



**Introduction to Magellan's Adopted Clinical Practice Guidelines
For the Assessment and Treatment of Patients
With Substance Use Disorders**

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Magellan Health Services Clinical Practice Guideline Task Force

Robert Ciaverelli, M.D.
Kathleen K. Frampton, R.N., B.S.N., M.P.H.
Gary Henschen, M.D.
Daniel P. McCarthy, Ph.D.
Lawrence J. Nardoizzi, M.M.M., M.D., D.F.A.P.A., C.P.E.
Anna Scherzer, M.D., F.A.A.P., F.A.A.C.A.P., F.A.P.A.
Charles Wadle, D.O.

Purpose of This Document

Magellan Health Services (Magellan) has adopted the American Psychiatric Association's (APA) *Practice Guideline for the Treatment of Patients With Substance Use Disorders, Second Edition* (2006),¹ *Treating Substance Use Disorders: A Quick Reference Guide* (2006),² and *Guideline Watch (April 2007): Practice Guideline for the Treatment of Patients With Substance Use Disorders, 2nd Edition*³ to serve as an evidence-based framework for practitioners' clinical decision-making with adult patients who have a substance use disorder. The APA guideline and reference guide are among the most comprehensive, evidence-based clinical practice guidelines (CPGs) for these disorders, and are widely used. The guideline and reference guide cover most areas of psychiatric management of patients with these disorders, covering topics from clinical features and epidemiology to numerous aspects of treatment approach and planning. Since this guideline and its reference guide are broadly accepted by managed behavioral health care organizations (MBHOs), this adoption will minimize the burden on practitioners participating in multiple MBHOs.

As with all guidelines, these adopted guidelines and Magellan's Introduction are intended to augment, not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to the treatment guidelines should be noted in the member's record. Additionally, this guideline does not supersede Food and Drug Administration (FDA) determinations or other actions regarding withdrawal or approval for specific medications or devices, and their uses. It is the responsibility of the treating clinician to remain current on medication/device alerts and warnings that are issued by the FDA and other regulatory and professional bodies, and to incorporate such information in his or her treatment decisions.

Content of These Adopted Guidelines

The APA 2006 substance use disorders guidelines cover the assessment and treatment of substance use disorders for the following major substances of abuse:

- Nicotine
- Alcohol
- Marijuana
- Cocaine
- Opioids

Additional Recommendations Based on Recent Literature Review

The APA guideline is based on a literature review through February 2005. Magellan conducted a further review of the clinical literature on assessment and treatment of substance use disorders – including use or abuse of alcohol, cocaine, cannabis, tobacco and opioids – published through June 2010. Key relevant recommendations from this more recent review are summarized below. Magellan encourages providers to become familiar with this information, as well as the information in the APA guideline.

Disease Definition, Natural History, and Course and Epidemiology

After publication of the APA guideline, more analysis of national survey data augmenting the discussion on substance abuse epidemiology in the United States has occurred. A clinical review by Compton et al., summarizing additional observations on findings of recent large surveys on substance use (i.e., National Survey on Drug Use and Health: National Findings 2002 and the Monitoring the Future Study: National Survey Results on Drug Use, 1975-2003 Survey), indicated shifts in the landscape of illicit drugs used over the past 30 years. The authors summarized findings of these major national studies, which revealed that illicit drug use in the United States escalated in the 1970s, decreased in the 1980s, increased again around 1992, reached a relative peak around 1997, and has subsequently leveled off, or in some cases, declined. Compton et al. also stressed several important findings from these surveillance studies as follows: (1) a marked increase in the use of opioid medications (oxycodone and hydrocodone) and an even greater increase in the problems associated with their use; (2) an increase in marijuana abuse and dependence – especially among younger black and Hispanic people, possibly related to an increase in marijuana’s potency; (3) an increased availability of high-purity heroin, and an increase in heroin use by smoking and other non-injection routes; (4) an increase in initial use of 3, 4-methylenedioxymethamphetamine (MDMA or ecstasy); (5) an expansion of the use of “club drugs” other than ecstasy, including ketamine and gamma-hydroxybutyrate; (6) a decline in the use of LSD; and (7) a stabilization and some signs of decline in the use of cocaine. (Compton et al. 2005)

The most recent findings from the 2009 National Survey on Drug Use and Health (NSDUH) indicated that an estimated 22.5 million persons (8.9 percent of the population aged 12 or older) were classified with substance dependence or abuse in the past year based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorder, 4th edition (DSM-IV). Of these, 3.2 million were classified with dependence on or abuse of *both* alcohol and illicit drugs, 3.9 million were dependent on or abused illicit drugs but not alcohol, and 15.4 million were dependent on or abused alcohol but not illicit drugs. The specific illicit drugs that had the highest levels of past year dependence or abuse in 2009 were marijuana (4.3 million), pain relievers (1.9 million) and cocaine (1.1 million). (Substance Abuse and Mental Health Administration [SAMHSA], 2009)

Other more recently published data from the Research Update - National Institute on Drug Abuse (NIDA) and SAMHSA also confirmed that prescription drug abuse is a significant emerging problem in the United States. The statistics show that in both 2006 and 2009, approximately 7 million persons (2.8 percent of the U.S. population) were current users of psychotherapeutic drugs or other agents targeting the central nervous system. (SAMHSA, 2009; NIDA, 2008) The abuse and diversion of prescription drugs is particularly problematic among adolescents due to the broad availability of prescription drugs and misconceptions about their safety. The most commonly abused

prescription drugs are opioids to treat pain, central nervous system depressants to treat anxiety and sleep disorders, and stimulants used to treat certain sleep disorders and attention deficit/hyperactivity disorder. (Bright 2010; SAMHSA, 2009; NIDA, 2008)

The abuse of illegal steroids as performance enhancing drugs has also become a health problem in the U.S. The Centers for Disease Control and Prevention (CDC) reported that 4.4 to 5.7 percent of boys and 1.9 to 3.8 percent of girls (grades 9 through 12) have used illegal steroids to enhance performance, energy and work capacity in an effort to gain a competitive edge. Most of these users are non-athletes or recreational body builders who began abusing anabolic steroids as teenagers. (Fernandez et al., 2009)

The use of smokeless tobacco products (i.e., snuff or chewing tobacco) was not specifically addressed in the APA guideline although they contain nicotine and are highly addictive. A team of epidemiologists from the United Kingdom noted a decline in usage of oral and nasal smokeless tobacco products in Europe and North America during most of the 20th century. However, these investigators reported a reverse trend in prevalence for their usage in the past few decades, especially among people who are under 40 years of age. (Boffetta and Straif, 2009) While these products are marketed as a safer alternative to cigarettes with small or negligible risks to health, they are carcinogenic in humans and may be associated with an increased risk of fatal myocardial infarction and stroke. (Boffetta and Straif, 2009; National Cancer Institute, 2010)

The use of cannabis for medicinal purposes (“medical marijuana”) was not a focus of review in the APA guideline. Already, 14 states have enacted laws legalizing the medical use of marijuana for a variety of indications such as pain management, treatment of nausea/vomiting, weight loss associated with debilitating disease, neurologically induced spasticities and other uses (e.g., glaucoma). (Seamon, 2010; Procon.org 2010) Medical societies have indicated that the decision to legalize marijuana for medical purposes was made in the absence of strong evidence supporting its efficacy and was based largely on animal data and anecdotal human reports. (Degenhardt et al., 2008; Burgess 2007) Similarly, 11 states and the District of Columbia have pending legislation to legalize its use for medical reasons and two states have passed laws favorable toward its usage for medical reasons while not formally legalizing its use for such purposes. (Burgess 2007; Procon.org 2010) The impact of the wider availability of cannabis for ostensibly medical purposes on the incidence of substance use disorders in the general population remains to be seen. Moreover, there is an urgent need for studies involving patients who smoke cannabis for medical purposes to assess the increased risk for cannabis dependence, cancer, cardiovascular disease and psychosis. (Degenhardt et al., 2008)

Proposed new goals of the U.S. Public Health Service’s Healthy People 2020 initiative are to increase both the proportion of adolescents who disapprove of substance abuse and perceive the great risks associated with it. (HHS, 2010) Studies published after release of the APA guideline have explored preventive interventions for substance abuse that exploit a window of opportunity in adolescent development to shape behaviors. Findings from these more recent studies have shown that prevention programs developed for teenagers can contribute to significant reductions in illicit substance abuse in this age group. Successful prevention intervention efforts included: (1) group sessions for adolescents on coping skills targeting personality types (i.e., traits of hopelessness, anxiety sensitivity, impulsivity and sensation seeking) (2) child/parent programs addressing family risk and protective factors (i.e., parent nurturing, child management skills, involvement in family activity and adolescent social skill development) and (3) other combination packages of formal school and community-based prevention programs (e.g., Lion’s Quest Skills for Adolescence,

Olweus Bullying Prevention Program, Big Brothers/Sisters, Parents Who Care, etc.). (Conrod et al., 2010; Hawkins et al., 2009; Spoth et al., 2009)

General Treatment Principles - Somatic Treatments

The APA guideline section titled “Somatic Treatments” discusses medication therapies for substance use disorders (SUD) as effective adjuncts to behavioral therapies and self-help groups, which may be employed in the entire range of treatment levels and settings. This section discusses the appropriateness and effectiveness of medications to treat SUDs and categorizes them as those to treat: (1) intoxication states; (2) withdrawal syndromes; (3) unpleasant withdrawal syndromes and cravings associated with abstinence – i.e., agonist maintenance therapies; (4) physiological and/or subjective reinforcing effects of substances – i.e., antagonist therapies; (5) relapse prevention and abstinence-promotion; and (6) co-occurring psychiatric conditions.

