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

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Purpose of This Document

Magellan Healthcare has adopted the American Psychiatric Association's (APA) *Practice Guideline for the Treatment of Patients With Substance Use Disorders, Second Edition* (2006), *Treating Substance Use Disorders: A Quick Reference Guide* (2006), and *Guideline Watch (April 2007): Practice Guideline for the Treatment of Patients With Substance Use Disorders, 2nd Edition.* These guidelines 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, including 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 healthcare organizations (MBHOs), this adoption will minimize the burden on practitioners participating in multiple MBHOs. The adopted guidelines and Guideline Watch are 10 and 9 years old, respectively, and the APA has not yet updated them. Magellan has updated this Introduction to reflect current knowledge and practice.

As with all guidelines, the adopted guidelines and Magellan's Introduction augment, but do not replace, sound clinical judgment. As a matter of good practice, clinically sound exceptions to the treatment guidelines are 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 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
- Novel Drugs of Abuse

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, opioids, and novel drugs – published through November 2016. Key relevant recommendations from this more recent review are included and summarized below. Magellan encourages providers to become familiar with this information as well as the information in the APA Guideline and Guideline Watch.

Executive Summary

(Discussion of changes/new information in this updated guideline)

Epidemiology

The national epidemic of prescription opioid abuse and heroin use has been recently addressed in the United States by the Comprehensive Addiction and Recovery Act of 2016 (CARA). Congress acted due to the large number of overdoses from heroin, prescription drugs, and opioid pain relievers that surpassed car accidents as the leading cause of injury-related death in the United States (https://www.govtrack.us/congress/bills/114/s524). Information from the most recent National Survey on Drug Use and Health (NSDUH) provides key substance use indicators in the United States (SAMHSA, 2016).

The Substance Abuse and Mental Health Services Administration (SAMHSA, 2016) has made changes to the *2015 National Survey on Drug Use and Health (NSDUH)* to improve the quality of data collected. This "break in trends" leads to difficulty in comparing current estimates with those from earlier years; a new baseline for some substances begins with this latest survey (SAMHSA, 2016). For marijuana, cocaine, and heroin use, trends continue for estimates considered comparable with those in past years. The new survey includes changed questions about particular measures as well as changes in eligibility of respondents (SAMHSA, 2016). The new report also includes information on new topics not included in past surveys. Some of the changes are:

- Instead of separate questions about chewing tobacco and snuff, these are combined into questions about smokeless tobacco; new smokeless tobacco questions include questions about "snus" (smokeless tobacco pouches placed under top lip).
- To ensure consistency with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the 2015 NSDUH lowered the threshold for determining binge alcohol use for females from five to four or more drinks on an occasion (the threshold remains at five or more drinks on an occasion for males).
- Questions for "Molly" (Ecstasy), ketamine, tryptamines, alpha-methyltryptamine, "Foxy" (5-MeO-DIPT), and salvia divinorum are now included in the hallucinogens section rather than the special drugs section.
- The inhalant section includes estimates beginning with 2015 data for specific inhalants, i.e., felt-tip pens and computer keyboard cleaner ("air duster").
- Questions about methamphetamine are now separate from the prescription drug items in the 2015 survey because most of it is both produced and consumed illicitly in the U.S.; a new baseline begins with 2015 for estimates of dependence or abuse of methamphetamine.
- Changes to prescription drug measures necessitated a new baseline for measures in the four categories of prescription drugs, i.e., pain relievers, tranquilizers, stimulants, and sedatives. Questions for prescription drug misuse now refer to a 12-month reference period rather than a lifetime reference period. In the 2015 survey, misuse of prescription drugs refers to using the drug "in any way a doctor did not direct you to use it" (e.g., in a greater amount than prescribed or for a longer period of time) (SAMHSA, 2016).

A summary of key findings from SAMHSA's 2015 NSDUH follows below:

- **Illicit Drug Use** – Questions about seven of ten illicit drug categories (hallucinogens, inhalants, methamphetamine, prescription pain relievers [misuse of], tranquilizers, stimulants, and sedatives) include changes in measurements affecting comparability with earlier years. The 2015 estimates show 10.1 percent of Americans aged 12 and older used an illicit drug in the past 30 days (27.1 million people), and among young adults aged 18-25, approximately 1 in 5 were current users of illicit drugs (22.3%). Key measurements did not change for **marijuana, cocaine, and heroin**, and estimates of the use of these are comparable with those from past years (SAMHSA, 2016).

    - ***Hallucinogens*** include LSD, PCP, peyote, mescaline, psilocybin mushrooms, "Ecstasy" (MDMA or "Molly"), ketamine, "FOXY" (DMT/AMT), and *Salvia divinorum*. An estimated 1.2 million people representing 0.5% of the population aged 12 or older were current users of hallucinogens in 2015. The age group with the largest percentage of its members using hallucinogens was the 18-25 years of age group (SAMHSA, 2016).
    - ***Inhalants*** used to get high include substances, e.g., computer keyboard cleaner, felt-tip pens, glue, nitrous oxide, cleaning fluids, spray paint, etc. Approximately half a million people aged 12 or older were current users of

inhalants in 2015, representing 0.2% of that population. The age group with the most common use was the 12-17 years of age group (SAMHSA, 2016).

- Currently, in the U.S. the production and distribution of most ***methamphetamine*** is illicit rather than through the pharmaceutical industry. An estimated 897,000 people aged 12 or older were current users of methamphetamine in 2015, representing 0.3% of this population. The age groups with the largest percentage of members using methamphetamine were the 18 to 25 and the 26 or older age groups (SAMHSA, 2016).
- In 2015, 1.4% of people aged 12 or older were misusers of ***prescription pain relievers,*** which represents 3.8 million people aged 12 or older. Out of this group, those with the highest percentage of misusing pain relievers in the past 30 days were from 18 to 25 years of age (SAMHSA, 2016).
- Among people aged 12 or older in 2015, ***tranquilizers*** were misused by an estimated 1.9 million people, who represented 0.7% of that age group. Within this age group, the 18-25 year-old group had the largest percentage of its members misusing tranquilizers (SAMHSA, 2016).
- ***Stimulants*** were currently misused in 2015 in an estimated 1.7 million people aged 12 or older, representing 0.6 percent of this population. The 18-25 year-old age group had the largest percentage of its members misusing stimulants (SAMHSA, 2016).
- In 2015, 0.2% of the population aged 12 or older misused ***sedatives***, representing an estimated 446,000 people. The 18-25 and 26 or older age groups had the largest percentages of their members misusing sedatives (SAMHSA, 2016).
- The 2015 illicit drug use estimate is highest for ***marijuana*** use (22.2 million current marijuana users aged 12 or older and 8.3% of people aged 12 or older). This is similar to the 2014 percentage and higher than the percentages from 2002-2013. The survey shows this increase in marijuana use among people 12 or older reflects the increase by adults aged 26 or older and, to not so great an extent, increases in use among those aged 18-25 (SAMHSA, 2016).
- Among people aged 12 or older in 2015, an estimated 1.9 million were current users of ***cocaine***; that number includes approximately 394,000 current users of crack cocaine. An estimated 0.7 percent of people aged 12 or older were current users of cocaine in 2015 while 0.1% currently used crack cocaine. These estimates were similar to estimates in years between 2007 and 2013, but were higher than the estimates in 2014. Additionally, the estimates of both cocaine and crack use in 2015 were lower than estimates between 2002 and 2006 (SAMHSA, 2016).
- In 2015, approximately 329,000 people aged 12 or older were current ***heroin*** users, corresponding to approximately 0.1 percent of the population of the same age. Approximately 0.3% of people aged 12 or older in 2015 had past-year use of heroin, representing approximately 828,000 people. Although the estimate of current heroin use in people aged 12 or older in 2015 was similar to the estimates between 2010 and 2014, it was higher than in most years between 2002 and 2009. Additionally, past-year heroin

use in 2015 was higher than during 2002-2008, but similar to 2009-2014. The survey indicates larger increases in heroin use among adults aged 26 or older and smaller increases among young adults aged 18 to 25 (SAMHSA, 2016).

The Centers for Disease Control and Prevention (CDC) reported increases in drug and opioid overdose death in the United States from 2000 – 2014 in the January 1, 2016 Morbidity and Mortality Weekly Report (*MMWR*). Information in the report noted significant increases in drug overdose deaths from 2013 to 2014, with opioid overdose deaths as the main factor in the increase. Increases in death rates were 9% for natural and semi-synthetic opioids, 26% for heroin, and 80% for synthetic opioids including illicit fentanyl and synthetic opioid pain relievers other than methadone (CDC, 2016).

- The CDC reported an epidemic of drug overdose (poisoning) deaths in the United States, with the rate of deaths from drug overdoses increasing 137% from the year 2000. The rate of overdose deaths involving opioids (opioid pain relievers and heroin) increased by 200% (CDC, 2016). Drug overdose deaths occurring the in the U.S. during 2014 totaled more than 47,000, representing a one-year increase of 6.5%, while opioid overdose deaths increased by 14% (CDC, 2016).
- In 2014, drug overdoses in the U.S. were greater than during any previous year on record. The number of drug overdose deaths in the U.S. in 2014 was approximately one and a half times more than the number of motor vehicle crashes. The main drugs associated with overdose deaths were opioids, primarily heroin and prescription pain relievers, (e.g., oxycodone and hydrocodone) (CDC, 2016). From 2013 to 2014, overdose death from oxycodone and hydrocodone increased by 9% (CDC, 2016).
- The increase in heroin use (tripling in 4 years) related to opioid pain reliever misuse **may** be due to increased availability, high purity, and relatively low price (CDC, 2016).
- Illicit fentanyl, often combined with heroin or sold as heroin, **may** be a contributor to the recent increases in drug overdose deaths involving heroin (CDC, 2016).

- **<u>Tobacco Use</u>**
  - As reported by SAMHSA, tobacco use continues to be the leading cause of preventable death in the U.S. Among people aged 12 or older in 2015, 66.3% of past-month tobacco users were current cigarette smokers, while not using any other tobacco products. Among past-month tobacco users in the same age group, 15% smoked cigarettes while also using other tobacco products and 18.8% used only tobacco products other than cigarettes (SAMHSA, 2016).
  - Among people aged 12 or older in 2015, about 20% were current **cigarette smokers** compared with 24% to 26% who were current cigarette smokers in years from 2002 to 2008. A decline in current use of cigarettes has occurred in adolescents aged 12 to 17, young adults aged 18 to 25, and in those aged

26 or older. NSDUH reports that part of this decline reflects the use of electronic vaporizing devices, e.g., e-cigarettes, for delivering nicotine (SAMHSA, 2016).

- In 2015, 4.7% and 0.8% of people aged 12 or older were current **cigar smokers** and **pipe tobacco smokers,** respectively. The 2015 percentage for cigar smokers was lower than in most of the years between 2002 and 2012 while similar to the percentages in 2013 and 2014. The percentage of people who were current pipe tobacco smokers in 2015 was similar to the percentages in most years between 2001 and 2014 (SAMHSA, 2016).
- About 3.4% of people aged 12 or older in 2015 were current users of **smokeless tobacco**, e.g., snuff, chewing tobacco, and snus. The 18-25 year-old age group had the largest percentage of its members using smokeless tobacco (SAMHSA, 2016).
- The U.S. Food and Drug Administration (FDA) finalized a rule, effective August 8, 2016, extending its authority to regulate the manufacturing, distribution, and marketing of all tobacco products, including e-cigarettes, cigars, hookah (waterpipe tobacco), pipe tobacco, nicotine gels, and dissolvables (FDA, 2016). The FDA's goal is the protection of Americans from disease and death related to tobacco use. Although the FDA recognizes that some tobacco products **may** have less toxicity, it also notes a need for more evidence. For example, the FDA acknowledges both benefits and risks of products, e.g., e-cigarettes, which **may** be less harmful than conventional cigarettes, but they **may** prompt young people to become addicted to nicotine. Vaporizers, vape pens, hookah pens, e-cigarettes, e-pipes and other Electronic Nicotine Delivery Systems (ENDS) are affected by the FDA regulation.

- **<u>Alcohol Use</u>**
  - In 2015, more than half (51.7%) of people aged 12 and older reported any use of **alcohol** in the past month. This estimate of current alcohol use was similar to the estimate in the years from 2005 to 2013, but it was lower than the estimate in 2014 (SAMHSA, 2016).
  - In 2015, approximately 25% of people aged 12 or older were estimated to be binge alcohol users. **Binge alcohol use** for males is defined as drinking five or more drinks on the same occasion on at least one day in the past 30 days; for females, the threshold is four drinks rather than five drinks. About 5.8% of adolescents aged 12 to 17 years were current binge drinkers in 2015, and an estimated 39% of young adults aged 18 to 25 were current binge alcohol drinkers in the past month. Almost 25% of adults aged 26 or older were also current binge alcohol drinkers (SAMHSA, 2016).
  - The 2015 NSDUH defines **heavy alcohol use** as "binge drinking on 5 or more days in the past 30 days" based on the thresholds described above (SAMHSA, 2016; p. 18). The estimated percentage of the population aged 12 or older who were heavy alcohol users in 2015 was 6.5%. Percentages for specific age groups in 2015 were 0.9%, 10.9%, and 6.4% for adolescents aged 12 to 17,

young adults aged 18 to 25, and adults aged 26 or older, respectively (SAMHSA, 2016).
    - Although **underage alcohol use** is prohibited in all 50 states and the District of Columbia, 20.3% of people aged 12 to 20 were reported drinking alcohol in the past month (lower than the percentages in 2002 through 2014). Among this age group, 13.4% and 3.3% were binge drinkers or heavy drinkers, respectively (SAMHSA, 2016).

- **Substance Use Disorders**
    - In 2015 among people aged 12 or older, 7.8% had a substance use disorder (SUD) in the past year. Out of this group, approximately 75% had an alcohol use disorder and about 33.3% had an illicit drug use disorder. Of those who had SUDs in the past year, approximately 12.5% had both an alcohol use disorder as well as an illicit drug use disorder (SAMHSA, 2016).
    - In 2015 among people aged 12 or older who had a past-year illicit drug use disorder, the largest numbers of people had disorders related to the use of marijuana and the misuse of prescription pain relievers (SAMHSA, 2016).

An October 2015 News Release by the National Institutes of Health (NIH) reported that surveys conducted by the National Institute on Alcohol Abuse and Alcoholism show that, "marijuana use in the United States has risen rapidly over the past decade, with about 3 in 10 people who use marijuana meeting the criteria for addiction" (NIH, 2015). The report discussed how the "changing cultural norms related to marijuana use" may create "public health challenges related to addiction, drugged driving and access to effective treatment" (NIH, 2015).

Marijuana is the most commonly used illicit drug. On August 11, 2016, the United States Drug Enforcement Administration (DEA) denied petitions to reschedule marijuana under the Controlled Substances Act (Drug Enforcement Administration, 2016). Marijuana continues its classification as a Schedule 1 controlled substance with high dependency potential and no accepted medical use. Although marijuana is illegal under federal law, its recreational use is legal in eight states and the District of Columbia. Currently 28 states, the District of Columbia, Guam and Puerto Rico have enacted laws to legalize the medical use of marijuana for indications such as pain management, treatment of nausea/vomiting, glaucoma, etc. (ProCon.Org, 2016). Additionally, limited-access marijuana products (low tetrohydrocannabidiol [THC]/high cannabidiol [CBD] are approved in 17 states for "medical reasons in limited situations or as a legal defense" (National Conference of State Legislatures, 2016). The DEA has expanded the number of DEA-registered marijuana manufacturers to foster research on its use. The American Medical Association (AMA) continues to support further studies of medical marijuana use in patients who have serious conditions where evidence **suggests** possible efficacy.

General Treatment Principles – Somatic Treatments

A recent article discussed the role of medication-assisted treatment for alcohol use disorders and opioid dependence in primary care (Lee et al., 2015). With primary care as

the entry point for many patients suffering from chronic substance related and addictive disorders, primary care health providers can address substance use disorders by screening, prevention, diagnosis, and disease management, including the use of pharmacotherapies in combination with counseling and behavioral therapies, and relapse prevention. Due to the national public health crisis surrounding opioid misuse and abuse, the importance in providing evidence-based effective prevention, care, and treatment is paramount. At present, many patients are referred to specialty care providers, but they often are lost in "the gap between primary care and specialty treatment systems" (Lee et al., 2015, p. 1). They may either undergo detoxification without transition to a treatment/support program or receive psychosocially-based treatment only, after which they relapse to substance use. Authors noted a clinical trial comparing alcohol care management delivery in primary care to specialty addiction treatment, which found that the intensive care and pharmacotherapy in a primary care setting provides "better clinical outcomes for patients with alcohol use disorders than those obtained in addiction specialty care" (Lee et al, 2015, p. 2).

The epidemic of opioid-related deaths with its rising death toll compares to the acquired immune deficiency syndrome (AIDS) crisis in that it requires a large scale, highly coordinated response (Williams and Bisaga, 2016). Patients with opioid use disorder (OUD) receive medical treatment for withdrawal during detoxification, followed by discharge referrals to medication-free outpatient or residential care; most of the patients not receiving medication-assisted treatment (MAT) relapse and are at risk of overdose death. Williams and Bisaga discussed "enlargement of the network of professionals authorized to deliver treatment and broadened access to MAT through such avenues as specialized community pharmacies, telemedicine, and hub-and-spoke systems of care" (Williams and Bisaga, p. 814).

General Treatment Principles – Psychosocial Treatments

Past studies have shown that a computer-based therapeutic education system (TES) including media technologies, e.g., internet and mobile devices, **may** be effective in the treatment of problematic substance use disorders. A recent trial examined how baseline demographic and behavioral characteristics of participants from a methadone maintenance treatment program (n=169) predict treatment outcomes of TES (Kim et al., 2015). Participants were randomized to one of two groups: (1) standard treatment (i.e., counseling once per week during first 4 weeks, followed by every other week over 52 weeks) alone, or (2) reduced standard treatment plus TES, where TES replaced the first half of each counseling session. Analyses showed baseline characteristics of subgroups who most benefit from the reduced standard plus TES condition compared to the standard alone treatment: employed patients, highly anxious patients, and those ambivalent about substance use (Kim et al., 2015).

General Treatment Principles – Clinical Factors Affecting Treatment

A recent study compared smoking status over four years between individuals (n=311,466) with and without behavioral health conditions in a large, integrated healthcare delivery

system providing access to tobacco treatment (Young-Wolff et al., 2016). In 2010, 10.4% of patients without behavioral health conditions were smokers whereas 20.1% of those with behavioral conditions were current smokers. Although smoking prevalence dropped significantly for both groups from 2010–2013, 33.3% of patients with a substance use disorder continued to smoke in 2013 compared to only 9.2% of those with no behavioral health condition who continued to smoke. The most commonly used tobacco cessation medication used was the nicotine patch, with very low use of bupropion. The use of bupropion did not differ significantly between those with and without a behavioral health condition. Authors highlighted results showing continuing large disparities in smoking between the two groups, noting that access to healthcare does not equate to utilization of tobacco cessation treatments. They further **suggested** use of tobacco cessation treatment within substance use and psychiatry specialty clinics, especially since "quitting smoking is associated with long-term reductions in depression, anxiety, and stress and with improvements in well-being" (Young-Wolff, p. 1000). Authors concluded the need to address the increasing disparities in smoking among those with behavioral health conditions, especially substance use disorders, and "to better facilitate access to, and use of, appropriate and effective tobacco cessation medications as part of standard behavioral health treatment (Young-Wolff, p. 1002).

Other issues related to smoking and mental illness addressed in recent studies include the effect of tobacco use and cessation on psychiatric medications. The dosing of many psychiatric medications is affected when patients quit smoking as well as when they relapse to smoking, and clinicians should watch for related side effects (Ziedonis et al., 2015). Authors provided clinical recommendations for psychiatrists, e.g., listing "tobacco use/tobacco use disorder" in the treatment plan; consideration of a CO meter to assess ongoing progress; and creation of system changes to integrate evidence-based practices and enhance patients' quality of life (Ziedonis et al., 2015). A 2016 study reviewed randomized controlled smoking cessation treatment intervention trials in smokers with serious mental illness (SMI) to provide evidence on both the safety and efficacy of smoking cessation interventions for individuals with serious mental illness (Evins et al, 2015). Authors noted that individuals with SMI should receive treatment to quit smoking, as they smoke with greater prevalence, die earlier due to smoking-related illnesses, and want to and can quit smoking. They concluded that effective treatment for smokers with schizophrenia spectrum disorder includes combined behavioral treatment and varenicline or bupropion with or without nicotine replacement therapy (NRT). Authors noted the need to establish an evidence base for clinical practice guidelines for smoking cessation treatment for subgroups of smokers, e.g., those with major depressive disorders, and bipolar disorder. They also noted the need for future research addressing types of behavioral treatment (Evins et al, 2015). A recent study assessed the effects of elevated depression symptoms among nicotine-dependent smokers during smoking cessation efforts (Reid and Ledgerwood, 2016). In this small controlled trial including nicotine-dependent smokers (n=81), authors found that smokers with greater vs. fewer depressive symptoms experienced increased withdrawal and craving while trying to quit smoking even at the start of treatment (monitoring of expired carbon dioxide and brief counseling), with the discomfort making quitting difficult.

Another clinical condition that affects the treatment of tobacco use disorder is obesity. A recent literature review explored the complex relationship between nicotine and body weight regulation (Rupprecht et al., 2015). Authors presented a simplistic model of the relationship between obesity and smoking. Obese smokers are especially susceptible to smoking due to several factors: clustering of unhealthy behaviors, smoking to reduce weight, and enhanced reward seeking. They noted how nicotine increases insulin resistance, central obesity and fat accumulation while contributing to obesity, and proposed "these factors create a cycle promoting nicotine-seeking in the obese population" (Rupprecht et al., p. 291). Authors further reported how reduction of nicotine content in cigarettes **may** "result in the development of obesity and its associated co-morbidities in a subset of smokers." According to the authors, nicotine-reduction policy currently studied as a strategy to reduce the harm caused by tobacco smoke must carefully consider this vulnerable population of obese smokers.

Patients with coronary heart disease (CHD) benefit from psychosocial smoking cessation interventions. Authors examined the efficacy of psychosocial interventions, e.g., counseling, telephone support, and self-help material, for smoking cessation in patients with CHD in an updated Cochrane review including 40 randomized controlled trials (Barth et al., 2015). From this review, authors concluded that psychosocial interventions over a period of more than one month were effective in promoting abstinence for up to one year, whereas brief interventions of less than one-month duration and of low intensity were not effective. Authors **suggested** the need for more studies comparing additional benefits of combined pharmacological interventions, e.g., bupropion and NRT, and psychosocial interventions compared with pharmacological or psychosocial interventions alone in patients with CHD.

Although alcohol dependence and major depressive disorder frequently co-occur, the disorders usually receive separate treatment, resulting in many individuals having poor access to specialized psychiatric treatment (Awan et al., 2015). In a recent report, authors described a pilot implementation and use of integrated care pathways (ICPs) for patients with co-occurring alcohol dependence and major depressive disorder in a clinical setting. The intervention included: psychopharmacological intervention, non-pharmacological intervention, interdisciplinary collaboration, and a project management approach. Authors emphasized the "bottom up" approach, including the "inclusion and engagement of frontline clinicians from the start" and allowing the clinicians to "own" the processes and be accountable for both results and accountability (Awan et al., 2015). Non-psychiatrist physicians specialized in addictions received guidance in assessment and treatment of major depressive disorder, and in complex cases, they were partners with the team psychiatrist. An evaluation of this pilot program showed reduction of symptoms for both alcohol dependence and depression. Authors **suggested** that the ICP is a potentially effective approach in the treatment of concurrent alcohol dependence and major depressive disorder at an academic tertiary care hospital; they noted the need for further research to establish applicability in a variety of settings (Awan et al., 2015).

As a number of states are legalizing both medicinal and recreational marijuana, studies have addressed an important concern about how adolescent marijuana use may affect the development of psychotic symptoms, e.g., hallucinations and paranoia. In a 2016

longitudinal study, researchers examined whether adolescents regularly using marijuana, i.e., weekly or more often, experienced a systematic increase in their subclinical psychotic symptoms during a period of regular use. They also examined whether the increase was short-lived or sustained following abstinence (Bechtold et al., 2016). The study sample included boys (n=1009) who self-reported frequency of marijuana use, subclinical psychotic symptoms, other substance use, e.g., alcohol, or other illicit drug use, and internalizing and externalizing problems. These were recorded annually from age 13 to 18, with researchers using within-individual change modeling to analyze whether the adolescents reported "an increase in their subclinical psychotic symptoms as a function of their recent and/or cumulative history of regular marijuana use and whether effects were sustained following abstinence" (Bechtold et al., p. 781). Researchers further examined the information for specific features of psychosis. Results found evidence **suggesting** an adolescent's risk of experiencing persistent subclinical psychotic symptoms **may** be increased by regular marijuana use, with this association remaining significant after controlling for changes in current marijuana use and other illicit drug use. Even when adolescents remained abstinent for a year, the effect of prior weekly marijuana use on subclinical psychotic symptoms did not go away, with pronounced effect for paranoia and hallucinations. Researchers concluded that, based on the results of this study, "adolescents are more likely to experience subclinical psychotic symptoms (particularly paranoia) during and after years of regular marijuana use" …and that "perhaps the most concerning finding is that the effect of prior weekly marijuana use persists even after adolescents have stopped using for 1 year" (Bechtold et al., p. 788). They noted the importance of policies and programs "to keep adolescents from engaging in regular marijuana use, as chronic use seems to increase their risk of developing persistent subclinical psychotic symptoms" (Bechtold et al., 2016).

Treatment of Nicotine Dependence

Effective treatments to stop smoking include both behavioral support and pharmacotherapies, either alone or combined. A 2016 review of 53 randomized or quasi-randomized trials from the Cochrane Library compared combined behavioral support (brief advice and counseling) and medication (nicotine replacement therapy [NRT], varenicline, nortriptyline, and bupropion) to usual care or brief advice to determine whether the treatment effect, i.e., abstinence from smoking after 6 months, differed depending on the intervention (Stead et al., 2016). Studies (n=53) included participants (n=more than 25,000) who were smokers recruited from both community and healthcare settings. The analysis, including 52 pooled studies, showed that the combination of behavioral support and pharmacotherapies increased smoking cessation success more than the minimal intervention or usual care. Researchers concluded that combined interventions of pharmacotherapy and behavioral support should be encouraged by clinicians for smokers (Stead et al., 2016).

Another 2016 study reviewed randomized controlled trials (n=29), from the Cochrane Library, comparing the efficacy of nicotine receptor partial agonists, e.g., varenicline and cytisine, to placebo, for helping people (n=13,562) stop smoking (Cahill et al., 2016). Trials comparing the treatment drugs with bupropion and nicotine patches were also included if

available. The follow-up period in all the trials was at least six months from start of treatment and all trials reported at least a follow-up period of six months from the start of treatment. Abstinence from smoking at the longest follow-up was the main outcome measured with results biochemically confirmed (by testing blood or bodily fluids). Cytisine increased the chances of quitting with only modest quit rates. Key results showed that varenicline doubled the chances of quitting smoking compared with placebo while it also reduced side effects. Varenicline was also more effective in stopping smoking than bupropion or NRT. Researchers reported, "Varenicline delivers one extra successful quitter for every 11 people treated, compared with smokers trying to quit without varenicline" (Cahillet al., 2016, p. 3). According to the researchers, recent evidence is not in support of a link between varenicline and depressed mood or suicidal ideation, although smokers treated with varenicline who also have a past or current psychiatric illness **may** be at a higher risk. They also noted unclear evidence about a linkage between varenicline and increased heart and circulatory problems in people already with these risks, necessitating future research (Cahill et al., 2016).

In a 2015 study, researchers noted that not all cigarette smokers are ready to quit abruptly, but **may** be willing to reduce smoking with the goal of quitting (Ebbert et al., 2015). Researchers indicated that past studies have shown that an average of two quit attempts annually are made by 40% of cigarette smokers, with surveys showing that 44% of daily cigarette smokers prefer to quit through reducing the number of cigarettes rather than abruptly quitting (Ebbert et al., 2015). The purpose of this randomized, blinded, placebo-controlled, multinational clinical trial was to determine efficacy as well as the safety of varenicline to increase smoking abstinence rates through smoking reduction in a "reduce-to-quit" approach. Participants (n=1510) included those who smoked 10 or more cigarettes per day without an abstinence period greater than 3 months in the past year and who agreed to reduce smoking and try to quit within 3 months. They were randomized to varenicline or placebo during a 24-week treatment period during which they were asked to reduce their smoking rate by 50% and 75% by week 4 and week 8, respectively, to meet a goal of quitting by week 12. Participants received counseling training to help them quit smoking. Within the varenicline group, 32% achieved continuous abstinence during weeks 15 through 24 compared with only 7% of those receiving placebo. Those in the varenicline treatment group were more than three times more likely to maintain abstinence six months after treatment than the placebo group. Adverse events rates did not differ between the groups. Researchers concluded that varenicline effectively increases long-term smoking cessation (Ebbert et al., 2015).

In a recent study, smokers (n=1086) were randomized to varenicline only, nicotine patch only, or combination nicotine replacement therapy (C-NRT), i.e., nicotine patch plus nicotine lozenge over a 12-week period (Baker et al., 2016). Treatment in all groups included counseling. The primary outcome measure was self-reported 7-day point-prevalence abstinence at 26 weeks, confirmed by exhaled carbon monoxide. No significant differences in rates of smoking abstinence occurred at 26 or 52 weeks. Researchers noted that although varenicline and C-NRT have been considered superior to the nicotine patch in effectiveness, the current findings "raise questions about the relative effectiveness of intense smoking pharmacotherapies" (Baker et al., 2016).

A recent large randomized, double-blind, triple-dummy, placebo-controlled trial, Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES), compared the smoking cessation efficacy and safety of varenicline (1 mg twice a day), bupropion (150 mg twice a day), and transdermal nicotine patch (21 mg per day with taper) in smokers (n=8144) with and without a psychiatric disorder (Anthenelli al, 2016). Participants were randomized to one of the treatment groups or placebo for a 12-week treatment phase followed by a 12-week non-treatment phase. Results showed no evidence of significant increase in rates of moderate-to-severe neuropsychiatric adverse events with varenicline or bupropion relative to nicotine patch or placebo in those with or without psychiatric disorders. The efficacy of varenicline was superior to bupropion, nicotine patch, and placebo in both those with and without a psychiatric disorder, and both bupropion and nicotine patch were superior in efficacy to placebo. The researchers **implied** that "the available evidence, substantially boosted by this study, clearly shows the efficacy of all three first-line smoking cessation medications with varenicline having the largest effect, in smokers with and without psychiatric disorders" (Anthenelli et al, p. 2508).

The FDA advisory panel recommended the removal of a serious warning about neuropsychiatric side effects of varenicline on Sept. 14, 2016. However, it is uncertain whether the FDA will follow the recommendation of the advisory committee to remove the Black Box warning. The FDA advisory panel reviewed results of the Anthenelli study (above) that suggested the drug does not appear to increase the risk of moderate to severe neuropsychiatric adverse events relative to nicotine patch or placebo, but an FDA medical review team was skeptical of the study. An FDA briefing document noted that "the evidence from the existing observational studies alone is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use" (FDA, 2016).

Authors assessed the effects of behavioral and pharmacologic interventions for the treatment of smokeless tobacco (ST) use in a 2015 systematic review (Ebbert et al., 2015). They obtained evidence from 34 randomized trials enrolling smokeless tobacco users (n = 16,000). Based upon their analyses, authors **suggested** that varenicline and nicotine lozenges appear to increase tobacco abstinence rates among those using smokeless tobacco, but the efficacies of these pharmacotherapies are lower in treatment of those using smokeless tobacco than among cigarette smokers attempting to quit smoking. Nicotine patch and nicotine gum did not increase abstinence. Authors also noted inconclusive evidence for the effect of bupropion SR in the treatment of smokeless tobacco use. From their analyses, authors found that behavioral interventions, including telephone counseling as a component of the intervention, increase tobacco abstinence among users of smokeless tobacco, regardless of whether they are motivated to stop using. Authors **suggested** further research including "placebo-controlled comparisons of different NRT doses, forms, and durations of therapy," combination therapies using both non-nicotine pharmacotherapy and NRT," and the "influence of different types of ST (e.g., snuff, chew, betel quid) on abstinence outcomes" (Ebbert et al., p. ii).

A 2016 meta-analysis examining whether electronic cigarettes are safe and effective in smoking cessation included two randomized trials involving smokers (n=662) (Hartmann-Boyce et al., 2016). The studies compared electronic cigarettes with placebo electronic cigarettes (lack of nicotine). Researchers found that participants using electronic cigarettes were more likely to have abstained from smoking for at least six months compared with those using the non-nicotine electronic cigarettes. One of the studies also compared electronic cigarettes to nicotine patch and did not find significant differences in 6-month abstinence rates. Neither study reported serious adverse events related to the use of the electronic cigarettes; mouth and throat irritation were the most frequent adverse conditions. Researchers noted the need for additional studies due to low quality of overall evidence (Hartmann-Boyce et al., 2016).

Although electronic cigarettes have been advertised as a safe replacement to aid smoking cessation or a supplement to traditional cigarettes, a recent study supported by the National Institutes of Health (NIH) **suggested**, "E-cigarette vapor, both with and without nicotine, is cytotoxic to epithelial cell lines and is a DNA strand break-inducing agent" (Yu et al., 2016). In exposing normal epithelial cells and head and neck cell carcinoma cell lines to nicotine-containing and nicotine-free vapor extract from two e-cigarette brands for up to 8 weeks, researchers found cytotoxic effects of e-cigarette vapor mediated through nicotine as well as non-nicotine components. The cytotoxic effects included cellular damage, i.e., increased DNA strand breaks, cell death, and decreased survival in both cell lines independent of nicotine content. Researchers indicated a need for further research "to definitively determine the long-term effects of e-cig usage, as well as whether the DNA damage shown in our study as a result of e-cig exposure will lead to mutations that ultimately result in cancer" (Yu et al., 2016).

A randomized, open-label study evaluated whether the use of electronic cigarettes, either alone or with dual use of conventional cigarettes, significantly reduces exposure to chemicals commonly associated with conventional cigarettes (D'Ruiz et al., 2016). Smokers of conventional cigarettes (n=105) were randomized to one of three groups: exclusive electronic cigarette use group, dual use group, or cessation group. After 5 days, measurement of blood, urine and toxicants in exhaled breath showed exposures to harmful smoke toxicants were lower in smokers who had either completely or partially replaced their conventional cigarettes with electronic cigarettes. However, researchers cautioned that reduced toxic and carcinogenic smoke does not necessarily reduce risks for chronic, smoking-caused diseases in this population. They noted the need for "epidemiologic or other types of investigations involving long term use populations" (D'Ruiz et al., 2016).

Treatment of Alcohol Related Disorders

Although highly prevalent, highly disabling, and associated with both physical and psychiatric disorders, alcohol use disorder (AUD) is often untreated, with only approximately 20 percent of those with the disorder seeking treatment (Grant et al., 2015). A 2015 study presenting results from the National Epidemiologic Survey on Alcohol and Related Conditions III found significant associations between AUD and other disorders, such as major depressive disorder, bipolar disorder, and other substance use disorders.

