findings will be reported elsewhere.

**PROTOCOL DEVELOPMENT**

The first step in the trial was to establish a team to develop
the study protocol. Initially, representatives from the University of Miami’s Center for Family Studies and from four community agencies across the State of Florida made up the entire team. Over time, however, the team expanded to include individuals from universities and community agencies across the Nation. With the goal of obtaining the widest possible array of research and community viewpoints, we welcomed any professionals from community agencies who expressed an interest in developing the protocol, whether or not their agency planned to participate in the study. Collectively, the team of 12, led by BSFT developer José Szapocznik, had expertise in conducting clinical trials with scientific integrity and also in administering community-based treatments.

The team’s first challenge was to determine the appropriate community treatment setting for examining BSFT. Community providers on the team considered three potential designs: (1) BSFT integrated into standard residential treatment, (2) BSFT as a followup intervention for adolescents released from residential programs, and (3) BSFT as an outpatient intervention. The first design was rejected, because the trials that had established BSFT’s efficacy had all tested it as a stand-alone intervention. The second and third designs were adopted.

The protocol team also had to select an appropriate comparison condition. Most prior family therapy effectiveness studies have compared the trial intervention with a specific alternative treatment regimen; however, the results of such studies are applicable mainly to treatment programs that use the particular regimen used as a comparison and so have limited potential impact on public health. The team instead adopted the community providers’ suggestion that treatment programs and policymakers would be most interested in a comparison of BSFT with the participating programs’ treatment as usual. Because the programs varied in the services they offered substance-abusing adolescents, this approach would yield information about how BSFT compared with a broad range of services (e.g., individual, group, intensive day treatment, or case management) that adolescents typically receive.

A design variant that had considerable appeal would have deployed BSFT as an add-on intervention and compared treatment as usual versus treatment as usual plus BSFT. Among its advantages, this design would have provided a within-site control, required no changes to be made to treatment as usual, omitted the need to randomize the therapists, and would have been the easiest approach to implement. However, the increased burden for clients and therapists (potentially double the number of sessions) and costs associated with providing two treatments would have threatened the sustainability of the intervention for community programs. Hence, the final consensus was to implement BSFT as a stand-alone intervention.

Throughout the planning and carrying out of the study, the researchers and community practitioners of the protocol team worked together as equal partners rather than in a hierarchical relationship. Level partnership established a basis for the team members to maintain effective communication throughout the project’s development and implementation. Communication occurred via weekly conference calls that included all collaborators, as well as weekly calls with the University of Miami research team and research assistants at the sites. Calls were dedicated to identifying problems and developing solutions. Changes to the research protocol were implemented only after they were discussed and a consensus achieved. These procedures are consistent with the components that were previously identified as essential for the successful dissemination of EBTs (Reback et al., 2002).

ASSEMBLING RESEARCH TEAMS IN COMMUNITY PROGRAMS

The first step in moving from discussion to implementation was to create a research structure at each community treatment program that would enable the program to carry out the complex study protocol. Each program identified a site principal investigator, a research coordinator, and research assistants. Four programs already
had research departments and experience in conducting clinical trials: They could use their existing personnel and organizational structures and, as one research coordinator noted, they “did not need to sell the importance of the study to anyone on the project team.” The other four sites had to create new research infrastructures and educate their staff concerning what research involves and its value. In the end, the advantage enjoyed by sites with research experience was relative: The scope and complexity of the BSFT trial—as illustrated, for example, by its use of 14 different assent/consent forms—was daunting for even the most research-savvy agencies. Although sites varied in how quickly they integrated new procedures into their daily activities, ultimately they all successfully implemented the research protocol and contributed data that were used in the final analysis.

The principal investigator at each agency was responsible for onsite monitoring and oversight of the study protocol. Among the challenges principal investigators addressed during the trial were coping with competition among different agency programs for new clients, negotiating BSFT protocol demands versus agency therapist productivity pressures (e.g., number of hours billed and completion of paperwork), securing adequate funding and other resources for both study implementation and agency clinical services, and promoting the benefits of the project to all involved agency departments. The principal investigator became the most important factor determining each program’s degree of success in implementing the protocol. In general, the more involved the principal investigator was with the daily activities of the protocol, the more quickly the program identified potential problems and developed solutions. Similarly, the stronger his or her leadership position was before the study, the more successful the site was in overcoming barriers.