In a published clinical review, O’Brien emphasizes that relapse is the major problem facing clinicians who treat patients with addictive disorders. However, in this review it is noted that anti-craving medications for relapse prevention are not well known and are underused by clinicians. O’Brien discusses addiction as a heterogeneous condition with variability in reactivity to the drug of abuse and to the medications available to treat it. The author further contends that recent developments in pharmacogenetics may result in improved selection of medications based on genotype. The author also reports that there are no medications approved by the FDA for the indication of cocaine addiction as there are for heroin, alcohol and nicotine, and that anti-craving drugs approved for one indication are used in clinical practice for other drug addictions, including cocaine. (O’Brien 2005)

In an effort to evaluate somatic treatment options for patients with co-occurring psychiatric conditions and substance use disorders, a randomized control trial was conducted by Riggs et al. to assess the effect of fluoxetine vs. placebo in adolescents with concomitant major depressive disorder, substance use disorder and conduct disorder (CD) receiving cognitive behavioral therapy (CBT) designed for treatment of SUD. The results of this study indicated that fluoxetine combined with CBT may have similar safety and efficacy for depression in adolescents with active SUD to that reported for depressed adolescents without SUD. However, the treatment was not associated with greater reduction in self-reported substance use and CD symptoms compared with placebo combined with CBT (substance abuse). Results showed that co-occurring depression may improve or remit without antidepressant pharmacotherapy. (Riggs et al. 2008)

General Treatment Principles - Psychosocial Treatments

The APA guideline section titled “Psychosocial Treatments” categorizes the major psychotherapeutic treatments that have been studied in patients with substance use disorders as cognitive-behavioral, psychodynamic/interpersonal and recovery-oriented therapies. The adopted guideline notes that efficacy data show no one particular type of psychotherapy has been found to be consistently superior when compared with other active psychotherapies for treating substance use disorders. The APA guideline indicates that although the techniques and theories of the therapeutic action vary, they address one or more of these common tasks as specified: (1) enhancing motivation to stop or reduce substance use; (2) teaching coping skills; (3) changing reinforcement contingencies; (4) fostering management of painful affects; and (5) enhancing social supports and interpersonal functioning.

Current substance abuse treatment research continues to evaluate and compare various psychosocial treatment modalities. A large meta-analysis of psychosocial interventions conducted by Dutra et al. reviewed some 34 studies of well-controlled treatment conditions for cannabis, cocaine, opioid and polysubstance use, and reviewed their effect sizes, abstinence and treatment-retentions rates. Psychosocial treatments evaluated in this review included contingency management, relapse prevention, general CBT, and treatments combining CBT and contingency management. Among the disorders under treatment, interventions for cannabis and cocaine yielded the largest effect sizes, whereas treatment targeting polysubstance use yielded the lowest effect size and lowest percent post-treatment abstinence. Overall, the highest effect size estimates were obtained for contingency management techniques, followed by relapse prevention and other cognitive behavioral therapy approaches. Researchers concluded that this review of psychosocial treatments revealed promising findings, whereby the aggregate effect size for active treatment showed that the average patient undergoing psychosocial interventions achieves acute outcomes better than approximately 67 percent of the patients in control conditions. (Dutra et al. 2008)

The APA guideline stresses that co-occurring psychiatric and substance use disorders are common in all treatment settings. Bellack notes that the lifetime prevalence of substance use is very high for the population of patients with severe and persistent mental illness (SPMI) – approximately 65 percent, and that it is one of the most significant problems facing the public mental health system. (Bellack et al. 2008) A randomized controlled clinical trial conducted by Bellack et al. compared a new behavioral treatment for drug abuse in people with SPMI called Behavioral Treatment for Substance Abuse in SPMI (BTSAS), and a supportive treatment termed Supportive Treatment for Addiction Recovery (STAR). Participants were outpatients meeting DSM-IV criteria for drug dependence (cocaine, heroin, or cannabis) and serious mental illness (schizophrenia or schizoaffective disorder, major affective disorder or other Axis I disorders). The BTSAS program is a social learning intervention that includes motivational interviewing, a urinalysis contingency (i.e., increasing monetary payments for clean urines paid to the client after a motivational interviewing session) and social skills training. The control condition, STAR, is a supportive group discussion treatment. Results of this study showed that the BTSAS program was significantly more effective than STAR in percentage of “clean” urine test results, survival in treatment and attendance at sessions. The BTSAS program also had significant effects on important community-functioning variables such as decreased hospitalizations and arrests, more money available for daily expenses and improved quality of life. (Bellack et al. 2008)

The population of disadvantaged women with substance use disorders represents a minority of those receiving welfare support, but these women experience more severe and persistent barriers to employment and are less likely to become employed than their counterparts without SUDs. (Morgenstern et al., 2009) Investigators examined abstinence rates among substance-dependent women (n=302) in New Jersey receiving Temporary Assistance for Needy Families (TANF) who participated in intensive case management (ICM) over 24 months or the usual alternative program of screen-and-refer (i.e., usual care). The ICM intervention was a manualized program where the case managers identified tangible barriers to treatment entry and provided needed services including giving treatment vouchers as incentives for attending SUD treatment. Additionally, ICM was provided through the 24-month follow-up period. These study results were promising where the ICM group had higher abstinence rates and employment days and greater odds of full-time employment status than the usual care group. (Morgenstern et al., 2009)

The APA guideline examined computer-based psychosocial therapies only within the context of self-help treatment. The guideline indicates that internet-based self-help therapies may be effective for those at high-risk for a SUD or substance-related medical consequences, but these therapies may not be sufficient for those who already meet criteria for a substance use disorder. More research on computer-based applications of other therapeutic modalities has been conducted since publication of the guideline. One such randomized controlled study by Carroll et al. (n=77) compared treatment as usual (TAU), consisting of weekly individual and group general drug counseling, against TAU and additional outpatient computer-based training in CBT over eight weeks for patients with a SUD (i.e., alcohol, cocaine, opioids or marijuana abuse). The CBT modules referred to by the acronym, “CBT4CBT” (short for cognitive-behavioral therapy for computer-based training), were developed specifically for multimedia interactive delivery on the internet. The CBT4CBT intervention covers core concepts in understanding/changing patterns of substance abuse, coping with craving, problem-solving and learning ways to refuse offers of drugs and alcohol. Results were promising for this new technique by showing that participants assigned to the CBT4CBT group submitted significantly more urine specimens that were negative for any type of drugs and had longer continuous periods of abstinence during treatment. Also, in the CBT4CBT group, outcome was more strongly associated with treatment engagement than in TAU, and completion of homework assignments significantly correlated with outcome and was a predictor of treatment involvement. (Carroll et al., 2008)

General Treatment Principles - Clinical Factors Affecting Treatment

Included in the APA guideline section titled “Clinical Features Influencing the Treatment Plan,” are discussions on co-morbid psychiatric conditions that affect both the planning and implementation of treatment. These sections stress the importance of careful diagnostic distinction between substance abuse symptoms and those of other co-occurring psychiatric disorders as this dictates the selection of appropriate and targeted pharmacotherapy and psychosocial interventions. The adopted guideline recommends using the same medications for the treatment of a specific psychiatric disorder in most cases whether that disorder co-exists with a substance use disorder or not. However, the guideline indicates that clinicians must pay special attention to each medication’s tolerability and safety profile as well as its abuse potential.

Since publication of the APA guideline and watch, and relevant to a discussion on use of psychotropic medications, is a FDA Alert that clinicians should consider when treating elderly patients. Specifically, this FDA Alert was issued notifying healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly treated for dementia-related psychosis (FDA Alert 6/16/08). This alert may also have particular relevance because the APA guideline acknowledges the significant problem of alcohol abuse and dependence/abuse of prescribed medications (e.g., benzodiazepines, sedative-hypnotics and opioids) among the elderly— particularly those who live alone. The guideline also stresses that alcohol-related cognitive impairment, co-occurring depressive disorder, dementia, post-stroke syndromes and other conditions among the elderly may impair their ability to obtain or adhere to treatment regimens for medical, psychiatric or substance abuse disorders.