After a review of the data, authors indicated the "urgent need to educate the public and policy makers about AUD and its treatment alternatives, to destigmatize the disorder, and to encourage those who cannot reduce their alcohol consumption on their own, despite substantial harm to themselves and others, to seek treatment" (Grant et al., p. 757).

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) reported in *Medication for the Treatment of Alcohol Use Disorder: A Brief Guide* that medication-assisted treatment (MAT) should be offered on a routine basis to patients with moderate or severe alcohol-related problems (NIAAA/SAMHSA, 2015). The brief guide discussed how alcohol use disorder continues to be associated with social exclusion, affecting both the patient with the AUD and the healthcare professionals providing care, and it encouraged physicians to recognize that alcohol use disorder is a treatable medical disorder. The brief guide summarized current evidence on the effectiveness of the following medications approved by the Food and Drug Administration (FDA) for treating AUDs: disulfiram, oral naltrexone and extended release injectable formulations, and acamprosate delayed-release tablets. Authors of the guide recommended that a comprehensive treatment approach include counseling and other psychosocial therapies along with participation in Alcoholics Anonymous or other similar programs.

A systematic review and meta-analysis evaluated FDA-approved medications, mostly acamprosate and oral naltrexone, in the treatment of adults with alcohol use disorders in outpatient settings (Jonas et al., 2014). This review included participants (n=22,803) in 122 randomized controlled trials and one cohort study. All of the trials included at least 12 weeks of treatment and included a variety of different psychosocial co-interventions. Evidence was not sufficient to determine whether off-label medications used in some of the trials were associated with reduced consumption, whereas evidence showed an association of topiramate with fewer drinking days, fewer heavy drinking days, and fewer drinks per drinking day. Nalmefene was associated with fewer heavy drinking days per month and drinks per drinking day. The analysis showed an association between valproic acid and improvement in consumption outcomes in a trial including people with bipolar disorder. Evidence was insufficient in determining whether medication treatment is associated with improvement in health outcomes. Researchers concluded that in this review, acamprosate and oral naltrexone (50mg/day) had the best evidence supporting their benefits, with no differences in outcomes established between the two medications. They noted that acamprosate, given three times daily, is less convenient than oral naltrexone, given only once daily. In patients with severe renal impairment, acamprosate is contraindicated and in those with acute hepatitis, liver failure, and concurrent opioid use, oral naltrexone is contraindicated. Researchers reported that no overall reductions in alcohol consumption resulted from the use of disulfiram. They also discussed how primary care providers have historically referred patients with alcohol use disorders for specialized treatment although not all patients have access or are willing to pursue it. They further discussed how offering treatment through primary care **may** reduce morbidity for many patients. Researchers concluded that "both acamprosate and oral naltrexone (50mg/d) were associated with reduction in return to drinking" and that "moderate evidence supports an association with

improvement in some consumption outcomes for nalmefene and topiramate (Jonas et al., 2014).

A recent article reviewed randomized clinical trials in Europe that compared the effects of nalmefene, an opioid antagonist not approved in the U.S. for treating alcohol use disorder, and placebo in patients (n=1697) with high consumption of alcohol, low physical dependence on alcohol, and lack of a need for immediate detoxification or inpatient treatment (Soyka, 2016). Fixed dosing regimens were not required as patients took the drug based on their own needs in a novel "as needed" approach. Alcohol drinking decreased more in the nalmefene groups than in the placebo groups although there was a higher dropout rate in the nalmefene group. Researchers **suggested** that patients with "high but not excessive mean alcohol consumption" and without severe physical dependence on alcohol benefit from treatment with nalmefine with side effects similar to those with naltrexone treatment, e.g., nausea, headache, and gastrointestinal effects (Soyka, 2016). Naudet et al., in a later review of studies comparing the use of nalmefene to placebo in alcohol treatment, noted that use of a "drug for people who continue to drink (especially if it is ineffective) **may** have seriously detrimental psychological and social implications" (Naudet et al, 2016). Authors noted the "inappropriate comparison with placebo when another treatment was available" and also **suggested** that instead of using alcohol consumption to determine treatment success, factors such as mortality and health outcomes, e.g., vehicle crashes, should be used (Naudet et al., 2016).

A recent study sought to uncover new insights about the usefulness of topiramate in the treatment of alcohol use disorders. Authors identified 22 studies including two meta-analyses and eight randomized controlled trials (Guglielmo et al., 2015). This review found beneficial effects of topiramate in the prevention of relapse as well as in reducing drinking behavior. Topiramate significantly reduced the number of drinks per day, the number of drinks per drinking day, the percentage of heavy drinking days and increased the number of abstinent days when compared to placebo. Authors noted that although the results were positive for topiramate, the longest trial was only 14 weeks. Compared to naltrexone, topiramate was more effective, reducing alcohol intake and craving. However, it was not more efficacious than disulfiram. Authors provided caution about the topiramate adverse effects that appeared to be dose-related and prominent. These included paresthesia, taste perversion, anorexia, difficulty with concentration/attention, and pruritus. Authors **suggested**, in their conclusions, that "topiramate, in the dosage range of 75-300 mg/day, **might** represent an efficacious and safe pharmacological option for the treatment of AUDs." They acknowledged the lack of evidence about the use of topiramate in alcohol withdrawal syndrome (Guglielmo et al., 2015).

Several herbal remedies have a history of use for the treatment of alcohol use disorders (Liang and Olsen, 2014). In a recent review, authors noted clinical studies suggesting that traditional herbal medications **may** have positive effects in treatment. Although kudzu, hovenia and salvia miltiorrhiza have shown anti-alcohol effects and have been used for many years, especially in China and Korea, authors concluded that "more time and effort are needed to understand the mechanisms and the safety/toxicity and to establish regulatory policies for using natural or other types of herbs" in the treatment of alcohol

disorders (Liang and Olsen, 2014). In a later, placebo-controlled, double-blind study including participants (n=32) with self-reported drinking patterns of 15 drinks per week or binge drinking 2 or more times per week, a single dose of kudzu extract significantly reduced alcohol consumption without noxious side effects (Penetar et al., 2015). Authors concluded, "This study provides additional evidence that an extract of the kudzu root significantly reduces alcohol consumption by human participants and confirms that this botanical medication **may** be a safe and effective adjunct pharmacotherapy for treating alcohol use disorders" (Penetar et al., 2015, p. 10). **Magellan does not recommend the use of kudzu extract for the treatment of alcohol disorders and recommends more studies to determine its effectiveness**.

A 2015 study analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to determine perceived barriers to treatment for alcohol problems (Schuler et al., 2015). The most commonly reported barriers to treatment among participants (n = 11,843), treatment naïve adults with a lifetime alcohol disorder and a perceived treatment need, were attitudinal barriers, e.g., feelings of being strong enough to handle it alone and that the problem will resolve by itself. Authors **suggested** that "interventions to reduce the stigma of alcohol treatment and to increase motivation for behavior change **may** be effective and sufficient for the majority of individuals with perceived treatment barriers. To this end, we endorse the use of Screening, Brief Intervention, and Referral to Treatment (SBIRT) in primary care" (Schuler et al., 2015).

A 2015 double-blind, randomized trial examined how cognitive bias modification, including exposure to alcohol-related stimuli and images, affects neural alcohol cue reactivity in inpatients (n=32) with alcohol use disorder, and whether it **may** reduce alcohol craving and relapse rates (Wiers et al., 2015). Researchers noted that as individuals transition from voluntary to habitual drinking, "alcohol cues engender motivational responses in alcohol-dependent patients, which are triggered relatively automatically" and are involved in craving and relapse. They reported studies showing that the exposure to alcohol cues in patients with alcohol use disorder activates mesolimbic areas of the brain (brain rewards pathways) and **may** result in an impulsive response toward the drug cues. In this study, patients received either cognitive bias modification training or sham training; functional MRI (fMRI) scans measured neural cue reactivity both before and after cognitive bias modification training. The training, an adapted version of the approach-avoidance task, included six sessions over a period of three weeks. In both groups, participants were instructed to push or pull a joystick while viewing alcohol and soft drink cues, depending on whether the cue format was in landscape or portrait format. Pushing the joystick decreased the size of the image while pulling it increased the size of the image. The pushing and pulling of the joystick, decreasing or increasing the size, created a visual impression of avoidance and approach, respectively. In the cognitive bias modification group, participants learned to push away and avoid the cues; they pushed away and pulled 90% and 10%, respectively, of the alcohol cues while the ratios in the sham group were 50/50. A functional MRI (fMRI) measured neural cue reactivity before and after the training period using the same images. "After the training period, the bias modification training group showed significantly greater reductions in cue reactivity in the amygdala bilaterally as compared to the control group. The difference between activation in the right amygdala

before and after training was significantly correlated with the decrease in alcohol craving for the modification bias training group but not for control" (Recovery Research Institute, 2015). Researchers concluded that this study provides evidence that cognitive bias modification reduces alcohol-cue induced mesolimbic brain activity (Wiers et al., 2015). In a review of the Wiers study, Obrien **suggested** that more randomized controlled trials are needed "to determine conclusively whether focusing on the brain does in fact result in improved overall outcomes for patients with alcohol use disorders (O'Brien, 2015).

Another recent study compared the SMART Recovery (SR) program with Overcoming Addictions (OA), both programs based on cognitive behavioral interventions for problem drinkers (Campbell et al., 2016). The SR program (a social modality) is an online and in-person mutual help group, whereas the self-directed OA program is a structured online intervention based on the principles and practices of the SR program. The SR program focuses on the following: motivation for change; managing urges, thoughts, feelings and behavior; and reaching a balanced lifestyle. Its website is a resource serving as a portal for an SR community (encourages meetings), and although SR does not include a formal treatment manual, it provides a workbook including descriptions of SR principles and exercises. The OA program, a self-directed web-based intervention, includes four modules: Building and Maintaining Motivation for Change; Dealing with Urges and Cravings; Self-Managing Thoughts, Behaviors, and Feelings; and Lifestyle Balance for Preventing Relapse. OA can be used as either standalone or as a complement to SR. In this study, heavy drinkers (n=188) were randomized to SR only or to OA + SR. Results showed that participants in both groups, over a six-month follow-up period, significantly increased the percentage of days of abstinence, significantly decreased the number of drinks consumed on drinking days, and also experienced a reduction in alcohol-related problems. However, there was no added benefit of OA over the SR intervention. Researchers noted that the evidence showed that OA **may** be a feasible alternative to SR, with advantages of access, reach and cost-effectiveness, suggesting that "web-based interventions work particularly well for individuals who are actively making changes to their drinking behavior" (Campbell et al., 2016).

A recent literature review of eight studies, including adults (n=1849) using alcohol, examined the efficacy of mobile technology interventions for the treatment of alcohol-dependent and nondependent alcohol users (Fowler et al., 2016). Seven of the studies included either a control or a comparison group. The interventions, delivered through text messages, smartphone applications, and mobile websites, were designed around theoretical frameworks, e.g., Self-Determination Theory, Motivational Interviewing, Cognitive-Behavioral Treatment, Health Belief Model, Theory of Reasoned Action, and Information Motivation Behavior Model. The length of interventions varied from two weeks to 32 weeks. Outcome measures included both behavioral, e.g., reduction in risky drinking days, as well as cognitive measures, e.g., readiness to change. This review found preliminary evidence for the efficacy of mobile technology-based technology while provided caution related to "the dearth of research in this potentially very promising field" (Fowler et al., 2016).

Treatment of Marijuana-Related Disorders

In a study analyzing data from *National Surveys on Drug Use and Health* from 2002 to 2014, authors found that the use of marijuana increased from 10.4% to 13.3% in adults while the **perceived** harm from using marijuana decreased during the same period from 50.4% to 33.3% (Compton et al., 2016). Authors **suggested** an association between both of these findings and the effects of the gradual legalization of marijuana in several states. However, no increase in marijuana use disorders was found; between 2002 and 2014, the percentage of adults with marijuana use disorders was stable at about 1.5%. Authors urged the targeting of reduction in the perceived harm of using marijuana in future prevention efforts, and **suggested** a need for more education about the risks of smoking marijuana (Compton et al., 2016).

A 2015 review of literature focused on the potential physical and mental adverse effects associated with the non-medicinal use of cannabis, mostly consumed as marijuana, which is the most widely consumed illegal substance in the world (Hoch et al., 2015). Key messages in their review are:

- Cannabis is the most commonly used illicit drug worldwide.
- Of all cannabis users, 9% become dependent; 17% of those beginning cannabis use in adolescence become dependent; and 25 to 50% of those who consume cannabis daily become dependent.
- Increased risks of various medical conditions, e.g., panic attacks, psychotic symptoms, motor incoordination and nausea, can arise after cannabis use.
- High doses of cannabis over several years or beginning use of cannabis during adolescence can be associated with various disorders of mental and physical health, e.g., substance dependence, cognitive impairment, psychosis, and respiratory and cardiovascular conditions.
- THC, the principal psychotropic substance in cannabis, delta-9-tetrahydrocannabinol, has increased in the past 10 years and is thought to be related to the increased risk of cannabis (Hoch et al., 2015).

Authors reviewed 40 meta-analyses and several systematic reviews demonstrating "short interventions (6 to 12 sessions) with combinations of measures to promote motivation, cognitive behavioral therapy, and contingency management (learning via systematic rewards)" as psychotherapeutic interventions having the greatest effect in treatment of cannabis-related disorders. They noted that reducing the frequency and intensity of cannabis consumption is more successful than attempting to achieve abstinence. The U.S. Food and Drug Administration (FDA) has not approved any pharmaceuticals for the treatment of cannabis disorder, although drugs, e.g., gabapentin, benzodiazepines, and sedative antipsychotics, treat severe withdrawal symptoms. Psychoses or panic attacks **may** be treated with antipsychotics, or benzodiazepines and sedative antipsychotics, respectively (Hoch et al., 2015).

A recent systematic review assessed the evidence of the effectiveness of psychosocial and psychological interventions for cannabis cessation in adults (Chatters et al., 2016). Researchers presented the definition of cannabis dependence by the International Classification of Disorders as "a cluster of physiological, behavioral, and cognitive phenomena in which the use of cannabis takes on a much higher priority for a given individual than other behaviors that once had greater value" (Chatters et al., p. 93). When ascertaining if a user is dependent or just a frequent user, researchers noted that the quantity of cannabis consumed per day and the level of harm sustained are the most important factors. This review included 25 randomized controlled trials measuring the effect of intervention(s) on cannabis usage:

- Ten studies assessing cognitive behavioral therapy (CBT) vs. wait-list, motivational interviewing (MI), or another intervention
- Five studies assessing contingency management (CM) vs. CBT or another intervention
- Nine studies assessing MI vs. wait-list or another intervention
- One study assessing web-based counseling.

Outcome measures of the effect of the intervention on cannabis usage were cannabis usage, severity of dependence, number of dependence symptoms, and number of cannabis problems via self-report, number of cannabis related problems, or session attendance. Results showed that CBT significantly improved short-term outcomes compared with wait-list at post-treatment in half of the studies and at nine months in one study with later follow-up. CBT over long courses showed improvement over shorter MI. Researchers concluded, despite a disparate evidence base, that CBT improved outcomes, although the long-term effect of the intervention is unknown. Brief MI showed improved outcomes at post-treatment not sustained in the long term. Combined with CBT, CM enhanced long-term outcomes (Chatters et al., 2016).

Another study, utilizing The Cochrane Database of Systematic Reviews, evaluated the efficacy of psychosocial interventions for cannabis disorders (Sabioni et al., 2016). It included 23 randomized controlled trials involving adults (n=4045) in outpatient or community settings. CBT and motivational enhancement therapy (MET) were effective in reducing the frequency of cannabis use, quantity used per occasion, and severity of dependence. In improving cannabis-related problems, CBT and MET were not more effective than no treatment. The most effective treatments for cannabis disorders were high intensity interventions, particularly MET combined with CBT, of more than four sessions and those longer than one month. Researchers **suggested** that CM combined with CBT, or with MET + CBT, improved both cannabis use frequency and severity of dependence (Sabioni et al., 2016).

A recent randomized controlled trial compared the efficacy of a web-based self-help intervention, Can Reduce, alone or in combination with individual brief chat counseling sessions based on MI and CBT approaches in the treatment of problematic cannabis use (Schaub et al., 2015). The study also included a third arm, a classical waiting list. Outcome

measures included the recorded quantity of cannabis use in the previous seven days (primary outcome measure) along with secondary outcome measures based on use of outcome instruments, e.g., the Cannabis Use Disorders Identification Test (CUDIT), Severity of Dependence Scale (SDS), Cannabis Withdrawal Scale (CWS), and the Cannabis Craving Symptoms questionnaire (CCS-7). Assessments were at baseline and at three-month follow-up. Results showed that participants randomized to Can Reduce with chat group reduced their frequency of cannabis use more than the Can Reduce without chat and the wait list groups. At follow-up, abstinence was higher in the group receiving the additional chat counseling. Not all participants in the self-help with chat group actually chose to receive a chat session, and interestingly, even they had greater reduction in the frequency of cannabis use than participants in the group receiving self-help without chat sessions. Researchers referred to the Supportive Accountability model and **suggested** knowledge of a possibility to have a chat appointment improved this outcome. However, participants in the self-help with chat group who actually received at least one chat counseling session reduced use of cannabis more than participants of the same group who did not receive chat counseling. Researchers related this to "expecting better outcomes due to a reciprocal relationship, through which the patient can derive explicit benefits" (Schaub et al, p. 12). For patients not seeking outpatient addiction counseling services for reasons such as the fear of stigmatization, researchers concluded that brief chat counseling in addition to web-based self-help **may** reduce cannabis use in problematic cannabis users.

Treatment of Cocaine-Related Disorders

The FDA has not approved any clearly effective pharmacotherapies for the treatment of cocaine use disorder. However, studies have found three promising categories of drugs for reducing cocaine use: dopaminergic agents, e.g., levodopa-carbidopa, dextroamphetamine, and lisdexamfetamine; noradrenergic agents, e.g., disulfiram, doxazosin, and nepicastat; and drugs with mixed mechanism agents, e.g., modafinal. A recent article discussed combined medication-behavioral treatment as a promising approach for treating cocaine and cannabis use disorders (Dakwar and Nunes, 2016). Authors conceptualized medications for SUDs, including cocaine, as "facilitating specific behavioral interventions, rather than as standalone interventions" (Dekwar and Nunes, p. 62). They reported studies showing that dopaminergic agents, e.g., levodopa-carbidopa, **may** enhance contingency management and help promote abstinence in cocaine-dependent individuals. Authors reported a study finding that cocaine-dependent individuals receiving combined slow-release amphetamine treatment and relapse prevention therapy including cognitive behavioral therapy exhibited higher rates of abstinence than those receiving combined relapse prevention therapy and placebo. They **suggested** a need for further studies to test whether the benefit of the drug was dependent on the behavioral treatment. Authors emphasized the importance of finding which type of behavioral interventions **may** "synergize best with the medication" (Dekwar and Nunes, 2016).

A recent randomized, double blind, placebo-controlled parallel group study evaluated lisdexamfetamine (LDX) in treatment of cocaine-dependent individuals (n=43) (Mooney et al., 2015). Previous studies **suggested** that LDX may have less abuse potential than amphetamine. In this study, participants received either placebo or LDX (70 mg/day) along

with a manual-based cognitive behavioral therapy emphasizing relapse prevention and coping skills provided one hour each week during the 14-week intervention. Although those receiving LDX reported significantly less craving for cocaine than those receiving placebo, no differences in cocaine use rates were found between LDX and placebo-treated individuals. Researchers noted that LDX was generally safe and well tolerated although the LDX group reported higher rates of diarrhea, headaches, and anxiety compared to the placebo group. They concluded, "Whether LDX, or any agonist-like strategy **may** realistically be considered for development and receive regulatory approval for stimulant use disorders remains to be determined" (Mooney et al., p. 103).

Based on the results of an eight-week, double blind, placebo-controlled trial of modafinil for the treatment of cocaine dependence without comorbid alcohol dependence, researchers concluded that modafinal **may** be an efficacious treatment for cocaine dependence (Kampman et al., 2015). In this study, individuals with cocaine dependence (n=94) received either 300 mg of modafinil or placebo daily combined with weekly individual therapy. Researchers noted that previous studies have shown that modafinal **may** reduce cocaine withdrawal symptoms and reduce the high associated with cocaine use by blocking the dopamine transporter. Cocaine use measured by self-report and confirmed by twice-weekly urine tests was the primary outcome measure. Results showed that individuals who received modafinal were significantly more likely to be abstinent from cocaine during the last three weeks of the trial and reported significantly lower levels of both craving intensity and duration. Researchers concluded that modafinal **may** be effective for a large number of cocaine-dependent patients, especially in those without comorbid alcohol dependence (Kampman et al., 2015).

A recent Cochrane Database Systematic Review discussed the use of antipsychotic medications for cocaine dependence (Indave et al., 2016). Authors discussed how the use of cocaine and dependence is associated with problems for both individual and public health, including medical, psychological, and social problems. Using cocaine is associated with the spread of AIDS, hepatitis, and tuberculosis as well as crime, violence and neonatal drug exposure. Cocaine can also induce hallucination and paranoia. This review included 14 randomized trials involving individuals with cocaine dependence (n= 719). Trials randomizing participants to receive a single drug versus placebo or versus another drug included risperidone, quetiapine, lamotrigine, olanzapine, haloperidol, olanzapine, aripiprazol, ropirinol, and placebo. Results showed no evidence supporting the clinical use of antipsychotic medications in the treatment of cocaine dependence (Indave, 2016).

Opioids

The recent increase in misuse of prescription analgesics, e.g., hydrocodone and oxycodone; the easy accessibility of affordable opioids such as heroin; and the opioid overdose epidemic underscore the importance of preventing the abuse of prescription painkillers as well as understanding best treatments for opioid use disorders. The clinical course of opioid use disorder is much like that of other chronic relapsing conditions, e.g., diabetes and hypertension, where control of symptoms is difficult and treatment adherence **may** be

incomplete. Opioid use disorder is associated with early death from accidental overdose, trauma suicide, or infectious disease (Schuckit, 2016).

Deaths from drug overdose are the leading cause of injury death in the United States, having risen steadily over the past twenty years (Department of Health and Human Services [HHS], 2015). Deaths related to opioid analgesics nearly quadrupled from 1999 to 2013, and deaths related to heroin increased by 39% between 2012 and 2013. While people who initiated abuse of opioids in the 1960s initiated with heroin, 75% of those who began abusing opioids in the 2000s initiated their abuse with prescription opioids. A shift to heroin use is related to heroin's easy accessibility as well as to its being cheaper, easier to inhale/inject, and its greater potency than prescription opioids (HHS, 2015). Overdose and death significantly increase with extended release/long-acting (ER/LA) formulations of prescription opioids. Overdose deaths also link to the combination of prescription opioids with other prescriptions drugs, e.g., benzodiazepines.

The Secretary of the U.S. Department of Health and Human Services (HHS) has targeted three priority areas to combat opioid abuse: 1) "opioid prescribing practices to reduce opioid use disorders and overdose; 2) expanded use and distribution of naloxone; and 3) expansion of medication-assisted treatment (MAT) to reduce opioid use disorders and overdose" (HHS, 2015).

"The Centers for Disease Control and Prevention's (CDC's) Guideline for ***Prescribing*** Opioids for Chronic Pain include the following recommendations:

- Non-opioid therapy is preferred for treatment of chronic pain; consider opioid therapy only if benefits are anticipated to outweigh risks; combine opioids with non-pharmacologic therapy and non-opioid pharmacologic therapy as appropriate;
- Before beginning treatment, establish treatment goals with patients and consider how opioids will be discontinued;
- Discuss with patients known risks and benefits and responsibilities for managing therapy;
- Prescribe immediate-release opioids instead of extended-release/long-acting opioids when starting therapy for chronic pain;
- Prescribe lowest effective dosage when starting opioids; reassess before increasing dosage;
- When prescribed for acute pain, prescribe lowest effective dose of immediate-release opioids and no greater quantity than needed (three or fewer days often sufficient);
- Evaluate benefits and harms of continued opioid therapy within 1–4 weeks of starting opioid therapy and evaluate every three months or more;
- Before initiating therapy and during continuation of opioid therapy, evaluate risk factors for opioid related harms;
- Review patient's history of controlled substance prescriptions when starting opioid therapy and periodically during therapy;
- Use urine drug testing before beginning opioid therapy and at least annually;

- Avoid prescribing combined opioid pain medication and benzodiazepines whenever possible; and
- Offer/arrange medication-assisted treatment with buprenorphine, methadone, or extended-release injectable naltrexone, in combination with counseling and behavioral therapies, for patients with opioid use disorder (CDC, 2015).

FDA approved and encourages the use of naloxone delivery systems, e.g., auto-injectors, for lay use outside of healthcare settings to reverse overdose from both prescription opioids and heroin. Naloxone reverses the effects of other opioids and can restore normal respiration when breathing has slowed due to heroin or prescription opioid overdose (FDA, 2014).

Prescription opioids are the second most commonly initiated drugs, second only to marijuana (Brady et al., 2016). Recently, the Office of National Drug Control Policy expanded the National Drug Control Strategy by including the following recommendations:

- Educating patients as well as providers about risks associated with misuse and abuse of opioids;
- Enhancing Prescription Drug Monitoring Programs (PDMP) that are state run;
- Increasing proper disposal of prescription drugs; and
- Addressing enforcement to prevent diversion via doctor shopping and "pill mills" (Brady et al., 2016).

Brady et al. advised that all patients receive screening for potential risk of abuse prior to starting opioid therapy, as well as education about safe use, storage, and disposal of opioid medications. Monitoring on a regular basis **may** identify escalation of opioid use; any negative impact on the patients' ability to function at work, home, and in social settings; and the existence of aberrant behaviors during therapy (Brady et al., 2016). ***The Collaborative Care Model of integrating mental health services within primary care services*** *may* ***facilitate the implementation of these steps to decrease prescription opioid abuse and misuse.***

A 2015 study reviewed the evidence for medication-assisted treatment (MAT) of opioid use disorder (Connery, 2015). Authors noted that the recommended treatment of an individual with opioid use disorder and physiological dependence includes one of the FDA-approved medications, i.e., buprenorphine, naltrexone, and methadone, for preventing opioid relapse and for stabilization/maintenance treatment of opioid use disorder. The approved medications should be prescribed as a part of a comprehensive treatment approach including counseling and other behavioral therapies delivered by a psychiatrist, psychologist, or professional counselor. The American Society of Addiction Medicine emphasized that the patient and the clinician share in the choice of treatment option (ASAM, 2015).

Connery noted that the strongest evidence for efficacy in both reducing opioid use and retaining patients in care is for agonist treatment, with methadone maintenance

considered the gold standard of care for many years (Connery, 2015). In a review of randomized controlled trials comparing tolerability and convenience of MAT, author noted that an adverse effect of full agonist methadone is dose-dependent respiratory depression, whereas the partial agonist buprenorphine has a "ceiling effect" on respiratory depression and does not induce euphoria in opioid-tolerant individuals. Buprenorphine reduces opioid withdrawal symptoms and decreases pleasurable effects of other opioids. Trials found comparatively weak evidence for antagonist naltrexone extended release (ER). Patient convenience for dosing was most burdensome with programs prescribing methadone or buprenorphine maintenance with required observed daily dosing in early phases of recovery, while monthly injections of naltrexone ER or monthly maintenance visits with office-based buprenorphine/naloxone were least burdensome. Compared to placebo or no medication, all three FDA approved medications showed improved retention in treatment in trials. Methadone demonstrated higher rates of treatment retention compared to buprenorphine. Data in studies cited by Connery also suggest that buprenorphine, methadone, and naltrexone ER, are important in preventing accidental opioid-overdose death during active treatment. MAT added to relapse-prevention counseling and mutual help groups, e.g., Narcotics Anonymous, increased the effectiveness of those interventions (Connery, 2015). Studies have shown that longer term, abstinence-based residential treatment not including MAT has limited effectiveness, with increased risk of fatal overdose.

On Nov. 18, 2015, the FDA approved Narcan nasal spray, the first approved nasal spray version of naloxone hydrochloride, to temporarily stop or reverse the effects of an opioid overdose (FDA, 2015). Narcan nasal spray, administered by first responders, medical professionals, family members, or caregivers, can counter overdose effects quickly, usually within two minutes, saving many lives. This user-friendly, needle-free delivery system, when used as directed, delivers a consistent and measured dose. Although the FDA has not approved an over-the-counter version of this nasal spray, many state regulations allow pharmacies to provide the nasal spray from pharmacy counters under collaborative practice agreements between the pharmacy and practitioners/physicians/prescribers (Regulatory Affairs Professionals Society, 2016).

On May 26, 2016, the FDA approved the first buprenorphine implant, Probuphine® for the maintenance treatment of opioid dependence (FDA, 2016). This drug, as an implant under the skin on the inside of the upper arm, provides a constant, low-level dose of buprenorphine over six months in patients already stable on low-to-moderate doses of other forms of buprenorphine in a treatment program. This new, innovative treatment option provides improved convenience as patients gain control of their lives, no longer needing to take medication on a daily basis. The director of the National Institute on Drug Abuse at the National Institutes of Health said, "Scientific evidence **suggests** that maintenance treatment with these medications in the context of behavioral treatment and recovery support are more effective in the treatment of opioid use disorder than short-term detoxification programs aimed at abstinence. This product will expand the treatment alternatives available to people suffering from an opioid use disorder" (FDA, 2016). An unpublished randomized clinical trial demonstrated the safety and efficacy of Probuphine in the treatment of adults (n=177) with opioid dependence. Common side effects included

implant-site discomfort, headache, depression, constipation, nausea, vomiting, back pain, toothache and oropharyngeal pain. Of the Probuphine-treated patients, 63% had no evidence of illicit opioid use throughout the six months of treatment compared to 64 percent of those using sublingual buprenorphine. The FDA announcement included a boxed warning with safety information that included a warning about the risk of implant migration, protrusion, expulsion and nerve damage associated with insertion and removal of Probuphine. A potential for accidental exposure or intentional misuse and abuse occurs if the implant comes out of the skin (FDA, 2016). The FDA advises that patients should be seen at least once monthly for continued counseling and psychosocial support in addition to a visit during the first week after insertion.

On June 6, 2014, the FDA approved Bunavail®, a buccal film formulation of buprenorphine/naloxone for the maintenance treatment of opioid dependence (FDA, 2014). The manufacturer of Bunavail claimed that the product is more convenient to administer than the earlier approved sublingual tablet and film formulation (Suboxone®) of the same combination, and that it is better absorbed into the blood, permitting lower doses of use. Findings from a 23-week, open-label, uncontrolled trial including opioid-dependent individuals (n=249) previously stabilized on Suboxone showed that the buccal film "appeared to be efficacious in maintenance treatment of opioid dependence, but 52 patients withdrew before the end of the study" (The Medical Letter, 2015). The Medical Letter concluded that this new form of buprenorphine/naloxone permits lower doses, but establishment of its clinical advantages, e.g., lower incidence of constipation, has not been evidenced in well controlled clinical trials (The Medical Letter, 2015).

A rule by the Health and Human Services Department, published in the Federal Register on July 8, 2016 (Medication Assisted Treatment for Opioid Use Disorders Reporting Requirements) authorizes eligible practitioners to request approval to treat up to 275 patients in an office-based setting with buprenorphine and the combination buprenorphine/naloxone (Federal Register, 2016). This rule thus increases access to MAT in the office-based setting. It requires that practitioners provide information about their patient caseload by month, including the number of patients receiving behavioral health services and the number referred to behavioral health services. This is "to ensure that patients receive the full array of services that comprise evidence-based MAT and minimize the risk that the medications provided for treatment are misused or diverted" (Federal Register, 2016). The features of the practitioner's diversion control plan must also be provided.

A 2015 double-blind, placebo-controlled randomized clinical trial evaluated the efficacy of clonidine as an adjuvant to buprenorphine in increasing the duration of abstinence, time to opioid lapse and relapse, and percent opioid-negative urine tests (Kowalczk et al., 2015). Opioid-dependent patients (n=208) began sublingual buprenorphine maintenance treatment (8-24 mg/day) at enrollment and continued for up to 28 weeks at an outpatient research clinic; individual counseling was provided once a week. At 7 weeks, participants (n=118) who were abstinent from illicit opioids during weeks 5 and 6 were randomly assigned to receive either clonidine or placebo concurrent with the daily dose of buprenorphine. (Note: those who did not meet abstinence were switched to methadone for

4 weeks after which they received an 8-week medication taper, or transferred to a community treatment program). The clonidine schedule included 0.1 mg for 7 days, 0.2 mg for the next 7 days, and 0.3 from weeks 9 through 20. During the intervention period from weeks 9-20, participants, most of whom completed this phase, were maintained on a stable dose of buprenorphine along with either daily clonidine or placebo. The maintenance phase was from weeks 21-28 during which the clonidine dosage was tapered to zero over the first 14 days and at the end of week 28, buprenorphine dosages were tapered over another 8 weeks, or patients transferred to another treatment program. Results showed duration of consecutive days of abstinence for opioids during the intervention phase were 34.8 days and 25.5 days for the clonidine group and the placebo group, respectively. Secondary outcomes measures showed that during the intervention phase, the clonidine group was more likely to test negative for THC although there was no significant difference in percentage of cannabis smokers at baseline in each group. No group difference in cocaine use was found during the intervention phase. Researchers noted that the longer duration of consecutive days of abstinence from opioids in the group receiving clonidine has important implication suggesting that "the longer the duration of abstinence, the greater the likelihood that it will be sustained" (Kowalczk et al., p. 764). They also noted that findings support clonidine's ability to increase participants' mean durations of abstinence. The study also found that participants in the clonidine group were less likely to report heroin craving at moderately high levels of stress than the placebo group. Researchers concluded that the study demonstrates efficacy of clonidine for relapse prevention in treatment-seeking opioid users and that it is "modestly effective in decoupling stress from lapses" (Kowalczk et al., p. 764).

According to SAMHSA, "Medication-assisted treatment has shown much promise in reducing nonmedical use of opioids and restoring patients to a healthier life" (SAMHSA, 2015). SAMHSA further noted that evidence and consensus among experts support the use of MAT in primary care settings, particularly for individuals unable to access treatment in specialized settings (SAMHSA, 2015).

In a systematic review, which summarized 55 articles, authors focused on comparisons of medications and behavioral therapies to identify factors associated with high rates of retention in MAT for opiate dependence (Timko, 2016). Retention, a primary outcome in treating opiate dependence, is associated with the achievement of decreased drug use, improved social functioning and quality of life, and reduced mortality. Findings included the following: patients receiving naltrexone or buprenorphine had better retention rates than those receiving no medication or a placebo; patients receiving methadone were more likely to be retained in MAT at 4- and 6-month follow-ups than those receiving buprenorphine/naloxone; and heroin-assisted treatment was associated with better retention than methadone among patients who were treatment refractory. Studies also found that contingency management (CM) was the only behavioral therapy showing promise to increase retention in MAT for opiate dependence, although it does not address the underlying causes of addiction. Authors concluded the need for additional randomized controlled trials addressing longer-term association between medications and behavioral therapies (greater than one year) and outcomes (Timko, 2016).