Research assistants were critical to the protocol’s success as well. They helped to recruit participants, conduct assessments, and relay completed measures to data management. The protocol team encouraged sites to hire research assistants who were proficient in attending to the details of research forms and procedures but could also engage and interact simultaneously with several family members, some of whom had serious mental or behavioral problems or were at odds with each other. Another goal in recruiting research assistants was to find individuals who possessed a specific set of clinical skills that included communicating enthusiasm about treatment and the study, listening and validating each person’s concerns, working around family conflicts, and providing appropriate care in chaotic home environments. The assistants would have to overcome considerable client ambivalence and resistance because adolescents and their families typically do not see themselves as being in need of change.

THERAPIST SELECTION

Community treatment programs that have training slots available—whether for BSFT, another family therapy, or other interventions—generally offer them to their “best” or most appropriate clinicians. Doing so enables the programs to obtain the maximum benefit from their investments in training. We were concerned, however, that if the community programs in our study selected their most skilled clinicians to learn and deliver BSFT, our results would be biased in favor of BSFT. To prevent this, the study conducted formal assessments of agency clinicians’ interpersonal skills, willingness to participate in intensive training, and other factors necessary to provide treatment as usual and to learn BSFT. Only therapists whose scores on these assessments demonstrated aptitude for both interventions were accepted into the study. We assigned these therapists randomly to either receive training and deliver BSFT or provide treatment as usual. By randomizing their assignments, we ensured that the range of aptitudes was similar among the therapists in both treatment groups.

Some participating agencies’ adolescent outpatient departments were too small to supply the minimum of four therapists that we needed to be able to distinguish BSFT effects from therapist effects independently at each study site. To make up the difference, these agencies recruited volunteers who worked in other departments or in the community, or who had not previously treated adolescents with substance abuse problems. This liberal approach should enhance the generalizability of our results to programs whose therapists may have less experience treating adolescent substance abuse. Because of it, our study results may suggest how much therapists with a wide range of skill levels can achieve with BSFT, while underrepresenting what programs that follow normal practices for therapist selection and training might achieve.

When a site recruited therapists who were not from its adolescent outpatient department into the study, its principal investigator had to reorganize staff to meet both the agency’s contractual obligations and the requirements of the protocol. For example, the protocol required BSFT therapists to devote approximately 20 percent of

The principal investigator became the most important factor determining each program’s degree of success.
a full-time work week to BSFT training, supervision, and study-related paperwork. Some agencies could draw from a pool of part-time staff to fill the personnel gaps created by this shift in BSFT therapists’ responsibilities. However, the allocation of time to the research protocol presented a major challenge to agencies whose clinical staff were already spread thin covering existing obligations. When therapists added BSFT training to their full existing caseloads, their workloads became unmanageable, and this impeded implementation of the intervention.

THERAPIST TRAINING
The BSFT training process evolved over the course of the project in response to challenges faced by the therapists. At the beginning of the trial, we provided therapist training as specified in the protocol:

- a 4-day workshop consisting of a 3-day overview of BSFT and 1 day of training on research forms and study procedures;
- three additional 1-day workshops over the next 13 weeks;
- weekly group supervision sessions delivered in 3-hour conference calls with a certified BSFT trainer/supervisor at the University of Miami.

However, high rates of therapist turnover at all the sites forced us to adapt and condense the training program for replacements so that they could be deployed promptly. For example, a trainer traveled to one agency and delivered the first and second workshops back-to-back and then returned a month later to give the third and fourth workshops back-to-back.

Therapist training times during the study ranged from 4 to 12 months. Some of the variability represents a downside of our “open” therapist selection process. The length of training was burdensome to the community treatment programs because every delay in certifying therapists translated into delays in other research activities. We originally estimated that we would require 6 months to train the study therapists, and we scheduled the shorter research assistant training to begin later and end simultaneously, at which time we would also begin enrolling study participants. At the first four sites, however, therapist training took longer than anticipated, and programs ended up retaining research assistants while they waited for the therapists to attain certification. This had direct implications for the budget, and research assistants’ newly learned skills may have atrophied during the long wait to put them into practice. Despite these experiences, therapists successfully implemented BSFT in a manner consistent with the theoretical underpinnings of the therapy. Independent ratings of therapy sessions revealed that the therapists adhered to the core techniques of BSFT. They also, however, documented substantial variability in the quality of therapy sessions across therapists and even for the same therapist between cases and over time. This finding is consistent with our own observations, during supervision, that therapists waxed and waned in the quality of sessions. Thus, as other research teams have substantiated (Henggeler et al., 2002), adherence to systemic family therapies may be difficult to maintain in community agencies without intensive monitoring and supervision. Another indicator of therapist effectiveness was that client and family engagement and retention rates were similar to those in a recent BSFT efficacy trial (Santisteban et al., 2003).