In order to understand better the clinical features that have an impact on substance use conditions, Goldstein et al. examined the relationship between age at onset of bipolar 1 disorder and illness characteristics among adults identified in the 2001-2002 National Epidemiologic Survey on Alcohol

and Related Conditions. Researchers concluded from these data that drug use disorders were more prevalent among childhood-onset and adolescent-onset (13-18 years old), as compared with adult-onset (19 years and older) subjects. Also, these findings corroborate previous reports that the illness characteristics among adults with childhood-onset bipolar disorder are similar to those described in children with bipolar disorder. (Goldstein and Levitt 2006)

Another analysis of the association between substance abuse disorders and bipolar disorder was performed where subjects with bipolar I or bipolar II (n=3,750) enrolled in the **S**ystematic **T**reatment **E**nhancement **P**rogram for **B**ipolar **D**isorder (STEP-BD) were followed prospectively for up to two years. In their design, investigators prospectively observed and identified depressive episodes. During follow-up 2,154 subjects developed a new onset major depressive episode and 457 of these individuals switched to a manic, hypomanic or mixed episode prior to recovery. Study findings showed that current or past substance use disorders were not associated with longer time to recovery from depression but may contribute to greater risk of switch into manic, mixed or hypomanic states. Further study is warranted to understand more fully the mechanism involved in the increased risk for this group of bipolar subjects. (Ostacher et al., 2010)

Another study of co-occurring psychiatric and substance use disorders included an in-depth analysis of a stratified sample of the Australian National Survey of Mental Health and Well-Being (1997), which revealed that SUD plus posttraumatic stress disorder (PTSD) was experienced by a significant minority (0.5 percent) of the Australian population. Among those with PTSD, the most common SUD was an alcohol use disorder (24.1 percent), whereas among those with a SUD, PTSD was most common among individuals with an opioid use disorder (33.2 percent). Although those with SUD plus PTSD were more likely to have a chronic health condition and had a greater number of health conditions than those with PTSD alone, the two groups shared a remarkably similar clinical profile. These findings indicate that the additional morbidity seen among individuals with substance use disorder plus PTSD may be attributed largely to PTSD. (Mills et al. 2006)

A more recent study examined the temporal course of improvement in PTSD and substance abuse among some 353 women in outpatient substance abuse treatment who were diagnosed with both disorders. Participants were randomized to receive 12 sessions of trauma-focused or health education group treatment. The investigators found that PTSD severity reductions were more likely to be associated with substance use improvement. There was minimal evidence of substance use symptom reduction improving PTSD symptoms. Additionally, the results supported the self-medication model of coping with PTSD symptoms in populations with co-morbid PTSD and addictive disorders. (Hein et al., 2010)

As discussed in the APA guideline, personality disorders and substance use disorders commonly co-occur with lifetime prevalence co-existence rates as high as 50-60 percent, particularly for borderline personality disorder (BDD) and antisocial personality disorder (ASPD). The adopted guideline acknowledges the efficacy of dialectical behavioral therapy in treating patients with BDD, with or without a co-occurring SUD, but notes that it is not always effective in improving substance use outcomes. More recently, Dynamic Deconstructive Psychotherapy (DDP) was studied by Gregory et al., as an individual, time-limited intervention in the BPD subpopulation with co-occurring SUD that can also be used in conjunction with adjunctive modalities (e.g., group therapy, family therapy, self-help groups and medications). (Gregory et al, 2010) The evidence-based DDP treatment model was developed by Gregory and Remen at SUNY Upstate Medical University in 2008 specifically for patients with BPD and co-morbid substance use or antisocial personality disorders. The DDP

intervention was designed to remediate deficits seen in the aberrant processing of emotional experiences through the contributing neurocognitive functions of association, attribution and alterity. Researchers described the stage-related tasks in their treatment as: (1) establish and maintain the therapeutic alliance, (2) integrate polarized and distorted attributions towards self and others, (3) accept limitations of self and others, and (4) differentiate from the therapist. Initial study findings and follow-up results (at 18 and 30 months) showed that compared with optimized community care (i.e., combination of individual psychotherapy, medication management, alcohol/drug counseling, professional or self-help groups and/or case management), patients who received DDP demonstrated large sustained treatment effects over a broad range of outcomes and achieved significantly greater improvement in core BPD symptoms (i.e., depression, parasuicide and recreational drug use). (Gregory et al., 2010)

Antisocial personality disorder (ASPD) co-occurring with substance use disorders presents unique treatment challenges for this subgroup of patients who frequently have severe mental illness requiring high psychiatric service usage and assistance with housing. (Frisman et al., 2009) Secondary analysis of a randomized clinical trial was conducted to compare the effectiveness of Assertive Community Treatment (ACT) versus standard clinical case management (SCCM) in the delivery of integrated dual disorder treatment (IDDT) for dually disordered patients with (n=36) and without (n=88) ASPD. Investigators described the ACT model's distinction from SCCM in that it has a lower clinician-patient ratio, provides services in the community rather than the clinic, shares caseloads between team members, provides rather than brokers services and assumes 24-hour responsibility for each client. Results of this study provided preliminary evidence that the ACT model may be a more effective way to offer IDDT for co-occurring disorders than SCCM. Additionally, among patients with ASPD, ACT was more effective in reducing alcohol use over the three-year treatment period than SCCM and resulted in fewer incarcerations. Researchers also specified that among patients who did not have ASPD, ACT and SCCM did not differ in their impact on substance abuse and incarceration. (Frisman et al., 2009)

Also included in the APA guideline section titled "Clinical Features Influencing the Treatment Plan" are discussions on co-morbid medical conditions that affect treatment planning and delivery of services. The guideline emphasizes that medical problems are further complicated by the use of multiple substances and the resultant nutritional deficiencies. In addition, the guideline indicates that patients with substance use problems often do not seek or receive adequate care for a variety of reasons including their disorganized and chaotic lifestyles. The APA guideline also stresses the critical need for pregnant women to receive treatment for their substance use disorders because it affects the health of the pregnant woman, the course of the pregnancy, fetal development, child development and future parenting behavior. Since publication of the adopted guideline, the American College of Obstetricians and Gynecologists (ACOG) Committee on Ethics published an updated Committee Opinion entitled, *At-Risk Drinking and Illicit Drug Use: Ethical Issues in Obstetric and Gynecologic Practice*. Clinicians are referred to this document for more information on the need for universal screening, referral and treatment in this population in order to meet the ethical obligation of providing patients and families with comprehensive and effective treatment. The ACOG Committee Opinion stresses that "the most effective safeguard for children is treatment for family members who have a substance abuse problem." (ACOG Committee Opinion No. 422, December 2008, p. 9)

Treatment of Nicotine Dependence

According to both the 2009 National Survey on Drug Use and Health (NSDUH) and the Monitoring the Future Survey (MFS), smoking rates are at the lowest point in the history of the survey. However, in the past year, smoking prevalence among students in the 8th, 10th and 12th grades remain unchanged. From 2002 to 2008, the rate of past-month cigarette use fell from 13.0 percent to 9.1 percent among 12- to 17-year-olds and there was a decline in cigarette use by young adults aged 18 to 25 years from 40.8 percent to 35.7 percent in the same period. (NIDA, 2010; SAMHSA, 2009)

The APA guideline recommends that any of the FDA-approved forms of nicotine replacement therapies (NRT) – i.e., patch, gum, lozenge, nasal spray and inhaler, can be used as first-line treatments for any individual who wishes to stop smoking. The guideline indicates that when nicotine gum or lozenges are used, scheduled dosing (e.g., one 2-mg lozenge or piece of gum every hour) rather than ad libitum dosing is often best. The guideline recommends the 4-mg dose for heavy smokers (defined as > 25 cigarettes/day) or more nicotine-dependent smokers. One randomized controlled study investigated the efficacy of 4-mg nicotine gum or placebo as desired for up to 12 months for heavy smokers (at least 20 cigarettes per day) who were not ready to quit but were willing to reduce their smoking intensity. The findings showed that the nicotine gum had a statistically significant rate of success in smoking reduction by at least 50 percent compared to placebo. (Batra et al. 2005) More recently, the use of 2-mg nicotine gum was found to be safe and effective when combined with individual smoking cessation counseling in a clinical trial of pregnant women smokers (n=194) and was associated with a modest reduction in smoking. Other noteworthy findings from this study showed that NRT was associated with a lower risk of preterm delivery, greater infant birth weight, a trend for reduced infant length of stay and likelihood of neonatal intensive care admission and higher Apgar scores at five minutes. (Oncken et al., 2008) In addition, newer NRT research findings from a randomized trial (n=568) suggested that extended therapy with the transdermal nicotine patch (21 mg) for 24 weeks may be superior to the standard regimen of eight weeks of treatment and warrants further study. (Schnoll et al, 2010)

The APA guideline also categorizes bupropion as a first-line pharmacological agent with nortriptyline and clonidine as second-line treatments for smokers who want to quit their habit. As well, the APA guideline indicates combining first-line pharmacological treatments (e.g., NRTs plus bupropion) may improve outcomes. A more recent comparative effectiveness trial demonstrated that two combination pharmacotherapies (i.e., bupropion hydrochloride sustained release [SR] plus nicotine lozenge and nicotine patch plus nicotine lozenge combinations) for smoking cessation were superior to three monotherapies – nicotine patch, bupropion ST and nicotine lozenge. Investigators noted that the bupropion SR plus lozenge was significantly effective relative to the monotherapies with an approximate doubling of abstinence rates at eight weeks and six months. (Smith et al., 2009). Another more recently published clinical review of the literature specified that combination pharmacotherapy may be indicated for patients who have failed an attempt(s) with monotherapy, experience breakthrough cravings, are highly dependent and experience nicotine withdrawal symptoms. (Laniado-Labrin et al. 2010).

The adopted guideline also notes that other agents such as naltrexone, mecamylamine, buspirone, monoamine oxidase inhibitors (MAOI) and selective serotonin re-uptake inhibitor (SSRI) antidepressants have been studied, but their efficacy for smoking cessation has not been established.