Although only a small percentage of those both seeking and needing treatment for substance use disorders receive MAT treatment, the trend for its use in medical or psychiatric practice settings is increasing. Barriers to utilization of MAT include reluctance of patients to take medications, side effects of medication, and costs. Due to a belief that "one is simply transferring addiction from one drug to another," both substance abuse and MAT retain a negative social stigma (Magellan, 2016). More education on evidence-based MAT protocols for treatment providers are needed to address preconceived notions of their ineffectiveness and to address reduction in patient motivation to comply with behavioral treatments and counseling programs. More time devoted to patient management while employing MAT protocols in this population is likely to reduce the possibility of relapse and/or readmission to an inpatient/residential rehabilitation program (Magellan, 2016). Current research has shown that the best treatment is at the least intensive level of care that manages the patient safely and comfortably and where the patient can be engaged in continued treatment leading to a sustained recovery from addiction. MAT can promote return to the community, employment and full contribution to society (Magellan, 2016).

Novel Drugs of Abuse

Novel or atypical drugs have become more popular over the past few years in the United States, posing difficulties for healthcare providers in diagnosis and treatment. A recent article, including a review of literature on new classes of drugs of abuse, discussed the pharmacology and both clinical and adverse effects of these new psychoactive substances (Rech et al, 2015). Although law enforcement agencies have rendered the most common synthetic cannabinoids and cathinones illegal, they are widely advertised in gas stations as well as on the internet and marketed as "legal highs" (Rech et al., 2015). Authors noted that there is no current tracking or reporting on many new illicit drugs of abuse, making it difficult to understand how their use negatively affects society.

Synthetic cathinones, derived from the active stimulant in the khat plant and often referred to as "bath salts," produce stimulant effects, e.g., euphoria, increased energy, openness, empathy, alertness, and increased libido (Rech et al., 2015). They are available at low cost as white or light brown powder, pills, or capsules, with doses ranging from a few milligrams to more than one gram. Sold as names, e.g., Khat, Bath Salts, Meow, MCAT, Ivory Wave, Bubbles, Vanilla Sky, Cloud 9, Explosion and White Lightning, they have a "glamour aura" (Karila et al, 2015). Some of the most common synthetic cathinones are Mephedrone, Methylone, MDPH, Ethylone, Butylone, Buphedrone, and Pentedrone. The most common routes of administration are snorting and oral ingestion. Other routes sometimes include "bombing" (powder wrapped in cigarette paper and swallowed) and "keying" (snorting powder off the surface of a key). Poison centers have reported common findings of agitation, confusion, hallucinations, tachycardia, hypertension, tremor and fever; more serious effects of the use of synthetic cathinones include electrolyte abnormalities, seizures, "excited delirium," renal failure, and death. A physical withdrawal syndrome may occur in cyclic binge users. Authors reported that intoxication from these agents may be suspected when patients show acute onset altered mental status, excited delirium, renal failure, and sympathomimetic symptoms (Rech et al., 2015).

The National Institute on Drug Abuse has issued a warning about the abuse of flakka, a dangerous synthetic cathinone similar to "bath salts" which may be snorted, injected, vaporized or eaten. This designer drug, with its use surging in the U.S., presents a risk of easy overdose as it enters the bloodstream very quickly when vaporized in an e-cigarette. It may cause "excited delirium" involving paranoia, hallucinations, and hyperstimulation. Deaths by suicide as well as by heart attack have been linked to its use. Additionally, it has been reported to dangerously raise body temperature leading to kidney damage or failure (NIH, 2016).

Synthetic cannabinoids, similar to synthetic cathinones, are also widely available, and increasing in popularity, especially among adolescents. Marketed frequently in foil packets marked "not for human consumption," these cannabinoids have methods of administration including inhalation, ingestion, and injection. Containing the active ingredient in marijuana, Tetrahydrocannabinol (THC), they produce similar psychotropic effects, e.g., euphoria and alteration in mood and sensorium (Rech et al., 2015). Abuse of synthetic cannabinoids is increasing every year and the agents are multiplying in number, with hundreds of combinations developed. The most reported adverse events are psychosis and anxiety; others include paranoia, hallucinations, seizures and sedation. Nausea, vomiting and acute kidney injury **may** also result from use. Rech et al. reported no long-term effects of synthetic cannabinoids.

Kemp et al. advised that synthetic cannabinoids should not be confused with marijuana/ cannabis, as they are a "collection of numerous laboratory chemicals that interact with the cannabinoid receptor in the brain to mimic marijuana to induce a marijuana-like high" (Kemp et al., 2016). Street names for synthetic cannabinoids include Spice, Spice Gold, Spice Diamond, Spice Silver, K2, Krypton, Aztec Fire, Bombay Blue, Fake Weed, and Yucatan Fire (Rech et al., 2015). Kemp et al. also **suggested** that Spice is more potent than marijuana, interacting with receptors in the brain other than those with which marijuana interacts. They cited news reports describing users so agitated that they tore off their clothes and sweated heavily. Kemp et al. concluded that synthetic cannabinoids are dangerous substances that result in many emergency department visits and fatalities (Kemp et al., 2015).

A systematic review of adverse events arising from the use of synthetic cannabinoids examined data from poison centers and drug monitoring systems in Europe, the United Kingdom, the U.S., and Australia. Authors advised that physicians be aware of adverse effects including severe cardiovascular, cerebrovascular, neurological, psychiatric and renal effects (Tait et al., 2016). Another recent study, a retrospective chart review of patients (n=676) admitted to a Dual Diagnosis psychiatric unit from March 2014 to February 2015, found that the use of synthetic cannabinoids was "strongly associated with more psychotic presentations and agitation compared to cannabis use" (Nia et al, 2016). Users of synthetic cannabinoids received higher doses of antipsychotic medications while spending longer time in hospital (Nia et al., 2016).

The National Institute on Drug Abuse has reported the abuse/diversion of pharmaceutical fentanyl in forms including patches, lozenges, tablets, and films. Non-pharmaceutical fentanyl analogs, e.g., illicitly-produced desmethyl fentanyl, can be snorted or injected as a powder, or swallowed in pill form (NIDA, 2015). Users abuse these drugs, linked to overdose deaths in the United States, to experience short-term highs and feelings of euphoria (DEA, 2015). Fentanyl is often marketed and disguised as white powder heroin and is many times more potent than either heroin or morphine by weight (DEA, 2012).

Other drugs or products that are abused include the following: club drugs, e.g., GHB, Rohypnol®, ketamine, MDMA (Ecstasy), Methamphetamine, and LSD (ACID); hallucinogens, e.g., ayahuasca, DMT, D-lysergic acid diethylamide (LSD), peyote (mescaline), 4-phosphoryloxy-N, N-dimethyltryptamine (psilocybin) and; salvia divinorum; inhalants, e.g., spray paints, markers, glues, and cleaning fluids; and anabolic steroids, e.g., Gear, Juice, Roids, and Stackers (National Institute on Drug Abuse, 2016). A nonprescription herbal medication available on the internet but not widely used in the United States, kratom is sometimes used as a replacement for methadone as it is more easily available and lacks the stigma of methadone (Rech et al., 2015).

Conclusions

In a landmark report, Facing Addiction in America: *The Surgeon General's Report on Alcohol, Drugs, and Health*, U.S. Surgeon General Vivek Murthy refers to this current addiction crisis as "a moral test for America," comparing it with the past tobacco epidemic. As "one of the most pressing public health crises of our time," Murthy notes how substance misuse and substance use disorders "prevent people from living healthy and productive lives. And just as importantly, they have profound effects on families, friends, and entire communities" (U.S. Dept. of Human Health and Services, 2016). He recommends additional policies and programs to increase access to effective treatment for this chronic illness (which is not a character flaw), and an expansion of the scientific evidence base for prevention, treatment and recovery. The report discusses recent changes in healthcare policy and law, which create incentives for the implementation of the collaborative care model integrating treatment of substance use disorder with general healthcare. Some of the key findings of the report include the following (U.S. Dept. of Human Health and Services, 2016):

- A majority of patients with substance use disorders do not receive any treatment;
- Recovery is achievable with comprehensive continuing care;
- Early intervention and treatment services are beginning to be delivered into general healthcare practice under the collaborative care model;
- Integration between primary care and specialty care is needed, as are additional treatment options within primary care;
- Medications are currently under-used in treatment of substance use disorders, although scientific evidence shows that medications can be effective along with behavioral therapies, and recovery support services;

- Treatment goals for substance use disorders are the same as those for treatment of other chronic illness: reduction of symptoms and improvement of health and functional status; and
- The use of electronic technologies, e.g., telehealth and electronic medical records, **may** improve treatment of those with substance use disorders.

The Surgeon General's report cites studies that have demonstrated the efficacy of MAT in both the reduction of illicit drug use and overdose deaths as well as in improving retention in treatment. It reports studies finding that patients who receive MAT for fewer than 90 days have not shown improved outcomes and that those receiving MAT for less than three years are more likely to relapse than those in treatment for three or more years (U.S. Dept. of Human Health and Services, 2016).

The American Society of Addiction Medicine's (ASAM) comprehensive set of guidelines, *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, Third Edition* (2013) describes the continuum of addiction health service (Mee-Lee, 2013). The ASAM Criteria refers to withdrawal management rather than detoxification services. It emphasizes that altering the course of the patient's illness toward wellness, recovery, and productive functioning in family, workplace and society are the goals of addiction treatment. Treatment is described by the ASAM Criteria as a continuum including broad levels of service and an early intervention level, with levels of care determined by an individual's needs. Severity of illness, level of function, and progress determine the length of stay in each level. Treatment is individualized and responsive to a patient's specific needs and progress in treatment (Mee-Lee, 2013).

Introduction

Disease Definition, Natural History, Course and Epidemiology

The national epidemic of prescription opioid abuse and heroin use has been recently addressed in the United States by the Comprehensive Addiction and Recovery Act of 2016 (CARA). Congress acted due to the large number of overdoses from heroin, prescription drugs, and opioid pain relievers that surpassed car accidents as the leading cause of injury-related death in the United States (https://www.govtrack.us/congress/bills/114/s524). Information from the most recent National Survey on Drug Use and Health (NSDUH) provides key substance use indicators in the United States (SAMHSA, 2016).

The Substance Abuse and Mental Health Services Administration (SAMHSA, 2016) has made changes to the *2015 National Survey on Drug Use and Health (NSDUH)* to improve the quality of data collected. This "break in trends" leads to difficulty in comparing current estimates with those from earlier years; a new baseline for some substances begins with this latest survey (SAMHSA, 2016). For marijuana, cocaine, and heroin use, trends continue for estimates considered comparable with those in past years. The new survey includes changed questions about particular measures as well as changes in eligibility of

respondents (SAMHSA, 2016). The new report also includes information on new topics not included in past surveys. Some of the changes are:

- Instead of separate questions about chewing tobacco and snuff, these are combined into questions about smokeless tobacco; new smokeless tobacco questions include questions about "snus" (smokeless tobacco pouches placed under the top lip).
- To ensure consistency with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the 2015 NSDUH lowered the threshold for determining binge alcohol use for females from five to four or more drinks on an occasion (the threshold remains at five or more drinks on an occasion for males).
- Questions for "Molly" (Ecstasy), ketamine, tryptamines, alpha-methyltryptamine, "Foxy" (5-MeO-DIPT), and salvia divinorum are now included in the hallucinogens section rather than the special drugs section.
- The inhalant section includes estimates beginning with 2015 data for specific inhalants, i.e., felt-tip pens and computer keyboard cleaner ("air duster").
- Questions about methamphetamine are now separate from the prescription drug items in the 2015 survey because most of it is both produced and consumed illicitly in the U.S.; a new baseline begins with 2015 for estimates of dependence or abuse of methamphetamine.
- Changes to prescription drug measures necessitated a new baseline for measures in the four categories of prescription drugs, i.e., pain relievers, tranquilizers, stimulants, and sedatives. Questions for prescription drug misuse now refer to a 12-month reference period rather than a lifetime reference period. In the 2015 survey, misuse of prescription drugs refers to using the drug "in any way a doctor did not direct you to use it" (e.g., in a greater amount than prescribed or for a longer period of time) (SAMHSA, 2016).

A summary of key findings from SAMHSA's 2015 NSDUH follows below:

- **Illicit Drug Use** – Questions about seven of ten illicit drug categories (hallucinogens, inhalants, methamphetamine, prescription pain relievers [misuse of], tranquilizers, stimulants, and sedatives) include changes in measurements affecting comparability with earlier years. The 2015 estimates show 10.1 percent of Americans aged 12 and older used an illicit drug in the past 30 days (27.1 million people), and among young adults, aged 18-25, approximately 1 in 5 were current users of illicit drugs (22.3%). Key measurements did not change for **marijuana, cocaine, and heroin**, and estimates of the use of these are comparable with those from past years (SAMHSA, 2016).

    - ***Hallucinogens*** include LSD, PCP, peyote, mescaline, psilocybin mushrooms, "Ecstasy" (MDMA or "Molly"), ketamine, "FOXY" (DMT/AMT), and *Salvia divinorum*. An estimated 1.2 million people representing 0.5% of the population aged 12 or older were current users of hallucinogens in 2015. The age group with the largest percentage of its members using hallucinogens was the 18-25 years-of-age group (SAMHSA, 2016).

- ***Inhalants*** used to get high include substances, e.g., computer keyboard cleaner, felt-tip pens, glue, nitrous oxide, cleaning fluids, spray paint, etc. Approximately half a million people aged 12 or older were current users of inhalants in 2015, representing 0.2% of that population. The age group with the most common use was the 12-17 years-of-age group (SAMHSA, 2016).
- Currently, in the U.S. the production and distribution of most ***methamphetamine*** is illicit rather than through the pharmaceutical industry. An estimated 897,000 people aged 12 or older were current users of methamphetamine in 2015, representing 0.3% of this population. The age groups with the largest percentage of members using methamphetamine were the 18 to 25 and the 26-or-older age groups (SAMHSA, 2016).
- In 2015, 1.4% of people aged 12 or older were misusers of ***prescription pain relievers****,* which represents 3.8 million people aged 12 or older. Out of this group, those with the highest percentage of misusing pain relievers in the past 30 days were from 18-25 years of age (SAMHSA, 2016).
- Among people aged 12 or older in 2015, ***tranquilizers*** were misused by an estimated 1.9 million people who represented 0.7% of that age group. Within this age group, the 18-25 year-old group had the largest percentage of its members misusing tranquilizers (SAMHSA, 2016).
- ***Stimulants*** were currently misused in 2015 in an estimated 1.7 million people aged 12 or older, representing 0.6 percent of this population. The 18-25 year-old age group had the largest percentage of its members misusing stimulants (SAMHSA, 2016).
- In 2015, 0.2% of the population aged 12 or older misused ***sedatives***, representing an estimated 446,000 people. The 18-25 and 26-or-older age groups had the largest percentages of their members misusing sedatives (SAMHSA, 2016).
- The 2015 illicit drug use estimate is highest for ***marijuana*** use (22.2 million current marijuana users aged 12 or older and 8.3% of people aged 12 or older). This is similar to the 2014 percentage and higher than the percentages from 2002-2013. The survey shows this increase in marijuana use among people 12 or older reflects the increase by adults aged 26 or older and, to not so great an extent, increases in use among those aged 18-25 (SAMHSA, 2016).
- Among people aged 12 or older in 2015, an estimated 1.9 million were current users of ***cocaine***; that number includes approximately 394,000 current users of crack cocaine. An estimated 0.7 percent of people aged 12 or older were current users of cocaine in 2015, while 0.1% currently used crack cocaine. These estimates were similar to estimates in years between 2007 and 2013, but were higher than the estimates in 2014. Additionally, the estimates of both cocaine and crack use in 2015 were lower than estimates between 2002 and 2006 (SAMHSA, 2016).
- In 2015, approximately 329,000 people aged 12 or older were current ***heroin*** users, corresponding to approximately 0.1 percent of the population of the same age. Approximately 0.3% of people aged 12 or older in 2015 had past-year use of heroin, representing approximately 828,000 people.

Although the estimate of current heroin use in people aged 12 or older in 2015 was similar to the estimates between 2010 and 2014, it was higher than in most years between 2002 and 2009. Additionally, past-year heroin use in 2015 was higher than during 2002-2008, but similar to 2009-2014. The survey indicates larger increases in heroin use among adults aged 26 or older and smaller increases among young adults aged 18 to 25 (SAMHSA, 2016).

The Centers for Disease Control and Prevention (CDC) reported increases in drug and opioid overdose death in the U.S. from 2000–2014 in the Jan. 1, 2016 Morbidity and Mortality Weekly Report (*MMWR*). Information in the report noted significant increases in drug overdose deaths from 2013 to 2014, with opioid overdose deaths as the main factor in the increase. Increases in death rates were 9% for natural and semi-synthetic opioids, 26% for heroin, and 80% for synthetic opioids including illicit fentanyl and synthetic opioid pain relievers other than methadone (CDC, 2016).

- The CDC reported an epidemic of drug overdose (poisoning) deaths in the U.S., with the rate of deaths from drug overdoses increasing 137% from the year 2000. The rate of overdose deaths involving opioids (opioid pain relievers and heroin) increased by 200% (CDC, 2016). Drug overdose deaths occurring the in the U.S. during 2014 totaled more than 47,000, representing a one-year increase of 6.5%, while opioid overdose deaths increased by 14% (CDC, 2016).
- In 2014, drug overdoses in the U.S. were greater than during any previous year on record. The number of drug overdose deaths in the U.S. in 2014 was approximately one and a half times more than the number of motor vehicle crashes. The main drugs associated with overdose deaths were opioids, primarily heroin and prescription pain relievers, (e.g., oxycodone and hydrocodone) (CDC, 2016). From 2013 to 2014, overdose death from oxycodone and hydrocodone increased by 9% (CDC, 2016).
- The increase in heroin use (tripling in four years) related to opioid pain reliever misuse may be due to increased availability, high purity, and relatively low price (CDC, 2016).
- Illicit fentanyl, often combined with heroin or sold as heroin, may be a contributor to the recent increases in drug overdose deaths involving heroin (CDC, 2016).

- **<u>Tobacco Use</u>**
  - As reported by SAMHSA, tobacco use continues to be the leading cause of preventable death in the U.S. Among people aged 12 or older in 2015, 66.3% of past-month tobacco users were current cigarette smokers, while not using any other tobacco products. Among past-month tobacco users in the same age group, 15% smoked cigarettes while also using other tobacco products, and 18.8% used only tobacco products other than cigarettes (SAMHSA, 2016).

- Among people aged 12 or older in 2015, about 20% were current **cigarette smokers** compared with 24% to 26% who were current cigarette smokers in years from 2002 to 2008. A decline in current use of cigarettes has occurred in adolescents aged 12 to 17, young adults aged 18 to 25, and in those aged 26 or older. NSDUH reports that part of this decline reflects the use of electronic vaporizing devices, e.g., e-cigarettes, for delivering nicotine (SAMHSA, 2016).
- In 2015, 4.7% and 0.8% of people aged 12 or older were current **cigar smokers** and **pipe tobacco smokers**, respectively. The 2015 percentage for cigar smokers was lower than in most of the years between 2002 and 2012 while similar to the percentages in 2013 and 2014. The percentage of people who were current pipe tobacco smokers in 2015 was similar to the percentages in most years between 2001 and 2014 (SAMHSA, 2016).
- About 3.4% of people aged 12 or older in 2015 were current users of **smokeless tobacco**, e.g., snuff, chewing tobacco, and snus. The 18-25 year-old age group had the largest percentage of its members using smokeless tobacco (SAMHSA, 2016).
- The U.S. Food and Drug Administration (FDA) finalized a rule, effective August 8, 2016, extending its authority to regulate the manufacturing, distribution, and marketing of all tobacco products, including e-cigarettes, cigars, hookah (waterpipe tobacco), pipe tobacco, nicotine gels, and dissolvables (FDA, 2016). The FDA's goal is the protection of Americans from disease and death related to tobacco use. Although the FDA recognizes that some tobacco products **may** have less toxicity, it also notes a need for more evidence. For example, the FDA acknowledges both benefits and risks of products, e.g., e-cigarettes, which **may** be less harmful than conventional cigarettes, but they **may** prompt young people to become addicted to nicotine. Vaporizers, vape pens, hookah pens, e-cigarettes, e-pipes and other Electronic Nicotine Delivery Systems (ENDS) are affected by the FDA regulation.

- **<u>Alcohol Use</u>**
  - In 2015, more than half (51.7%) of people aged 12 and older reported any use of **alcohol** in the past month. This estimate of current alcohol use was similar to the estimate in the years from 2005 to 2013, but it was lower than the estimate in 2014 (SAMHSA, 2016).
  - In 2015, approximately 25% of people aged 12 or older were estimated to be binge alcohol users. **Binge alcohol use** for males is defined as drinking five or more drinks on the same occasion on at least one day in the past 30 days; for females, the threshold is four drinks rather than five drinks. About 5.8% of adolescents, aged 12 to 17 years, were current binge drinkers in 2015 and an estimated 39% of young adults aged 18 to 25 were current binge alcohol drinkers in the past month. Almost 25% of adults aged 26 or older were also current binge alcohol drinkers (SAMHSA, 2016).
  - The 2015 NSDUH defines **heavy alcohol use** as "binge drinking on five or more days in the past 30 days" based on the thresholds described above

(SAMHSA, 2016; p. 18). The estimated percentage of the population aged 12 or older who were heavy alcohol users in 2015 was 6.5%. Percentages for specific age groups in 2015 were 0.9%, 10.9%, and 6.4% for adolescents aged 12 to 17, young adults aged 18 to 25, and adults aged 26 or older, respectively (SAMHSA, 2016).

- Although **underage alcohol use** is prohibited in all 50 states and the District of Columbia, 20.3% of people aged 12 to 20 reported drinking alcohol in the past month (lower than the percentages in 2002 through 2014). Among this age group, 13.4% and 3.3% were binge drinkers or heavy drinkers, respectively (SAMHSA, 2016).

- **Substance Use Disorders**
  - In 2015 among people aged 12 or older, 7.8% had a substance use disorder (SUD) in the past year. Out of this group, approximately 75% had an alcohol use disorder and about 33.3% had an illicit drug use disorder. Of those who had SUDs in the past year, approximately 12.5% had both an alcohol use disorder as well as an illicit drug use disorder (SAMHSA, 2016).
  - In 2015 among people aged 12 or older who had a past-year illicit drug use disorder, the largest numbers of people had disorders related to the use of marijuana and the misuse of prescription pain relievers (SAMHSA, 2016).

An Oct. 2015 News Release by the National Institutes of Health (NIH) reported that surveys conducted by the National Institute on Alcohol Abuse and Alcoholism show that "marijuana use in the United States has risen rapidly over the past decade, with about 3 in 10 people who use marijuana meeting the criteria for addiction" (NIH, 2015). The report discussed how the "changing cultural norms related to marijuana use" **may** create "public health challenges related to addiction, drugged driving and access to effective treatment" (NIH, 2015).

Marijuana is the most commonly used illicit drug. On August 11, 2016, the United States Drug Enforcement Administration (DEA) denied petitions to reschedule marijuana under the Controlled Substances Act (Drug Enforcement Administration, 2016). Marijuana continues its classification as a Schedule 1 controlled substance with high dependency potential and no accepted medical use. Although marijuana is illegal under federal law, its recreational use is legal in eight states and the District of Columbia. Currently 28 states, the District of Columbia, Guam and Puerto Rico have enacted laws to legalize the medical use of marijuana for indications such as pain management, treatment of nausea/vomiting, glaucoma, etc. (ProCon.Org, 2016). Additionally, limited-access marijuana products (low tetrohydrocannabidiol [THC]/high cannabidiol [CBD] are approved in 17 states for "medical reasons in limited situations or as a legal defense" (National Conference of State Legislatures, 2016). The DEA has expanded the number of DEA-registered marijuana manufacturers to foster research on its use. The American Medical Association (AMA) continues to support further studies of medical marijuana use in patients who have serious conditions where evidence **suggests** possible efficacy.

After publication of the APA guideline, more analysis of national survey data augmenting the discussion on substance abuse epidemiology in the U.S. 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 (NSDUH): National Findings 2002 and the Monitoring the Future Study: National Survey Results on Drug Use, 1975-2003) 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 U.S. 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 first release of 2013 NSDUH estimates contained in *The NSDUH Report* (2014) reported the following: an estimated 24.6 million individuals aged 12 or older were current illicit drug users in 2013 compared with 23.9 million in 2012. In 2013, 8.8% of youths aged 12 to 17 were current illicit drug users compared to 9.3% in 2008. In 2013, an estimated 60.1 million individuals aged 12 or older were past-month binge alcohol users compared with 59.7 million in 2012, and 21.6 million (8.2% of the population aged 12 or older) had a past-year substance use disorder. This represents an increase from the number in 2011 (20.6 million) and a decrease from the number in 2012 (22.2 million). Further, this report indicated that of the estimated 22.7 million individuals aged 12 or older in 2013 needing treatment for an illicit drug or alcohol use problem, 2.5 million were treated at a specialty facility. It also reported that in 2013, 1.4 percent of adolescents had co-occurring SUD and major depressive episode; 3.2 percent of adults had co-occurring any mental illness and substance use disorder; and 1.0 percent of adults had co-occurring serious mental illness and substance use disorder (Substance Abuse and Mental Health Administration [SAMHSA], 2014).

The 2013 NSDUH estimated that 2.6 million persons aged 12 or older were dependent on or abused *both* illicit drugs and alcohol; 4.3 million were dependent on or abused illicit drugs but not alcohol; and 14.7 million were dependent on or abused alcohol but not illicit drugs. The survey found that illicit drugs with the largest numbers of persons with past-year dependence or abuse in 2013 were marijuana, pain relievers, and cocaine. The number of persons with marijuana dependence or abuse was similar from 2002 to 2013 (4.2 million) and the number with pain reliever dependence or abuse was similar from 2006 to 2013 (1.9 million). Those with cocaine dependence or abuse declined from 1.7 million in 2006 to 0.9 million in 2013, while those with heroin dependence or abuse more

than doubled from 2002 (214,000) to 2013 (517,000) (SAMHSA, 2014). A recent study examined recent trends in heroin initiation among persons aged 12 to 49. Using data pooled from the 2012 NSDUH, the study found a heroin incidence rate in the 12 months preceding interview that was 19 times higher among those who reported prior nonmedical pain reliever use than among those who did not. Further, 79.5 percent of the recent heroin initiates previously used nonmedical pain relievers, while only 1.0 percent of recent users of nonmedical pain relievers had prior use of heroin. However, only 3.6 percent of nonmedical pain relievers initiated heroin use within a 5-year period following their first use of pain relievers (Muhuri et al., 2013).

The 2013 NSDUH reported that marijuana was the most commonly used illicit drug in 2013, with 19.8 million past month users among those aged 12 or older. The rate of past month users increased from 5.8 to 7.5 percent between 2002 and 2013. In the same report, marijuana was also the illicit drug with the largest numbers of persons with past year dependence or abuse. In 2013, the number of persons with past year dependence or abuse of marijuana was 4.2 million (SAMHSA, 2014).

The use of cannabis for medicinal purposes ("medical marijuana") was not a focus of review in the APA guideline. To date, 23 states and the District of Columbia 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 (Procon.org, 2014). Similarly, two states have pending legislation to legalize its use for medical reasons (Procon.org, 2014). 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). 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). According to an American Medical Association (AMA) policy statement on medical marijuana, "our AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence **suggests** possible efficacy and the application of such results to the understanding and treatment of disease" (Procon, 2014).

In November 2012, Washington and Colorado became the first two states to legalize the recreational use of marijuana, decriminalizing its use. In 2014, voters in Alaska and Oregon approved a ballot measure to legalize the recreational use of marijuana to be effective in 2015, and voters in Washington, D.C. also approved a ballot initiative which is subject to Congressional review. A recent report by the American Medical Association's (APA's) Council on Science and Public Health and approved by AMA delegates asserts that "cannabis is a dangerous drug and as such is a public health concern, [that] sale and possession of marijuana should not be legalized, [and that] public health based strategies,

rather than incarceration, should be utilized in the handling of individuals possessing cannabis for personal use," (Psychiatryonline, 2014).

Other published data from the 2013 NSDUH also confirmed that prescription drug abuse is a significant emerging problem in the United States. NSDUH combines prescription-type drugs, i.e., pain relievers, tranquilizers, stimulants, and sedatives, into the broad category of psychotherapeutics. Methamphetamines are included under stimulants (SAMHSA 2013). The percentage of persons aged 12 or older using prescription-type psychotherapeutic drugs for nonmedical reasons in the past month in 2013 was 2.5 percent, compared to 2.4 percent in 2011 (SAMHSA, 2014). Abuse and diversion of prescription drugs are 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).

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 (Bofetta and Straif, 2009). The 2013 NSDUH reported that the rate of past-month use of smokeless tobacco use among persons aged 12 or older in 2013 was 3.4 percent, compared to the corresponding rate in 2002 of 3.3 percent (SAMHSA, 2014). 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 (Bofetta and Straif, 2009; National Cancer Institute, 2010). The 2013 NSDUH reported that the rate of current use of any tobacco product among those aged 12 or older in 2013 (25.5 %) was similar to the rate in 2011 (26.5 %). Past month use of any tobacco product among persons aged 12 or older decreased between 2002 and 2013 from 30.4 to 25.5 percent. Past month pipe tobacco was unchanged at 0.8 percent in 2002 and in 2013 while rates of past month use of cigars decreased from 5.4 % in 2002 to 4.7 % in 2013 (SAMHSA, 2014). An analysis of the results from the National Longitudinal Alcohol Epidemiologic Survey and the National Epidemiologic Survey on Alcohol and Related Conditions found higher rates of past-year daily tobacco use in individuals with substance use disorder or major depressive disorder and in Native Americans (Secades-Villa et al, 2013).

The use of electronic cigarettes (e-cigarettes), battery-operated devices delivering nicotine and other additives via inhaled vapor, is rapidly increasing among adolescents and adults. According to the National Youth Tobacco Survey (NYTS), ever use of e-cigarettes among youths (grades 6-12) doubled between 2011 and 2012, from 3.3 % to 6.8 % (Dutra and Glantz, 2014). More than 75 % of youth who smoked e-cigarettes also smoked conventional cigarettes. The authors reported a web-based survey showing that in 2010 and 2011, the percentage of adults who had ever used e-cigarettes was 3.3 and 6.2 % respectively. Among

both adolescents and adults, dual use of e-cigarettes and conventional cigarettes is high and increasing rapidly (Dutra and Glantz, 2014). On April 24, 2014, the U.S. Food and Drug Administration (FDA) announced its proposal of a new rule extending its tobacco authority to cover additional tobacco products, e.g., e-cigarettes, cigars, pipe tobacco, nicotine gels, and waterpipes. Conventional cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco are currently regulated by the FDA (FDA, 2014).

The abuse of illegal steroids as performance enhancing drugs also remains 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 bodybuilders who began abusing anabolic steroids as teenagers (Fernandez et al., 2009). The CDC's 2013 National Youth Risk Behavior Survey reports that 3.2 percent of high school students have taken steroid pills or shots without a doctor's prescription one or more times. The percentage increased from 2.7 percent in 1991 to 6.1 percent in 2003 and has been declining since 2003 (CDC, 2013). Evidence related to anabolic-androgenic steroids (AAS) is summarized in a position by Kersey et al. as a reference for healthcare professionals and interested others. They indicated that the non-medicinal abuse of AAS often begins in adolescence and sometimes even in middle school. Most AAS abusers administer doses beyond medicinal levels or "stack" multiple AAS. In addition to the negative health effects of AAS, e.g., associated mood disorders and AAS dependence, the authors reported results from several studies suggesting AAS abusers **may** be more likely to develop other forms of drug dependence, e.g., opioid dependence. Kersey et al. **suggested** that adolescent educational AAS abuse-prevention programs (e.g., Adolescents Training and Learning to Avoid Steroids [ATLAS] and Athletes Targeting Healthy Exercise and Nutrition Alternatives [ATHENA]) provide high-quality evidence about how to best educate adolescents about doping and its consequences. They also advised referral and counseling to avoid consequences of AAS abuse (Kersey et al., 2012).

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 (Department of Health and Human Services [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 (Conrod et al., 2010; Hawkins et al., 2009; Spoth et al., 2009). Griffin and Botvin (2010) reviewed the epidemiology, risk and

protective factors, and evidence-based approaches that have been found to be most effective in preventing adolescent substance use and abuse. They described evidence-based approaches to drug abuse prevention for adolescents at the school, family and community levels, stressing the need for flexible prevention efforts that are responsive to changing trends, e.g., the abuse of prescription and over the counter medications where multiple stakeholders including parents, physicians, and pharmacists must play a role (Griffin et al., 2010).

Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published in 2013, includes several changes to addictions, substance-related disorders, and alcohol. Key changes include the addition of gambling disorder as a behavioral addiction, and the combination of substance abuse and substance dependence into single substance use disorders, further divided into mild, moderate, and severe subtypes based on the number of criteria endorsed. Accompanying the diagnostic criteria for substance use disorder are criteria for intoxication, withdrawal, substance-induced disorders, and unspecified substance-related disorders, where relevant. Diagnostic criteria for substance use disorder fit within overall groupings: impaired control, social impairment, risky use, and pharmacological criteria. Two or more of the 11 criteria must be met within a 12-month period for a diagnosis of a substance use disorder in DSM-5; one or more criteria were required for diagnosis of substance abuse and three or more required for diagnosis of substance dependence in DSM-IV. A new criterion, i.e., "craving or a strong desire or urge to use a substance", has been added, and the "recurrent legal problems" criterion has been removed from DSM-5. New specifiers include "in a controlled environment" and "on maintenance therapy." Other new disorders in DSM-5 are cannabis withdrawal and caffeine withdrawal (American Psychiatric Association, 2013).

General Treatment Principles - Somatic Treatments

A recent article discussed the role of medication-assisted treatment for alcohol use disorders and opioid dependence in primary care (Lee et al., 2015). With primary care as the entry point for many patients suffering from chronic substance related and addictive disorders, primary care health providers can address substance use disorders by screening, prevention, diagnosis, and disease management, including the use of pharmacotherapies in combination with counseling and behavioral therapies, and relapse prevention. Due to the national public health crisis surrounding opioid misuse and abuse, the importance in providing evidence-based effective prevention, care, and treatment is paramount. At present, many patients are referred to specialty care providers, but they often are lost in "the gap between primary care and specialty treatment systems" (Lee et al., 2015, p. 1). They **may** either undergo detoxification without transition to treatment/ support programs or receive psychosocially based treatment only, after which they relapse to substance use. Authors noted a clinical trial comparing alcohol care management delivery in primary care to specialty addiction treatment which found that the intensive

care and pharmacotherapy in a primary care setting provides "better clinical outcomes for patients with alcohol use disorders than those obtained in addiction specialty care" (Lee et al, 2015, p. 2).

The epidemic of opioid-related deaths with its rising death toll compares to the acquired immune deficiency syndrome (AIDS) crisis in that it requires large scale, highly coordinated response (Williams and Bisaga, 2016). Patients with opioid use disorder (OUD) receive medical treatment for withdrawal during detoxification, followed by discharge referrals to medication-free outpatient or residential care; most of the patients not receiving medication-assisted treatment (MAT) relapse and are at risk of overdose death. Williams and Bisaga discussed "enlargement of the network of professionals authorized to deliver treatment and broadened access to MAT through such avenues as specialized community pharmacies, telemedicine, and hub-and-spoke systems of care" (Williams and Bisaga, p. 814).