PATIENT SELECTION AND RECRUITMENT
We set patient inclusion and exclusion criteria to include most of the adolescents referred for drug abuse treatment at the participating community agencies. For example, we accepted youths who had used illicit drugs in the 30 days preceding baseline assessment even if they did not meet diagnostic criteria for drug abuse or dependence, as had been required for participation in the efficacy trials. After we launched the protocol, we learned that many youths were being excluded because they had been referred from residential treatment settings or juvenile detention facilities where they did not have opportunities to use drugs, and we expanded our criteria to include these adolescents. To account for differences in the level of use for youths being referred from restricted settings, we included “referral for drug treatment from an institution” as a covariate in planned analyses. In other ways as well, we redesigned our analyses of drug outcomes in response to the considerable variability in baseline drug abuse among youths referred to outpatient services in community settings.

In another departure from the inclusion and exclusion standards of the efficacy trial, we did not take into account co-occurring psychiatric disorders. Consequently, our sample included youths with a mix of co-occurring psychiatric disorders, which is representative of most community programs.

The most important factor for successful participant recruitment was the systematic integration of the protocol into the community agencies’ existing intake procedures. We recommended that the research staff
conduct or at least attend all intake interviews to ensure that every potential participant who entered the agency received information about the study. We observed that research staff who were committed to the study were most successful in engaging adolescents and family members into the protocol.

Most agencies, we found, did not highlight family services among the constellation of services provided, even though all eight considered family therapy a critical component of their treatment of adolescents. Working closely with each site’s principal investigator, we developed a strategic plan that included integrating the presentation of family services into the initial discussions with potential participants. This approach helped promote the agency, as well as the study, to each family. Principal investigators also helped to convey the emphasis on family involvement to agency staff.

Court mandates provided an important referral stream of adolescents for many of the agencies. However, the courts sometimes required much more stringent treatment parameters than BSFT uses. For example, the court that sent adolescents to one agency usually recommended one of two programs: three treatment sessions per week for 6 months or an intensive program of five sessions per week for 1 year. In this instance, the site principal investigator met with the primary referring judge to present BSFT as a viable treatment alternative. He highlighted the national study, the voluntary nature of participation, the research showing that family therapy was an efficacious treatment for drug-using adolescents, and the lack of evidence that intensive interventions are more efficacious than less intensive ones. The judge agreed to permit court-referred cases to be enrolled in the study.

**AGENCY ACCOMMODATION OF RESEARCH AND BSFT**

The community treatment programs had to adjust various practices to integrate BSFT into their service offerings. Although many changes were logistical and concrete in nature, such as securing the equipment and room for group supervision conference calls, others involved a philosophical shift.

**Strengthening the Family Focus**

Although all the agencies acknowledged the importance of family involvement in the treatment of adolescents, most had few clinical staff with training, or even experience, working with families. Treatment as usual typically consisted of individual and group therapy; even when parents participated, the treatment models tended to be cognitive and behavioral rather than focused on family systems. This lack of orientation to family led to challenges in several areas of the project, including recruitment of families into the study.

To address this issue, the research team at the University of Miami worked with sites individually to elicit their views on the role of families in the treatment of drug-using adolescents. At several sites, the principal investigator expressed strong agency commitment to involving families in treatment, but admissions staff did not always communicate this to families being recruited for the study. Consequently, many parents opted not to participate based on the misunderstanding that the treatment as usual did not require family involvement. This was particularly the case for families experiencing high levels of conflict and families that viewed the adolescent as the primary problem. To remedy this situation, site principal investigators were encouraged by the research team at the University of Miami to meet regularly with their admissions teams and research assistants to inform them about all the services, including family services, provided at the agency. These conversations were essential for integrating the study into the agency’s daily activities and convincing agency staff of the value of the research.