Furthering the APA discussion on these investigational agents, a controlled trial of naltrexone augmentation of NRT for smoking cessation compared doses of 0, 25, 50 or 100 mg/day oral naltrexone along with a 21 mg nicotine patch. These study results showed that the 100 mg dose of naltrexone demonstrated the most promise for augmenting the efficacy of the nicotine patch on smoking cessation outcomes but requires further study. (O'Malley et al. 2008) Another promising treatment for nicotine dependence is oral topiramate when used to promote smoking abstinence among alcohol-dependent smokers. Results of a subgroup analysis of a larger randomized double-blind trial demonstrated that topiramate recipients (up to 300 mg/day) were significantly more likely than placebo recipients to abstain from smoking. (Johnson et al. 2005)

The Magellan-adopted *APA Guideline Watch 2007* discusses the selective $\alpha 4\beta 2$ nicotinic receptor partial agonist, varenicline, as an effective and well-tolerated pharmacotherapy aid for patients who are engaged in behavioral treatment for smoking cessation. The guideline watch indicated that further research was needed to determine its relative efficacy compared with already established drugs such as bupropion and alternate NRT agents. A randomized controlled trial by Nides et al. studied the efficacy and tolerability of three varenicline doses (at 0.3 mg once daily, 1.0 mg once daily or 1.0 mg twice daily) for six weeks, compared to 150 mg sustained-release bupropion twice daily for seven weeks or placebo for seven weeks. The results of the study demonstrated both short-term (at both 1mg once daily and 1 mg twice daily) and long-term efficacy of varenicline (at 1 mg twice daily) with better confirmed continuous quit rates than bupropion or placebo. (Nides et al. 2006)

On May 16, 2008, the FDA issued a MedWatch (a Safety Alert for Drugs, Biologicals, Medical Devices and Dietary Supplements) and noted the following:

FDA informed healthcare professionals and patients that as the Agency's review of Chantix® (varenicline) safety data has progressed, it appears increasingly likely that there is an association between Chantix® and serious neuropsychiatric symptoms. Prescribing information for Chantix® was revised to include this safety information in the WARNINGS and PRECAUTIONS sections of the label, and a Medication Guide for patients is also available. If patients, their families, or caregivers notice agitation, depressed mood, or changes in behavior that are not typical for the patient or if the patient has suicidal thoughts or actions, the patient should stop taking Chantix® and contact their healthcare professional. (FDA MedWatch 5/16/08)

Since publication of the APA guideline, varenicline (1 mg) was compared against placebo for safety and efficacy in a large multicenter, randomized clinical trial of 714 smokers with stable cardiovascular disease. Findings showed that varenicline was well tolerated and did not increase cardiovascular events or mortality while demonstrating superiority to placebo in achieving abstinence from smoking. (Rigotti et al, 2009)

A very large meta-analysis was conducted by Eisenberg et al. examining 69 randomized trials involving a total of 32, 908 patients in an effort to compare a variety of treatments for nicotine dependence. Their findings demonstrated that varenicline, bupropion and the NRTs (nicotine gum, transdermal patch, inhaler, tablet and nasal spray) were more efficacious than placebo and that varenicline was superior to bupropion. Additionally, this meta-analysis showed that despite the documented efficacy of these agents, the absolute number of patients abstinent from smoking at 12

months was low - i.e., 30 percent among patients in the treatment groups. (Eisenberg et al., 2008) Another more recent study examined the effectiveness of a triple-medication combination (i.e., nicotine patch, nicotine oral inhaler, and bupropion ad libitum) against a standard 10-week tapering course of the nicotine patch in a group of patients (n=127) with a predetermined medical illness (i.e., cardiovascular disease, cancer, chronic obstructive lung disease, diabetes, hyperlipidemia and psychiatric/substance use disorders). Results of this study showed that the combination therapy improved abstinence rates (35 percent vs. 19 percent) but caused more insomnia and anxiety than the nicotine patch alone. Investigators argued that medically ill smokers are often highly addicted and at great risk for complications from continued smoking and may benefit from such a flexible triple-combination therapy. (Steinberg et al., 2009)

According to our adopted guideline, rates of smoking in patients with schizophrenia are much higher (58 percent to 88 percent) than in the general population. The guideline emphasizes that in the presence of a co-occurring psychiatric disorder, smoking cessation may be more difficult for psychiatric patients and they appear to have more withdrawal symptomatology when they do stop smoking. This may be a function of their higher levels of nicotine dependence and smoking consumption. The guideline also notes that there has been little study of psychosocial smoking cessation interventions or NRTs in the chronic psychiatric population. Baker et al. performed a study to compare an integrated psychological and NRT intervention against routine care for people with a psychotic disorder. The integrated approach under study included eight 1-hr. sessions of motivational interviewing, CBT, NRT, treatment as usual (i.e., access to general practitioners and publicly funded community mental health teams) and the provision of booklets for smoking cessation. Results showed no overall differences in abstinence rates between the treatment group and the comparison group who received treatment as usual. However, a significantly higher proportion of smokers who completed all treatment sessions stopped smoking or achieved continuous abstinence at three months. Also, one-half of those who completed the intervention program achieved a 50 percent or greater reduction in daily cigarette consumption across the follow-ups. (Baker et al. 2006) Although the APA guideline did not specifically address the prison population, smoking prevalence rates among incarcerated individuals are also much higher than the general population. (Cropsey et al., 2008) A more recent clinical trial tested the efficacy of a combined pharmacologic and behavioral smoking cessation intervention among women (n=539) in a state prison in the southern United States. Ten group sessions of behavioral mood management training to prevent smoking relapse was provided along with the nicotine patch as the active intervention offered to all women in the crossover study design. Investigators reported that the intervention was effective and that point prevalence quit rates for the intervention group were consistent with outcomes from other community smoking cessation programs, confirming that female prisoners were interested in this type of treatment. (Cropsey et al., 2008)

The APA guideline acknowledges there is extensive evidence of the efficacy of individual and group psychosocial therapies (i.e., social support, brief behavioral, cognitive-behavioral and self-guided therapy) for treating individuals with nicotine dependence and recommends behavioral therapies as first-line treatment for smoking cessation. The guideline describes these psychosocial therapies as typically provided in a multimodal package of several specific treatments aimed at providing patients with the skills to quit smoking and avoid smoking in high-risk situations. Moreover, the guideline indicates the best outcomes are achieved through combined psychosocial and pharmacological therapy.

The adopted guideline discusses the supportive evidence for social support by a spouse, partner or through specific interventions such as a buddy system. This was further demonstrated in A Stop Smoking in Schools Trial (ASSIST) study, which showed that this specific peer supporter training program was more effective than usual smoking education in achieving a sustained reduction of regular smoking in adolescents for two years after its delivery. (Campbell et al. 2008) Similarly, a study evaluated the effects of a home-based anti-smoking socialization program, *Smoke-Free Kids*, for children on the initiation of smoking from their parents who smoke. Findings indicated that children in the pre-initiation phase of smoking who took part in this program from their parents were less likely to initiate smoking. (Jackson and Dickinson 2008)

Since the release of the APA guideline, disease management programs have been developed to assist those wishing to stop smoking by offering repeated interventions to support quit attempts and treat relapses. The impact of a disease management program on smoking cessation was recently studied in a large randomized clinical trial with 750 primary care patients smoking more than 10 cigarettes per day. Participants were offered free pharmacotherapy consisting of either a six-week course of 21 mg/day nicotine patch or a seven-week course of bupropion SR (150 mg twice daily) and were randomized to one of three groups: pharmacotherapy management alone, pharmacotherapy supplemented with either moderate-intensity disease management (two counseling calls) or high-intensity disease management (up to six counseling calls). Findings showed that after a full 24 months of treatment, the higher intensity disease management was associated with increased abstinence. Investigators suggested that a disease management approach can reach a large number of patients by offering free pharmacotherapy and pharmacotherapy management and noted that the majority of smokers will make one or more attempts to quit. (Ellerbe et al., 2009) Findings from another randomized trial showed that using a pay-for-performance intervention for clinics (i.e., offering clinics a \$5,000 bonus for 50 referrals) can substantially increase the number of smoker referrals made by staff members to tobacco telephone counseling (“quitline”) services. (Lawrence et al, 2008)

Studies published after release of the APA guideline found that hospital admissions provided a unique opportunity to help people stop smoking. One meta-analysis reviewed some 33 clinical trials where smoking cessation interventions (behavioral counseling and/or pharmacotherapy) began during hospitalization with a minimum of six months of follow-up. Investigators reported robust positive findings in that such programs increased the odds of smoking cessation by 65 percent at six to 12 months over what was achieved by hospitalization alone. (Rigotti et al., 2008) Another clinical trial of patients (n=117) scheduled to undergo elective surgery demonstrated that a smoking cessation intervention of four weekly meetings/telephone counseling sessions and free NRT (i.e., client preference of nicotine patch, gum or microtab) was superior to the control condition of standard pre-operative care. In this study, 36 percent of the intervention patients vs. two percent of the control group became completely abstinent throughout the peri-operative period. Moreover, a lower nicotine dependence (Fagerström Tolerance Scale score <4) and obesity (BMI ≥ 30 kg.m⁻²) were predictors of long-term smoking abstinence in this study. (Azodi et al., 2009)