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. A recent Informational Bulletin provides information on "Medication Assisted Treatment" (MAT) of persons with SUD (Mann et al., 2014). Authors noted that 105 individuals in the U.S. die each day as result of drug overdoses, and 6,748 individuals seek treatment in emergency departments each day for misuse or abuse of drugs. They suggest that the use of medications combined with behavioral therapies to treat SUD helps to reduce cravings and prevent relapse. Authors reported findings that individuals with untreated alcohol disorders use twice as much healthcare as those with treated alcohol use disorders. MAT is associated with fewer inpatient admissions in those with alcohol dependence (Mann et al., 2014).

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).

A study evaluating somatic treatment options for patients with co-occurring psychiatric conditions and substance use disorders was conducted in adult outpatient individuals

(n=12) with comorbid major depression and alcohol dependence (Cornelius et al, 2012). Participants received 15 mg of mirtazapine during the first two weeks of the trial and 30 mg during the last six weeks of the medication trial. Motivation Enhancement Therapy focusing on medication compliance and compliance was also provided. Depressive symptoms (participant rated) were assessed with the Beck Depression Inventory and drinking behavior was evaluated using the timeline follow-back method (TLFB). Results demonstrated significant improvement in both depressive symptoms and in level of alcohol consumption by participants during the course of the medication trial. Researchers noted that this is the first study reporting a significant decrease in level of drinking in individuals with a comorbid major depressive disorder/alcohol dependence who are treated with mirtazapine (Cornelius et al, 2012).

General Treatment Principles - Psychosocial Treatments

Past studies have shown that a computer-based therapeutic education system (TES) including media technologies, e.g., internet and mobile devices, **may** be effective in the treatment of problematic substance use disorders. A recent trial examined how baseline demographic and behavioral characteristics of participants from a methadone maintenance treatment program (n=169) predict treatment outcomes of TES (Kim et al., 2015). Participants were randomized to one of two groups: (1) standard treatment (i.e., counseling once per week during first four weeks, followed by every other week over 52 weeks) alone, or (2) reduced standard treatment plus TES, where TES replaced the first half of each counseling session. Analyses showed baseline characteristics of subgroups who most benefit from the reduced standard plus TES condition compared to the standard alone treatment: employed patients, highly anxious patients, and those ambivalent about substance use (Kim et al., 2015).

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).

A recent study evaluated the long-term efficacy of mindfulness-based relapse prevention (MBRP) compared with cognitive-behavioral relapse prevention (RP) and treatment as usual (TAU) in an SUD aftercare program (Bowen et al., 2014). TAU included 12-step programming and psychoeducation. Participants (n=286) were randomly assigned to 8 weekly sessions of one of the treatments, with assessments at baseline and at 3, 6, and 12 months. Results showed no between-group differences at the 3-month follow-up, whereas at the 6-month follow-up, both RP and MBRP participants had a significantly reduced risk of relapse to both drug use and heavy drinking compared with the TAU group. MBRP participants reported significantly fewer drug use days and less probability of engaging in heavy drinking compared with RP participants at the 12-month follow-up. Researchers noted that MBRP "increases awareness of individual internal and environmental events that precipitate relapse and alter responses to craving and negative affect through exposure-based processes facilitated through mindfulness practice" (Bowen et al., 2013, p. 554).

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). Another study of the SPMI population by Brown et al. used data from a randomized trial of

substance use disorder treatment in outpatients with dual severe mental illness and SUD to analyze factors predicting initiation and engagement of substance use disorder treatment. The researchers found that the likelihood of initiating treatment was decreased in individuals with schizophrenia and in the male gender. There was less likelihood of engaging in treatment among individuals with current drug dependence and recent arrest, while positive feelings about family relationships increased the likelihood of engaging in treatment (Brown et al., 2011).

The population of disadvantaged women with substance use disorders represents a minority of those who receive 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 computer-based training for cognitive-behavioral therapy) 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, 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). Using data from the randomized clinical trial by Carroll et al., other investigators examined the quality of coping responses acquired during CBT4CBT (Kiluk et al., 2010). Investigators measured quality of coping using an adapted version of the Cocaine Risk Response Test (CRRT) finding that the quality of coping responses to high-risk situations

increased during the treatment period for participants receiving CBT4CBT compared to those receiving treatment as usual. This increase was also evident at treatment termination and at the 3-month follow-up. The authors **suggested** the need for future studies to better understand the role that coping skills play in the relationship between CBT and substance use treatment outcomes (Kiluk et al., 2010).

Carrol, Kiluk et al. conducted a later eight-week trial evaluating CBT4CBT in a more homogenous sample including only cocaine-dependent individuals (n=101) maintained on methadone (Carroll et al., 2014). Participants were randomly assigned to methadone maintenance combined with weekly access to CBT4CBT or to standard methadone maintenance only. Participants in the CBT4CBT group were significantly more likely to attain three or more consecutive weeks of abstinence within the treatment period than those in the standard methadone maintenance only group (36% compared with 17%, respectively). Drug-free urine specimens were greater in the CBT4CBT group compared to the methadone maintenance alone (24% compared with 19%). This replication study of a computer-assisted therapy for addiction also showed continued improvement (6 months after treatment) for the participants assigned to the CBT4CBT group relative to those assigned to standard methadone maintenance treatment alone (Carroll et al., 2014).

The APA guideline also indicates that while "psychotherapy can enhance the effectiveness of pharmacotherapy," it also stresses that "pharmacotherapy enhances the efficacy of psychotherapy since these two treatments have different mechanism of action and targeted effects that can counteract the weaknesses of either treatment alone" (p.38). In concert with the APA guideline, The SAMHSA *Treatment Improvement Protocol (TIP) 49 – Incorporating Alcohol Pharmacotherapies into Medical Practice* supports integrating behavioral interventions and counseling with an appropriate medication as this "can have a synergistic or additive effect and improve outcome" (p.6, CSAT 2009). The *TIP 49* further notes..."Medication can reduce the cravings that disrupt recovery. When cravings are decreased, counseling is more likely to strengthen the individual's coping resources, which are necessary to promote medication adherence and behavioral change" (p.6, CSAT, 2009). Further, medication-assisted treatment (MAT) of alcohol use disorder and opioid dependence can be administered in physician office-based settings, making treatment more available, and can improve continuity and accessibility of care. Medication-assistant treatment of these disorders is "reasonable, practical and a desirable trend that should be greatly expanded" (p.7, CSAT, 2009).

General Treatment Principles - Clinical Factors Affecting Treatment

A recent study compared smoking status over four years between individuals (n=311,466) with and without behavioral health conditions in a large, integrated healthcare delivery system providing access to tobacco treatment (Young-Wolff et al., 2016). In 2010, 10.4% of patients without behavioral conditions were smokers, whereas 20.1% of those with behavioral health conditions were current smokers. Although smoking prevalence dropped significantly for both groups from 2010–2013, 33.3% of patients with a substance use disorder continued to smoke in 2013 compared to only 9.2% of those with no behavioral

health condition who continued to smoke. The most commonly used tobacco cessation medication used was the nicotine patch, with very low use of bupropion. The use of bupropion did not differ significantly between those with and without a behavioral health condition. Authors highlighted results showing continuing large disparities in smoking between the two groups, noting that access to healthcare does not equate to utilization of tobacco cessation treatments. They further **suggested** tobacco cessation treatment within substance use and psychiatry specialty clinics, especially since "quitting smoking is associated with long-term reductions in depression, anxiety, and stress and with improvements in well-being" (Young-Wolff, p. 1000). Authors concluded the need to address the increasing disparities in smoking among those with behavioral health conditions, especially substance use disorders, and "to better facilitate access to, and use of, appropriate and effective tobacco cessation medications as part of standard behavioral health treatment (Young-Wolff, p. 1002).

Other issues related to smoking and mental illness addressed in recent studies include the effect of tobacco use and cessation on psychiatric medications. The dosing of many psychiatric medications is affected when patients quit smoking as well as when they relapse to smoking, and clinicians should watch for related side effects (Ziedonis et al., 2015). Authors provided clinical recommendations for psychiatrists, e.g., listing "tobacco use/tobacco use disorder" in the treatment plan; consideration of a CO meter to assess ongoing progress; and creation of system changes to integrate evidence-based practices and enhance patients' quality of life (Ziedonis et al., 2015). A 2016 study reviewed randomized controlled smoking cessation treatment intervention trials in smokers with serious mental illness (SMI) to provide evidence on both the safety and efficacy of smoking cessation interventions for individuals with serious mental illness (Evins et al, 2015). Authors noted that individuals with SMI should receive treatment to quit smoking, as they smoke with greater prevalence, die earlier due to smoking-related illnesses, and want to and can quit smoking. They concluded that effective treatment for smokers with schizophrenia spectrum disorder includes combined behavioral treatment and varenicline or bupropion with or without nicotine replacement therapy (NRT). Authors noted the need to establish an evidence base for clinical practice guidelines for smoking cessation treatment for subgroups of smokers, e.g., those with major depressive disorders, and bipolar disorder. They also noted the need for future research addressing types of behavioral treatment (Evins et al, 2015). A recent study assessed the effects of elevated depression symptoms among nicotine-dependent smokers during smoking cessation efforts (Reid and Ledgerwood, 2016). In this small controlled trial including nicotine-dependent smokers (n=81), authors found that smokers with greater vs. fewer depressive symptoms experienced increased withdrawal and craving while trying to quit smoking even at the start of treatment (monitoring of expired carbon dioxide and brief counseling), with the discomfort making quitting difficult.

Another clinical condition that affects the treatment of tobacco use disorder is obesity. A recent literature review explored the complex relationship between nicotine and body weight regulation (Rupprecht et al., 2015). Authors presented a simplistic model of the relationship between obesity and smoking. Obese smokers are especially susceptible to smoking due to several factors: clustering of unhealthy behaviors, smoking to reduce

weight, and enhanced reward seeking. They noted how nicotine increases insulin resistance, central obesity and fat accumulation while contributing to obesity, and proposed "these factors create a cycle promoting nicotine-seeking in the obese population" (Rupprecht et al., p. 291). Authors further reported how reduction of nicotine content in cigarettes **may** "result in the development of obesity and its associated co-morbidities in a subset of smokers." According to the authors, nicotine reduction policy currently studied as a strategy to reduce the harm caused by tobacco smoke must carefully consider this vulnerable population of obese smokers.

Patients with coronary heart disease (CHD) benefit from psychosocial smoking cessation interventions. Authors examined the efficacy of psychosocial interventions, e.g., counseling, telephone support, and self-help material, for smoking cessation in patients with CHD in an updated Cochrane review including 40 randomized controlled trials (Barth et al., 2015). From this review, authors concluded that psychosocial interventions over a period of more than one month were effective in promoting abstinence for up to one year, whereas brief interventions of less than one-month duration and of low intensity were not effective. Authors **suggested** the need for more studies comparing additional benefits of combined pharmacological interventions, e.g., bupropion and NRT, and psychosocial interventions compared with pharmacological or psychosocial interventions alone in patients with CHD.

Although alcohol dependence and major depressive disorder frequently co-occur, the disorders usually receive separate treatment, resulting in many individuals having poor access to specialized psychiatric treatment (Awan et al., 2015). In a recent report, authors described a pilot implementation and use of integrated care pathways (ICPs) for patients with co-occurring alcohol dependence and major depressive disorder in a clinical setting. The intervention included: psychopharmacological intervention, non-pharmacological intervention, interdisciplinary collaboration, and a project management approach. Authors emphasized the "bottom up" approach, including the "inclusion and engagement of frontline clinicians from the start" and allowing the clinicians to "own" the processes and be accountable for both results and accountability (Awan et al., 2015). Non-psychiatrist physicians specialized in addictions received guidance in assessment and treatment of major depressive disorder, and in complex cases, they were partners with the team psychiatrist. An evaluation of this pilot program showed reduction of symptoms for both alcohol dependence and depression. Authors **suggested** that the ICP is a potentially effective approach in the treatment of concurrent alcohol dependence and major depressive disorder at an academic tertiary care hospital; they noted the need for further research to establish applicability in a variety of settings (Awan et al., 2015).

As a number of states are legalizing both medicinal and recreational marijuana, studies have addressed an important concern about how adolescent marijuana use may affect the development of psychotic symptoms, e.g., hallucinations and paranoia. In a 2016 longitudinal study, researchers examined whether adolescents regularly using marijuana, i.e., weekly or more often, experienced a systematic increase in their subclinical psychotic symptoms during a period of regular use. They also examined whether the increase was short-lived or sustained following abstinence (Bechtold et al., 2016). The study sample included boys (n=1009) who self-reported frequency of marijuana use, subclinical

psychotic symptoms, other substance use, e.g., alcohol, or other illicit drug use, and internalizing and externalizing problems. These were recorded annually from age 13 to 18, with researchers using within-individual change modeling to analyze whether the adolescents reported "an increase in their subclinical psychotic symptoms as a function of their recent and/or cumulative history of regular marijuana use and whether effects were sustained following abstinence" (Bechtold et al., p. 781). Researchers further examined the information for specific features of psychosis. Results found evidence suggesting an adolescent's risk of experiencing persistent subclinical psychotic symptoms may be increased by regular marijuana use, with this association remaining significant after controlling for changes in current marijuana use and other illicit drug use. Even when adolescents remained abstinent for a year, the effect of prior weekly marijuana use on subclinical psychotic symptoms did not go away, with pronounced effect for paranoia and hallucinations. Researchers concluded that, based on the results of this study, "adolescents are more likely to experience subclinical psychotic symptoms (particularly paranoia) during and after years of regular marijuana use" …and that "perhaps the most concerning finding is that the effect of prior weekly marijuana use persists even after adolescents have stopped using for 1 year" (Bechtold et al., p. 788). They noted the importance of policies and programs "to keep adolescents from engaging in regular marijuana use, as chronic use seems to increase their risk of developing persistent subclinical psychotic symptoms" (Bechtold et al., 2016).

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.

A recent review of studies evaluating outcomes of patients with both a mood and a substance use disorder who received a single medication for their mood disorder showed inconsistent results in determining the effectiveness of mood-resolving medications to reduce mood symptoms and substance use (Pettinati et al., 2013). Researchers reported results from several double-blind placebo-controlled studies showing tricyclics and SSRIs alleviated depression in the majority of cases, but had little effect on reducing drinking. A review examining eight double-blind placebo-controlled trials of antidepressants and counseling for patients with a depressive disorder and alcohol dependence showed that six of the studies reported a relationship between the medication and reductions in depressive symptoms, irrespective of type of antidepressant. Only three of the studies showed an advantage for the medication over placebo in the reduction of drinking. In another study, a tricyclic (desipramine) reduced depressive symptoms as well as the amount of drinking in depressed alcoholics, and the same effects were found in another study where alcohol dependent patients with primary depression and suicidal ideation were treated with an

SSRI (fluoxetine). A larger trial included patients (n=345) with major depression and alcohol dependence who were treated with sertraline or placebo for 10 weeks with no advantage of sertraline over placebo for alleviating depression or for reducing drinking. Pettinati et al. conducted a 14-week double-blind-placebo-controlled trial with patients (n=170) with major depression and alcohol who were treated with sertraline (for depression), naltrexone (for alcohol dependence), a combination of sertraline and naltrexone, or placebo. All of the patients received weekly cognitive-behavioral therapy. Results found that patients treated with the combination of drugs achieved greater abstinence from alcohol and delayed relapse to heavy drinking compared to those treated with only one or the medications or with placebo. Additionally, those treated with the combination of medications also had a lower likelihood of being depressed at end of treatment compared with those receiving only one of the medications or placebo. Researchers noted that despite the fact that four medications (disulfiram, oral naltrexone, long-acting injectable (LAI) naltrexone, and acamprosate) have been approved by the FDA for alcohol dependence, few clinicians prescribe medications to treat alcohol dependence while treating mood disorders (Pettinati et al., 2013).

Since the publication of the APA guideline and watch, and relevant to a discussion on use of psychotropic medications, an FDA Alert appeared for clinicians to 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 better understand 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 post-traumatic 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).

A clinician's view of manualized therapies relevant to PTSD/SUD was assessed using a nationwide survey of Veterans Affairs (VA) staff (n=205) working with veterans who had PTSD/SUD, many having returned from duty in Iraq or Afghanistan. Of the 11 different therapy models addressed, ratings of the overall helpfulness of each model showed the four treatment models considered most helpful were: supportive therapy (seeking safety), relapse prevention, motivational interviewing, and CBT. Clinicians stressed the difficulty in striking a balance between teaching coping skills and allowing a veteran to talk about their experience when it distresses them so much that they relapse. Some clinicians advised treating both PTSD and SUD at the same time, but delaying trauma-based intensive therapy until SUD is stable for 3-6 months (Najavitis et al., 2011).

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 (BPD) and antisocial personality disorder (ASPD). The adopted guideline acknowledges the efficacy of dialectical behavioral therapy in treating patients with BPD, with or without a co-occurring SUD, but notes that it is not always effective in improving substance use outcomes. The relationship between improvements in emotion regulation and substance use problems following dialectical

behavioral therapy in women (n=27) with substance dependence and borderline personality disorder was investigated by Axelrod et al. (2011). Measurable improvement in emotion regulation was demonstrated in women with substance dependence and borderline personality disorder who received dialectical behavioral therapy. The results also correlated improved emotion regulation with decreased substance use. The researchers cautioned that it is not possible to make conclusive interpretations of causality, but **suggested** that this study shows improved emotion regulation can account for improvement in impulsive, maladaptive behavior, e.g., substance abuse (Axelrod et al., 2011).

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).

The APA guideline discusses blending psychosocial therapies used to treat specific substance use disorders with psychosocial treatment approaches for other psychiatric diagnoses (e.g., CBT for depression). According to Watkins et al., few individuals entering treatment for substance use disorders have access to effective depression treatment (Watkins et al., 2011). In their non-randomized, quasi-experimental study, patients (n=299) with persistent depressive symptoms and substance abuse problems received usual residential care or usual residential care plus CBT. Results of the study showed that CBT was associated with significant improvements in both depression and substance use outcomes. Patients receiving usual residential care plus CBT reported fewer depressive symptoms at the 3- and 6-month post-baseline interviews and reported fewer drinking days at 6-months and fewer days of problem substance use compared to patients receiving usual residential care. Researchers **suggested** that these results provide support for a new model of integrated care for substance abuse programs, suggesting future studies addressing challenges associated with the implementation of this model of integrated care (Watkins et al., 2011).

A large segment of the population being treated for SUD is made up of young adults with co-occurring substance use and psychiatric disorders (COD). A recent study investigated differences between two groups of young adults attending psychiatrically-integrated residential SUD treatment: young adults with co-occurring SUD and psychiatric disorders (n=141); and SUD only young adults (n=159) (Bergman et al., 2014). The most common SUDs were alcohol and cannabis use while the most common psychiatric disorders were major depressive disorder, generalized anxiety disorder, and/or social phobia. At treatment intake, significantly greater levels of dependence severity and substance use consequences were reported in the COD group. The residential treatment program employed 12-step facilitation, cognitive-behavioral therapy, and motivational enhancement therapies. Psychiatric assessment, psychotropic medication, and evidence-based psychological interventions for psychiatric disorders were integrated into patient care. Results showed that COD patients improved as much during treatment as the SUD only group. Researchers **suggested** that clinicians consider a residential program integrating evidence-based psychosocial and psychopharmacological interventions for treatment of young adults with COD (Bergman et al., 2014).

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).

ACOG later published Committee Opinion Number 538, *Nonmedical Use of Prescription Drugs*, which indicates that all women should be screened annually and early in pregnancy for nonmedical prescription drug use. The ACOG Committee Opinion advises physicians to offer referrals for treatment to mitigate withdrawal symptoms and address drug-seeking behavior. It also instructs women's healthcare providers to: "follow suggestions on prescribing to reduce drug abuse and diversion; educate patients who have been prescribed medications to be the sole user of the drug; give instruction for safe medication storage and disposal; consider referral to a pain management expert for women with chronic pain; and be aware of state laws addressing the prescribing of opioids and other potential drugs of addiction" (ACOG Committee Opinion Number 538, October 2012, p. 5).

A recent large study to assess possible associations between mild traumatic brain injury (TBI) and substance use disorders analyzed the demographic, medical and military data for more than a half million active duty U.S. Air Force service members, including active-duty airmen (n=5,065) meeting criteria for a mild TBI (Miller et al. 2013). An increased risk for alcohol dependence, nondependent abuse of drugs or alcohol, and nicotine dependence was found in the first 30 days following mild TBI. Researchers **suggested** that alcohol dependence **may** be a longer-lasting adverse outcome following mild TBI as it continued past the first 30 days. Researchers noted that their results suggest that routine care for mild TBI should include screening for addiction-related disorder during the first 30 days post-mild TBI, as well as repeat alcohol screening for at least 6 months following the TBI (Miller et al, 2013).

Treatment of Nicotine Dependence

Effective treatments to stop smoking include both behavioral support and pharmacotherapies, either alone or combined. A 2016 review of 53 randomized or quasi-randomized trials from the Cochrane Library compared combined behavioral support (brief advice and counseling) and medication (nicotine replacement therapy [NRT], varenicline, nortriptyline, and bupropion) to usual care or brief advice to determine whether the treatment effect, i.e., abstinence from smoking after six months, differed depending on the intervention (Stead et al., 2016). Studies (n=53) included participants (n=more than 25,000) who were smokers recruited from both community and healthcare settings. The analysis, including 52 pooled studies, showed that the combination of behavioral support and pharmacotherapies increased smoking cessation success more than the minimal intervention or usual care. Researchers concluded that combined interventions of pharmacotherapy and behavioral support should be encouraged by clinicians for smokers (Stead et al., 2016).

Another 2016 study reviewed randomized controlled trials (n=29), from the Cochrane Library, comparing the efficacy of nicotine receptor partial agonists, e.g., varenicline and cytisine, to placebo, for helping people (n=13,562) stop smoking (Cahill et al., 2016). Trials comparing the treatment drugs with bupropion and nicotine patches were also included if available. The follow-up period in all the trials was at least six months from start of treatment, and all trials reported at least a follow-up period of six months from the start of treatment. Abstinence from smoking at the longest follow-up was the main outcome measured, with results biochemically confirmed (by testing blood or bodily fluids). Cytisine increased the chances of quitting with only modest quit rates. Key results showed that varenicline doubled the chances of quitting smoking compared with placebo while it also reduced side effects. Varenicline was also more effective in stopping smoking than bupropion or NRT. Researchers reported, "varenicline delivers one extra successful quitter for every 11 people treated, compared with smokers trying to quit without varenicline" (Cahillet al., 2016, p. 3). According to the researchers, recent evidence is not in support of a link between varenicline and depressed mood or suicidal ideation, although smokers treated with varenicline who also have a past or current psychiatric illness **may** be at a higher risk. They also noted unclear evidence about a linkage between varenicline and increased heart and circulatory problems in people already with these risks, necessitating future research (Cahill et al., 2016).

In a 2015 study, researchers noted that not all cigarette smokers are ready to quit abruptly, but **may** be willing to reduce smoking with the goal of quitting (Ebbert et al., 2015). Researchers indicated that past studies have shown that an average of two quit attempts annually are made by 40% of cigarette smokers, with surveys showing that 44% of daily cigarette smokers prefer to quit through reducing the number of cigarettes rather than abruptly quitting (Ebbert et al., 2015). The purpose of this randomized, blinded, placebo-controlled, multinational clinical trial was to determine efficacy as well as the safety of varenicline to increase smoking abstinence rates through smoking reduction in a "reduce-to-quit" approach. Participants (n=1510) included those who smoked 10 or more cigarettes per day without an abstinence period greater than three months in the past year and who agreed to reduce smoking and try to quit within three months. They were randomized to varenicline or placebo during a 24-week treatment period during which they were asked to reduce their smoking rate by 50% and 75% by week 4 and week 8, respectively, to meet a goal of quitting by week 12. Participants received counseling training to help them quit smoking. Within the varenicline group, 32% achieved continuous abstinence during weeks 15 through 24 compared with only 7% of those receiving placebo. Those in the varenicline treatment group were more than three times more likely to maintain abstinence six months after treatment than the placebo group. Adverse events rates did not differ between the groups. Researchers concluded that varenicline effectively increases long-term smoking cessation (Ebbert et al., 2015).

In a recent study, smokers (n=1086) were randomized to varenicline only, nicotine patch only, or combination nicotine replacement therapy (C-NRT), i.e., nicotine patch plus nicotine lozenge over a 12-week period (Baker et al., 2016). Treatment in all groups included counseling. The primary outcome measure was self-reported 7-day point-

prevalence abstinence at 26 weeks, confirmed by exhaled carbon monoxide. No significant differences in rates of smoking abstinence occurred at 26 or 52 weeks. Researchers noted that although varenicline and C-NRT have been considered superior to the nicotine patch in effectiveness, the current findings "raise questions about the relative effectiveness of intense smoking pharmacotherapies" (Baker et al., 2016).

A recent large, randomized, double-blind, triple-dummy, placebo-controlled trial, Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES), compared the smoking cessation efficacy and safety of varenicline (1 mg twice a day), bupropion (150 mg twice a day), and transdermal nicotine patch (21 mg per day with taper) in smokers (n=8144) with and without a psychiatric disorder (Anthenelliet al, 2016). Participants were randomized to one of the treatment groups or placebo for a 12-week treatment phase followed by a 12-week non-treatment phase. Results showed no evidence of significant increase in rates of moderate-to-severe neuropsychiatric adverse events with varenicline or bupropion relative to nicotine patch or placebo in those with or without psychiatric disorders. The efficacy of varenicline was superior to bupropion, nicotine patch, and placebo in both those with and without a psychiatric disorder, and both bupropion and nicotine patch were superior in efficacy to placebo. The researchers **implied** that "the available evidence, substantially boosted by this study, clearly shows the efficacy of all three first-line smoking cessation medications with varenicline having the largest effect, in smokers with and without psychiatric disorders" (Anthenelliet et al, p. 2508).

The FDA advisory panel recommended the removal of a serious warning about neuropsychiatric side effects of varenicline on Sept. 14, 2016. However, it is uncertain whether the FDA will follow the recommendation of the advisory committee to remove the Black Box warning. The FDA advisory panel reviewed results of the Anthenelli study (above) that suggested the drug does not appear to increase the risk of moderate to severe neuropsychiatric adverse events relative to nicotine patch or placebo, but an FDA medical review team was skeptical of the study. An FDA briefing document noted that "the evidence from the existing observational studies alone is of insufficient quality to either rule in or rule out an increased neuropsychiatric risk associated with either varenicline use or bupropion use" (FDA, 2016).

Authors assessed the effects of behavioral and pharmacologic interventions for the treatment of smokeless tobacco (ST) use in a 2015 systematic review (Ebbert et al., 2015). They obtained evidence from 34 randomized trials enrolling smokeless tobacco users (n = 16,000). Based upon their analyses, authors **suggested** that varenicline and nicotine lozenges appear to increase tobacco abstinence rates among those using smokeless tobacco, but the efficacies of these pharmacotherapies are lower in treatment of those using smokeless tobacco than among cigarette smokers attempting to quit smoking. Nicotine patch and nicotine gum did not increase abstinence. Authors also noted inconclusive evidence for the effect of bupropion SR in the treatment of smokeless tobacco use. From their analyses, authors found that behavioral interventions, including telephone counseling as a component of the intervention, increase tobacco abstinence among users of smokeless tobacco, regardless of whether they are motivated to stop using. Authors **suggested** further research including "placebo-controlled comparisons of different NRT

doses, forms, and durations of therapy," combination therapies using both non-nicotine pharmacotherapy and NRT," and the "influence of different types of ST (e.g., snuff, chew, betel quid) on abstinence outcomes" (Ebbert et al., p. ii).

A 2016 meta-analysis examining whether electronic cigarettes are safe and effective in smoking cessation included two randomized trials involving smokers (n=662) (Hartmann-Boyce et al., 2016). The studies compared electronic cigarettes with placebo electronic cigarettes (lack of nicotine). Researchers found that participants using electronic cigarettes were more likely to have abstained from smoking for at least six months compared with those using the non-nicotine electronic cigarettes. One of the studies also compared electronic cigarettes to nicotine patch and did not find significant differences in six-month abstinence rates. Neither study reported serious adverse events related to the use of the electronic cigarettes; mouth and throat irritation were the most frequent adverse conditions. Researchers noted the need for additional studies due to low quality of overall evidence (Hartmann-Boyce et al., 2016).

Although electronic cigarettes have been advertised as a safe replacement to aid smoking cessation or a supplement to traditional cigarettes, a recent study supported by the National Institutes of Health (NIH) **suggested**, "E-cigarette vapor, both with and without nicotine, is cytotoxic to epithelial cell lines and is a DNA strand break-inducing agent" (Yu et al., 2016). In exposing normal epithelial cells and head and neck cell carcinoma cell lines to nicotine-containing and nicotine-free vapor extract from two e-cigarette brands for up to eight weeks, researchers found cytotoxic effects of e-cigarette vapor mediated through nicotine as well as non-nicotine components. The cytotoxic effects included cellular damage, i.e., increased DNA strand breaks, cell death, and decreased survival in both cell lines independent of nicotine content. Researchers indicated a need for further research "to definitively determine the long-term effects of e-cig usage, as well as whether the DNA damage shown in our study as a result of e-cig exposure will lead to mutations that ultimately result in cancer" (Yu et al., 2016).

A randomized, open-label study evaluated whether the use of electronic cigarettes, either alone or with dual use of conventional cigarettes, significantly reduces exposure to chemicals commonly associated with conventional cigarettes (D'Ruiz et al., 2016). Smokers of conventional cigarettes (n=105) were randomized to one of three groups: exclusive electronic cigarette use group, dual use group, or cessation group. After five days, measurement of blood, urine and toxicants in exhaled breath showed exposures to harmful smoke toxicants were lower in smokers who had either completely or partially replaced their conventional cigarettes with electronic cigarettes. However, researchers cautioned that reduced toxic and carcinogenic smoke does not necessarily reduce risks for chronic, smoking-caused diseases in this population. They noted the need for "epidemiologic or other types of investigations involving long term use populations" (D'Ruiz et al., 2016).

According to the 2013 National Institute of Drug Abuse (NIDA) Monitoring the Future Survey (MFS), the substance abused most frequently and used on a daily basis by high school students since the beginning of the survey in 1975 has been cigarettes. Cigarette smoking rates among teens are at the lowest point in the history of the survey, which began

in 1975. However, the smoking rate has been declining much slower since 2002 in 8th, 10th and 12th graders who are also using other tobacco products, e.g., smokeless tobacco, at high levels. The National Survey on Drug Use and Health (NSDUH) reports that from 2002 to 2013, the rate of past-month cigarette use fell from 13.0 percent to 5.6 percent among 12- to 17-year-olds, and past-month cigarette use by young adults aged 18 to 25 years declined from 40.8 percent to 30.6 percent (SAMHSA, 2014).

In a recent study, researchers compared smoking trends between 2004 and 2011 among individuals with mental illness (n=32,156) and without mental illness (n=133,113) using a nationally representative, non-institutionalized sample of adults from the Medical Expenditure Panel Survey (MEPS) (Cook et al., 2014). Although smoking cessation efforts have led to reduced prevalence of tobacco use among the general population from 2004 to 2011, the decline in smoking was significantly less among those with mental illness. Results found smoking rates declined between 2004 and 2011 for adults without mental illness from 19.5 to 15.6 % while the rates declined from 28.8 % to 27.0 % for those with mental illness. This study further found that individuals receiving treatment for mental illness are both less likely to smoke as well as more likely to quit than those not receiving treatment. Researchers **suggested** that an explanation for the difference in the decline in smoking between the two groups **may** be limited adoption of integrated treatment as well as barriers to smoking cessation treatment in mental health settings. Barriers discussed included: a belief that smoking cessation **may** adversely affect psychiatric treatment; lack of the same cessation opportunities provided to general population; lack of confidence that individuals with mental illness are either willing or able to quit; and the normalized smoking culture in some treatment settings where cigarettes have been provided to psychiatric patients (Cook et al., 2014). Another recent study assessed associations between smoking cessation behaviors, cessation-related social norms, and mental health treatment in adult current smokers (n=18,939) from the 2000, 2005, and 2010 National Health Interview Survey (Shi, 2014). This study found that smokers (n=1,897) who had sought mental health treatment were more likely to quit in the past year as well as more likely to have used cessation aids, e.g., NRT, prescription medication, counseling. Researchers concluded that there is a need for integrative tobacco-control policies and smoking cessation treatments in smokers with severe mental illness (Shi, 2014).

According to our adopted guideline, rates of smoking in patients with schizophrenia are much higher (from 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).

In a study by Williams et al., smokers (n=87) with schizophrenia were randomized to one of two groups receiving nicotine transdermal patch as well as one of two different intensities of behavioral counseling: Treatment of Addiction to Nicotine in Schizophrenia (TANS) or Medications Management (MM). TANS, a high-intensity treatment of 24 sessions (45 minutes) delivered over 26 weeks, incorporated motivational interviewing skills, social skills training, and relapse prevention techniques. MM, a moderate-intensity treatment of 9 sessions (20 minutes) delivered over 26 weeks, focused on smoking cessation including medication compliance and education as well as monitoring psychiatric symptoms and understanding medication interactions with tobacco. No differences in treatment outcomes between lower and higher intensity treatment were found in this comparison of two psychosocial treatments. Results of this study showed that smokers in both groups significantly reduced cigarette use and that clinicians in mental health settings can effectively help smokers with schizophrenia or schizoaffective disorder using individual counseling and NRT (Williams et al., 2010).

A recent randomized, double-blind, placebo-controlled, parallel-group, relapse-prevention clinical trial evaluated the efficacy of 40 weeks of maintenance pharmacotherapy with varenicline and relapse-prevention cognitive behavioral therapy (CBT) in smokers (n=203) with schizophrenia or bipolar disease for the prevention of relapse (Evins et al., 2014). Smokers who attained initial abstinence at week 12 of treatment with varenicline and CBT were randomly assigned to a group receiving one of two treatments from week 12 to 52: maintenance varenicline combined with CBT or placebo combined with CBT. Results showed that maintenance pharmacotherapy with varenicline and CBT improved tobacco abstinence rates compared with placebo and CBT after a year of treatment as well as 6 months after end of treatment in patients with severe mental illness (Evins et al., 2014).

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, 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 Magellan-adopted *APA Guideline Watch 2007* discusses the selective α4β2 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).

On October 24, 2011 the FDA posted an update of Chantix® (varenicline) and its risk of neuropsychiatric adverse events. In this communication, the FDA announced that it had reviewed the results from two FDA-sponsored epidemiological studies that evaluated the risk of neuropsychiatric adverse events associated with varenicline and specified that neither study found a difference in risk of neuropsychiatric hospitalizations between Chantix and nicotine replacement therapy. However, the FDA did not rule out an increased risk of other neuropsychiatric events with varenicline and advised healthcare professionals and patients to continue to follow the recommendations to monitor for neuropsychiatric symptoms when prescribing this drug (FDA 2011).

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). An exploratory pilot study was designed to estimate and characterize neuropsychiatric adverse events (NPAEs) in abstinent smokers treated with varenicline or placebo. Smokers (n=110) with no history of psychiatric illness or unstable medical illness were randomized to receive either varenicline or placebo for a 12-week treatment period. Results of the study showed rates of neuropsychiatric adverse events were not significantly different between treatment groups (Garza et al., 2011).

The results of a meta-analysis of clinical trials comparing patients who received Chantix to those who received a placebo were released by the FDA on December 12, 2012. The results of this study evaluating the cardiovascular safety of the drug noted the following: a higher occurrence of major adverse cardiovascular events in patients using Chantix compared to placebo; the adverse cardiovascular events were uncommon in both groups; and the increased risk in the Chantix group was statistically insignificant. Healthcare professionals were again advised to weigh the risks of Chantix against the benefits of its use (FDA, 2012).