The early difficulty in recruiting families served as a warning sign. We put into place procedures to avoid this problem with sites that began training later and during the study. For example, research assistants were required to complete a weekly tracking list that included
information about all new referrals to the agency and an update on the research assistants’ contact with each of them. Members of the University of Miami research team reviewed this tracking list weekly.

**Billing for Family Services**

Clinics need to know not only whether they will be able to achieve desirable outcomes with a new therapy but also whether they can sustain it financially. Therefore, in contrast to efficacy trials, where the research sponsors typically pay for the treatment, our BSFT effectiveness study did not fund any clinical services. Agencies were reimbursed for time that therapists spent in training and supervision on par with the financial support that hundreds of national and international agencies have received for training and supervision in empirically based family therapy over the past decade through local, State, and Federal contracts or grants and private foundations. Therapists in the study received a $3,000 incentive to participate in training and complete research forms.

Most of the community programs in the study already had a standard line on their billing forms for family therapy, but some had to revise their procedures to bill for BSFT. Likewise, some agencies had to modify their billing practices to reimburse for family sessions in which the adolescent participant was not present, but the therapist worked with the parents on issues that affect the adolescent.

A BSFT therapist often will go to a family’s home during the evening or on a weekend. To support this flexibility, the agencies in the BSFT protocol needed to allow therapists to work atypical hours and reimburse for transportation, insurance, mileage, and other incidental expenses.

Some agencies expel patients whose urine tests positive for drug use. Successful integration of the BSFT intervention, however, required that the community treatment programs in our study allow adolescents to remain in treatment even after numerous positive urine screens. Further, the research team at the University of Miami consulted with each site about potential BSFT clinical terminations, reviewing the efforts to engage the adolescent or family and recommending intensified engagement efforts when appropriate.

**CONCLUSION**

The BSFT trial was designed to evaluate the effectiveness of an evidence-based family intervention with adolescent substance abusers and their families in community treatment centers. In the process of designing and implementing the study, key features of efficacy studies (e.g., intensive therapist training and ongoing supervision, assessment of treatment fidelity) were combined with features that are more characteristic of effectiveness research (e.g., inclusion of participants with co-occurring disorders, recruitment of therapists...
already employed at the agencies). Close collaboration between university-led research training centers and community providers sought to ensure that the protocol not only met the highest standards of scientific integrity, but also yielded results that are generalizable to community practitioners. The strategies described in this paper are particularly relevant for furthering implementation research focused on family-based treatments of adolescent drug abuse (Dennis et al., 2004; Henggeler, 2004; Liddle et al., 2006; Schoenwald, Brown, and Henggeler, 2000).

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MICHAEL S. SHOPSHIRE, Ph.D., is quality assurance and regulatory affairs coordinator for the California-Arizona (CA-AZ) Node of the NIDA Clinical Trials Network at the University of California, San Francisco. He has extensive experience in regulatory affairs coordinating NIDA/SAMHSA and other federal, state, and local contracts and grants.

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GREG BRIGHAM, Ph.D., is chief research officer at Maryhaven, a substance abuse treatment facility in Columbus, Ohio, and a research scientist at the University of Cincinnati. Dr. Brigham has specialized in addiction treatment and prevention since 1982. He has developed and implemented a wide range of behavioral and medication-assisted treatment programs. He is active in local, State, and national efforts for the adoption of evidence-based practices and has participated in the development and implementation of numerous clinical trials of community-based substance abuse treatments.

SLADE DODRILL, Ph.D., is an assistant professor and staff psychologist at the Michael E. Debakey Veterans Affairs Medical Center at Baylor College of Medicine. He also is a member of the Motivational Interviewing Network of Trainers. Dr. Dodrill’s experience includes roles in several randomized controlled trials funded by the National Institutes of Health, the Centers for Disease Control and Prevention, and the Health Resources and Services Administration. He is currently involved in studies to reduce environmental tobacco smoke in the homes of infants who received neonatal intensive care, to use expressive writing as an intervention for depressed clients court-referred for alcohol and drug treatment, and to increase management of opioid addiction by using buprenorphine in primary care.

VITKA EISEN, Ed.D., M.S.W., is chief executive officer for Walden House, Inc., in San Francisco, one of the largest providers of behavioral health care to poor and uninsured Californians. She oversees Walden House’s network of substance abuse and mental health treatment, re-entry, and prevention services throughout California for incarcerated men and women, ex-offenders, and other substance abusers and their families in the community. Dr. Eisen has served on the faculty of San Francisco State University’s School of Social Work and Porterville Community College. She has over 20 years of experience in the human services field and a lifelong commitment to supporting people struggling with addiction and incarceration.