Similarly, a study of 101 parents tested the feasibility and acceptability of introducing an intervention to address mothers’ and fathers’ smoking during the postpartum hospitalization. This program consisted of one 15-minute in-person counseling session delivered by trained study staff working from adapted materials and messages specifically tailored for parental smokers. In addition, parents were referred to a telephone quitline and letters were faxed to the parents’ primary care provider and the mother’s obstetrician. Findings showed that both self-reported 24-hour quit attempts and

cotinine-confirmed seven-day abstinence rates were higher in the intervention group than the usual care control group. Investigators suggested that birth of an infant presented a unique occasion to teach parents and provide cessation assistance, along with offering staff a systematic method for addressing smoking with parents of newborns. (Winickoff et al., 2010, p. 518)

Treatment of Alcohol-Related Disorders

Alcohol use disorders are common and, as noted in the APA guideline, the 12-month prevalence rates for alcohol abuse is 4.65 percent and 3.61 percent for alcohol dependence. In 2009, nearly one quarter (23.7 percent) of persons aged 12 or older participated in binge drinking (i.e., five or more drinks on the same occasion on at least one day per month), which translates to about 59.6 million people. The rate of binge drinking was 41.7 percent among young adults aged 18 to 25 years. (SAMHSA, 2009) The guideline also indicates that the first episode of alcohol intoxication is likely to occur in the mid-teens and that the age at onset of alcohol dependence peaks at ages 18 to 25. Following on these observations, Hingson et al. retrospectively analyzed data from the 2001-2002 National Institute on Alcohol Abuse and Alcoholism. These researchers found that among persons who were ever alcohol dependent, those diagnosable before age 25 were less likely to seek alcohol-related help or treatment and were also more likely to experience indicators of chronic relapsing alcohol dependence, including multiple dependence episodes and longer episodes with a wider variety of symptoms. (Hingson et al. 2006)

The APA guideline recommends all patients undergoing a psychiatric evaluation should be screened for a substance abuse disorder, regardless of their age, presentation or referral source, using empirically validated screening tools (e.g., Alcohol Use Disorders Identification Test, Drug Abuse Screening Test and CAGE). The adopted guideline also stresses that the clinician's approach to assessing a substance use disorder will differ depending on the context in which an individual presents for treatment and how amenable he or she is to questions. In this regard, one multi-center descriptive study of parents visiting their children's pediatrician revealed that the majority of parents were accepting to being screened for alcohol problems in this setting either by the pediatrician or via a computer-based or paper-and-pencil questionnaire. In addition, parents who screened positive preferred that the pediatrician discuss the problem further and present treatment options for referral. (Wilson et al., 2008) Another more recent meta-analysis compared the widely used 10-item Alcohol Use Disorder Identification Test (AUDIT) against its abbreviated three-item version, Alcohol Use Disorder Identification Test – Consumption (AUDIT-C) in accurately detecting unhealthy alcohol use in adults. Findings showed that there were not statistically significant differences in the overall accuracy between the instruments for detecting risky drinking, alcohol use disorder or unhealthy alcohol use but that the AUDIT might be better than the AUDIT-C for identifying severe conditions – i.e., alcohol dependence. (Kriston et al. 2008).

Also relevant to understanding the characteristics of people who develop problems with alcohol use is current research interest in both the genetic and environmental factors which play a crucial role in both vulnerability and protection against alcoholism. A study by Volkow et al. found that the higher-than-normal D₂ receptor availability in the brain (caudate and ventral striatum) in non-alcoholic members of alcoholic families supports the hypothesis that high levels of D₂ receptors and their association with metabolism in frontal regions may protect against alcoholism. (Volkow et al. 2008)

The APA guideline discusses the pharmacological treatment of moderate to severe withdrawal from alcohol and supports the use of fluids and benzodiazepines to reduce withdrawal severity and the incidence of seizures and delirium. The guideline notes that beta-blockers, clonidine, carbamazepine and neuroleptics may diminish the severity of alcohol withdrawal symptoms but have not been proven to prevent delirium and seizures. Therefore, the guideline suggests these drugs should be used as adjunctive agents. A small randomized clinical trial compared the use of oral diazepam (0.5-0.75mg/kg/day for six consecutive days, tapering the dose by 25 percent daily from day seven to day 10) to oral doses of the selective GABA_B receptor agonist, baclofen (30 mg/day for 10 consecutive days), in the treatment of uncomplicated alcohol withdrawal symptoms (AWS). Results of this study showed that both drugs significantly decreased AWS without significant differences between the two drug treatments. (Addolorato et al. 2006)

Three FDA-approved anti-alcoholism agents were discussed in the adopted guideline as effective treatments for abuse and dependence – disulfiram, naltrexone and acamprosate. Promising results of an initial topiramate treatment study reported by Johnson et al. showed that this drug (up to 300 mg vs. placebo) significantly reduced drinking among alcohol-dependent individuals. Unlike previous studies with other medications, participants were currently drinking when they entered the study. Results also showed that topiramate reduced the percentage of heavy drinking days, the number of drinks per day and the laboratory measure of alcohol consumption (plasma γ -glutamyltransferase). Researchers indicated that hypothetically topiramate, a sulfamate-substituted fructopyranose derivative, can decrease alcohol reinforcement and propensity to drink. (Johnson et al. 2007) In a more recently published clinical review of pharmacological interventions used to treat alcohol craving and dependence, Leggio discussed the use of baclofen in the treatment of alcohol dependence. (Leggio, 2010) The author postulated the involvement of the GABA_B receptor in the neural substrate mediating alcohol intake and alcohol motivational properties. Results of initial small studies by Addolorato et al. highlighted in this review showed the effectiveness of baclofen in reducing anxiety and daily alcohol intake in patients who continued to drink and in both achieving and maintaining abstinence in patients with alcohol dependence and liver cirrhosis. Another randomized controlled trial (n=80) compared baclofen versus placebo over 12 weeks of combined treatment with a low-intensity psychosocial intervention. In contrast, results of this study did not show baclofen demonstrating clinical outcomes superior to placebo for differences in percentage of heavy drinking days, abstinence days, time to first drink or time to relapse to heavy drinking, with the exception of an association with a significant reduction in anxiety (Leggio, 2010; Garbutt et al., 2010)

Naltrexone has been found to be more effective than placebo and moderately effective in promoting abstinence, reducing heavy drinking days and decreasing rates of relapse, and is categorized in the APA guideline as one of the most widely studied drugs for the treatment of alcohol dependence. Two clinical trials have suggested that naltrexone's effectiveness may be moderated by variations in an individual's μ -opioid receptor gene (OPRM1). (Anton et al. 2008; Ray and Hutchinson 2008) Published findings from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) Study confirmed and extended the observation that the functionally significant OPRM1 Asp40 allele predicts naltrexone treatment response in alcoholic individuals. Researchers here suggest that OPRM1 genotyping in alcoholic individuals might be useful to assist in selecting treatment options. (Anton et al. 2008) Another study by Ray and Hutchinson showed that lower relapse rates among carriers of the A118G single nucleotide polymorphism (SNP) of the OPRM1 gene after treatment with naltrexone may be due to a more

pronounced naltrexone-induced reduction in alcohol reward in these individuals. (Ray and Hutchinson 2008)

Another more recently published clinical trial of naltrexone and sertraline compared the treatment outcomes for patients with co-occurring depression and alcohol dependence. A total of 170 patients were randomly assigned to receive 14 weeks of treatment with sertraline 200mg/day (n=40), naltrexone 100mg/day (n=49), the combination of sertraline plus naltrexone (n=42) or double placebo (n=39) while receiving weekly cognitive-behavioral therapy. Investigators reported that the sertraline plus naltrexone combination produced a higher alcohol abstinence rate (54.7 percent) and demonstrated a longer delay before relapse to heavy drinking (median delay = 98 days). These findings compared with naltrexone alone (abstinence rate: 21.3 percent; delay = 29 days), sertraline alone (abstinence rate: 27.5 percent; delay = 23 days), and placebo (abstinence rate: 23.1 percent; delay = 26 days). The study also showed that the number of patients in the medication combination group not depressed by the end of treatment (83.3 percent) approached significance when compared with the other treatment groups. Researchers acknowledged that further replication of these findings is necessary before instituting this protocol in clinical practice for this highly prevalent and difficult to treat population of patients. (Pettinati et al., 2010)

As noted earlier in this section, binge drinking is both a highly prevalent and serious problem in the U.S population. A recent large (n=752) randomized controlled trial conducted in Spain examined the effectiveness of an intervention by primary care physicians specifically targeting only binge drinkers versus providing patients with educational materials. A brief intervention protocol by the physician consisted of two short counseling sessions delivered four weeks apart. Each 10-15 minute face-to-face counseling session was offered as part of a routine office visit. The physician used a scripted workbook which included the following components: (1) alcohol-related health effects, (2) a pie chart displaying the different types of at-risk drinkers, (3) a list of methods for cutting down drinking, (4) a treatment contract, and (5) cognitive-behavioral exercises. The control group received a booklet on general health issues with follow-up at six and 12 months. Investigators reported that at the end of the 12-month follow-up period, there were significant reductions ($P<.001$) in binge drinking status (52.2 percent vs. 67.2 percent), number of episodes of binge drinking (1.14 vs. 1.56), number of drinks weekly (19.2 vs. 22.4) and frequency of excessive alcohol intake in seven days (49.9 percent vs. 66.6 percent). Authors also noted that while both men and women benefited from the experimental intervention, the greatest reduction in alcohol consumption over time occurred among women. (Rubio et al., 2010)