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 that 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).

In a recent double-blind, parallel-arm adaptive treatment study, researchers evaluated a treatment regimen in which smokers (n=606) initially received nicotine patch treatment two weeks before the quit date (Rose and Behm, 2013). In Phase 1 of the study, participants who did not respond adequately to the nicotine patch treatment in the first week were randomly assigned to one of three treatments: nicotine patch, bupropion plus nicotine patch, or varenicline. Abstinence rates during weeks 8-11 after the quit date were significantly higher in the group receiving bupropion augmentation of nicotine patch, compared with nicotine patch only. The change from nicotine patch to varenicline did not result in a significant effect during the same period of time, although point abstinence at 6 months was significantly higher than with the nicotine patch alone. Researchers **suggested** smokers who do not respond adequately to nicotine patch before the quit date can benefit from augmenting nicotine patch treatment with bupropion. In Phase 2 of the study, researchers explored the potential of post-quit date adaptive changes in treatment.

Smokers who responded adequately to the nicotine patch treatment in the first week but who lapsed after the quit date were randomly assigned to one of three treatments: nicotine patch, bupropion plus nicotine patch, or varenicline. Researchers found that postquit adaptive changes in treatment had no significant effects on abstinence outcomes (Rose and Behm, 2013).

A recent randomized, blinded, placebo-controlled clinical trial evaluated the efficacy and safety of combining varenicline and a nicotine patch compared to varenicline alone in smoking cessation (Koegelenberg et al., 2014). Smokers (n=446) were randomized to receive varenicline plus placebo patch or varenicline plus nicotine patch. Nicotine or placebo patch was begun 2 weeks prior to the quit date continuing for another 12 weeks while varenicline was begun 1 week prior to the quit date, continuing for a further 12 weeks, tapering off during week 13. Results showed that varenicline combined with nicotine patch was more effective than varenicline combined with placebo patch in achieving abstinence at both 12 weeks and 6 months (Koegelenberg et al., 2014).

Much of the research on adolescent smoking has focused on psychosocial interventions. In a randomized trial by Gray et al., individual and combined effects of contingency management (CM) along with pharmacological treatments were evaluated. Adolescent smokers (n=134) were randomized into one of four treatment groups (bupropion SR with CM, bupropion SR without CM, placebo with CM, or placebo without CM). Results of this study indicated that combined treatment with bupropion SR and CM is superior to placebo and non-CM during treatment. The researchers suggest that combined treatment **may** also be superior to either bupropion SR or CM alone during treatment. To determine the long-term efficacy of this treatment, further research is needed (Gray et al., 2011).

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 and 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 APA guideline does not address smoking cessation treatments specifically for HIV-infected persons. In an open label, nonrandomized study (n=36), Cui et al. examined the safety and tolerability of varenicline as a smoking cessation aid in persons with HIV. Researchers found that, although adverse events were common, there was no adverse effect on HIV treatment outcome. By comparing results in their study with randomized controlled trials conducted in HIV-negative, generally healthy smokers from published

literature, they found that varenicline was as safe and effective in HIV-infection smokers as in HIV-negative smokers. The researchers concluded that treatment with varenicline, along with appropriate counseling, appears to be both safe and effective for smoking cessation among HIV-infected persons and encouraged further research (Cui et al., 2012).

The APA guideline refers to studies that suggest the efficacy of pharmacotherapy treatment (i.e., bupropion SR) for smoking cessation in users of smokeless tobacco. Since publication of the APA guideline, a study has been published suggesting varenicline **may** also be effective for smokeless tobacco cessation along with an acceptable safety profile (Fagerstrom et al., 2010). In this double blind, placebo controlled, randomized clinical trial conducted in Norway, smokeless tobacco users (n=432) were randomized to varenicline or placebo treatment. At the end of two treatment periods (i.e., 9-12 weeks and 9-26 weeks in length), the continuous abstinence rate was significantly higher in the varenicline group than in the placebo group. Neuropsychiatric adverse events in both treatment groups occurred at the same rate, except for sleep disorder, abnormal dreams, and insomnia, which are known side effects associated with varenicline. Researchers suggested the need for more studies with longer follow-up and including behavioral interventions (Fagerstrom et al., 2010).

Since publication of the APA guideline, researchers have investigated the efficacy of other pharmacological agents (e.g., methylphenidate and atomexetine) typically used in the treatment of attention deficit hyperactivity disorder (ADHD) in smoking cessation. A controlled trial of adult smokers (n=253) with ADHD randomized to receive methylphenidate or placebo had results showing a positive response to methylphenidate relative to placebo among non-white smokers only. Investigators **suggested** that methylphenidate **may** be an effective smoking cessation treatment for a subset of smokers and cautioned that future studies are needed (Covey et al., 2010). Methylphenidate was studied in a randomized, double-blind, placebo-controlled study (n = 80), but results did not support treatment efficacy of this agent in helping non-ADHD smokers stop smoking (Hurt et al., 2011). A randomized, double-blind study measuring the effects of atomoxetine HCL on high risk behaviors, including tobacco use, in adolescents with ADHD (n=267) demonstrated that atomoxetine treatment was associated with significant improvement in high-risk behaviors including smoking. Authors recommended the need for additional larger, prospective, well-controlled studies to better understand the mechanisms for this effect and the complex inter-relationships between high-risk behaviors and the core symptoms of ADHD (Saylor et al., 2010).

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).

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 were 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 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 that the best outcomes are achieved through combined psychosocial and pharmacological therapy. In a study highlighting two potential psychological predictors of abstinence following treatment for nicotine dependence (i.e., self-efficacy to quit and perceived control over withdrawal symptoms), Schnoll et al. analyzed the results of a clinical trial that randomized treatment-seeking smokers to either transdermal nicotine patches or nicotine lozenge along with individual smoking cessation behavioral counseling sessions. Results showed that smokers with a greater increase in self-efficacy to quit smoking and perceived control over withdrawal symptoms were significantly more likely to have quit smoking following behavioral counseling and nicotine replacement therapy (Schnoll et al., 2011).

Since publication of the APA guideline, several studies been published examining various psychosocial treatments for smoking cessation. Hettema and Hendricks conducted a meta-analysis (31 trials; total n=8,165) to examine motivational interviewing (MI) as a treatment for smoking cessation (Hettema, 2010). As a result of these analyses, they concluded that MI outperforms or does as well as other behavioral approaches for the treatment of tobacco dependence among most individuals. Findings included particular promise for individuals residing outside the U.S., smokers with medical co-morbidities, adolescents and

people who are low in motivation. The author **suggested** that although the effects of MI on smoking **may** be small in magnitude, the intervention has the potential to significantly impact public health (Hettema and Hendricks, 2010).

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).

The effectiveness of a social cognitive theory-based intervention (STUB IT), a role-model-based multimedia mobile phone intervention for smoking cessation, was assessed by Whittaker et al. In this clinical trial, participants (n = 226) were randomized to an intervention group receiving video and text messages tailored to self-selected quit date, role models and timing of messages or to a control group which received simple general health video messages via mobile phone. Researchers concluded that the complex video messaging mobile phone intervention did not demonstrate a statistically significantly effect compared with the simple general health video messages via mobile phone. However, the researchers concluded that further investigation is warranted due to the positive feedback about the support obtained by observing the role models in the program (Whittaker et al., 2011).

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 (Ellerbeck 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).

A study by Japuntich et al. examined how nicotine dependence, demographics, and life context are related to the achievement of three smoking-cessation milestones (e.g., achieving initial abstinence, lapse risk, and lapse-relapse transition). Smokers (n = 1504) were randomized to one of six treatment conditions: bupropion SR, nicotine lozenge, nicotine patch, nicotine patch + nicotine lozenge combination therapy, bupropion SR + nicotine lozenge combination, or placebo. The study found that higher nicotine dependence predicted worse outcomes across each of the cessation milestones. Many of the demographic variables (i.e., level of education, marital status, ethnicity, gender, age) and contextual variables (i.e., smoking in the home or at work, number of smokers in the social network, social support, and stress) affected achievement of initial abstinence and lapse, but not the lapse-relapse transition. Only nicotine dependence and gender predicted the risk of transition from lapse to relapse. Japuntich et al. **suggested** increasing the nicotine replacement dose after lapse as a treatment to reduce lapse-relapse transitions and encouraged future research to determine why women are at extra risk of failure at the third milestone. Since demographic and contextual variables seemed to affect initial abstinence and lapse, researchers **suggested** cue avoidance/coping training and intratreatment support (Japuntich et al., 2011).

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 $\geq$ 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).

The APA guideline does not discuss the role of dental hygienists in tobacco control efforts. A study by Studts et al. examined the results of a survey collecting information from practicing dental hygienists (n = 308) regarding their demographic, clinical characteristics and knowledge, attitudes and clinical practices related to tobacco cessation treatment. This study showed that although dental hygienists have opportunities to play a substantive role in smoking cessation treatment, more training in evidence-based tobacco cessation treatment is necessary for them to maximize their impact to reduce smoking (Studts et al., 2011).

The APA guideline reports on studies suggesting no difference in the outcomes of abrupt versus gradual cessation. It also acknowledges that the gradual approach **may** be considered if the patient is historically uninterested or unable to quit smoking. In a randomized, controlled trial on NRT-aided gradual cessation (n = 297) vs. abrupt cessation (n = 299) in smokers actively trying to quit, Hughes et al. unexpectedly found that gradual cessation did not produce higher quit rates than abrupt cessation, even when participants were smokers who wanted to quit gradually. They **suggested** that there is a need for further randomized controlled trials of gradual vs. abrupt cessation (Hughes et al., 2010).

Abstaining from tobacco and nicotine entirely is difficult for many smokers who continue smoking despite the risk of adverse health consequences. Electronic cigarettes (e-cigarettes), introduced into the U.S. market in recent years, are battery operated devices delivering nicotine and flavorings into an aerosol inhaled by the user. These electronic nicotine delivery devices have been marketed as smoking cessation aids although "little is known about the health impact of the product or the extent of its use" (King et al., 2013, p. 1623). A recent study by King et al. assessed the prevalence and correlates of awareness and use of e-cigarettes among U.S. adults (n=6,689 and 4,050 in 2010 and 2011, respectively) using data obtained from the *HealthStyles* survey, a national consumer-based survey of U.S. adults aged ≥ 18 years old. Results showed that awareness of e-cigarettes increased from 2010 to 2011, and ever use of e-cigarettes was significantly higher among current smokers vs. former and never-smokers. Approximately 20 % of current smokers reported having ever used e-cigarettes in 2011 (King et al., 2013).

In an August 25, 2014 press release, the Centers for Disease Control and Prevention (CDC) reported a study showing that more than 263,000 youth who had never smoked a traditional cigarette used e-cigarettes in 2013 (CDC, 2014). This number reflects a three-fold increase from 2011 according to data from 2011, 2012, and 2013 National Youth Tobacco surveys of middle and high school students. An intention to smoke traditional cigarettes was expressed by 43.9 % of those who had used e-cigarettes compared with 21.5 % of those who had never used e-cigarettes. The CDC report also noted evidence that nicotine's effects on brain development of adolescents could result in lasting deficits in cognitive function.

A potential exists for e-cigarettes to cause acute nicotine toxicity (Morbidity and Mortality Weekly Report, 2014). An analysis of data on calls to U.S. poison centers from September 2010 through February 2014 compared the number and characteristics of e-cigarette exposure calls with those of traditional tobacco cigarette exposure calls. In September,

2010, e-cigarette calls accounted for 0.3 % of combined monthly e-cigarette and traditional cigarette exposure calls, and this percentage increased to 41.7 % in February, 2014. The e-cigarette exposures were reported more often as inhalations, eye exposures, and skin exposures compared with ingestions for cigarettes. Adverse health effects in e-cigarette calls were vomiting, nausea and eye irritation. Further, 51.1 % e-cigarette-related exposures were among young children (Morbidity and Mortality Weekly Report, 2014).

In a recent policy statement, the American Heart Association (AHA) cautioned that although e-cigarettes have none or lower levels of potentially harmful constituents compared with cigarettes, their use has the potential to maintain or initiate nicotine addiction, sustain dual use of both e-cigarettes and cigarettes, serve to reinitiate smoking by ex-smokers, and erase gains in smoking cessation. The AHA supports the regulation of e-cigarettes under existing laws relating to the use and marketing of tobacco products. They also advise doctors to encourage patients to quit smoking and use nicotine-replacement products that are approved by the FDA (Bhatnagar et al., 2014).

The FDA currently regulates cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco products. In a FDA News Release on April 24, 2014, the FDA announced its proposed new rule extending its tobacco authority to include additional tobacco products, e.g., e-cigarettes, cigars, pipe tobacco, nicotine gels, waterpipes, and dissolvables in an attempt "to make the next generation tobacco-free" (FDA 2014). Under the proposed rule, provisions applying to newly "deemed" tobacco products would include restrictions to prevent sales to underage youth; health warning labels; and prohibition of vending machine sales in facilities that admit youth. The FDA proposal is expected to correct misperceptions by consumers that e-cigarettes are safe alternatives to traditional cigarettes.

Treatment of Alcohol-Related Disorders

Although highly prevalent, highly disabling, and associated with both physical and psychiatric disorders, alcohol use disorder (AUD) is often untreated, with only approximately 20 percent of those with the disorder seeking treatment (Grant et al., 2015). A 2015 study presenting results from the *National Epidemiologic Survey on Alcohol and Related Conditions III* found significant associations between AUD and other disorders such as major depressive disorder, bipolar disorder, and other substance use disorders. After a review of the data, authors indicated the "urgent need to educate the public and policy makers about AUD and its treatment alternatives, to destigmatize the disorder, and to encourage those who cannot reduce their alcohol consumption on their own, despite substantial harm to themselves and others, to seek treatment" (Grant et al., p. 757).

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) reported in *Medication for the Treatment of Alcohol Use Disorder: A Brief Guide* that medication-assisted treatment (MAT) should be offered on a routine basis to patients with moderate or severe alcohol-related problems (NIAAA/SAMHSA, 2015). The brief guide discussed how alcohol use disorder

continues to be associated with social exclusion, affecting both the patient with the AUD and the healthcare professionals providing care, and it encouraged physicians to recognize that alcohol use disorder is a treatable medical disorder. The brief guide summarized current evidence on the effectiveness of the following medications approved by the Food and Drug Administration (FDA) for treating AUDs: disulfiram, oral naltrexone and extended release injectable formulations, and acamprosate delayed-release tablets. Authors of the guide recommended that a comprehensive treatment approach include counseling and other psychosocial therapies along with participation in Alcoholics Anonymous or other similar programs.

A systematic review and meta-analysis evaluated FDA-approved medications, mostly acamprosate and oral naltrexone, in the treatment of adults with alcohol use disorders in outpatient settings (Jonas et al., 2014). This review included participants (n=22,803) in 122 randomized controlled trials and one cohort study. All of the trials included at least 12 weeks of treatment and included a variety of different psychosocial co-interventions. Evidence was not sufficient to determine whether off-label medications used in some of the trials were associated with reduced consumption, whereas evidence showed an association of topiramate with fewer drinking days, fewer heavy drinking days, and fewer drinks per drinking day. Nalmefene was associated with fewer heavy drinking days per month and drinks per drinking day. The analysis showed an association between valproic acid and improvement in consumption outcomes in a trial including people with bipolar disorder. Evidence was insufficient in determining whether medication treatment is associated with improvement in health outcomes. Researchers concluded that in this review, acamprosate and oral naltrexone (50mg/day) had the best evidence supporting their benefits, with no differences in outcomes established between the two medications. They noted that acamprosate, given three times daily, is less convenient than oral naltrexone, given only once daily. In patients with severe renal impairment, acamprosate is contraindicated and in those with acute hepatitis, liver failure, and concurrent opioid use, oral naltrexone is contraindicated. Researchers reported that no overall reductions in alcohol consumption resulted from the use of disulfiram. They also discussed how primary care providers have historically referred patients with alcohol use disorders for specialized treatment, although not all patients have access or are willing to pursue it. They further discussed how offering treatment through primary care **may** reduce morbidity for many patients. Researchers concluded that "both acamprosate and oral naltrexone (50mg/d) were associated with reduction in return to drinking" and that "moderate evidence supports an association with improvement in some consumption outcomes for nalmefene and topiramate (Jonas et al., 2014).

A recent article reviewed randomized clinical trials in Europe that compared the effects of nalmefene, an opioid antagonist not approved in the U.S. for treating alcohol use disorder, and placebo in patients (n=1697) with high consumption of alcohol, low physical dependence on alcohol, and lack of a need for immediate detoxification or inpatient treatment (Soyka, 2016). Fixed dosing regimens were not required as patients took the drug based on their own needs in a novel "as needed" approach. Alcohol drinking decreased more in the nalmefene groups than in the placebo groups although there was a higher dropout rate in the nalmefene group. Researchers **suggested** that patients with

"high but not excessive mean alcohol consumption" and without severe physical dependence on alcohol benefit from treatment with nalmefine with side effects similar to those with naltrexone treatment, e.g., nausea, headache, and gastrointestinal effects (Soyka, 2016). Naudet et al., in a later review of studies comparing the use of nalmefene to placebo in alcohol treatment, noted that use of a "drug for people who continue to drink (especially if it is ineffective) **may** have seriously detrimental psychological and social implications" (Naudet et al, 2016). Authors noted the "inappropriate comparison with placebo when another treatment was available" and also **suggested** that instead of using alcohol consumption to determine treatment success, mortality and health outcomes, e.g., vehicle crashes, should be used (Naudet et al., 2016).

A recent study sought to uncover new insights about the usefulness of topiramate in the treatment of alcohol use disorders. Authors identified 22 studies including two meta-analyses and eight randomized controlled trials (Guglielmo et al., 2015). This review found beneficial effects of topiramate in the prevention of relapse as well as in reducing drinking behavior. Topiramate significantly reduced the number of drinks per day, the number of drinks per drinking day, the percentage of heavy drinking days and increased the number of abstinent days when compared to placebo. Authors noted that although the results were positive for topiramate, the longest trial was only 14 weeks. Compared to naltrexone, topiramate was more effective, reducing alcohol intake and craving. However, it was not more efficacious than disulfiram. Authors provided caution about the topiramate adverse effects that appeared to be dose related and prominent. These included paresthesia, taste perversion, anorexia, difficulty with concentration/attention, and pruritus. Authors **suggested**, in their conclusions, that "topiramate, in the dosage range of 75-300 mg/day, **might** represent an efficacious and safe pharmacological option for the treatment of AUDs." They acknowledged the lack of evidence about the use of topiramate in alcohol withdrawal syndrome (Guglielmo et al., 2015).

Several herbal remedies have a history of use for the treatment of alcohol use disorders (Liang and Olsen, 2014). In a recent review, authors noted clinical studies suggesting that traditional herbal medications **may** have positive effects in treatment. Although kudzu, hovenia and salvia miltiorrhiza have shown anti-alcohol effects and have been used for many years, especially in China and Korea, authors concluded that "more time and effort are needed to understand the mechanisms and the safety/toxicity and to establish regulatory policies for using natural or other types of herbs" in the treatment of alcohol disorders (Liang and Olsen, 2014). In a later placebo-controlled, double-blind study including participants (n=32) with a self-reported drinking patterns of 15 drinks per week or binge drinking two or more times per week, a single dose of kudzu extract significantly reduced alcohol consumption without noxious side effects (Penetar et al., 2015). Authors concluded, "This study provides additional evidence that an extract of the kudzu root significantly reduces alcohol consumption by human participants and confirms that this botanical medication **may** be a safe and effective adjunct pharmacotherapy for treating alcohol use disorders" (Penetar et al., 2015, p. 10). **Magellan does not recommend the use of kudzu extract for the treatment of alcohol disorders and recommends more studies to determine its effectiveness**.

A 2015 study analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to determine perceived barriers to treatment for alcohol problems (Schuler et al., 2015). The most commonly reported barriers to treatment among participants (n = 11,843), treatment naïve adults with a lifetime alcohol disorder and a perceived treatment need, were attitudinal barriers, e.g., feelings of being strong enough to handle it alone and that the problem will resolve by itself. Authors **suggested** that "interventions to reduce the stigma of alcohol treatment and to increase motivation for behavior change **may** be effective and sufficient for the majority of individuals with perceived treatment barriers. To this end, we endorse the use of Screening, Brief Intervention, and Referral to Treatment (SBIRT) in primary care" (Schuler et al., 2015).

A 2015 double-blind randomized trial examined how cognitive bias modification, including exposure to alcohol-related stimuli and images, affects neural alcohol cue reactivity in inpatients (n=32) with alcohol use disorder, and whether it may reduce alcohol craving and relapse rates (Wiers et al., 2015). Researchers noted that as individuals transition from voluntary to habitual drinking, "alcohol cues engender motivational responses in alcohol-dependent patients, which are triggered relatively automatically" and are involved in craving and relapse. They reported studies showing that the exposure to alcohol cues in patients with alcohol use disorder activates mesolimbic areas of the brain (brain rewards pathways) and **may** result in an impulsive response toward the drug cues. In this study, patients received either cognitive bias modification training or sham training; functional MRI (fMRI) scans measured neural cue reactivity both before and after cognitive bias modification training. The training, an adapted version of the approach-avoidance task, included six sessions over a period of three weeks. In both groups, participants were instructed to push or pull a joystick while viewing alcohol and soft drink cues, depending on whether the cue format was in landscape or portrait format. Pushing the joystick decreased the size of the image while pulling it increased the size of the image. The pushing and pulling of the joystick, decreasing or increasing the size, created a visual impression of avoidance and approach, respectively. In the cognitive bias modification group, participants learned to push away and avoid the cues; they pushed away and pulled 90% and 10%, respectively, of the alcohol cues, while the ratios in the sham group were 50/50. A functional MRI (fMRI) measured neural cue reactivity before and after the training period using the same images. "After the training period, the bias modification training group showed significantly greater reductions in cue reactivity in the amygdala bilaterally as compared to the control group. The difference between activation in the right amygdala before and after training was significantly correlated with the decrease in alcohol craving for the modification bias training group but not for control" (Recovery Research Institute, 2015). Researchers concluded that this study provides evidence that cognitive bias modification reduces alcohol-cue induced mesolimbic brain activity (Wiers et al., 2015). In a review of the Wiers study, Obrien **suggested** that more randomized controlled trials are needed "to determine conclusively whether focusing on the brain does in fact result in improved overall outcomes for patients with alcohol use disorders (O'Brien, 2015).

Another recent study compared the SMART Recovery (SR) program with Overcoming Addictions (OA), both programs based on cognitive behavioral interventions for problem drinkers (et al., 2016). The SR program (a social modality) is an online and in-person

mutual help group, whereas the self-directed OA program is a structured online intervention based on the principles and practices of the SR program. The SR program focuses on the following: motivation for change; managing urges, thoughts, feelings and behavior; and reaching a balanced lifestyle. Its website is a resource serving as a portal for an SR community (encourages meetings), and although SR does not included a formal treatment manual, it provides a workbook including descriptions of SR principles and exercises. The OA program, a self-directed web-based intervention, includes four modules: Building and Maintaining Motivation for Change; Dealing with Urges and Cravings, Self-Managing Thoughts, Behaviors, and Feelings, and Lifestyle Balance for Preventing Relapse. OA can be used as either standalone or as a complement to SR. In this study, heavy drinkers (n=188) were randomized to SR only or to OA + SR. Results showed that participants in both groups, over a six-month follow-up period, significantly increased the percentage of days of abstinence, significantly decreased the number of drinks consumed on drinking days, and also experienced a reduction in alcohol-related problems. However, there was no added benefit of OA over the SR intervention. Researchers noted that the evidence showed that OA **may** be a feasible alternative to SR, with advantages of access, reach and cost-effectiveness, suggesting that "web-based interventions work particularly well for individuals who are actively making changes to their drinking behavior" (Campbell et al., 2016).

A recent literature review of eight studies, including adults (n=1849) using alcohol, examined the efficacy of mobile technology interventions for the treatment of alcohol-dependent and nondependent alcohol users (Fowler et al., 2016). Seven of the studies included either a control or a comparison group. The interventions, delivered through text messages, smartphone applications, and mobile websites, were designed around theoretical frameworks, e.g., Self-Determination Theory, Motivational Interviewing, Cognitive-Behavioral Treatment, Health Belief Model, Theory of Reasoned Action, and Information Motivation Behavior Model. The length of interventions varied from two weeks to 32 weeks. Outcome measures included both behavioral, e.g., reduction in risky drinking days, as well as cognitive measures, e.g., readiness to change. This review found preliminary evidence for the efficacy of mobile technology-based technology while provided caution related to "the dearth of research in this potentially very promising field" (Fowler et al., 2016).

Alcohol use disorders are common and, as noted in the APA guideline, the 12-month prevalence rate for alcohol abuse is 4.65 percent, and 3.61 percent for alcohol dependence. In 2013, nearly one quarter (22.9 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 60.1 million people. The rate in 2013 is similar to the rate in 2012 (23.0 percent).The rate of binge drinking was 43.3 percent among young adults aged 21to 25 years (SAMHSA, 2013). The APA 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). In a later study, Guttmannova et al. examined the association between age at alcohol use onset and adult alcohol misuse and dependence (Guttmannova et al., 2011). Data from this longitudinal study followed students (n=808) from elementary school to adulthood. Results showed that the onset of alcohol use before age 11, when compared with onset during early adolescence, was associated with increased chronicity of adult alcohol dependence. Authors **suggested** the importance of delaying the onset of alcohol use through prevention efforts during elementary school. In addition, the study also found that the onset of regular drinking at any age before 21 years was predictive of later alcohol dependence (Guttmannova et al., 2011).

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, e.g., 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 D_2 receptor availability in the brain (caudate and ventral striatum) in non-alcoholic members of alcoholic families supports the hypothesis that high levels of D_2 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 later open-label controlled study, alcohol dependent participants (n=90) were assigned to either a standard alcohol detoxification group or to a topiramate augmentation group (Paparrigopoulos et al., 2011). Topiramate was found to reduce alcohol craving, as well as symptoms of depression and anxiety, and it helped participants to abstain from drinking during the first 16-week detoxification period (Paparrigopoulos et al., 2011).

In a double-blind, placebo-controlled study of another anticonvulsant drug, zonisamide, alcohol-dependent subjects (n = 40) were randomized to one of two groups: treatment with zonisamide or placebo in a 12-week trial (Arias et al., 2010). Results of the study showed a reduction in heavy drinking days (small effect) and a reduction in number of drinks per week (moderate effect), but no effect of zonisamide on number of abstinent days for the treatment compared to placebo. Researchers **suggested** further studies, both larger and with longer duration of treatment, of zonisamide for the treatment of alcohol dependence, are warranted (Arias et al., 2010).

In a 2010 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).

A recent study reviewed the results of three separate randomized, double-blind, multinational trials investigating the effectiveness of nalmefene, an opioid system modulator approved in the European Union to reduce alcohol consumption, in the treatment of alcohol dependence (Keating, 2013). In two trials, participants (n=1322) were randomized to receive nalmefene 18 mg or placebo for 24 weeks while also taking part in a motivational and adherence-enhancing intervention. In both trials, the number of heavy drinking days from baseline to month 6 decreased significantly more for those receiving treatment with nalmefene. In one of the trials, total alcohol consumption was decreased significantly more for the group receiving nalmefene than for those receiving placebo. In a third trial, participants (n=675) were randomized to receive nalmefene or placebo while also taking part in motivation and adherence-enhancing intervention. Results from this trial showed no significant difference in number of heavy drinking days or total alcohol consumption between those receiving nalmefene and those receiving placebo at month 6. However, at week 52, the number of heavy drinking days from baseline to one year decreased significantly more for those receiving nalmefene while total alcohol consumption was also decreased for this group. This study reported that as-needed nalmefene was well tolerated, with most commonly occurring adverse events including dizziness, nausea and fatigue. The author noted that the achievement of abstinence and prevention or reducing relapse have traditionally been the treatment goals for alcohol-dependent patients. They stressed that a reduction in alcohol consumption reduces harm, the risk of morbidity and mortality. Authors also pointed out that pharmacological treatment should be combined with psychological intervention (Keating, 2013).

A 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 the necessity of further replication of these findings before instituting this protocol in clinical practice for this highly prevalent and difficult-to-treat population of patients (Pettinati et al., 2010).

The APA guideline discusses the possibility of new psychotherapeutic options that may be developed depending on the genetic makeup or genetic etiology of treatment responsiveness of substance use disorders, including alcohol dependence. A recent study demonstrated that the medication, ondansetron, **may** be effective treatment for alcohol-dependent people with certain serotonin transporter gene variants, i.e., LL variant and TT gene variant (Johnson et al., 2011). In this controlled trial, participants (n = 283) were randomly assigned to receive ondansetron or an inactive placebo for 11 weeks, plus standardized cognitive behavioral therapy. Results showed that individuals with the LL genotype who received ondansetron had fewer drinks per day on average and a higher percentage of days abstinent than those who received placebo. Also, participants with the LL genotype had fewer drinks per day and more days without a drink than those without the variant. Researchers concluded that much of the trial and error in prescribing medicine can be eliminated by genetic screening before treatment and that personalized medicine allows clinicians to better predict a successful treatment option (Johnson et al., 2011).

In a later study, Johnson et al. examined polymorphisms in the HTR3A and HTR3B genes which regulate the function and binding of 5-HT_3 to ondansetron (Johnson et al., 2013). Researchers used the same sample including alcohol dependent individuals (n=283) as in the 2011 study. Throughout the three-month treatment period, they examined genetic associations with drinking patterns, identifying three genotypes in the HTR3A and HTR3B genes that were associated with ondansetron treatment response. Researchers assessed the effect of genotype on three alcohol consumption measures: drinks per drinking day, percentage of heavy drinking days, and percentage of days abstinent. Findings showed that individuals carrying polymorphisms in the HTR3A and HTR3B genes had improved outcomes when treated with ondansetron for alcohol dependency. Researchers **suggested** that a combined five-marker genotype panel may help predict whether ondansetron **may** improve improves treatment results in persons with alcohol dependence. They **suggested** further randomized controlled trials to test the replicability of their findings (Johnson et al., 2013).

A more recent study by Kranzler et al. examined the efficacy and tolerability of topiramate in reducing drinking to safe levels in European American heavy drinkers whose goal is the reduction of drinking instead of abstinence (Kranzler et al., 2014). This 12-week study also examined whether the effects of topiramate are moderated by a single nucleotide

polymorphism in GRIK1, thus assisting in the identification of which patients are most likely to respond to topiramate therapy. Heavy drinkers (n=138) were randomized to receive a daily maximum of 200 mg of topiramate or matching placebo while both groups also received brief counseling to reduce drinking and increase abstinent days. Results showed that the patients receiving topiramate reduced heavy drinking days significantly more than those receiving placebo, while also decreasing heavy drinking more rapidly than placebo patients. Patients receiving topiramate reported more abstinent days than those receiving placebo. Researchers noted that a single nucleotide polymorphism (SNP) in GRIK1 (rs2832407) moderated the effects of topiramate on heavy drinking days. They **suggested** further studies to evaluate the effects of topiramate and the moderating effects of rs2832407 in other populations as an effort in the personalization of the pharmacological treatment of heavy drinking (Kranzler et al., 2014).

An earlier clinical trial examined the interaction of age of onset of alcohol use and variation in 5-HTTLPR genotype with the efficacy of sertraline alcohol dependence (Kranzler et al., 2011). In this 12-week placebo-controlled trial, participants (n = 134) were randomly assigned to sertraline treatment or to placebo. Individuals who had late-onset alcohol dependence and who carried the long allele of 5-HTTLPR genotype reported fewer drinking and heavy drinking days when treated with sertraline than those with early onset alcohol dependence. Participants carrying the short allele of 5-HTTLPR had no significant effects of sertraline (Kranzler et al., 2011).

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).

A recent analysis of the 16-week Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study (a multisite controlled study of interventions for alcohol dependence evaluating the individual and combined effects of acamprosate and naltrexone versus placebo, with or without a concurrently delivered behavioral intervention) examined whether pretreatment drinking goals, i.e., reductions in drinking or complete

abstinence, affect treatment outcomes (Dunn and Strain, 2013). In the new study, each of the participants (n=340) from the Combine study who had selected a goal of reducing but not abstaining from drinking was matched with a participant with an abstinent drinking goal, creating a sample of 680 participants. In creating the sample for their study, researchers conducted matching of variables that could affect treatment results: treatment received, gender, and number of pre-baseline heavy drinking days. Results of the analysis showed that participants with an abstinence goal when entering treatment had significantly greater reductions in drinking during the intervention than those who entered treatment with a non-abstinent drinking goal, independent of the treatment condition to which they had been assigned. Researchers **suggested** the need for future studies of the association between drinking goal and outcomes (Dunn and Strain, 2013).

In an unblended randomized controlled trial, researchers explored whether a smartphone-based application could provide effective personalized care for individuals leaving residential treatment for alcohol use disorder (Gustafson et al, 2014). Upon leaving residential treatment, patients (n=349) with alcohol dependence at the time they entered residential treatment were randomized to treatment as usual (TAU) plus a smartphone with "Addiction-Comprehensive Health Enhancement Support System" (A-CHESS) or to TAU alone. A-CHESS, based on self-determination theory, provided monitoring, communication, information and emotional and instrumental services to patients for 8 months with a follow-up period of 4 months whereas TAU offered no coordinated continuing care to patients after discharge. Significantly fewer risky drinking days during the 8 months of the intervention and 4 months of follow-up were reported by those in the A-CHESS group compared to the TAU group. Researchers **suggested** that if other studies confirm this result, smartphone interventions hold promise for the continuing care of alcohol use disorders (Gustafson et al, 2014).

Kelly et al. analyzed data from the National Institute on Alcohol Abuse and Alcoholism initiated *Project Match* (Matching Alcoholism Treatment to Client Heterogeneity) to examine how Alcoholics Anonymous (AA) affects abstinence and recovery. Individuals (n=1,726) with alcohol dependence or abuse participating in a randomized controlled trial were assessed at intake, and at 3, 9 and 15 months to test whether changes in four network variables (i.e., pro-abstinent network ties, pro-drinking network ties, drinking activities, and abstinent activities) **may** help explain AA's success. The analyses showed that AA was associated with significant increases in pro-abstinence social network ties and abstinent activities as well as with significant decreases in pro-drinking social network ties and drinking activities. Researchers **suggested** that AA is able to effectively mobilize adaptive social changes that result in better alcohol use outcomes (Kelly et al., 2011).

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

In a study analyzing data from *National Surveys on Drug Use and Health* from 2002 to 2014, authors found that the use of marijuana increased from 10.4% to 13.3% in adults while the **perceived** harm from using marijuana decreased during the same period from 50.4% to 33.3% (Compton et al., 2016). Authors **suggested** an association between both of these findings and the effects of the gradual legalization of marijuana in several states. However, no increase in marijuana use disorders was found; between 2002 and 2014, the percentage of adults with marijuana use disorders was stable at about 1.5%. Authors urged the targeting of reduction in the perceived harm of using marijuana in future prevention efforts, and **suggested** a need for more education about the risks of smoking marijuana (Compton et al., 2016).