RON JACKSON, M.S.W., is the executive director of Evergreen Treatment Services (ETS), a private non-profit organization in Seattle, Washington, that provides outpatient opioid treatment to more than 1,500 patients in clinics in Seattle and Olympia. Mr. Jackson has investigated various types of interventions for individuals dependent on opiates, cocaine, and marijuana. He is currently a co-principal investigator for the Pacific Northwest Node of NIDA’s Clinical Trials Network and is an affiliate professor at the University of Washington’s School of Social Work.

MICHAEL LEVY, Ph.D., is the director of clinical treatment services at CAB Health & Recovery Services, an organization that offers a full continuum of care for clients with substance use disorders. Dr. Levy has written numerous articles and book chapters and has given many workshops that focus on working with clients with substance use disorders and those with co-occurring disorders. In 2007 he published the book, Take Control of Your Drinking … And You May Not Need to Quit.

MICHAEL S. SHOPSHIRE, Ph.D., is quality assurance and regulatory affairs coordinator for the California-Arizona (CA-AZ) Node of the NIDA Clinical Trials Network at the University of California, San Francisco. He has extensive experience in regulatory affairs coordinating NIDA/SAMHSA and other federal, state, and local contracts and grants.
Graphic Evidence

ADOLESCENT DECISIONMAKING: STILL A MYSTERY

Scientists have proposed various theories to explain why adolescents are more likely than children or adults to make decisions that result in accidents, suicide, homicide, addiction, and other negative outcomes. According to one theory, the part of the brain that says, “That’ll feel good—go for it” matures before the part that says, “Hold on, there could be a downside here.” Another theory holds that these adolescents are trying to do what adults do, but before society is ready for them to be adults and before they have the experience and skills that enable adults to hedge the attendant dangers.

A recent NIDA-funded study lent support to the latter theory. Dr. C. Monica Capra and colleagues at the Emory School of Medicine in Atlanta found that, in brain development, adolescents who made risky decisions—about sex, glue sniffing, drinking and driving, and other activities—were more like adults than those who played it safer.

The researchers assessed risk-taking behaviors of 91 boys and girls, 12 to 18 years old, using questions from the standardized Adolescent Risk Questionnaire (ARQ). The results indicated that children younger than 14 uniformly took few risks (Figure 1). Both the overall level of risk taking and the amount of divergence between individual risk levels increased steadily from age 14 to 18.

The researchers adjusted the ARQ responses statistically to eliminate the effects of age and sex (males had scores that were 10 percent higher on the risk-taking scale), then compared the adjusted responses with diffusion tensor brain images of the 60 youths who were aged 14 to 18. The youths who made riskier decisions had greater nerve fiber density and more myelination in tracts connecting the two sides of the prefrontal cortex (red areas, Figure 2A) and emanating from the prefrontal cortex to brain motor areas via the corona radiata (yellow and red areas, Figure 2B–2D). Increases in fiber density and myelination in cortical tracts are features of brain maturation that enhance the volume and rapidity of nerve transmission.

The prefrontal cortex is a center of judgment. The study findings suggest that the right and left prefrontal cortex may be better coordinated and exert stronger influence on risk-taking teens than their more conservative peers.

The Emory team says that its findings counter the idea that adolescent risk taking reflects immature cortical tracts but raise another question: Does precocious brain development predispose adolescents to take risks, or does engaging in risky activities at a young age affect brain development?

Continuing Education Quiz for Counselors

Substance abuse counselors can earn two nationally certified continuing education (CE) hours by reading the indicated articles and completing the multiple-choice quiz below. This is an open-book exam. Complete the quiz by circling one of the multiple-choice answers. Be sure to answer all questions; unanswered questions will be scored as incorrect. You must score at least 70 percent to earn CE hours. Please note that we must receive your quiz by March 31, 2011.

Addiction and Cognition—Page 4
1. In the two-stage model of addiction, the first stage is predominantly characterized by:
   a. alterations in signals carried by the neurotransmitter glutamate;
   b. heightened susceptibility to drug cues during periods of abstinence;
   c. protein synthesis pathways between neurons are also involved in drug-seeking behaviors;
   d. craving.