For in-depth review of the evaluation and treatment of substance use disorders in children and adolescents, the APA guideline refers the reader to the American Academy of Child and Adolescent Psychiatry's (AACAP) *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Substance Use Disorders* (2005). The AACAP practice parameter indicates that "in-treatment factors that are predictive of outcome are time in treatment, involvement of family, use of practical problem solving, and provision of comprehensive services such as housing, academic assistance, and recreation. Posttreatment variables that are thought to be the most important determinants of outcome include association with non-using peers and involvement in leisure time activities, work and school. Variables reported to be most consistently related to successful outcome are treatment completion, low pretreatment use, and peer and parent social support and nonuse of substances." The AACAP Practice Parameter also reported that the most empirical evidence of efficacy supported family therapy approaches and individual CBT, alone and in combination with

motivational enhancement. (AACAP, 2005, page 614) More recent meta-analytic findings from 26 studies assessing the effectiveness of substance use interventions in their ability to reduce adolescent substance abuse concluded that interventions with large effect sizes were: (1) brief motivational interviewing, (2) CBT with 12 steps, (3) CBT with aftercare, (4) multidimensional family therapy, (5) brief intervention with adolescent, and (6) brief intervention with adolescent and a parent. (Tripodi et al., 2010)

Treatment of Marijuana-Related Disorders

The APA guideline indicates that marijuana, as the most widely used illicit drug in the United States and in the world, is not a benign substance as widely believed, and is associated with a number of psychological, behavioral and social problems. In 2009, there were 16.7 million past month users. Among persons aged 12 or older, the rate of past month marijuana use and the number of users in 2009 (6.6 percent or 16.7 million) were higher than in 2008 (6.1 percent or 15.2 million) and in 2007 (5.8 percent or 14.4 million). (SAMHSA, 2009)

A prospective longitudinal study by Aharonovich et al. examined cannabis use and its relationship to remission and relapse of cocaine, alcohol and heroin in individuals after inpatient drug abuse treatment for these substances. Findings showed that about one-third (N=73) of the patients used cannabis after hospital discharge. This continued marijuana use increased the risk of relapse to alcohol and cocaine, but did not significantly affect remission and relapse to heroin-dependent patients. Researchers suggest that cannabis use during period of sustained remission from dependence on another substance should be addressed as a possible risk or warning sign of impending relapse to use of substances on which patients were formerly dependent. (Aharonovich et al. 2005) Another large systematic review of cannabis studies by Moore et al. showed that there was an increased risk of any psychotic outcome in individuals who had ever used cannabis where findings were consistent with a dose-response effect and greater risk in people who used cannabis more frequently. The findings were inconclusive with respect to depression, suicidal thought and anxiety outcomes. Researchers concluded that there was sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life. (Moore et al. 2007) There also have been two more recently published large systematic reviews of epidemiological, clinical and laboratory studies examining the association between non-medical cannabis use and adverse outcomes by researchers from Australia. One review reported that the most probable adverse effects of cannabis use include a dependence syndrome, increased risk of motor vehicle crashes, impaired respiratory function, cardiovascular disease and adverse effects of regular use on adolescent psychosocial development and mental health. (Hall et al., 2009) Another review also specified an association with altered bone metabolism, teratogenic effects on the developing brain following perinatal exposures and increased risk of cancer. (Reece, 2009)

Treatment of Cocaine-Related Disorder

Cocaine use and abuse of methamphetamine have become significant public health problems in the United States. According to 2009 NSDUH data, there were 1.6 million current cocaine users aged 12 or older, comprising 0.7 percent of the population. These estimates were similar to the number and rate in 2008 (1.9 million or 0.7 percent) but were lower than the estimates in 2006 (2.4 million or 1.0 percent). This same survey showed that the number of past month methamphetamine users decreased between 2006 and 2008, but then increased in 2009. The numbers were 731,000 (0.3

percent) in 2006, 529,000 (0.2 percent) in 2007, 314,000 (0.1 percent) in 2008, and 502,000 (0.2 percent) in 2009. (SAMHSA, 2009)

As discussed in the previous section, Treatment of Alcohol-Related Disorders, similar interest exists in researching the genetic and environmental factors that contribute to both the vulnerability and protection against cocaine dependency. A study by Martinez et al. investigated the association between deficits in pre-synaptic dopamine and the choice for cocaine vs. monetary reward in their model of relapse. As in the cited Volkow study, cocaine dependence was found to be associated with impairment of pre-synaptic dopamine functioning by playing a role in maintaining the habitual, maladaptive patterns of behavior that are indicative of addiction. Specifically, blunted dopamine transmission in the ventral striatum and anterior caudate was predictive of the choice for cocaine over money. (Martinez et al. 2007) There also has been an interest in understanding the effects of prenatal cocaine exposure (PCE) on children's growth and development. A published review of research by Ackerman et al. looked at 32 studies of children and adolescents that examined the effects of PCE on growth, cognitive ability, academic functioning and brain structure and function among school-aged children. The findings indicated that PCE had significant negative associations with sustained attention and behavioral self-regulation but not with other related impairments because the association was small and attenuated by numerous environmental variables. (Ackerman et al., 2009)

The APA guideline notes that pharmacology treatment is not ordinarily indicated as an initial treatment for cocaine dependency, but that drugs may be used in severe forms of dependency and when patients do not respond to psychosocial interventions. The guideline also notes that no drugs have FDA indications for the treatment of cocaine dependence. The guideline indicates that clinical study results showed that – for those who fail to respond to psychosocial treatment alone – topiramate, baclofen, tiagabine (a GABA reuptake blocker) or modafinil may be promising when integrated into these interventions. This discussion also includes data on the efficacy of bupropion, which showed some benefit in small studies, but did not demonstrate superiority to placebo in larger trials. Following on these findings, a randomized controlled trial by Poling et al. compared the efficacy of bupropion and contingency management in a sample of combined cocaine/opioid-abusing individuals currently maintained on methadone. Results showed that contingency management augmented with bupropion 300 mg/day was effective for cocaine abuse, but not opioid use, as evidenced by abstinence. (Poling et al. 2006)

Since publication of the guideline, clinical trials have been published on both modafinil and vigabatrin and their use in treating cocaine dependence. The use of morning-dosed modafinil (400 mg) vs. placebo promoted nocturnal sleep, normalized sleep architecture and decreased daytime sleepiness in abstinent cocaine users. The research team of Morgan et al. acknowledged that further study is indicated, but suggested these findings may be relevant to sleep improvement and its association with effective treatments for cocaine dependence. (Morgan et al., 2010)

The first randomized, double-blind, placebo-controlled trial of cocaine addicted patients (n=103) was conducted comparing fixed titration of vigabatrin against placebo for nine weeks of treatment and three weeks of follow-up. Results showed that full end-of-trial abstinence was achieved in 28 percent (n=14) of the vigabatrin-treated subjects versus 7.5 percent (n=4) of the placebo arm subjects. Abstinence through follow-up was achieved in 12 subjects in the vigabatrin group and 2 subjects in the placebo group. The retention rate was 62 percent in the vigabatrin arm and 41.5 percent in the placebo arms. Additionally, for subjects with pre-study alcohol use, vigabatrin was

superior to placebo for self-reported abstinence from alcohol (43.5 percent versus 6.3 percent). However, investigators reported that there were no differences between the two groups in drug craving, depressed mood, anxiety or Clinical Global Impression severity scores. The authors also cautioned this study did not evaluate binge cocaine usage and that careful study is still required to evaluate associated risk of visual field defects in long-term treatment with vigabatrin. (Brodie et al., 2009)

Findings from a preliminary randomized clinical trial of the immunogenicity, safety and efficacy of a novel cocaine vaccine (succinylornocaine) to treat cocaine dependence revealed that attaining high ($\geq 43 \mu\text{g/mL}$) IgG anti-cocaine antibody levels was associated with significantly reduced cocaine use in 109 methadone-maintained subjects. Unfortunately, results showed that only 38 percent of the vaccinated patients attained these IgG levels and they had only two months of adequate cocaine blockade. Investigators acknowledged the need to further improve vaccines for this indication. (Martell et al., 2009)

A range of general medical conditions are associated with cocaine. The APA guideline discusses several comorbid conditions that develop based on the route of administration of the drug – intranasal use, smoking and the Valsalva-like maneuver that is performed to better absorb the drug. Complications can include conditions such as sinusitis, nasal septum perforation, bronchitis, pneumonitis and barotraumas (e.g., pneumothorax, pneumomediastinum and pneumopericardium). Medical conditions that can develop independently of administration route include weight loss and malnutrition, myocardial infarction and stroke. An analysis of hospital discharges in Texas (2000-2003) by Westover et al. concluded that when controlling for risk factors, amphetamine abuse was associated with twice the risk of hemorrhagic stroke as cocaine abuse. In contrast, Westover notes that amphetamine abuse was not associated with an increased risk of ischemic stroke, while cocaine abuse was associated with increased risk. Also, amphetamine abuse, but not cocaine abuse, was associated with increased risk of death after a hemorrhagic stroke. (Westover et al. 2007) Datillo et al. conducted a retrospective analysis of consecutive patients who had positive urine toxicology test results for cocaine and were admitted to telemetry units, ICUs, or coronary care units of a municipal hospital. Researchers noted that most physicians believe that sole β -blockade should be avoided in patients with clinical evidence of cocaine toxicity because of the risk of unopposed α receptor stimulation and that β -blockers should be avoided in any patient with chest pain and a history of cocaine abuse. However, these study findings revealed that administration of β -blockers was associated with a reduction, rather than an increase, in the risk of death and myocardial infarction. (Datillo et al. 2008)