A 2015 review of literature focused on the potential physical and mental adverse effects associated with the non-medicinal use of cannabis, mostly consumed as marijuana, the most widely consumed illegal substance in the world (Hoch et al., 2015). Key messages in their review are:

- Cannabis is the most commonly used illicit drug worldwide.
- Of all cannabis users, 9% become dependent; 17% of those beginning cannabis use in adolescence become dependent; and 25 to 50% of those who consume cannabis daily become dependent.
- Increased risks of various medical conditions, e.g., panic attacks, psychotic symptoms, motor incoordination and nausea, can arise after cannabis use.
- High doses of cannabis over several years or beginning use of cannabis during adolescence can be associated with various disorders of mental and physical health, e.g., substance dependence, cognitive impairment, psychosis, respiratory and cardiovascular conditions.
- THC, the principal psychotropic substance in cannabis, delta-9-tetrahydrocannabinol, has increased in the past 10 years and is thought to be related to the increased risk of cannabis (Hoch et al., 2015).

Authors reviewed 40 meta-analyses and several systematic reviews demonstrating "short interventions (6 to 12 sessions) with combinations of measures to promote motivation, cognitive behavioral therapy, and contingency management (learning via systematic rewards)" as psychotherapeutic interventions having the greatest effect in treatment of cannabis-related disorders. They noted that reducing the frequency and intensity of cannabis consumption is more successful than attempting to achieve abstinence. The U.S. Food and Drug Administration (FDA) has not approved any pharmaceuticals for the treatment of cannabis disorder, although drugs, e.g., gabapentin, benzodiazepines, and sedative antipsychotics, treat severe withdrawal symptoms. Psychoses or panic attacks **may** be treated with antipsychotics, or benzodiazepines and sedative antipsychotics, respectively (Hoch et al., 2015).

A recent systematic review assessed the evidence of the effectiveness of psychosocial and psychological interventions for cannabis cessation in adults (Chatters et al., 2016). Researchers presented the definition of cannabis dependence by the International Classification of Disorders as "a cluster of physiological, behavioral, and cognitive phenomena in which the use of cannabis takes on a much higher priority for a given individual than other behaviors that once had greater value" (Chatters et al., p. 93). When ascertaining if a user is dependent or just a frequent user, researchers noted quantity of cannabis consumed per day and the level of harm sustained are the most important factors. This review included 25 randomized controlled trials measuring the effect of intervention(s) on cannabis usage:

- Ten studies assessing Cognitive Behavioral therapy (CBT) vs. wait-list, motivational interviewing (MI), or another intervention
- Five studies assessing contingency management (CM) vs. CBT or another intervention
- Nine studies assessing MI vs. wait-list or another intervention
- One study assessing web-based counseling.

Outcome measures of the effect of the intervention on cannabis usage were cannabis usage, severity of dependence, number of dependence symptoms, and number of cannabis problems via self-report, number of cannabis related problems, or session attendance. Results showed that CBT significantly improved short-term outcomes compared with wait-list at post-treatment in half of the studies and at nine months in one study with later follow-up. CBT over long courses showed improvement over shorter MI. Researchers concluded, despite a disparate evidence base, that CBT improved outcomes, although the long-term effect of the intervention is unknown. Brief MI showed improved outcomes at post-treatment not sustained in the long term. Combined with CBT, CM enhanced long-term outcomes (Chatters et al., 2016).

Another study, utilizing The Cochrane Database of Systematic Reviews, evaluated the efficacy of psychosocial interventions for cannabis disorders (Sabioni et al., 2016). It included 23 randomized controlled trials involving adults (n=4045) in outpatient or

community settings. CBT and motivational enhancement therapy (MET) were effective in reducing the frequency of cannabis use, quantity used per occasion, and severity of dependence. In improving cannabis-related problems, CBT and MET were not more effective than no treatment. The most effective treatments for cannabis disorders were high intensity interventions, particularly MET combined with CBT, of more than four sessions and those longer than one month. Researchers **suggested** that CM combined with CBT or with MET + CBT improved both cannabis use frequency and severity of dependence (Sabioni et al., 2016).

A recent randomized controlled trial compared the efficacy of a web-based self-help intervention, Can Reduce, alone or in combination with individual brief chat counseling sessions based on MI and CBT approaches in the treatment of problematic cannabis use (Schaub et al., 2015). The study also included a third arm, a classical waiting list. Outcome measures included the recorded quantity of cannabis use in the previous seven days (primary outcome measure) along with secondary outcome measures based on outcome instruments, e.g., the Cannabis Use Disorders Identification Test (CUDIT), Severity of Dependence Scale (SDS), Cannabis Withdrawal Scale (CWS), and the Cannabis Craving Symptoms questionnaire (CCS-7). Assessments were at baseline and at three-month follow-up. Results showed that participants randomized to Can Reduce with chat group reduced their frequency of cannabis use more than the Can Reduce without chat and the wait list groups. At follow-up, abstinence was higher in the group receiving the additional chat counseling. Not all participants in the self-help with chat group actually chose to receive a chat session, and interestingly, even they had greater reduction in the frequency of cannabis use than participants in the group receiving self-help without chat sessions. Researchers referred to the Supportive Accountability model and **suggested** knowledge of a possibility to have a chat appointment improved this outcome. However, participants in the self-help with chat group who actually received at least one chat counseling session reduced use of cannabis more than participants of the same group who did not receive chat counseling. Researchers related this to "expecting better outcomes due to a reciprocal relationship, through which the patient can derive explicit benefits" (Schaub et al, p. 12). For patients not seeking outpatient addiction counseling services for reasons such as the fear of stigmatization, researchers concluded that brief chat counseling in addition to web-based self-help **may** reduce cannabis use in problematic cannabis users.

The APA guideline indicates that marijuana, as the most widely used illicit drug in the U.S. and in the world, is not a benign substance as widely believed, and is associated with a number of psychological, behavioral and social problems. From 2007 to 2013, the number of past months users aged 12 and older increased from 14.4 million (5.8 %) to 19.8 million (7.5 %). In 2013, 8.1 million persons used marijuana on 20 or more days in the past month compared to 5.1 million persons in 2005 to 2007. Marijuana was used by 80.6 % of current illicit drug users in 2013 (SAMHSA, 2014).

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).

As the landscape regarding the legalization of marijuana for both medical and recreational purposes rapidly shifts, recent attention has focused on the harmfulness of marijuana. A recent comprehensive review by Volkow et al. provided an overview, based on data from 77 studies and literature reviews, of the adverse effects of cannabis use (Volkov et al., 2013). Authors pointed to evidence indicating that long-term marijuana use can lead to addiction. The DSM-5 recognizes that an abrupt cessation of use of marijuana **may** result in the onset of cannabis withdrawal syndrome, including symptoms, e.g., anxiety, anger or aggression, depressed mood, irritability (APA, 2013). Authors noted special concerns of marijuana use during adolescence, due to its negative effect on the functional connectivity of the brain, reporting the finding of an association between significant declines in intelligence quotient (IQ). Also reported were studies finding that marijuana use was related to mental illness, e.g., psychoses; measurable and long-lasting cognitive impairments; and impaired driving ability. Effects on health were discussed, suggesting the possibility of a positive association between marijuana smoking and cancer. Another health concern noted was the association between marijuana smoking and inflammation of the large airways. Vascular conditions increasing the risks of myocardial infarction, stroke and transient ischemic attacks have also been associated with marijuana use. However, authors noted the complexity of the actual mechanisms underlying the effects of marijuana on the cardiovascular and cerebrovascular systems. Volkov et al. noted that the potency of marijuana has been increasing steadily, raising concerns that adverse effects of marijuana use may be worse now than in the past and raised questions about the current relevance of the findings of older studies assessing long-term outcomes. Referring to the report by the Institute of Medicine, Marijuana and Medicine (Joy et al., 1999), Volkov et al. noted the importance of research efforts focusing on the therapeutic potential of synthetic or pharmaceutically pure cannabinoids. They noted that as legal status of marijuana allows

for more widespread exposure, its use will increase along with the number of persons with negative health consequences (Volkov et al. 2014).

A recent integrative meta-analysis investigated the association between the maximum frequency of cannabis use before age 17 years and developmental outcomes, i.e., high-school completion, university degree earned, cannabis dependence, other illicit drug use, suicide attempt, depression, and welfare dependence, assessed up to age 30 years (Silins et al., 2014). Researchers integrated data from participants (n=2537 to n=3765, varying by outcome), in three large, long-running longitudinal studies from Australia and New Zealand. Findings showed that daily users before age 17 had reduced odds of completing high school along with increased odds of later marijuana dependence, other illicit drug use, and suicide attempts when compared with individuals who never used marijuana. Researchers **suggested** that the prevention or delay of marijuana use in adolescence **may** have broad health and social benefits (Silins et al, 2014).

Based on a time-series analysis of state laws establishing access to medical cannabis and state-level death certificate data in the U.S. from 1999 to 2010, researchers concluded that the laws were associated with lower rates of opioid overdose mortality in each year after implementation of the law (Bachhuber et al., 2014). They **suggested** further studies are needed to substantiate their findings before advocating for medical cannabis laws to reduce the risk of opioid analgesics. In another recent article, Kleber and DuPont discussed the current effort spreading the legalization of medical marijuana and cautioned that medical marijuana has not been approved by the FDA and is not a purified product available with prescriptions in pharmacies. Authors supported distribution of drugs through licensed pharmacies (rather than marijuana dispensaries) and encouraged support of the U.S.'s science-based drug approval system (Kleber and DuPont, 2012).

The APA guideline does not recommend any specific pharmacotherapies for marijuana withdrawal or dependence. In a randomized, double-blind, controlled clinical trial evaluating agonist substitution pharmacotherapy in cannabis-dependent adults (n = 156), Levin et al. found that dronabinol, a synthetic form of a naturally occurring pharmacologically active component of marijuana, was superior to placebo in promoting retention in treatment and reducing withdrawal symptoms. However, there was no evidence that dronabinol was superior to placebo in improvement of abstinence. Researchers **suggested** future trials to include higher doses of dronabinol or combinations of dronabinol and other medications (Levin et al., 2011).

In another study, researchers examined whether treatment with N-acetylcysteine, combined with contingency management and brief weekly cessation counseling, is associated with higher rates of abstinence in treatment-seeking cannabis-dependent adolescents than placebo combined with the same contingency management intervention and brief weekly cessation counseling (Gray et al., 2012). In this 8-week double-blind randomized controlled trial, cannabis-dependence adolescents (n=116) were randomized to receive either N-acetylcysteine 1200 mg or placebo twice daily. Both groups also included contingency management and brief weekly cessation counseling. This study found that participants receiving N-acetylcysteine had more than double the odds of negative

urine cannabinoid tests during the treatment period compared to those receiving placebo. In addition, N-acetylcysteine was well tolerated. Researchers **suggested** further studies to confirm the findings, suggesting that the positive effects of N-acetylcysteine **may** also be a potential medication for treatment of other substance use disorder (modulation of glutamate or other mechanisms) (Gray et al., 2012)

The APA guideline discusses psychosocial treatments for marijuana dependence, indicating that, in general, existing trials consistently support the efficacy of cognitive-behavioral relapse prevention group therapy, social support group treatment, contingency management therapies, motivational individualized assessment and intervention, and motivation enhancement therapy (MET). A study by Buckner and Carroll examined the impact of anxiety on marijuana treatment, using data from a large randomized trial (Marijuana Treatment Project) in which marijuana users (n = 450) were randomly assigned to one of three groups: MET alone, MET combined with CBT, or delayed treatment. Researchers found that reduction in anxiety during the course of the 9-month study was associated with reduction in marijuana problems and less marijuana use at 4- and 9-month follow-up, particularly in the MET combined with CBT condition. Researchers **suggested** that the preferred treatment for marijuana dependence, especially among patients with high levels of anxiety, **may** be CBT-MET (Buckner and Carroll, 2010).

In a recent multi-site, controlled trial, treatment-seeking individuals (n=279) with cannabis use disorder were randomized to an Active Treatment or a Delayed Treatment, both of which included ten 90-minute sessions of fully manualized individual psychotherapy combining CBT, motivational enhancement therapy and problem-solving training spanning a period from eight to twelve weeks (Hoch et al., 2014). Patients in the Delayed Treatment group were required to wait eight weeks before the beginning of treatment. The rate of negative urine screenings increased from 11.7 % at baseline to 46.3 % at post treatment in the Active Treatment group compared to an increase from 9.3 % to 17.7 % in the Delayed Treatment group. Researchers noted the growth of computer-assisted interventions for cannabis use disorders, but highlighted the value of in-person interventions in traditional outpatient treatment settings. They **suggested** that computer-delivered interventions will not become a total substitute for the in-person interventions of a live clinician (Hoch et al., 2014).

Treatment of Cocaine-Related Disorders

The FDA has not approved any clearly effective pharmacotherapies for the treatment of cocaine use disorder. However, studies have found three categories of promising categories of drugs for reducing cocaine use: dopaminergic agents, e.g., levodopa-carbidopa, dextroamphetamine, and lisdexamfetamine; noradrenergic agents, e.g., disulfiram, doxazosin, and nepicastat; and drugs with mixed mechanism agents, e.g., modafinal. A recent article discussed combined medication-behavioral treatment as a promising approach for treating cocaine and cannabis use disorders (Dakwar and Nunes, 2016). Authors conceptualized medications for SUDs, including cocaine, as “facilitating specific behavioral interventions, rather than as standalone interventions” (Dekwar and Nunes, p.

62). They reported studies showing that dopaminergic agents, e.g., levodopa-carbidopa, **may** enhance contingency management and help promote abstinence in cocaine-dependent individuals. Authors reported a study finding that cocaine-dependent individuals receiving combined slow-release amphetamine treatment and relapse prevention therapy including cognitive behavioral therapy exhibited higher rates of abstinence than those receiving combined relapse prevention therapy and placebo. They **suggested** a need for further studies to test whether the benefit of the drug was dependent on the behavioral treatment. Authors emphasized the importance of finding which type of behavioral interventions **may** "synergize best with the medication" (Dekwar and Nunes, 2016).

A recent randomized, double blind, placebo-controlled parallel group study evaluated lisdexamfetamine (LDX) in treatment of cocaine dependent individuals (n=43) (Mooney et al., 2015). Previous studies **suggested** that LDX may have less abuse potential than amphetamine. In this study, participants received either placebo or LDX (70 mg/day) along with a manual-based cognitive behavioral therapy emphasizing relapse prevention and coping skills provided one hour each week during the 14-week intervention. Although those receiving LDX reported significantly less craving for cocaine than those receiving placebo, no differences in cocaine use rates were found between LDX and placebo-treated individuals. Researchers noted that LDX was generally safe and well tolerated, although the LDX group reported higher rates of diarrhea, headaches, and anxiety compared to the placebo group. They concluded, "Whether LDX, or any agonist-like strategy **may** realistically be considered for development and receive regulatory approval for stimulant use disorders remains to be determined" (Mooney et al., p. 103).

Based on the results of an eight-week, double blind, placebo-controlled trial of modafinil for the treatment of cocaine dependence without co-morbid alcohol dependence, researchers concluded that modafinal **may** be an efficacious treatment for cocaine dependence (Kampman et al., 2015). In this study, individuals with cocaine dependence (n=94) received either 300 mg of modafinil or placebo daily combined with weekly individual therapy. Researchers noted that previous studies have shown that modafinal **may** reduce cocaine withdrawal symptoms and reduce the high associated with cocaine use by blocking the dopamine transporter. Cocaine use measured by self-report and confirmed by twice- weekly urine tests was the primary outcome measure. Results showed that individuals who received modafinal were significantly more likely to be abstinent from cocaine during the last three weeks of the trial and reported significantly lower levels of both craving intensity and duration. Researchers concluded that modafinal **may** be effective for a large number of cocaine-dependent patients, especially in those without comorbid alcohol dependence (Kampman et al., 2015).

A recent Cochrane Database Systematic Review discussed the use of antipsychotic medications for cocaine dependence (Indave et al., 2016). Authors discussed how the use of cocaine and dependence is associated with problems for both individual and public health, including medical, psychological, and social problems. Using cocaine is associated with the spread of AIDS, hepatitis, and tuberculosis as well as crime, violence and neonatal drug exposure. Cocaine can also induce hallucination and paranoia. This review included 14

randomized trials involving individuals with cocaine dependence (n= 719). Trials randomizing participants to receive a single drug versus placebo or versus another drug included risperidone, quetiapine, lamotrigine, olanzapine, haloperidol, olanzapine, aripiprazol, ropirinol, and placebo. Results showed no evidence supporting the clinical use of antipsychotic medications in the treatment of cocaine dependence (Indave, 2016).

Cocaine use and abuse of methamphetamine are significant public health problems in the United States. According to 2013 NSDUH data, there were 1.5 million current cocaine users aged 12 or older, or 0.6 percent of the population. These estimates were similar to the numbers and rates in 2009 to 2012 (1.4 million to 1.7 million, or 0.5 to 0.7 percent) but were lower than the estimates in 2002 to 2007 (2.0 million to 2.4 million, or 0.8 to 1.0 percent).

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 that 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 (succinylnorcocaine) to treat cocaine dependence revealed that attaining high ($\geq$ 43 μg/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).

The APA guideline discusses how individuals with bipolar disorder are at high risk for a co-occurring SUD and cautions that although lamotrigine **may** be used as a first-line pharmacological treatment, it should be used cautiously in patients who have both bipolar and SUD. The guideline specifies that these individuals may be inclined to take excess medication doses, thereby increasing the risk of rash. Recent studies, cited by Brown et al., noted the potential of lamotrigine as both a standard treatment for bipolar disorder and for reducing the use of cocaine (Brown et al., 2012). They conducted a randomized, double-blind, controlled study to determine the impact of lamotrigine therapy on cocaine use and craving, as well as manic and depressive symptoms. Adult outpatients with bipolar disorder, depressed or mixed mood state, and cocaine dependence (n = 112) were randomized to one of two conditions: lamotrigine treatment or placebo. Lamotrigine therapy was initiated at 25 mg/day and was slowly increased until at 5 weeks it reached 200 mg/day after which additional increases were made if well tolerated. Outcome measures of this study were dollars spent on cocaine and weekly urine drug screens. The

study found that during treatment with lamotrigine, the amount of money spent on cocaine (by participant report) was significantly decreased when compared with placebo. The percentage of cocaine-positive urines was smaller with lamotrigine than with placebo, although not significantly. Researchers reported that side effects were not different in the treatment groups and lamotrigine was well tolerated. They concluded that standard treatment (lamotrigine) for bipolar disorder **may** reduce cocaine use and **suggested** additional research with lamotrigine using a larger patient sample as well as more frequent urine drug screens (Brown et al., 2012).

A range of general medical conditions are associated with cocaine use. 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).

In a published clinical review focused on pharmacotherapies for dependence, Haile et al. concluded that there is evidence that medications acting on dopamine, norepinephrine, and glutamate neurotransmitter systems show promise in the treatment of cocaine dependence (Haile et al., 2012). These medications include modafinil, n-acetylcysteine, disulfiram, prazosin/doxazosin, sustained-release AMPH/METH, and methylphenidate. The APA guideline discusses disulfiram as a medication that **may** increase the aversive effects of cocaine, thereby reducing its use. The authors **suggested** the need for further research based upon the characterization of cocaine dependence as a brain disease with biologically identifiable pathologies and they stressed the need to develop efficacious treatments by using medications that reverse known neurochemical imbalances (Haile et al., 2012). Newton et al. assessed the impact of the treatment of a prototypical α_1R antagonist, doxazosin, on cocaine's effects using a double-blind, placebo controlled design, in cocaine dependent people (n=16). Positive subjective effects of cocaine were weakened by the doxazosin treatment. The researchers concluded that medications that block noradrenergic

α_1R receptors, e.g., doxazosin, should be further evaluated as they **may** be useful for cocaine dependence (Newton et al., 2012).

A double-blind, randomized, placebo-controlled, 12-week trial was recently conducted to determine the efficacy of topiramate as a treatment for cocaine dependence (Johnson et al, 2013). Cocaine-dependent adults (n=142) were randomized to one of two treatment groups: topiramate in escalating doses from 50 mg/d to 300 mg/d in weeks 6 to 12 or matching placebo capsules. Treatment in each group was combined with weekly cognitive-behavioral treatment. During the treatment period, participants in each group provided information on self-reported cocaine use and had their urine tested for cocaine's primary metabolite. Cocaine craving was measured on the Brief Substance Craving Scale while global functioning was measured with the Clinical Global Impression Scales. Compared with placebo, topiramate was more efficacious at increasing the weekly proportion of cocaine nonuse days, and was associated with increasing the likelihood of urinary cocaine-free weeks, decreasing craving, and improving global functioning significantly more than placebo. Researchers concluded that the data is promising as a building block from which topiramate **may** be established as an efficacious pharmacological treatment for cocaine dependence (Johnson et al., 2013).

A systematic review of randomized controlled trials (n=8) was performed to compare the effectiveness of cognitive-behavioral therapy (CBT) and contingency management (CM) for cocaine dependence (Farronato et al., 2013). In this review, researchers also examined whether the combination of CBT and CM results in additive effects. Findings showed that CM reduced cocaine use during active treatment and was superior to CBT alone. It was effective also in maintaining abstinence. CBT did not show measurable cocaine reduction during active treatment in trials, although sleeper effects were seen in some studies with a positive effect emerging post-treatment. Three of the trials found no additive effects of CM combined with CBT while two trials reported synergistic effects of the combination of CM and CBT. Authors **suggested** implementation of CM procedures in standard clinical treatment of patients with cocaine dependence, and that future studies address ethical concerns, e.g., CM procedures potentially associated with gambling behaviors (Farronato et al., 2013).

Treatment of Opioid-Related Disorders

The recent increase in misuse of prescription analgesics, e.g., hydrocodone and oxycodone; the easy accessibility of affordable opioids such as heroin; and the opioid overdose epidemic underscore the importance of preventing the abuse of prescription painkillers as well as understanding best treatments for opioid-use disorders. The clinical course of opioid-use disorder is much like that of other chronic relapsing conditions, e.g., diabetes and hypertension, where control of symptoms is difficult and treatment adherence **may** be incomplete. Opioid use disorder is associated with early death from accidental overdose, trauma suicide, or infectious disease (Schuckit, 2016).

Deaths from drug overdose are the leading cause of injury death in the U.S., having risen steadily over the past twenty years (Department of Health and Human Services [HHS], 2015). Deaths related to opioid analgesics nearly quadrupled from 1999 to 2013, and deaths related to heroin increased by 39% between 2012 and 2013. While people who initiated abuse of opioids in the 1960s initiated with heroin, 75% of those who began abusing opioids in the 2000s initiated their abuse with prescription opioids. A shift to heroin use is related to heroin's easy accessibility as well as to its being cheaper, easier to inhale/inject, and its greater potency than prescription opioids (HHS, 2015). Overdose and death significantly increase with extended release/long-acting (ER/LA) formulations of prescription opioids. Overdose deaths also link to the combination of prescription opioids with other prescriptions drugs, e.g., benzodiazepines.

The Secretary of the U.S. Department of Health and Human Services (HHS) has targeted three priority areas to combat opioid abuse: 1) "opioid prescribing practices to reduce opioid use disorders and overdose; 2) expanded use and distribution of naloxone; and 3) expansion of medication-assisted treatment (MAT) to reduce opioid use disorders and overdose" (HHS, 2015).

"The Centers for Disease Control and Prevention's (CDC) Guideline for ***Prescribing*** Opioids for Chronic Pain include the following recommendations:

- Non-opioid therapy is preferred for treatment of chronic pain; consider opioid therapy only if benefits are anticipated to outweigh risks; combine opioids with nonpharmacologic therapy and non-opioid pharmacologic therapy as appropriate;
- Before beginning treatment, establish treatment goals with patients and consider how opioids will be discontinued;
- Discuss with patients known risks and benefits and responsibilities for managing therapy;
- Prescribe immediate-release opioids instead of extended-release/long-acting opioids when starting therapy for chronic pain;
- Prescribe lowest effective dosage when starting opioids; reassess before increasing dosage;
- When prescribed for acute pain, prescribe lowest effective dose of immediate-release opioids and no greater quantity than needed (three or fewer days often sufficient);
- Evaluate benefits and harms of continued opioid therapy within 1-4 weeks of starting opioid therapy and evaluate every three months or more;
- Before initiating therapy and during continuation of opioid therapy, evaluate risk factors for opioid related harms;
- Review patient's history of controlled substance prescriptions when starting opioid therapy and periodically during therapy;
- Use urine drug testing before beginning opioid therapy and at least annually;
- Avoid prescribing combined opioid pain medication and benzodiazepines whenever possible; and

- Offer/arrange medication-assisted treatment with buprenorphine, methadone, or extended-release injectable naltrexone, in combination with counseling and behavioral therapies for patients with opioid user disorder (CDC, 2015).

FDA approved and encourages the use of naloxone delivery systems, e.g., auto-injectors, for lay use outside of healthcare settings to reverse overdose from both prescription opioids and heroin. Naloxone reverses the effects of other opioids and can restore normal respiration when breathing has slowed due to heroin or prescription opioid overdose (FDA, 2014).

Prescription opioids are the second most commonly initiated drugs, second only to marijuana (Brady et al., 2016). Recently, the Office of National Drug Control Policy expanded the National Drug Control Strategy by including the following recommendations:

- Educating patients as well as providers about risks associated with misuse and abuse of opioids;
- Enhancing Prescription Drug Monitoring Programs (PDMP) that are state run;
- Increasing proper disposal of prescription drugs; and
- Addressing enforcement to prevent diversion via doctor shopping and "pill mills" (Brady et al., 2016).

Brady et al. advised that all patients receive screening for potential risk of abuse prior to starting opioid therapy, as well as education about safe use, storage, and disposal of opioid medications. Monitoring on a regular basis **may** identify escalation of opioid use; any negative impact on the patients' ability to function at work, home, and in social settings; and the existence of aberrant behaviors during therapy (Brady et al., 2016). ***The Collaborative Care Model of integrating mental health services within primary care services*** *may* ***facilitate the implementation of these steps to decrease prescription opioid abuse and misuse.***

A 2015 study reviewed the evidence for medication-assisted treatment (MAT) of opioid use disorder (Connery, 2015). Authors noted that the recommended treatment of an individual with opioid use disorder and physiological dependence includes one of the FDA-approved medications, i.e., buprenorphine, naltrexone, and methadone, for preventing opioid relapse and for stabilization/maintenance treatment of opioid use disorder. The approved medications should be prescribed as a part of a comprehensive treatment approach including counseling and other behavioral therapies delivered by a psychiatrist, psychologist, or professional counselor. The American Society of Addiction Medicine emphasized that the patient and the clinician share in the choice of treatment option (ASAM, 2015).

Connery noted that the strongest evidence for efficacy in both reducing opioid use and retaining patients in care is for agonist treatment, with methadone maintenance considered the gold standard of care for many years (Connery, 2015). In a review of randomized controlled trials comparing tolerability and convenience of MAT, author noted

that an adverse effect of full agonist methadone is dose-dependent respiratory depression, whereas the partial agonist buprenorphine has a "ceiling effect" on respiratory depression and does not induce euphoria in opioid-tolerant individuals. Buprenorphine reduces opioid withdrawal symptoms and decreases pleasurable effects of other opioids. Trials found comparatively weak evidence for antagonist naltrexone extended release (ER). Patient convenience for dosing was most burdensome with programs prescribing methadone or buprenorphine maintenance, with required observed daily dosing in early phases of recovery, while monthly injections of naltrexone ER or monthly maintenance visits with office-based buprenorphine/naloxone were least burdensome. Compared to placebo or no medication, all three FDA-approved medications showed improved retention in treatment in trials. Methadone demonstrated higher rates of treatment retention compared to buprenorphine. Data in studies cited by Connery also suggest that buprenorphine, methadone, and naltrexone ER, are important in preventing accidental opioid-overdose death during active treatment. MAT added to relapse-prevention counseling and mutual help groups, e.g., Narcotics Anonymous, increased the effectiveness of those interventions (Connery, 2015). Studies have shown that longer term, abstinence-based residential treatment not including MAT has limited effectiveness, with increased risk of fatal overdose.

On Nov. 18, 2015, the FDA approved Narcan nasal spray, the first approved nasal spray version of naloxone hydrochloride, to temporarily stop or reverse the effects of an opioid overdose (FDA, 2015). Narcan nasal spray, administered by first responders, medical professionals, family members, or caregivers, can counter overdose effects quickly, usually within two minutes, saving many lives. This user-friendly, needle-free delivery system, when used as directed, delivers a consistent and measured dose. Although the FDA has not approved an over-the-counter version of this nasal spray, many state regulations allow pharmacies to provide the nasal spray from pharmacy counters under collaborative practice agreements between the pharmacy and practitioners/physicians/prescribers (Regulatory Affairs Professionals Society, 2016).

On May 26, 2016, the FDA approved the first buprenorphine implant, Probuphine® for the maintenance treatment of opioid dependence (FDA, 2016). This drug, as an implant under the skin on the inside of the upper arm, provides a constant, low-level dose of buprenorphine over six months in patients already stable on low-to-moderate doses of other forms of buprenorphine in a treatment program. This new, innovative treatment option provides improved convenience as patients gain control of their lives, no longer needing to take medication on a daily basis. The director of the National Institute on Drug Abuse at the National Institutes of Health said, "Scientific evidence **suggests** that maintenance treatment with these medications in the context of behavioral treatment and recovery support are more effective in the treatment of opioid use disorder than short-term detoxification programs aimed at abstinence. This product will expand the treatment alternatives available to people suffering from an opioid use disorder" (FDA, 2016). An unpublished randomized clinical trial demonstrated the safety and efficacy of Probuphine in the treatment of adults (n=177) with opioid dependence. Common side effects included implant-site discomfort, headache, depression, constipation, nausea, vomiting, back pain, toothache and oropharyngeal pain. Of the Probuphine-treated patients, 63% had no

evidence of illicit opioid use throughout the six months of treatment compared to 64 percent of those using sublingual buprenorphine. The FDA announcement included a boxed warning with safety information that included a warning about the risk of implant migration, protrusion, expulsion and nerve damage associated with insertion and removal of Probuphine. A potential for accidental exposure or intentional misuse and abuse occurs if the implant comes out of the skin (FDA, 2016). The FDA advises that patients should be seen at least once monthly for continued counseling and psychosocial support in addition to a visit during the first week after insertion.

On June 6, 2014, the FDA approved Bunavail®, a buccal film formulation of buprenorphine/naloxone for the maintenance treatment of opioid dependence (FDA, 2014). The manufacturer of Bunavail claimed that the product is more convenient to administer than the earlier approved sublingual tablet and film formulation (Suboxone) of the same combination and that it is better absorbed into the blood, permitting lower doses of use. Findings from a 23-week, open-label, uncontrolled trial including opioid-dependent individuals (n=249) previously stabilized on Suboxone, showed that the buccal film "appeared to be efficacious in maintenance treatment of opioid dependence, but 52 patients withdrew before the end of the study" (The Medical Letter, 2015). The Medical Letter concluded that this new form of buprenorphine/naloxone permits lower doses, but establishment of its clinical advantages, e.g., lower incidence of constipation, has not been evidenced in well controlled clinical trials (The Medical Letter, 2015).

A rule by the Health and Human Services Department, published in the Federal Register on July 8, 2016 (Medication Assisted Treatment for Opioid Use Disorders Reporting Requirements), authorizes eligible practitioners to request approval to treat up to 275 patients in an office-based setting with buprenorphine and the combination buprenorphine/naloxone (Federal Register, 2016). This rule thus increases access to MAT in the office-based setting. It requires that practitioners provide information about their patient caseload by month, including the number of patients receiving behavioral health services and the number referred to behavioral health services. This is "to ensure that patients receive the full array of services that comprise evidence-based MAT and minimize the risk that the medications provided for treatment are misused or diverted" (Federal Register, 2016). The features of the practitioner's diversion control plan must also be provided.

A 2015 double-blind, placebo-controlled randomized clinical evaluated the efficacy of clonidine as an adjuvant to buprenorphine in increasing the duration of abstinence, time to opioid lapse and relapse, and percent opioid-negative urine tests (Kowalczk et al., 2015). Opioid-dependent patients (n=208) began sublingual buprenorphine maintenance treatment (8-24 mg/day) at enrollment and continued for up to 28 weeks at an outpatient research clinic; individual counseling was provide once a week. At 7 weeks, participants (n=118) who were abstinent from illicit opioids during weeks 5 and 6 were randomly assigned to receive either clonidine or placebo concurrent with the daily dose of buprenorphine. (Note: those who did not meet abstinence were switched to methadone for 4 weeks after which they received an 8-week medication taper, or transferred to a community treatment program). The clonidine schedule included 0.1 mg for 7 days, 0.2 mg

for the next 7 days, and 0.3 from weeks 9 through 20. During the intervention period from weeks 9-20, participants, most of whom completed this phase, were maintained on a stable dose of buprenorphine along with either daily clonidine or placebo. The maintenance phase was from weeks 21-28 during which the clonidine dosage was tapered to zero over the first 14 days and at the end of week 28, buprenorphine dosages were tapered over another 8 weeks, or patients transferred to another treatment program. Results showed duration of consecutive days of abstinence for opioids during the intervention phase were 34.8 days and 25.5 days for the clonidine group and the placebo group, respectively. Secondary outcomes measures showed that during the intervention phase, the clonidine group was more likely to test negative for THC although there was no significant difference in percentage of cannabis smokers at baseline in each group. No group difference in cocaine use was found during the intervention phase. Researchers noted that the longer duration of consecutive days of abstinence for opioids in the group receiving clonidine has important implication, suggesting that "the longer the duration of abstinence, the greater the likelihood that it will be sustained" (Kowalczk et al., p. 764). They also noted that findings support clonidine's ability to increase participants' mean durations of abstinence. The study also found that participants in the clonidine group were less likely to report heroin craving at moderately high levels of stress than the placebo group. Researchers concluded that the study demonstrates efficacy of clonidine for relapse prevention in treatment-seeking opioid users and that it is "modestly effective in decoupling stress from lapses" (Kowalczk et al., p. 764).

According to SAMHSA, "Medication-assisted treatment has shown much promise in reducing nonmedical use of opioids and restoring patients to a healthier life" (SAMHSA, 2015). SAMHSA further noted that evidence and consensus among experts support the use of MAT in primary care settings, particularly for individuals unable to access treatment in specialized settings (SAMHSA, 2015).

In a systematic review which summarized 55 articles, authors focused on comparisons of medications and behavioral therapies to identify factors associated with high rates of retention in MAT for opiate dependence (Timko, 2016). Retention, a primary outcome in treating opiate dependence, is associated with the achievement of decreased drug use, improved social functioning and quality of life, and reduced mortality. Findings included the following: patients receiving naltrexone or buprenorphine had better retention rates than those receiving no medication or a placebo; patients receiving methadone were more likely to be retained in MAT at 4- and 6-month follow-ups than those receiving buprenorphine/naloxone; and heroin-assisted treatment was associated with better retention than methadone among patients who were treatment refractory. Studies also found that contingency management (CM) was the only behavioral therapy showing promise to increase retention in MAT for opiate dependence, although it does not address the underlying causes of addiction. Authors concluded the need for additional randomized controlled trials addressing longer-term association between medications and behavioral therapies (greater than one year) and outcomes (Timko, 2016).