2. Drug-stimulus associations persist over time because:
   a. communication pathways between neurons are reshaped during substance abuse;
   b. proteins that participate in cell signaling pathways between neurons are also involved in drug-seeking behaviors;
   c. substance abuse can alter brain areas that are responsible for long-term, declarative memory;
   d. all of the above.

3. Synaptic plasticity refers to:
   a. the reshaping of communication pathways between neurons;
   b. withdrawal symptoms during early abstinence;
   c. drug-related impaired cognitive performance;
   d. all of the above.

4. Some evidence-based treatments are based on use:
   a. cognitive-behavioral therapy;
   b. motivational interviewing;
   c. medications such as buprenorphine;
   d. all of the above.

5. The most effective method for training therapists to deliver an evidence-based therapy is:
   a. workshops that are reinforced with reviews of treatment manuals and handouts;
   b. clinical supervision of therapists, involving direct supervision of sessions and the use of performance feedback and individualized coaching;
   c. Web-based training and computer-assisted simulation programs;
   d. yet to be determined.

6. “Blended learning” refers to:
   a. evaluating the effectiveness of counseling methods through an analysis of patient outcomes;
   b. a combination of training techniques, such as manuals, workshops, and face-to-face supervision, which help counselors learn how best to use evidence-based treatments;
   c. training in a cross-cultural context;
   d. initial training in an evidence-based treatment followed by booster sessions.

7. The main theme of this article concerns:
   a. balancing scientific rigor and real-world applicability in a community-based trial of Brief Strategic Family Therapy;
   b. the best methods to retain a population of drug-abusing adolescents in a long-term research study;
   c. ways to develop fair and equitable reimbursement policies for therapists;
   d. all of the above.

8. Hybrid designs balance features that are typically associated with both:
   a. cognitive-behavioral therapy (CBT) and Brief Strategic Family Therapy (BSFT);
   b. clinical research (efficacy studies) and real-world intervention research (effectiveness studies);
   c. effectiveness studies and analyses of reimbursement policies;
   d. all of the above.

9. When designing and implementing the Brief Strategic Family Therapy (BSFT) protocol in community treatment programs, researchers were challenged to:
   a. develop a research structure that would enable each community treatment program to carry out the complex protocol;
   b. systematically integrate BSFT recruitment protocols into each agency’s existing intake procedures;
   c. encourage community treatment programs to make a philosophical shift regarding the nature of drug treatment for adolescents;
   d. all of the above.

This issue of Addiction Science & Clinical Practice has the following objectives for drug abuse treatment providers and researchers:
- to explain how drugs affect learning and memory, and the clinical implications of these effects;
- to review current knowledge concerning how well various training methods prepare therapists to deliver evidence-based treatments;
- to describe a multisite, community-based effectiveness trial of an evidence-based treatment, highlighting challenges faced and steps taken to meet them.

Please rate the following on a 1 to 5 scale, by circling the appropriate number:

1. To what extent did these articles accomplish these learning objectives?
   Completely Adequately Not at All
   1       2       3       4       5

2. To what extent did you learn something useful to your profession?
   Completely Adequately Not at All
   1       2       3       4       5

3. Was the information well presented?
   Completely Adequately Not at All
   1       2       3       4       5

Please print legibly, copy page, and mail with your $25 payment to: AS&CP CE Quiz, RTI International, 6110 Executive Boulevard, Suite 502, Rockville, MD 20852. Quiz and payment must be received by March 31, 2011.

Name ________________________________
Address ________________________________
City ____________________________ State ___ ZIP __________
Phone (   ) __________________________

Please rate the following on a 1 to 5 scale, by circling the appropriate number:

I certify that I have answered the test questions without any help.

Signed ____________________________ Date ___________

(  ) Check (  ) VISA (  ) MasterCard

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Signed ____________________________

Make checks payable to RTI International. In about 6 weeks you will receive notification of the results and, if you score 70 percent or higher, a certificate of completion. The National Institute on Drug Abuse, publisher of Addiction Science & Clinical Practice, is a NAADAC-approved provider of continuing education home study.
Addiction Science & Clinical Practice is published twice yearly to promote dialogue between researchers and providers with the aim of improving drug abuse treatment and research. The publication may also be viewed at NIDA’s Web site: www.drugabuse.gov.

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