Treatment of Opioid-Related Disorders

Large numbers of people in the United States use or misuse opiate drugs, which include both heroin and prescription pain relievers (e.g., hydromorphone, morphine, oxycodone, codeine, propoxyphene). The APA guideline discusses the size and seriousness of this problem and reports estimates from the Office of National Drug Control Policy (2003) that between 750,000 to 1,000,000 individuals are heroin-dependent, and that 943,000 individuals met the criteria for opioid dependence on opioids for non-medical use. In addition, the most recent (2003) National Survey on Drug Use and Health (NSDUH), indicated that an estimated 3.7 million people had used heroin at some time in their lives, and more than 119,000 of them reported using it within the month preceding the survey. (NIDA, 2005) The guideline indicates that treatments for opioid dependence,

opioid abuse, opioid intoxication and opioid withdrawal have been extensively studied and that these treatments are highly effective. However, the guideline stresses that despite the number of effective treatments for opioid dependence and the well-researched scientific basis for their efficacy and safety, the availability of treatment programs for this and other illicit drug use is limited.

A 2005 epidemiological study by Paulozzi has provided the most current information on the involvement of opioid analgesics in drug abuse deaths in American Metropolitan Areas. Analysis of data from the Drug Abuse Warning Network (DAWN) medical examiner and coroner surveillance system showed that multiple urban areas have experienced a dramatic increase in both drug abuse deaths and the involvement of opioid analgesics in those deaths between 1997 and 2002. Also, this report suggests that these metropolitan area data probably underestimate the current problem nationwide because sales of opioids continued to increase through the first half of 2004, and that there is increased diversion of some opioids (i.e., fentanyl and oxycontin) to abusers. Finally, Paulozzi cites alarming data from several recent reports (i.e., The Drug and Alcohol Services Information System-DASIS Report, 2002 update and the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report – MMWR, 2005) that show the fatal prescription drug overdose rates are even higher in rural areas. These rural areas also show the sharpest increase in admissions for substance abuse treatment involving narcotic pain killers. (Paulozzi 2006)

Studies have been conducted to understand better the prevalence of opioid abuse, and the associated risk factors and demographic characteristics of abusers. Carise et al. evaluated the prevalence and correlates of OxyContin use and abuse among a population of subjects admitted to 157 addiction treatment centers across the United States from 2001-2004. The main finding of this study was that most of the OxyContin use reported in the sample of individuals seeking addiction treatment did not originate from physician prescriptions, but rather from illicit sources, such as family, friends or other illegitimate sources as part of a broader and longer term pattern of multiple substance abuse. (Carise et al. 2007) Martell et al. conducted a systematic review to determine the prevalence of opioid treatment, whether opioid medications are effective, and the prevalence of substance use disorders among patients receiving opioid medications for chronic back pain. Results of the meta-analysis revealed that opioids are commonly prescribed for chronic back pain and may be efficacious for short-term pain relief, but the long-term efficacy (> 16 weeks) is unclear. Researchers note that substance use disorders are common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in up to 24 percent of cases. (Martell et al. 2007). Fletcher and a team of researchers conducted a study on opioid prescribing patterns in emergency rooms. Their findings confirmed that opioid prescribing for patients making a pain-related visit to the emergency department increased after national quality improvement initiatives in the late 1990s, but that differences in opioid prescribing by race and ethnicity have not diminished. Over the study years (2001-2005), white patients with pain were more likely to receive an opioid (31 percent) than black (23 percent), Hispanic (24 percent), or Asian/other patients (28 percent). These differences did not diminish over time, with opioid prescribing rate of 40 percent for white patients and 32 percent for all other patients in 2005. The differential prescribing by race/ethnicity was evident for all types of pain visits, was more pronounced with increasing pain severity, and was detectable for long-bone fracture and nephrolithiasis as well as among children. (Fletcher et al. 2008)

The APA guideline stresses that psychosocial treatments are an essential component of a comprehensive treatment program. The adopted guideline explains that psychosocial treatments attempt to counteract compulsive substance abuse by bringing about changes in patients' behaviors, thought processes, affect regulation and social functioning. As one of the recommended

psychosocial treatments, the guideline indicates that the community reinforcement approach (CRA) is based on the theory that environmental reinforcers for substance use perpetuate SUDs. Additionally, patients with substance use disorders lack positive environmental reinforcers for sober activities and pleasures. The guideline also notes that CRA treatment packages (e.g., to include conjoint marital therapy, training in finding a job, counseling on substance-free social and recreational activities and a substance-free social club) have been shown to be effective in treating alcohol dependence with adjunctive disulfiram treatment increasing its effectiveness. A clinical trial by Bickel et al. evaluated the efficacy of therapist-delivered CRA and computer-assisted CRA (both using voucher-based contingency interventions) against standard treatment with opioid dependent patients. Researchers found that both types of delivery yielded comparable weeks of continuous opioid and cocaine abstinence, and significantly greater weeks of abstinence than the standard intervention. (Bickel et al. 2008)

As summarized in the adopted guideline, acute opioid intoxication of a mild to moderate degree usually does not require specific treatment, but a severe opioid overdose requires emergency medical management to treat respiratory depression with naloxone. The APA guideline indicates that the following are effective strategies for managing opioid withdrawal by safely ameliorating acute symptoms and facilitating the patient's entry into a long-term treatment program for opioid use disorders: (1) methadone or buprenorphine substitution for the opioid, followed by gradual tapering; (2) abrupt discontinuation of opioids with use of clonidine to suppress withdrawal symptoms; and (3) clonidine-naltrexone detoxification. The guideline does *not* recommend using anesthesia-assisted rapid opioid detoxification (AROD) for this indication because of lack of proven efficacy and adverse risk-benefit ratios. Appropriate maintenance treatment is the use of methadone or buprenorphine for patients with a prolonged history (> one year) of opioid dependence using a stable maintenance dose of an opioid agonist.

Following on the APA guideline's pharmacotherapy treatment recommendations are results of a number of studies on various drugs used for opioid withdrawal and maintenance treatment. With the increasing prevalence of adolescents using opioids, a study of opioid-dependent adolescents was conducted by Marsch et al. to evaluate the relative efficacy of both buprenorphine- and clonidine-assisted withdrawal. Both medications were provided with thrice weekly behavioral counseling and incentives contingent on opioid abstinence during the detoxification. Adolescents who received buprenorphine were retained in treatment much longer and achieved markedly greater levels of abstinence from opioids relative to those who received clonidine. (Marsch et al. 2005) Another study of opioid addicted youth (aged 15 to 21 years) compared the outcomes of patients in a 12-week buprenorphine-naloxone regimen (prescribed up to 24 mg per day for nine weeks and then tapered to week 12) against a detox group (prescribed up to 14 mg per day then tapered to day 14). All study subjects were offered individual and group counseling. While more research is necessary in this age cohort, findings from this study favored the buprenorphine-naloxone group resulting in fewer opioid-positive urine test results, better retention in the clinical trial, less self-reported opioid use and injecting behavior along with less use of cocaine and marijuana. (Woody et al., 2008)

More recent research has focused on infants born to substance-dependent women and the resultant neonatal abstinence syndrome (NAS). The APA guideline indicates that methadone has a long history of use in pregnant women, with buprenorphine use showing comparable or better outcomes in reducing rates of NAS in this population. The research team of Kraft et al. discussed the challenges in treating NAS in infants since there is considerable variation in pharmacological treatment protocols (e.g., neonatal morphine solution, tincture of opium and methadone) as the

optimal treatment protocol has not been established. (Kraft et al., 2008) In a small (n=26) open label, active controlled study, Kraft et al. studied the use of sublingual buprenorphine versus oral neonatal opium solution (NOS) for the treatment of opiate withdrawal in this group of infants. Findings from this preliminary investigation showed that buprenorphine was safe, did not precipitate withdrawal due to its partial agonist/antagonist activity and was associated with a 31 percent reduction in length of treatment and a 29 percent reduction in length of stay. Nonetheless, three infants receiving buprenorphine and one infant receiving NOS reached protocol-specified maximum doses and required adjuvant therapy with phenobarbital. (Kraft et al., 2008)

Another large randomized controlled trial of 80 infants with moderate to severe NAS was conducted where all subjects received oral diluted tincture of opium and 40 infants were administered additional oral clonidine (1 µg/kg every four hours) and 40 infants received additional placebo. Findings showed that adding clonidine to the standard opioid therapy for detoxification from in utero exposure to methadone or heroin reduced the duration of pharmacotherapy for NAS without causing short-term cardiovascular outcomes. Also, higher doses of opium were required by 40 percent of the infants in the placebo group versus 20 percent in the clonidine group, along with treatment failure occurring in 12.5 percent of the infants in the placebo group versus none in the clonidine group. (Agthe et al., 2009)