Although only a small percentage of those both seeking and needing treatment for substance use disorders receive MAT treatment, the trend for its use in medical or

psychiatric practice settings is increasing. Barriers to utilization of MAT include reluctance of patients to take medications, side effects of medication, and costs. Due to a belief that "one is simply transferring addiction from one drug to another," both substance abuse and MAT retain a negative social stigma (Magellan, 2016). More education on evidence-based MAT protocols for treatment providers are needed to address preconceived notions of their ineffectiveness and to address reduction in patient motivation to comply with behavioral treatments and counseling programs. More time devoted to patient management while employing MAT protocols in this population is likely to reduce the possibility of relapse and/or readmission to an inpatient/residential rehabilitation program (Magellan, 2016). Current research has shown that the best treatment is at the least intensive level of care that manages the patient safely and comfortably and where the patient can be engaged in continued treatment leading to a sustained recovery from addiction. MAT can promote return to the community, employment and full contribution to society (Magellan, 2016).

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 dependence on opioids for non-medical use. In addition, the 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 2013 NSDUH reports that 517,000 persons had heroin dependence or abuse in 2013, similar to the numbers in 2009 to 2012 (361,000 to 467,000), while it was higher that the numbers in 2002-2008 (189,000 to 324,000). The percentage of persons with heroin dependence or abuse in 2013 was 0.2 percent, similar to the rates in 2006 and in 2009 to 2012 (from 0.1 to 0.2 percent). It was higher than the rate of 0.1 percent in 2002 through 2005, 2007 and 2008. The report shows the number of heroin users during the month preceding the survey increased from 266,000 in 2002 to 289,000 in 2013. The percentage of persons aged 12 and older who used prescription-type psychotherapeutic drugs nonmedically in the past month (2.5 %) was lower than the percentages in 2006, 2007, and 2009 (2.8 to 2.9 %), while it was similar to percentages in the all the other years from 2002 to 2012 (2.4 to 2.7 percent) (SAMHSA 2014).

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 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 (e.g., fentanyl and oxycodone) to abusers. Finally, Paulozzi cites alarming data from several recent reports (e.g., 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). According to the Centers for Disease Control Fact Sheet (CDC, October 17, 2014), drug overdose deaths have increased in the U.S. each year since 1979, with prescription opioid analgesics, cocaine, and heroin most commonly involved. This report indicates that drug overdose death rates in the U.S. increased threefold from 1990 to 2008 and the number of annual deaths increased to 41,502 in 2012. Pharmaceutical drugs were involved in about 53% of the drug overdose deaths (22,114). Of these, opioid pain relievers or prescription painkillers were involved in about 72 % of the deaths, and 30% involved benzodiazepines. The CDC recommended that public health agencies implement community-based opioid drug overdose prevention programs, including training and providing naloxone to address the high rates of opioid drug overdose deaths (CDC, 2012). Gil Kerlikowske, the director of the Office of National Drug Control Policy (DNDCP), responded to the data in the 2012 NSDUH by stating that "we actively support programs that encourage the use of naloxone among first responders" (CDC, 2014).

On April 3, 2014, the FDA approved Evzio (naloxone hydrochloride injection), a new hand-held auto-injector to reverse opioid overdose. This prescription treatment, designed to be given by family members or caregivers, is intended for the emergency treatment of known or suspected opioid overdose characterized by decreased breathing or heart rate, or loss of consciousness. The injection rapidly delivers a dose of the drug, standard treatment for overdose (FDA, 2014).

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).

Prescription opioid analgesics have gained acceptance as effective treatments for moderate-to-severe chronic non-cancer pain (Gudin, 2012). Along with greater prescription opioid utilization, Gudin discussed the parallel increase in misuse, abuse, and overdose that are associated with all opioid analgesics. The author focused on the multi-agency federal effort to address this growing problem which resulted in a risk evaluation and mitigation strategy (REMS) for extended-release (ER) and long-acting opioid medications (Gudin, 2012). The goal of REMS is to address the growing problem of prescription drug abuse and misuse by ensuring that healthcare professionals are educated to safely prescribe opioids and patients learn how to safely use the drugs. On July 9, 2012 the Food and Drug Administration announced its approval of the final REMS for opioid analgesics, including the following key components: (1) training for prescribers (voluntary prescriber continuing education supported financially by manufacturers and based on an FDA blueprint; patient education and counseling of patients by prescribers including how to recognize evidence of, and the potential for, opioid misuse, abuse, and addiction); (2) updated Medication Guide and counseling document (including consumer-friendly information on the safe use, storage and disposal of opioids, instructions on when to consult the physician, signs of potential overdose and advice on safe storage); and (3) periodic assessment/auditing of the implementation of the REMS and the success of the program in meeting its goals. REMS does not require that prescribers take the training; however, mandatory training programs on responsible opioid prescribing are a part of a comprehensive plan to address the epidemic of prescription drug abuse requiring legislative changes that are currently being pursued (FDA 2012).

The FDA, in recognition of both the importance of opioid analgesics in the management of modern pain and the abuse and misuse of these products, has worked to address these problems through REMS (Department of Health and Human Services, 2013). On September 10, 2013, the FDA announced safety labeling changes for all extended-release and long acting (ER/LA) opioid analgesics used to treat pain, indicating that these drugs should be reserved for use in patients for whom other treatment options are ineffective, not tolerated or otherwise inadequate in providing sufficient management of pain. It states that ER/LA drugs are indicated only when the pain is severe enough to require "daily, around-the-clock, long-term opioid treatment" (FDA, 2013). The FDA determined that the original formulation of OxyContin (Oxycodone hydrochloride) extended-release tablets was withdrawn from the market for safety reasons. They also determined that the reformulated version of OxyContin has abuse-deterrent properties. New labeling approved by the FDA on April 16, 2013 indicates that the properties of the reformulated version, both physical and chemical, make abuse via injection as well as intranasal route difficult. Another extended-release long acting opioid analgesic with recent FDA-approved labeling describing the product's abuse-deterrent properties is Targiniq ER (oxycodone hydrochloride and

naloxone hydrochloride) tablets (FDA, 2014). It should be prescribed only when alternative treatment options are ineffective, not tolerated or would otherwise not be adequate for sufficient pain management. A third extended-release opioid analgesic, Embeda (morphine sulfate and naltrexone hydrochloride) was approved by the FDA on October 17, 2014 with labeling describing its abuse-deterrent properties (FDA, 2014). Embeda, like Targiniq and OxyContin, is not approved for as-needed pain relief and should be used only when alternative treatment options are not effective, tolerated, nor adequate to provide sufficient pain management.

On October 25, 2013, the FDA approved Zohydro ER (hydrocodone bitartrate extended-release capsules) for management of severe pain (FDA, 2013). Zohydro ER is part of the extended release/long acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy. Olsen and Sharfstein noted how physicians are recognizing chronic pain and writing prescriptions for opioids more now than in the past, with a 10-fold increase in number of prescription written since 1990 (Olsen and Sharfstein, 2014). They also pointed to evidence that a path to addiction for some individuals may have started with a prescription for pain that progressed to heroin, and indicated that the rate of overdose deaths in the United States has more than tripled since 1990. Olsen and Sharfstein noted how FDA approval of the Zohydro ER capsule, without features to deter crushing and injecting, has resulted in a backlash against the drug by state officials who have asked the FDA to revoke its approval or make it harder to crush. They reported that the FDA has attempted to address the risks of addiction and overdose, e.g., relabeling prescription opioids with new warning as well as narrower indications and is encouraging development of effective non-opioid treatments for pain. Olsen and Sharfstein call for SAMHSA to provide guidance on the concurrent treatment of chronic pain and addiction among patients, e.g., providing guidance to physicians on appropriate ways of using methadone or buprenorphine to treat opioid disorder and chronic pain (Olsen and Sharfstein, 2014).

On August 21, 2014 the U.S. Drug Enforcement Administration (DEA) published a rule that moved hydrocodone combination products such as Vicodin to Schedule II (highest potential for harm) from Schedule III (less potential for harm), pointing out that adding a nonnarcotic substance such as acetaminophen to hydrocodone does not diminish its potential for abuse (DEA, 2014). On November 20, 2014, the FDA approved Hysingla ER, an extended-release, single-entity hydrocodone product with abuse deterrent properties, to treat pain severe enough to require long-term opioid treatment and for which there are no alternative treatment options. Properties of this product reduce abuse of the drug as it is difficult to crush, break, or dissolve as well as being difficult to prepare for injection (FDA, 2014).

In discussing the current prescription drug abuse and misuse problem, Volkow et al. noted that “a key driver of the overdose epidemic is underlying substance-use disorder” (Volkow et al., 2014). Authors discussed three types of medication-assisted therapies (MAT) used in treating patients with opioid addiction: methadone, buprenorphine, and naltrexone, noting that they are underutilized although considered safe, cost-effective, and reduce the risk of overdose. Authors reported the findings of a recent study that found an association between the decrease in number of fatal overdoses and the availability of methadone and

buprenorphine. Authors concluded by presenting essential steps for physicians in preventing prescription overdoses: the reduction of unnecessary or excessive opioid prescribing; routinely checking data from prescription-drug-monitoring programs to identify misusers of opioids; and utilization of MATs for persons with opioid addiction (Volkov el al., 2013).

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 that the standard intervention (Bickel et al., 2008).

The efficacy of intensive role induction (IRI) in the transitioning of opioid-dependent patients from detoxification to long-term treatment was evaluated in a study where patients (n=240) admitted to a buprenorphine detoxification were randomized to one of three treatment groups: (1) standard treatment (ST) including once weekly individual counseling services; (2) intensive role induction (IRI) including counseling focused on psycho-education about detoxification which emphasizes the value of continuing in treatment beyond detoxification; and (3) IRI plus case management (CM) including assistance from counselors in accessing community resources to support recovery efforts (Katz et al., 2011). Patients receiving IRI were more likely to complete detoxification, had more positive connection to their counselors, and continued treatment for a longer period following detoxification than participants receiving ST. IRI plus CM did not have the same effect; it was no more effective than ST treatment. This finding conflicted with the expectations of researchers, who **suggested** that the task of implementing two different interventions within the same counseling session **may** have reduced the quality of treatment and undermined the effectiveness of both interventions. Researchers concluded that IRI, readily adopted by counselor staff and easily integrated into routine treatment, is effective in enhancing patient involvement in detoxification and in long-term treatment following detoxification (Katz et al., 2011).

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 detoxification 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).

Secondary analyses of the above study of opioid-dependent youth (n = 152) were performed to identify factors, both baseline and during treatment, related to treatment success (Subramaniam et al., 2011). This study found that opioid-dependent youth with advanced illness who presented with previous 30-day injection drug use and more active medical/psychiatric problems were less likely to have a week-12 opioid positive urine. Researchers **suggested** that association between injection drug use/distressing psychiatric problems at treatment entry and better outcomes **may** be explained by increased motivation to get out of a downward spiral that consumed so much energy in obtaining and using drugs. Another finding showed that youth who received early treatment opioid abstinence, received ancillary treatments to augment study treatment, and remained in treatment for the full 12 weeks, were more likely to have lower rates of week-12 opioid positive urine. Researchers **suggested** that these findings **may** help to facilitate tailored treatments for opioid-dependent youth and that future studies are needed to replicate these findings (Subramaniam et al., 2011).

Additional 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 at a dose of 13.2 μg/kg/day in three divided doses 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). Researchers reported on a follow-up pilot study to optimize the dose of sublingual buprenorphine in neonates (Kraft et al., 2011). In this open-label, active-control clinical trial, infants (n=24) were randomized to one of two groups: treatment with sublingual buprenorphine (15.9 μg/kg/day in 3 divided doses) or treatment with morphine (0.4 μg/kg/day in 6 divided doses). Findings from this study showed that buprenorphine at an optimized dose was safe and effective and was associated with a 40% reduction in length of treatment and a 24% reduction in length of hospital stay. Researchers concluded that while this study indicated that buprenorphine has a therapeutic advantage over morphine, these results need to be verified in a double-blind clinical trial (Kraft et al., 2011).

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 (IM) 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). Since this study did not examine how the absence of regularly scheduled counseling during the 120 days affected treatment retention or reductions in illicit drug use, this investigator conducted an extension of his prior study of IM. Opioid-dependent adults (n=230) were randomly assigned to IM, standard methadone treatment (SM), or "restored" methadone treatment (RM), defined as standard methadone treatment with a counselor who has a reduced caseload. Researchers found that all three groups showed improvement in outcome measures, e.g., treatment retention, reductions in illicit drug and self-reported illegal activities, with results not favoring the counseling conditions. Although no evidence was found indicating that the IM participants were disadvantaged during the 4-month period in which only emergency counseling was available, the researchers cautioned that the amount of counseling patients received in SM and RM treatment was minimal and acknowledged that counseling or other psychosocial services are not without value in methadone treatment programs (Schwartz et al., 2011).

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).

More recently, Weiss et al. evaluated the efficacy of brief and extended buprenorphine-naloxone treatment, with different counseling intensities, in a randomized controlled trial conducted by the National Institute on Drug Abuse Clinical Trials Network (Weiss et al., 2011). Brief treatment included 2-week buprenorphine-naloxone stabilization, 2-week taper, and 8-week postmedication follow-up whereas extended treatment included 12-week buprenorphine-naloxone treatment, 4-week taper, and 8-week postmedication follow-up. Patients (n=653) were randomized to standard medical management (SMM) or SMM plus opioid dependence counseling and all patients received buprenorphine-naloxone treatment for prescription opioid dependence. Patients receiving SMM received counseling by physicians certified to prescribe buprenorphine while those receiving opioid dependence counseling in addition to SMM received counseling by trained substance abuse or mental health professionals covering coping with high-risk situations, managing emotions and dealing with relationships. Patients receiving extended treatment had a much higher rate of successful outcomes than those who had been tapered off the medication. The addition of opioid dependence counseling did not improve the outcomes. Researchers **suggested** that patients can be successfully treated using buprenorphine-naloxone with brief and extended weekly medical management visits. They also **suggested** that contingency management or some other alternative model of behavioral intervention might improve outcomes (Weiss et al., 2011).

In a recent article, authors reviewed the literature surrounding the use of buprenorphine-naloxone (Suboxone® and Zubsolv®) treatment in an inpatient or ambulatory setting for

acute detoxification and opioid substitution in patients with a mild-to-moderate dependence on opioids (Mauger et al., 2014). They found that, compared to methadone, buprenorphine-naloxone has a lower abuse potential, allows for more flexibility, and carries less stigma. In their review of studies, authors found that a buprenorphine-naloxone treatment combined with psychosocial counseling, prevention education, and recovery-support services was significantly superior in reducing dropout rates, decreasing relapses, and improving treatment compliance. Studies also found that although a buprenorphine-naloxone combination can be used for induction in most all patients, those who are either pregnant or on long-acting opioids such as methadone should be induced with buprenorphine monotherapy. However, authors cautioned that transitioning from methadone to buprenorphine **may** induce significant withdrawal during the induction procedure requiring a gradual tapering of the methadone dose prior to discontinuing methadone. Authors noted that buprenorphine-naloxone is the only office-based maintenance treatment for patients with opioid disorders, and that in the U.S. and Canada, a training program should be completed by physicians who wish to prescribe the treatment (Mauger et al., 2014).

In a recent study, patients (n=220) actively using heroin were treated with Suboxone during hospitalization and, upon discharge, were followed as outpatients for maintenance treatment and counseling (Sittambalam et al., 2014). Marketed as an office-based treatment option for prescription opioid abuse, researchers found that this drug has potential as an alternative to methadone. Hospitalization and emergency room visit rates for all 220 patients decreased by 45 and 23%, respectively, as compared to the year prior to beginning of treatment. Other findings included a decrease in legal charges for drug possession in the year after starting treatment, and increased quality of life, as perceived by the patient. Researchers emphasized that counseling should be made a mandatory part of treatment with Suboxone, allowing for treatment of mental and emotional aspects of heroin addiction. They also noted that other factors, e.g., other addictions, mental health issues, affect the course of treatment for heroin addiction, necessitating the need for individually tailoring treatment to the patient (Sittambalam et al., 2014).

Another recent study, a retrospective chart review of patients (n=356) who received buprenorphine for 6-month treatment of opioid dependence, investigated the primary care patient characteristics of completion of 6-month buprenorphine treatment (Neumann et al., 2013). Almost 75% of the patients abused prescription opioids rather than heroin. Results of this review showed that both counseling attendance, primarily on-site, and a past physical injury were associated with completion of the 6-month treatment. Authors **suggested** that patients with a past physical injury **may** have been more motivated to complete buprenorphine for its analgesic effects. They concluded that in a primary care office, buprenorphine treatment combined with counseling **may** be most effective in treating patients with opioid dependence, recommending combination of behavior and medical management of opioid addiction and chronic pain in a primary care setting (Neumann et al., 2013).

A recent article reviewed several meta-analyses or systematic reviews (n=7) and individual studies (n=19), most of which were randomized controlled trials, of the use of

buprenorphine maintenance treatment (BMT) as an alternative to methadone maintenance treatment (MMT) for opioid use disorders (Thomas et al., 2014). This review showed BMT to be as effective as MMT in reducing illicit opioid use, although MMT showed better treatment retention. However, BMT was associated with less risk of adverse events. BMT also was shown to be as effective in reducing illicit opioid use among pregnant women, and its use led to less neonatal abstinence syndrome than with MMT. Authors **suggested** due to the limited access to MMT as well as its more restrictive safety profile, BMT should be considered for the long-term management of opioid use disorders (Thomas et al., 2014).

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). Designating the regimen 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 non-opioid 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). In a later study, these investigators stressed the importance of using craving scores as a clinical assessment tool, and **suggested** the use of self-reported craving as an indicator of risk of relapse (Hulse et al., 2010).

In a study presented by Mannelli at the 43rd Annual Medical-Scientific Conference of the American Society of Addiction Medicine (ASAM), patients (n=174), of whom 83% were nicotine dependent, were randomized to sites that allowed or prohibited smoking during treatment. Comparisons of the two groups showed that patients who smoked during treatment had higher craving for opioids and cigarettes than those who did not smoke during treatment. Smokers also had lower detoxification completion rates and higher smoking rates in the week after discharge when compared with patients who did not smoke. The research **suggested** that stopping smoking during methadone detoxification **may** cut down on opioid withdrawal, craving, and relapse (Mannelli 2012).

Two studies focused on cardiac complications resulting from the use of methadone, levomethadyl acetate (LAAM; now off the U.S. market) 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 second½ 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 LAAM or methadone, and **may** be a safe alternative (Wedam et al., 2007).

In 2007, the Substance Abuse and Mental Health Services Administration convened an independent expert panel on the cardiac effects of methadone to evaluate the available evidence and make recommendations to enhance the cardiac safety of patients in opioid

programs (SAMHSA, 2009; Krantz et al., 2009). Based on a review of literature, this consensus panel acknowledged that oral and intravenous methadone is associated with QTc interval prolongation and torsade de pointes (Krantz et al., 2009). After reviews and discussions, in 2009 the panel concluded that methadone is effective and its benefits exceed its risks. However, the potential for QT prolongation must be recognized, patients must receive ECG screening at indicated intervals, and appropriate clinical action must be taken in the presence of significant QT prolongation (Martin et al., 2011). The panel members agreed that opioid treatment programs should have a cardiac risk management plan incorporating clinical assessment, ECG assessment, risk stratification, and drug interactions. The following conclusions of the panel provide general guidance to assist clinicians in developing cardiac safety standards for methadone induction and maintenance treatment:

1. Patients should be informed of arrhythmia risk when they are prescribed methadone.
2. Patients should be asked about any history of structural heart disease, arrhythmia, and syncope before being prescribed methadone.
3. A baseline ECG at the time of admission should be performed on all patients to measure the QTc interval.
4. A follow-up ECG within 30 days of admission should be performed **only** on patients with significant risk factors for QT prolongation.
5. Additional ECGs should be performed annually or if the methadone dosage exceeds 120 mg/day.
6. If the QTc interval is greater than 450 ms but less than 500 ms, potential risks and benefits should be discussed with patients and they should be monitored more frequently. If the QTc interval exceeds 500 ms, consider: (1) discontinuing or reducing the methadone dose; (2) eliminating contributing factors, such as drugs that promote hypokalemia; or (3) using an alternative therapy.
7. Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone (Krantz et al., 2009; Martin et al., 2011).

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). A later analysis, by Oviedo-Joekes, used data from the same randomized controlled trial to investigate treatment response and retention by gender, finding that medically prescribed diacetylmorphine is more effective than oral methadone among both long-term opioid dependent men and women who have not benefitted from previous treatment attempts. The researchers found that men receiving diacetylmorphine showed greater improvement than women who presented more vulnerabilities (e.g., higher rates of reported sexual and physical abuse, HIV and HCV infections, suicide attempts, sex work, cocaine use and less employment) than men at the beginning of the study (Oviedo-Joekes et al., 2010). Another study by Oviedo-Joekes et al. compared the effectiveness and safety of injectable hydromorphone and diacetylmorphine in the treatment of patients (n=140) with severe opioid addiction and found no differences. They **suggested** that hydromorphone **may** be a more feasible alternative than diacetylmorphine in the treatment due to less stigma and fewer regulatory barriers (Oviedo-Joekes et al., 2010). Marchand et al. analyzed data from a randomized controlled trial (n=232) comparing the effectiveness of oral methadone vs. injectable diacetylmorphine and found higher satisfaction among long-term chronic opioid users who received injectable diacetylmorphine (Marchand et al., 2011).

In a randomized, double-blind, placebo-controlled study in China, 216 patients with heroin addiction and acute heroin withdrawal syndrome were assigned to one of three treatment groups: 5μg tetrodotoxin (TTX), 10 μg TTX, or placebo to determine the efficacy and safety of TTX in the treatment of acute heroin withdrawal syndrome. TTX, extracted from the puffer fish, is a sodium channel blocker showing potential as an effective agent in detoxification as it produces no physical dependence and no withdrawal symptoms. This trial showed that TTX was effective in controlling opiate withdrawal symptoms and there was no significant difference in the incidence of adverse events among the three groups. The researchers **suggested** the need for further studies to confirm the findings (Song et al., 2011).

The APA guideline stresses that after achieving a stable dose of opioid agonist, 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). In a 12-week trial, patients receiving buprenorphine were assigned to one of two groups: physician management with weekly buprenorphine dispensing; or physician management and directly observed, thrice-weekly buprenorphine and cognitive behavioral therapy. Researchers found that CBT session attendance was associated with greater abstinence the following week and that the number of sessions was associated with improved outcome. Authors **suggested** that additional research to evaluate the

independent effect of directly observed medication and cognitive behavioral counseling is needed (Moore et al., 2011).

The more recent published meta-analytic review by Amato et al. evaluated psychosocial treatments (i.e., contingency management approaches, counseling and family therapy) combined with pharmacological treatments (buprenorphine and methadone) versus pharmacological treatments alone for opioid detoxification. Review of eleven controlled studies (n = 1,592) produced evidence that psychosocial treatments combined with pharmacological detoxification treatments reduced dropouts, use of opiates, and clinical absences during the treatment compared to pharmacological treatment alone (Amato et al., 2011). Another parallel review by these investigators of 35 randomized trials (n = 4,319) addressed whether a specific psychosocial treatment adds benefit to agonist maintenance treatments alone for the treatment of opioid dependence. These studies considered 13 different psychosocial interventions (e.g., behavioral, psychoanalytic oriented, counseling, other) and three pharmacological maintenance treatments: methadone, buprenorphine and LAAM. Based on a review of these studies, the authors concluded that adding specific psychosocial treatments to standard maintenance treatment does not add any additional benefits (i.e., treatment retention, abstinence, compliance, psychiatric symptoms, depression). To explain the difference in results between outcomes demonstrated in detoxification versus maintenance treatment, the authors emphasized that standard maintenance treatment routinely uses additional counseling, which is not typically included with detoxification. In addition, patients undergoing detoxification are less stable and have more psychological issues. Therefore, investigators **suggested** that further research should focus on measuring differences in clinical outcomes for specific, structured psychosocial interventions compared to standard psychosocial support that is typically integrated into comprehensive opioid maintenance treatment programs (Amato et al., 2011).

The Statement of the American Society of Addiction Medicine (ASAM) Consensus Panel on the Use of Buprenorphine in Office-Based Treatment of Opioid Addiction developed the following summarized recommendations: 1) medication-assisted therapies, e.g., buprenorphine, are more effective than other types of treatment for opioid dependence, especially when used along with psychosocial interventions; 2) pharmacotherapy must take place over an extended period of time to achieve management of the underlying disorder; 3) therapeutic outcomes for patients who select office-based buprenorphine treatment are comparable to those seen in patients treated with methadone programs; 4) there are few absolute contraindications to the use of buprenorphine; 5) a targeted assessment of every patient is important to confirm that the provider can meet the needs of the patient; 6) patients must be assessed for biopsychosocial needs in addition to opioid use/addiction; 7) buprenorphine/naloxone combination is preferred to the monoproduct in the absence of contraindications; 8) patients should be informed of potential for drug interactions; 9) physicians must obtain knowledge of applicable practice standards and guidelines before using buprenorphine to treat patients; and 10) physicians treating patients with buprenorphine must engage in continued medical education about medication-assisted therapies, included buprenorphine (Kraus et al., 2011).

ASAM supports "improving prescribing education, diversion control and expansion of qualified buprenorphine treatment providers nationwide" and is in favor of an "expansion of prescribing limit for qualified addiction treatment providers" (ASAM, 2014). The organization notes that this expansion "will have an immediate, positive impact on expanding opioid addiction patient access to a clinically and cost effective addiction pharmacotherapy." According to ASAM, "every day, in fact every 19 minutes, an American dies from an unintentional drug overdose. This epidemic is compounded by the vast gap in access to opioid addiction treatment. This does not have to be our patients' realities."

New legislation has been introduced in the U.S. to expand treatment for heroin and prescription drug addiction. The Recovery Enhancement for Addiction Treatment Act (S. 2645, TREAT Act) would increase the number of patients that can be provided access to medication-assisted treatments, lifting federal restrictions that currently limit access to life-saving therapies. It will lift the buprenorphine prescribing limit for addiction physician specialists and non-specialist providers, improving patient access to medications that treat opioid addiction. The legislation is endorsed by both the American Medical Association and the American Society for Addiction Medicine (American Society of Addiction Medicine, 2014).

Novel Drugs of Abuse

Novel or atypical drugs have become more popular over the past few years in the U.S., posing difficulties for healthcare providers in diagnosis and treatment. A recent article, including a review of literature on new classes of drugs of abuse, discussed the pharmacology and both clinical and adverse effects of these new psychoactive substances (Rech et al, 2015). Although law enforcement agencies have rendered the most common synthetic cannabinoids and cathinones illegal, they are widely advertised in gas stations as well as on the internet and marketed as "legal highs" (Rech et al., 2015). Authors noted that there is no current tracking or reporting on many new illicit drugs of abuse, making it difficult to understand how their use negatively affects society.

Synthetic cathinones, derived from the active stimulant in the khat plant and often referred to as "bath salts," produce stimulant effects, e.g., euphoria, increased energy, openness, empathy, alertness, and increased libido (Rech et al., 2015). They are available at low cost as white or light brown powder, pills, or capsules, with doses ranging from a few milligrams to more than one gram. Sold as names, e.g., Khat, Bath Salts, Meow, MCAT, Ivory Wave, Bubbles, Vanilla Sky, Cloud 9, Explosion, and White Lightning, they have a "glamour aura" (Karila et al, 2015). Some of the most common synthetic cathinones are Mephedrone, Methylone, MDPH, Ethylone, Butylone, Buphedrone, and Pentedrone. The most common routes of administration are snorting and oral ingestion. Other routes sometimes include "bombing" (powder wrapped in cigarette paper and swallowed) and "keying" (snorting powder off the surface of a key). Poison centers have reported common findings of agitation, confusion, hallucinations, tachycardia, hypertension, tremor and fever; more serious effects of the use of synthetic cathinones include electrolyte abnormalities, seizures, "excited delirium," renal failure, and death. A physical withdrawal syndrome may

occur in cyclic binge users. Authors reported that intoxication from these agents may be suspected when patients show acute onset altered mental status, excited delirium, renal failure, and sympathomimetic symptoms (Rech et al., 2015).

The National Institute on Drug Abuse has issued a warning about the abuse of flakka, a dangerous synthetic cathinone similar to "bath salts" which may be snorted, injected, vaporized or eaten. This designer drug, with its use surging in the U.S., presents a risk of easy overdose, as it enters the bloodstream very quickly when vaporized in an e-cigarette. It may cause "excited delirium" involving paranoia, hallucinations, and hyperstimulation. Deaths by suicide as well as by heart attack have been linked to its use. Additionally, it has been reported to dangerously raise body temperature leading to kidney damage or failure (NIH, 2016).

Synthetic cannabinoids, similar to synthetic cathinones, are also widely available, and increasing in popularity, especially among adolescents. Marketed frequently in foil packets marked "not for human consumption," these cannabinoids have methods of administration including inhalation, ingestion, and injection. Containing the active ingredient in marijuana, Tetrahydrocannabinol (THC), they produce similar psychotropic effects, e.g., euphoria and alteration in mood and sensorium, as marijuana (Rech et al., 2015). Abuse of synthetic cannabinoids is increasing every year and the agents are multiplying in number, with hundreds of combinations developed. The most reported adverse events are psychosis and anxiety; others include paranoia, hallucinations, seizures and sedation. Nausea, vomiting and acute kidney injury **may** also result from use. Rech et al reported no long-term effects of synthetic cannabinoids.

Kemp et al. advised that synthetic cannabinoids should not be confused with marijuana/cannabis, as they are a "collection of numerous laboratory chemicals that interact with the cannabinoid receptor in the brain to mimic marijuana to induce a marijuana-like high" (Kemp et al., 2016). Street names for synthetic cannabinoids include Spice, Spice Gold, Spice Diamond, Spice Silver, K2, Krypton, Aztec Fire, Bombay Blue, Fake Weed, and Yucatan Fire (Rech et al., 2015). Kemp et al. also **suggested** that Spice is more potent than marijuana, interacting with receptors in the brain other than those with which marijuana interacts. They reported news reports describing users so agitated that they tore off their clothes and sweated heavily. Kemp et al. concluded that synthetic cannabinoids are dangerous substances that result in many emergency department visits and fatalities (Kemp et al., 2015).

A systematic review of adverse events arising from the use of synthetic cannabinoids examined data from poison centers and drug monitoring systems in Europe, the United Kingdom, the U.S. and Australia. Authors advised that physicians be aware of adverse effects including severe cardiovascular, cerebrovascular, neurological, psychiatric and renal effects (Tait et al., 2016). Another recent study, a retrospective chart review of patients (n=676) admitted to a Dual Diagnosis psychiatric unit from March 2014 to February 2015, found that the use of synthetic cannabinoids was "strongly associated with more psychotic presentations and agitation compared to cannabis use" (Nia et al, 2016).

Users of synthetic cannabinoids received higher doses of antipsychotic medications while spending longer time in hospital (Nia et al., 2016).

The National Institute on Drug Abuse has reported the abuse/diversion of pharmaceutical fentanyl in forms including patches, lozenges, tablets, and films. Non-pharmaceutical fentanyl analogs, e.g., illicitly-produced desmethyl fentanyl, can be snorted or injected as a powder, or swallowed in pill form (NIDA, 2015). Users abuse these drugs, linked to overdose deaths in the U.S., to experience short-term highs and feelings of euphoria (DEA, 2015). Fentanyl is often marketed and disguised as white powder heroin and is many times more potent than either heroin or morphine by weight (DEA, 2012).

Other drugs or products that are abused include the following: club drugs, e.g., GHB, Rohypnol®, ketamine, MDMA (Ecstasy), Methamphetamine, and LSD (ACID); hallucinogens, e.g., ayahuasca, DMT, D-lysergic acid diethylamide (LSD), peyote (mescaline), 4-phosphoryloxy-N, N-dimethyltryptamine (psilocybin) and; salvia divinorum; inhalants, e.g., spray paints, markers, glues, and cleaning fluids; and anabolic steroids, e.g., Gear, Juice, Roids, and Stackers (National Institute on Drug Abuse, 2016). A nonprescription herbal medication available on the internet but not widely used in the U.S., kratom is sometimes used as a replacement for methadone, as it is more easily available and lacks the stigma of methadone (Rech et al., 2015).

Novel drugs, including synthetic cannabinoids, synthetic cathinones, synthetic hallucinogens, and Salvia divinorum, are available on the internet as well as in retail stores as substitutes for traditional illicit drugs, e.g., cannabis, cocaine, amphetamines (Vandrey et al., 2013). Packaging for the drugs may not list the drug contents and may suggest uses such as incense or bath salts, and may note that the products are "not for human consumption." Labeling of these recreational drugs include such names as Spice and K2 (synthetic cannabinoids), Vanilla Sky and Ivory Way (synthetic cathinones), N-Bomb and Smiles (synthetic hallucinogens) and Salvia (Salvia divinorum). Vandrey et al indicate that adolescents can buy these products containing psychoactive drugs with potency and efficacy that is often far greater than traditional drugs of abuse. Additionally these drugs may contain harmful contaminants. They emphasize that the current novel drug market represents a shift from past illicit drug markets, and caution that the market **may** expand to include additional classes of drugs of abuse. They emphasize how the medical field must be able to recognize this trend in drug use.

Synthetic cannabinoids use among 12th graders was the same in 2011 and 2012 at 11% (Vandrey et al., 2013). Authors noted informal reviews of internet sites indicating that the use of synthetic cannabinoids (packaged as incense or potpourri) initially was related to the belief (by users) that the product was a safe, legal alternative to cannabis and that it would not be detected in standard urine toxicology tests. With the use of synthetic cannabinoids, tolerance develops rapidly and withdrawal **may** occur. Some of the adverse effects following the use of these products include tachycardia, vomiting, drowsiness, confusion, agitation/irritability, hallucinations/delusions, dizziness, and chest pain. In some cases, an exacerbation or recurrence of ongoing psychosis **may** occur. Vandrey et al. caution that pharmacologically specific treatments for managing adverse reactions are not

available, requiring clinicians to develop a symptom-specific treatment strategy (Vandrey et al., 2013).

Synthetic cathinones, marketed as "bath salts," contain an amphetamine-like stimulant found naturally in the Khat plant. Although usually administered intranasally, other routes of administration have included oral, smoked, intravenously. Use of these products in the U.S. among students is at 0.8%, 0.6%, and 1.3% for grades 8, 10, and 12, respectively (National Institute on Drug Abuse, 2012). The predominant synthetic cathinone in the U.S. is MDPV (3,4-methylenedioxypyrovalerone). Others include mephedrone and methylone, but there are also many others. Mephedrone and MDPV became illegal in the U.S. in 2012. Bath salts, sold under names, e.g., "Ivory Wave," "Bloom," Cloud Nine," "Vanilla Sky,", and "Scarface," are related to severe intoxication and dangerous health effects. They raise the level of dopamine in brain circuits, producing euphoria, increased sex drive, paranoia, hallucinatory delirium and psychotic behavior. Users of bath salts **may** also have raised levels of serotonin. Other health effects of bath salts include racing heart, high blood pressure, chest pains, paranoia, hallucinations and panic attacks. Bath salts are highly addictive and users have reported intense cravings (National Institute on Drug Abuse, 2012).