Effective alternatives to long waiting lists for entry into methadone maintenance treatment were studied due to the inadequate methadone maintenance program capacity in the United States. This study, conducted by Schwartz et al., compared the effectiveness of interim methadone maintenance (i.e., consisting of an individually determined methadone dose and emergency counseling only for up to 120 days) with that of the usual waiting list condition. Results revealed that interim methadone maintenance results in a substantial increase in the likelihood of entry into comprehensive treatment and is also an effective means of reducing heroin use and criminal behavior among opioid-dependent individuals awaiting entry into a comprehensive methadone treatment program. (Schwartz et al. 2008)

A shift to buprenorphine-based approaches has the potential to reduce methadone overdose death due to its long-acting properties as a partial agonist at the μ -opioid sites. Also, buprenorphine may improve access to treatment since this agent is approved for office-based use in the United States. In comparing conventional methadone maintenance to a stepped-care strategy using buprenorphine/naloxone with escalation to methadone if needed, Kakko et al. found both drug regimens that included intensive behavioral treatment to be equally efficacious. Researchers suggest that in considering prior data on the advantageous safety of buprenorphine, broad implementation of strategies using buprenorphine as a first-line treatment should be considered. (Kakko et al. 2007)

Other investigators have acknowledged that development of mechanisms to deliver low and steady levels of buprenorphine is important in order to address the problems of low adherence, medication diversion and emergence of withdrawal symptoms with existing pharmacological treatments for opioid dependence. (Ling et al., 2010) Results from a more recently published clinical trial (n=163) conducted at 18 sites in the U.S. have been very encouraging in that buprenorphine implants compared to placebo resulted in less opioid use over 16 weeks in opioid dependent individuals as confirmed by urine samples. In this particular intervention, patients received either four buprenorphine implants (80 mg per implant) or four placebo implants after induction with sublingual buprenorphine-naloxone tablets. A fifth implant was available if a threshold for rescue use of sublingual buprenorphine-naloxone treatment was exceeded. Other positive clinical outcomes

for implanted buprenorphine in this study included fewer clinician-rated and patient-rated withdrawal symptoms, lower patient ratings of cravings and a greater change on clinician global ratings of severity of opioid dependence and global improvement. (Ling et al., 2010)

The APA guideline notes that while oral naltrexone is approved by the FDA for the treatment of opioid dependence, research data on its efficacy are mixed because clinical trials in outpatient settings fail to demonstrate a robust effect as seen in inpatient settings. However, interest in this drug remains where clinical studies have been conducted in both the injectable/sustained-release (depot) and implantable forms of naltrexone. A prospective clinical trial conducted by Comer et al. showed positive results for both the 192 mg and 384 mg doses of long lasting injectable formulations of naltrexone against placebo where treatment retention was robust and dose-related. (Comer et al. 2006) Designated as a priority review, the FDA approved extended-release injectable naltrexone in October 2010 for use in the treatment and prevention of relapse for patients with opioid dependence who have undergone detoxification treatment. Findings from a 24-week clinical trial conducted in Russia (n=250) revealed positive outcomes where the median percentage of opioid-free screens was 90 percent among patients taking 380 mg extended-release naltrexone, compared with 35 percent among patients taking placebo. Additionally, total abstinence was reported in 45 (35.6 percent) of treated patients vs. 28 (22.6 percent) in the placebo group, and a 50 percent mean reduction in cravings from baseline on the Visual Analog Scale (VAS) craving score was found for naltrexone-treated patients compared with no change for placebo-treated patients. (FDA, 2010; Laino 2010)

A retrospective longitudinal follow-up study by Ngo et al. conducted in Australia, where the naltrexone implantation is available, showed that naltrexone implants, but not methadone maintenance, had long-term benefits in reducing opioid-related hospital morbidity. However, researchers were concerned with the long-lasting and increased nonopioid drug-related morbidity that occurred following naltrexone implantation. (Ngo et al. 2008) A more recent randomized trial of heroin-dependent patients (n=70) compared the safety and efficacy of a single treatment sustained-release naltrexone implant (2.3 g) plus placebo tablets against daily oral naltrexone treatment of 50 mg per day for six months. Results indicated that more participants in the oral naltrexone group had subtherapeutic blood levels of naltrexone and returned to regular heroin use by six months and at an earlier stage. Investigators concluded that the naltrexone implant effectively reduced relapse to regular heroin use compared with oral naltrexone and was not associated with major adverse events. (Hulse et al., 2009)

Two studies focused on cardiac complications resulting from the use of methadone, levomethadyl acetate (LAAM) and buprenorphine in opioid maintenance treatment. The first systematic retrospective study by Ehret et al. compared active or former intravenous drug users receiving methadone and those not receiving methadone among all patients hospitalized over a five-year period in a tertiary care hospital. Results revealed that among 167 methadone patients, the prevalence of QTC prolongation to 0.50 second^{1/2} or longer was 16.2 percent compared with 0 percent in 80 control subjects - confirming that this is a frequent finding. Further analysis showed that methadone dose, presence of cytochrome P-450 3A4 inhibitors, potassium level and liver function, contribute to QT prolongation and that long QT syndrome can occur with low doses of methadone. (Ehret et al. 2006) Wedam et al. conducted a retrospective analysis of 12-lead electrocardiograms using electrocardiographic data from a previously published randomized control trial (Johnson et al. 2000) that compared the effects of three efficacious treatments for opioid addiction – methadone,

levomethadyl acetate and buprenorphine. (Note: FDA black box warnings on lethal cardiac arrhythmias led to the manufacturer withdrawing levomethadyl acetate from the market in 2003). Their analysis showed that buprenorphine is associated with less QTc prolongation than levomethadyl or methadone, and may be a safe alternative. (Wedam et al. 2007)

In 2009, at the suggestion of The Center for Substance Abuse Treatment, an independent expert panel developed cardiac safety recommendations for physicians prescribing methadone. (SAMHSA, 2009; Krantz et al., 2009) After a review of the evidence, this consensus panel acknowledged a large body of evidence suggesting that oral and intravenous methadone is associated with QTc interval prolongation and torsade de pointes and recommended the following: (Krantz et al., 2009, p. 392)

1. “Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
2. Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
3. Obtain a pretreatment electrocardiogram (ECG) for all patients to measure the QTc interval and a follow-up ECG within 30 days and annually. Additional ECG is recommended if the methadone dosage exceeds 100 mg per day or if patients have unexplained syncope or seizures.
4. If the QTc interval is greater than 450 ms but less than 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
5. Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.”

A Canadian research team studied the use of injectable diacetylmorphine, the active ingredient in heroin, as an alternative treatment for the estimated 15-25 percent of heroin-addicted patients who are refractory to oral methadone maintenance treatment. (Oviedo-Joekes et al., 2010) Long-term users of injectable heroin (n=226) who had not benefited from at least two previous attempts at treatment for addiction (including at least one methadone treatment) were randomly assigned to receive oral methadone (mean daily dose of 96.0 mg) or self-injected diacetylmorphine (up to 1000 mg) under medical supervision on a daily basis. Investigators reported that the rate of retention in addiction treatment in the diacetylmorphine group was 87.8 percent, compared with 54.1 percent in the methadone group. The reduction in rates of illicit-drug use or other illegal activity was 67.0 percent in the diacetylmorphine group versus 47.7 percent in the methadone group. Serious adverse effects were associated with diacetylmorphine injections in 10 patients who overdosed and in six patients who experienced seizures. In acknowledging the superior effectiveness of diacetylmorphine maintenance treatment outcomes, the research team suggested its use in the refractory subgroup of patients who do not benefit from methadone maintenance. (Oviedo-Joekes et al., 2010)

After achieving a stable dose of opioid agonist, the APA guideline stresses that the treating clinician should facilitate a patient’s engagement in a comprehensive program of rehabilitation, usually with the behavioral therapies (e.g., contingency management) and CBT components. Fiellin et al. conducted a study to determine the optimal level of counseling and frequency of attendance for buprenorphine-naloxone medication distribution in a primary care setting. The results showed that the efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice weekly dispensing. Researchers

concluded that strategies to improve buprenorphine-naloxone adherence are still needed. (Fiellin et al. 2006)

Obtaining Copies of the APA Guidelines

Copies of the APA *Practice Guideline for the Treatment of Patients With Substance Use Disorders, Second Edition*, and *Treating Substance Use Disorders: A Quick Reference Guide* may be obtained through the APA at <http://psych.org/>, by calling 800-368-5777, or by U.S. mail at:

American Psychiatric Publishing, Inc.
1000 Wilson Blvd., Suite 1825
Arlington, VA 22209-3901

Provider Feedback

Magellan welcomes feedback on adopted clinical practice guidelines. All suggestions and recommendations are taken into consideration in our ongoing review of the guidelines. Questions or comments may be submitted via mail or e-mail to:

Clinical Operations Coordinator

Re: CPG

Magellan Health Services
6950 Columbia Gateway Dr.
Columbia, Maryland 21046
CPG@MagellanHealth.com

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