Recently, a new deadly class of synthetic hallucinogen mimicking LSD is emerging as a LSD substitute (Medscape, 2014). This drug, 251-NBOMe, or simply NBOMe, is sold cheaply under the names "N-Bomb,", "Smiles," "251," or "25B." NBOMe, structural analogue of 2C phenethylamines, is sold on blotter sheets infused with the drug, much like LSD, and is extremely potent in very low doses. This drug has the potential for experiencing significant toxicity in users who are typically young (college aged) and who think they are using LSD. Overdoses occur, as doses **may** be miscalculated from the blotter. Some of the adverse events from NBOMe use are delirium, tachycardia, hypertension, severe aggression, respiratory acidosis, impaired renal function, and seizures. Treatment for overdose of NBOMe is unlike that of LSD. NBOMe overdose requires extended stays in the ICU. The effects of NBOMe can last up to 5 days compared with 8 hours for LSD (Medscape, 2014).

Salvinorin A is a psychoactive compound found in a plant with hallucinogenic effects, Salvia divinorum. Products containing this compound are typically smoked but **may** also be orally consumed in tea made from leaves. Among 12th grade students in the U.S., lifetime use has remained near 6% from 2009 through 2011 (Vandrey et al, 2014). The most adverse effect of using Salvia divinorum is behavioral toxicity associated with intense psychological effects, e.g., perceptual distortions, anxiety, panic, and psychotic episodes. Treatments include interpersonal reassurance and support, intravenous nalozone to reverse drug effects, benzodiazepines and antipsychotic agents (Vandrey et al, 2014).

Healthcare Effectiveness Data and Information Set (HEDIS) Measure: Initiation of Alcohol and Other Drug Dependence Treatment (IET)

The Healthcare Effectiveness Data and Information Set (HEDIS) is a set of performance measures developed and maintained by the National Committee for Quality Assurance

(NCQA). The HEDIS measure that includes substance use disorders is Initiation and Engagement of Alcohol and Other Drug Dependence Treatment (IET). This measure focuses on processes, rather than on outcome measures. NCQA uses the term alcohol and other drug dependence instead of the accepted industry term, substance use disorder (SUD). The IET measure requires that treatment of adolescents and adults, with a new episode of alcohol and other drug dependence per a claim, is initiated within 14 days of the identifying event per a claim. It also requires that adolescents and adults with an identifying event per a claim, who initiated treatment within 14 days, have two or more additional treatment services within 30 days of the initial treatment service.

Conclusions

In a landmark report, Facing Addiction in America: *The Surgeon General's Report on Alcohol, Drugs, and Health*, U.S. Surgeon General Vivek Murthy refers to this current addiction crisis as "a moral test for America," comparing it with the past tobacco epidemic. As "one of the most pressing public health crises of our time, Murthy notes how substance misuse and substance use disorders "prevent people from living healthy and productive lives. And just as importantly, they have profound effects on families, friends, and entire communities" (U.S. Dept. of Human Health and Services, 2016). He recommends additional policies and programs to increase access to effective treatment for this chronic illness (which is not a character flaw), and an expansion of the scientific evidence base for prevention, treatment and recovery. The report discusses recent changes in healthcare policy and law, which create incentives for the implementation of the collaborative care model integrating treatment of substance use disorder with general healthcare. Some of the key findings of the report include the following (U.S. Dept. of Human Health and Services, 2016):

- A majority of patients with substance use disorders do not receive any treatment;
- Recovery is achievable with comprehensive continuing care;
- Early intervention and treatment services are beginning to be delivered into general healthcare practice under the collaborative care model;
- Integration between primary care and specialty care is needed as are additional treatment options within primary care;
- Medications are currently under-used in treatment of substance use disorders, although scientific evidence shows that medications can be effective along with behavioral therapies, and recovery support services;
- Treatment goals for substance use disorders are the same as those for treatment of other chronic illness: reduction of symptoms and improvement of health and functional status; and
- The use of electronic technologies, e.g., telehealth and electronic medical records, **may** improve treatment of those with substance use disorders.

The Surgeon General's report cites studies that have demonstrated the efficacy of MAT in both the reduction of illicit drug use and overdose deaths as well as in improving retention in treatment. It reports studies finding that patients who receive MAT for fewer than 90

days have not shown improved outcomes and that those receiving MAT for less than three years are more likely to relapse than those in treatment for three or more years (U.S. Dept. of Human Health and Services, 2016).

The American Society of Addiction Medicine's (ASAM) comprehensive set of guidelines, *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions, Third Edition* (2013) describes the continuum of addiction health service (Mee-Lee, 2013). The ASAM Criteria refers to withdrawal management rather than detoxification services. It emphasizes that altering the course of the patient's illness toward wellness, recovery, and productive functioning in family, workplace and society are the goals of addiction treatment. Treatment is described by the ASAM Criteria as a continuum including broad levels of service and an early intervention level, with levels of care determined by an individual's needs. Severity of illness, level of function, and progress determine the length of stay in each level. Treatment is individualized and responsive to a patient's specific needs and progress in treatment (Mee-Lee, 2013).

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. We take all suggestions and recommendations into consideration in our ongoing review of the guidelines. Submit questions or comments via mail or email to:

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References

1. 11 States and DC with Pending Legislation or Ballot Measures to Legalize Marijuana Accessed website on July 7, 2010 http://medicalmarijuana.procon.org/view.resource.php?resourceID=002481.
2. 14 Legal Medical Marijuana States. Accessed website on July 7, 2010 http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.
3. Accessed website http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm on April 14, 2009.
4. Ackerman JP, Riggins T, Black MM. A Review of the Effects of Prenatal Cocaine Exposure Among School-Aged Children. Pediatrics Volume 125, Number 3, March 2010.
5. Addolorato G, Leggio L, Abenavoli L, Agabio R, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Baclofen in the Treatment of Alcohol Withdrawal Syndrome: A Comparative Study vs Diazepam. The American Journal of Medicine (2006) 119, 276.e13-276.e18.
6. Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, Lewis TR, Vaster M, Gauda EB. Clonidine as an Adjunct Therapy to Opioids for Neonatal Abstinence Syndrome: A Randomized, Controlled Trial. Pediatrics Volume 123, Number 5, May 2009.
7. Aharonovich E, Xinhua L, Samet S, Nunes E, Waxman R, Hasin D. Postdischarge Cannabis Use and Its Relationship to Cocaine, Alcohol and Heroin Use: A Prospective Study. Am J Psychiatry 162:8, August 2005.
8. Amato L, Minozzi L, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database of Systematic Reviews 2011; 9.
9. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database of Systematic Reviews 2011; 10.
10. American Psychiatric Association (2006). Practice guideline for the treatment of patients with substance use disorders, 2nd edition. Am J Psychiatry, 163(8) (Suppl):1-82, 2006.
11. American Psychiatric Association (2006). *Treating Substance Use Disorders: A Quick Reference Guide.*
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition DSM-5™. American Psychiatric Publishing, Washington, DC; London, England, 2013.
13. American Society of Addiction Medicine (ASAM). 2014. Accessed online on December 8, 2014 at http://www.asam.org/docs/default-source/advocacy/letters-and-comments/buprenorphine-expansion-act-markey-letter.pdf.
14. American Society of Addiction Medicine (ASAM). The national practice guideline for the use of medications in the treatment of addiction involving opioid use 2015. Accessed online at http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf.
15. An LC, Bluhm JH, Foldes SS, Alesci NL, Klatt CM, Center BA, Nersesian WS, Larson ME, Ahluwalia JS, Manley MW. A Randomized Trial of a Pay-for-Performance Program Targeting Clinician Referral to a State Tobacco Quitline. Arch Intern Med/Vol 168 (No. 18), Oct.13, 2008.
16. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. *The Lancet* 2016; 387: 2507-2520.

17. Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, Gold D. An Evaluation of μ-Opioid Receptor (OPRM1) as a Predictor of Naltrexone Response in the Treatment of Alcohol Dependence. Arch Gen Psychiatry/Vol. 65 (No. 2), Feb 2008.
18. Arias A, Feinn R, Oncken C, Covault J, Kranzler HR. Placebo-controlled trial of Zonisamide for the treatment of alcohol dependence. J Clin Psychopharmacol 2010; 30(3): 318-322.
19. Awan S, Samokhvalov AV, Aleem N, Hendershot CS, Irving JA, Kalvik A, Lefebvre L, Le FOll B, Quilty L, Voore P. Development and implementation of an ambulatory integrated care pathway for major depressive disorder and alcohol dependence. *Psychiatric Services* 2015; 66:12; 1265-1267.
20. Axelrod SR, Perepletchikova F, Holtzman K, Sinha R. Emotion regulation and substance use frequency in women with substance dependence and borderline personality disorder receiving dialectical behavior therapy. Am J Drug Alcohol Abuse 2011; 37(1):37-42.
21. Azodi OS, Lindstrom D, Adami J, Tonnesen H, Nasell H, Gilljam H, Wladis A. The efficacy of a smoking cessation programme in patients undergoing elective surgery – a randomized clinical trial. Anaesthesia, 2009, 64, pages 259-265.
22. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med* 2014;174(10): 1668-73.
23. Baker A, Richmond R, Haile M, Lewin TJ, Carr VJ, Taylor RL, Janson S, Wilhelm K. A Randomized Controlled Trial of a Smoking Cessation Intervention Among People with a Psychotic Disorder. Am J Psychiatry 2006; 163: 1934-1942.
24. Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, Fiore MC. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomized clinical trial. JAMA 2016; 315(4): 371-379.
25. Barth J, Jacob T, Daha I, Critchley JA. Psychosocial interventions for smoking cessation in patients with coronary heart disease (review). The Cochrane Collaboration 2015.
26. Batra A, Klinger K, Landfeldt B, Friederich H, Westin A, Danielsson T. Smoking Reduction with 4-mg Nicotine Gum: A Double-Blind, Randomized, Placebo-Controlled Study. Clinical Pharmacology and Therapeutics 2005; 78 (6) 689-96.
27. Bechtold J, Hipwell A, Lewis D, Loeber R, Pardini D. Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms. *Am J Psychiatry* 2016; 173(8): 781-789.
28. Bellack AS, Bennett ME, Gearon JS, Brown CH, Yang Y. A Randomized Clinical Trial of a New Behavioral Treatment for Drug Abuse in People with Severe and Persistent Mental Illness. Arch Gen Psychiatry/Vol. 63, April 2006.
29. Bergman BG, Greene MC, Slaymaker V, Heoppner BB, Kelly JF. Young adults with co-occurring disorders: substance use disorder treatment response and outcomes. *J Subst Abuse Treat* 2014; 46(4): 420-429.
30. Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, Robertson RM, McAuley T, Goff D, Benowitz N, American Heart Association. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation* 2014;30: 1419-36.
31. Bickel WK, Marsch LA, Buchhalter AR, Badger GJ. Computerized Behavior Therapy for Opioid-Dependent Outpatients: A Randomized Controlled Trial. Exp Clin Psychopharmacol. 2008 Apr; 16(2): 132-43.
32. Bofetta P, Straif K. use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. BMJ 2009, 339:b3060.
33. Bowen S, Witkiewitz K, Clifasefi SL, Grow J, Chawla N, Hsu SH, Carroll HA, Harrop E, Collins, SE, Lustyk MK, Larimer ME. Relative efficacy of mindfulness-based relapse prevention, standard relapse prevention, and treatment as usual for substance use disorders: a randomized clinical trial. *JAMA Psychiatry* 2014; 71(5): 547-556.

34. Brady KT, McCauley JL, Back SE. Prescription opioid misuse, abuse, and treatment in the United States: an update. *Am J Psychiatry* 2016; 173:1: 18-26.
35. Bright GM. Abuse of Medications for the Treatment of ADHD: A Survey. Accessed website on June 30, 2010 www.medscape.com/viewarticle/571996_6
36. Brodie JD, Case BG, Figueroa E, Dewey SL, Robinson JA, Wanderling JA, Laska EM. Randomized, Double-Blind, Placebo-Controlled Trial of Vigabatrin for the Treatment of Cocaine Dependence in Mexican Parolees. Am J Psychiatry 2009; 166: 1269-1277.
37. Brown CH, Bennett ME, Li L, Bellack AS. Predictors of initiation and engagement in substance abuse treatment among individuals with co-occurring serious mental illness and substance use disorders. Addict Behav 2011; 36(5): 439-447.
38. Brown ES, Sunderajan P, Hu LT, Sowell SM, Carmody TJ. A randomized, double-blind, placebo-controlled trial of lamotrigine therapy in bipolar disorder, depressed or mixed phase and cocaine dependence. Neuropsychopharmacology 2012; 37:2347-2354.
39. Buckner JD, Carroll KM. Effect of anxiety on treatment presentation and outcome: results from the Marijuana Treatment Project. Psychiatry Res 2010; 1788:493-500.
40. Burgess FW. New Research Findings in Chronic Pain. Accessed website on July 7, 2010 http://cme.medscape.com/viewarticle/553069
41. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation (Review). The Cochrane Library 2016.
42. Campbell R, Starkey F, Holliday J, Audrey S, Bloor M, Parry-Langdon N, Hughes R, Moore L. An Informal School-Based Peer-Led Intervention for Smoking Prevention in Adolescents (ASSIST): A Cluster Randomized Trial. Lancet. 2008 May 10; 371 (9624): 1595-1602.
43. Campbell W, Hester RK, Lenberg KL, Delaney HD. Overcoming addictions, a web-based application, and SMART Recovery, an online and in-person mutual help group for problem drinkers, Part 2: Six-month outcomes of a randomized controlled trial and qualitative feedback from participants. *J Med Internet Res* 2016; 18(10): 262.
44. Carise D, Leggett Dugosh K, McLellan AT, Camilleri A, Woody GE, Lynch KG. Prescription OxyContin Abuse Among Patients Entering Addiction Treatment. Am J Psychiatry 164:11, November 2007.
45. Carroll Km, Ball SA, Martino S, Nich C, Babuscio TA, Nuro KF, Gordon MA, Portnoy GA, Rounsaville BJ. Computer-Assisted Delivery of Cognitive-Behavioral Therapy for Addiction: A Randomized Trial of CBT4CBT. Am J Psychiatry. 2008 July: 165(7): 881-888.
46. Carroll KM, Kiluk BD, Nich, C, Gordon MA, Portnoy GA, Marino DR, Ball SA. Computer-assisted delivery of cognitive-behavioral therapy: efficacy and durability of CBT4CBT among cocaine-dependent individuals maintained on methadone. *Am J Psychiatry* 2014; 171(4):436-444.
47. CDC. Morbidity and mortality weekly report (MMWR); increases in drug and opioid overdose deaths – United States, 2000-2014. Accessed online on November 10, 2016 at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm.
48. Center for Disease Control and Prevention. 2011 Youth risk behavior survey (YRBS) results. Accessed at http://www.cdc.gov/healthyyouth/yrbs/slides/taodu_slides_yrbs.ppt
49. Center for Disease Control and Prevention. 2012 Morbidity and Mortality Weekly Report (MMWR) February 17, 2012. Accessed website at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6106a1.htm.
50. Center for Substance Abuse Treatment. Incorporating alcohol pharmacotherapies into medical practice (TIP) Series 49. DHHS Publication No. (SMA) 09-4380. Rockville, MD: Substance Abuse and Mental Health Services, 2009.
51. Centers for Disease Control and Prevention. Morbidity and mortality weekly report June 13 2014: Youth risk behavior surveillance – United States, 2013.

52. Centers for Disease Control and Prevention. Morbidity and mortality weekly report September 6, 2013: Electronic cigarette use among middle and high school students – United States, 2011-2012.
53. Centers for Disease Control and Prevention. Prescription drug overdose in the United States: fact sheet 2013. Accessed online on November 10, 2014 at http://www.cdc.gov/homeandrecreationalsafety/overdose/facts.html.
54. Centers for Disease Control Prevention Press Release August 25, 2014.. More than a quarter-million youth who had never smoked a cigarette used e-cigarettes in 2013. Accessed online on November 10, 2014 at http://www.cdc.gov/media/releases/2014/p0825-e-cigarettes.html.
55. Chantix® (varenicline) FDA MedWatch update May 16, 2008. Accessed Web site http://www.fda.gov/medwatch/SAFETY/2007/safety07.htm#Chantix on October 28, 2008.
56. Chatters R, Cooper K, Day E, Knight M, Lagundoye O, Wong R, Kaltenthaler E. Psychological and psychosocial interventions for cannabis cessation in adults: a systematic review. *Addiction Research & Theory* 2016; 24(2): 93-110.
57. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP. Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence. Arch Gen Psychiatry/Vol 63, Feb 2006.
58. Comprehensive Addiction and Recovery Act of 2016. Accessed online at www.govtrack.us/congress/bills/114/s524.
59. Compton WM, Han B, Jones CM, Blanco C, Hughes A. Marijuana use and use disorders in adults in the USA, 2002-14; analysis of annual cross-sectional surveys. *The Lancet* 2016; 3910): 954-64.
60. Compton WM, Thomas YF, Conway KP, Colliver JD. Developments in the Epidemiology of Drug Use and Drug Use Disorders. Am J Psychiatry 162:8, August 2005.
61. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harvard Review of Psychiatry* 2015; 23(2): 63-75.
62. Conrod PJ, Castellanos-Ryan N, Strang J. Brief, Personality-Targeted Coping Skills Interventions and Survival as a Non-Drug User Over a 2-Year Period During Adolescence. Arch Gen Psychiatry/Vol. 67 (No.1), January 2010.
63. Cook BL, Wayne GF, Kafali EN, Liu Z, Shu C, Flores M. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA* 2014; 311(2): 172-182.
64. Cornelius JR, Douaihy AB, Clark DB, Chung T, Wood DS, Daley D. Mirtazapine in comorbid major depression and alcohol dependence: an open-label trial. *J Dual Diagn* 2012; 8(3): 200-204.
65. Covey LS, Hu M, Winhusen T, Weissman J, Berlin I, Nunes E. OROS-methylphenidate or placebo for adult smokers with attention deficit hyperactivity disorder: Racial/ethnic differences. Drug Alcohol Depend 2010; 110:156-159.
66. Cropsey K, Eldridge G, Weaver M, Villalobos G, Stitzer M, Best A. Smoking Cessation Intervention for Female Prisoner: Addressing an Urgent Public Health Need. American Journal of Public Health. October 2008, Vol. 98, No. 10.
67. Cui Q, Robinson L, Elston D, Smaill F, Cohen J, Quan C, McFarland N, Thabane L, McIvor A, Zeidler J, Smieja M. Safety and tolerability of varenicline tartrate (Champix®/Chantix®) for smoking cessation in HIV-infected subjects: a pilot open-label study. Aids Patient Care and STDs 2012;26(1); 12-19.
68. D'Ruiz C, Graff DW, Robinson E. Reductions in biomarkers of exposure, impacts on smoking urge and assessment of product use and tolerability in adult smokers following partial or complete substitution of cigarettes with electronic cigarettes. *BMC Public Health* 2016.
69. Dakwar E and Nunes EV. New directions in medication-facilitated behavioral treatment for substance use disorders. *Curr Psychiatry Rep* 2016; 18:64.

70. Datillo PB, Hallpern SM, Fearon K, Sohal D, Nordin C. β-blockers Are Associated with Reduced Risk of Myocardial Infarction After Cocaine Use. Annals of Emergency Medicine Volume 51, No. 2: February 2008.
71. Degenhardt L, Hall WD. The adverse effects of cannabinoids: implications for use of medical marijuana. CMAJ 2008 June 17: 178 (13); June 17, 2008.
72. Department of Health and Human Services (DHHS): Determination that the OxyContin (Oxycodone Hydrochloride) drug products covered by new drug application 20-553 were withdrawn from sale for reasons of safety or effectiveness. Accessed online November 10, 2014 at http://www.gpo.gov/fdsys/pkg/FR-2013-04-18/html/2013-09092.htm.
73. Department of Health and Human Services (DHHS): Food and Drug Administration. Report on the standardization of risk evaluation and mitigation strategies; availability. *Federal Register* 2014; 79(184).
74. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain-United States 2016. *JAMA* 2016; 315 (15): 1625-1645.
75. Drug Enforcement Administration (U.S.) August 21, 2014. DEA to publish final rule rescheduling hydrocodone combination products. Accessed online on November 10, 2014 at http://www.dea.gov/divisions/hq/2014/hq082114.shtml.
76. Drug Enforcement Administration. DEA announces actions related to marijuana and industrial hemp Aug 11, 2016. Accessed online at https://www.dea.gov/divisions/hq/2016/hq081116.shtml.
77. Dunn KE, Strain EC. Pretreatment alcohol drinking goals are associated with treatment outcomes. *Alcohol Clin Exp Res* 2013; 37(10): 1745-1752.
78. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A Meta-Analytic Review of Psychosocial Interventions for Substance Use Disorders. Am J Psychiatry 165:2, February 2008.
79. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among US adolescents: a cross-sectional study. *JAMA Pediatr* 2013; 168(7): 610-617.
80. Ebbert JO, Elrashidi MY, Stead LF. Interventions for smokeless tobacco use cessation (Review). *Cochrane Database of Systematic Reviews* 2015.
81. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, Treadow J, Yu CR, Dutro MP, Park PW. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA* 2015; 313(7): 687-69444.
82. Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, Piguet V, Musset T, Gaspoz J, Perrier A, Dayer P, Desmeules JA. Drug-Induced Long QT Syndrome in Injection Drug Users Receiving Methadone. Archives of Internal Medicine Vol. 166 No. 12, June 26, 2006.
83. Eisenberg MJ, Filion KB, Yavin D, Belisle P, Mottillo S, Joseph L, Gervais A, O'Loughlin J, Paradis G, Rinfret S, Pilote L. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. CMAJ, 2008; 179(2): 135-44.
84. Ellerbeck EF, Mahnken JD, Cupertino P, Cox S, Greiner A, Mussulman LM, Nazir N, Shireman TI, Resnicow K, Ahluwalia JS. Impact of Varying levels of Disease Management on Smoking: A Randomized Trial. Ann Intern Med. 2009 April 6; 150(7): 437-446.
85. Emerging Issues in the Use of Methadone. Substance Abuse Treatment Advisory. The Center for Substance Abuse Treatment. Volume 8, Issue 1, Spring 2009.
86. Evins AD, Cather C, Laffer A. Treatment of tobacco use disorders in smokers with serious mental illness: toward clinical best practices. *Harv Rev Psychiatry* 2015; 23(2): 90-98.
87. Evins AE, Cather C, Pratt SA. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA* 2014; 311(2): 145-154.
88. Fagerstrom K, Gillljam H, Metcalfe M, Tonstad S, Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. BMJ 2010; 341:c6549.

89. Farronato NS, Dürsteler-MacFarland KM, Wiesbeck GA, Petitjean SA. *A systematic review comparing cognitive-behavioral therapy and contingency management for cocaine dependence*. J Addict Dis 2014; 32(4): 274-87.
90. FDA 2014. FDA approves new hand-held auto-injector to reverse opioid overdose. Accessed online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391465.htm.
91. FDA 2016. FDA approved first buprenorphine implant for treatment of opioid dependence. Accessed online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503719.htm.
92. FDA approves injectable drug to treat opioid-dependent patients. FDA New Release. Accessed website on December 8, 2010 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229109.htm.
93. FDA Briefing Document 2016. Accessed online at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM520103.pdf.
94. FDA introduces new safety measures for extended-release and long-acting opioid medication. FDA News and Events July 9 2012. Accessed website on November 1, 2012 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310870.htm.
95. FDA News Release. FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose. Accessed online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm.
96. FDA News Release April 2, 2014. FDA approves new hand-held auto-injector to reverse opioid overdose. Accessed online on November 10, 2014 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391465.htm.
97. FDA News Release April 24, 2014. FDA proposes to extend its tobacco authority to additional tobacco products, including e-cigarettes. Accessed online on November 10, 2014 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394667.htm.
98. FDA News Release October 17, 2014. FDA approves labeling with abuse-deterrent features for third extended-release opioid analgesic. Accessed November 10, 2014 online at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm419288.htm.
99. FDA News Release October 25, 2013. FDA approves extended-release, single-entity hydrocodone product. Accessed online on November 10, 2014 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm372287.htm.
100. FDA News Release September 10, 2013. FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics. Accessed online on November 10, 2014 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm.
101. FDA News Release: July 23, 2014). FDA approves new extended-release oxycodone with abuse-deterrent properties. Accessed online on November 10, 2014 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406407.htm.
102. FDA News Release: November 20, 2014. FDA approves extended-release, single-entity hydrocodone product with abuse-deterrent properties. Accessed online on November 10, 2014 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm423977.htm.
103. FDA safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events. FDA MedWatch November 24, 2011. Accessed website on November 1, 2012 at http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm.
104. FDA. Safety Announcement (12-12-2012): FDA Drug Safety Communication: Safety Review of Chantix (varenicline) and Risk of Cardiovascular Adverse Events. Accessed online on November 2014 at http://www.fda.gov/Drugs/DrugSafety/ucm330367.htm.

105. FDA. U.S. Food and Drug Administration News Release. FDA proposes to extend its tobacco authority to additional tobacco products, including e-cigarettes. Accessed online on November 10 from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394667.htm.
106. FDA. Vaporizers, e-cigarettes, and other electronic nicotine delivery systems (ENDS). Accessed online on November 10, 2016 at http://www.fda.gov/TobaccoProducts/Labeling/ProductsIngredientsComponents/ucm456610.htm.
107. Federal Register July 8, 2016. Accessed online at https://www.gpo.gov/fdsys/pkg/FR-2016-07-08/pdf/2016-16120.pdf.
108. Fernandez MM, Hosey RG. Performance-enhancing drugs snare nonathletes, too. J Fam Pract. 2009 Jan; 58 (1): 16-23.
109. Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor PG, Schottenfeld RS. N Eng J Med 355:4 July 27, 2006.
110. Fletcher MJ, Kertesz SG, Kohn MA, Gonzales R. Trends in Opioid Prescribing by Race/Ethnicity for Patients Seeking Care in US Emergency Departments. JAMA January 2, 2008 Vol. 299, No. 1.
111. Fowler LA, Holt SL, Joshi D. Mobile technology-based interventions for adult users of alcohol: a systematic review of the literature. *Addictive Behaviors* 2016; 25-34.
112. Frisman LK, Mueser KT, Covell NH, Lin HJ, Crocker A, Drake RE, Essock SM. Use of Integrated Dual Disorder Treatment Via Assertive Community Treatment Versus Clinical Case Management for Persons With Co-Occurring Disorders and Antisocial Personality Disorder. The Journal of Nervous and Mental Disease, Volume 197, Number 11, November 2009.
113. Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res. 2010 Nov; 34 (11): 1849-57.
114. Garza D, Murphy M, Tseng L, Riordan HJ, Chatterjee A. A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo. Biol Psychiatry 2011; 69:1075-1082.
115. Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L. Psychosocial interventions for cannabis use disorder (Review). *Cochrane Database of Systematic Reviews* 2016.
116. Goldstein BI, Levitt AJ. Further Evidence for a Developmental Subtype of Bipolar Disorder Defined by Age at Onset: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. Am J Psychiatry 163:9, September 2006.
117. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, Pickering RP, Ruan WJ, Smith SM, Huang B, Hasin DS. Epidemiology of DSM-5 alcohol use disorder results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry* 2015; 72(8): 757-766.
118. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, McRaeClark AL, Brady KT. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry* 2012; 169(8): 805-12.
119. Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW, Deas D, Upadhyaya HP. Bupropion SR and contingency management for adolescent smoking cessation. J Subst Abuse Treat 2011; 40(1):77-86.
120. Gregory RJ, DeLucia-Deranja E, Mogle JA. Dynamic Deconstructive Psychotherapy Versus Optimized Community for Borderline Personality Disorder Co-Occurring with Alcohol Use Disorders. The Journal of Nervous and Mental Disease, Volume 198, Number 4, April 2010.
121. Griffin KW, Botvin GJ. Evidence-based interventions for preventing substance use disorders in adolescents. Child Adolesc Psychiatr Clin N Am 2010; 19(3):505-526.

122. Gudin JA. The changing landscape of opioid prescribing: long-acting and extended-release opioid class-wide Risk Evaluation and Mitigation Strategy. Ther Clin Risk Manag 2012; 8:209-217.
123. Guglielmo R, Martinotti G, Quatrale M, Ioime L, Kadili I, Di Nicola M, Janiri L. Topiramate in alcohol use disorders: review and update. *CNS Drugs* 2015.
124. Gustafson DH, McTavish FM, Chih M, Atwood AK, Johnson RA, Boyle MG. A smartphone application to support recovery from alcoholism: a randomized controlled trial. *JAMA Psychiatry* 2014; 71(5): 566-572.
125. Guttmannova K, Bailey JA, Hill KG, Lee JO, Hawkins JD, Woods ML, Catalano RF. Sensitive Periods for Adolescent Alcohol Use Initiation: predicting the lifetime occurrence and chronicity of alcohol problems in adulthood. J Stud Alcohol Drugs 2011; 72(2); 221-231.
126. Haile CN, Mahoney JJ, Newton TF, Garza RDL. Pharmacotherapeutics directed at deficiencies associated with cocaine dependence: focus on dopamine, norepinephrine and glutamate. Pharmacol Ther 2012; 134(2):260-277.
127. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet Vol 374, October 17, 2009.
128. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Can electronic cigarettes help people stop smoking, and are they safe to use for this purpose? *Cochrane Database of Systematic Reviews* 2016.
129. Hawkins JD, Oesterle S, Brown E, Arthur MW, Abbott RD, Fagan AA, Catalano RF. Results of a Type 2 Translational Research Trial to Prevent Adolescent Drug Use Delinquency. Arch Pediatr Adolesc Med/Vol 163 (No.9), Sep 2009.
130. Health and Humar Services 2015. Opioid abuse in the U.S. and HHS actions to address opioid-drug related overdoses and deaths. Accessed online at https://aspe.hhs.gov/basic-report/opioid-abuse-us-and-hhs-actions-address-opioid-drug-related-overdoses-and-deaths.
131. Healthy People 2020: Understanding and Improving Health. Proposed Objectives for Substance Abuse. Washington, DC. US Department of Health and Human Services. http://www.healthypeople.gov/hp2020/Objectives/TopicArea.aspx?id=46&TopicArea=Substance+Abuse. Accessed website on October 18, 2010.
132. Hettema JE, Hendriks PS. Motivational interviewing for smoking cessation: a meta-analytic review. J Consult Clin Psychol 2010; 78(6):868-884.
133. Hien DA, Jaiang H, Campbell ANC, Hu M, Miele GM, Cohen LR, Brigham GS, Capstick C, Kulaga A, Robinson J, Suarez-Morales L, Nunes EV. Do treatment improvements in PTSD severity affect substance use outcomes? A secondary analysis from a randomized clinical trial in NIDA's Clinical Trials Network. Am J Psychiatry, 2010 January; 167 (1): 95-101.
134. Hingson RW, Heeren T, Winter MR. Age of Alcohol-Dependence Onset: Associations with Severity of Dependence and Seeking Treatment. Pediatrics Volume 118, Number 3, September 2006.
135. Hoch E, Bonnet U, Thomasius R, Ganzer F, Havemann-Reinecke U, Preuss UW. Risks associated with the non-medicinal use of cannabis. *Dtsch Arztebl Int* 2015; 112: 271-8.
136. Hoch E, Bühringer G, Pixa A, Dittmer K, Henker J, Seifert A, Wittchen HU. CANDIS treatment program for cannabis use disorders: Findings from a randomized multi-site translational trial. *Drug Alcohol Depend* 2014; 185-93.
137. Hughes JR, Solomon LJ, Livingston AE, Callas PW, Peters EN. A randomized, controlled trial on NRT-aided gradual vs. abrupt cessation in smokers actively trying to quit. Drug Alcohol Depend 2010; 111(1-2):105-113.
138. Hulse GK, Morris N, Arnold-Reed D, Tait L, Lewis T RJ. Improving Clinical Outcomes in Treating Heroin Dependence. Arch Gen Psychiatry. 2009; 66 (10): 1108-1115.
139. Hulse GK, NGO HTT, Tait RJ. Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone. Biol Psychiatry 2010; 68:296-302.

140. Hurt RD, Ebbert JO, Croghan IT, Schroeder DR, Sood A, Hays JT. Methylphenidate for treating tobacco dependence in non-attention deficit hyperactivity disorder smokers: a pilot randomized placebo-controlled trial. J Negat Results Biomed 2011; 10:1.
141. Indave B, Minozzi S, Pani PP, Amato L. Antipsychotic medications for cocaine dependence. *Cochrane Database Syst Rev* 2016; 19;3.
142. Jackson C, Dickinson D. Enabling Parents Who Smoke to Prevent Their Children from Initiating Smoking. Arch Pediatr Adolesc Med/Vol. 160, Jan. 2006.
143. Japuntich SJ, Leventhal AM, Piper ME, Bolt DM, Roberts LJ, Fiore MC, Baker TB. Smoker characteristics and smoking-cessation milestones. Am J Prev Med 2011; 40(3):286-294.
144. Johnson BA, Ait-Daoud N, Fatema A, Akhtar MS, Javors MA. Use of Oral Topiramate to Promote Smoking Abstinence Among Alcohol-Dependent Smokers A Randomized Controlled Trial. Arch Intern Med. 2005: 165:1600-1605.
145. Johnson BA, Nassima AD, Wang XQ, Penberthy JK, Javors MA, Seneviratne C, Liu L. Topiramate for the treatment of cocaine addiction. *JAMA Psychiatry* 2013; 70(12): 1338-1346.
146. Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, McKay A, Ait-Daoud N, Anton RF, Ciraulo DA, Kranzler HR, Mann K, O'Malley SS, Swift RM for the Topiramate for Alcoholism Advisory Board and the Topiramate for Alcoholism Study Group. Topimate for Treating Alcohol Dependence. JAMA, October 10, 2007. Vol. 298, No. 14.
147. Johnson BA, Seneviratne C, Wang X, Ait-Daoud N, Li MD. Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT_3 antagonist Ondansetron. *Am J Psychiatry* 2013; 170: 1020-1031.
148. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine and methadone for opioid dependence. N Engl J Med. 2000; 343 (18): 1290-1297.
149. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014; 311(18): 1889-1900.
150. Kakko J, Gronbladh L, Dybrandt Svanborg K, von Wachenfeldt J, Ruck C, Rawlings B, Nilsson BH, Heilig M. A Stepped Care Strategy Using Buprenorphine and Methadone Versus Conventional Methadone Maintenance in Heroin Dependence: A Randomized Controlled Trial. Am J Psychiatry 164:5, May 2007.
151. Kampman KM, Lynch KG, Pettinati HM, Spratt K, Wierzbicki MR, Dackis C, O-Brien CP. A double blind, placebo controlled trial of modafinil for the treatment of cocaine dependence without co-morbid alcohol dependence. *Drug and Alcohol Dependence* 2015; 105-110.
152. Karila L, Megarbane B, Cottencin O, Lejoyeux M. Synthetic cathinones: a new public health problem. *Current Neuropharmacology* 2015; 13: 12-20.
153. Katz EC, Brown BS, Schwartz RP, O'Grady KE, King SD, Gandhi D. Transitioning opioid-dependent patients from detoxification to long-term treatment: efficacy of intensive role induction. Drug Alcohol Depend 2011; 117:24-30.
154. Keating GM. Nalmefene: a review of its use in the treatment of alcohol dependence*. CNS Drugs* 2013; 27:761-772.
155. Kelly JF, Stout RL, Magill M, Tonigan JS. The role of alcoholics anonymous in mobilizing adaptive social network changes: a prospective lagged mediational analysis. Drug Alcohol Depend 2011: 114(2-3): 119-126.
156. Kemp AM, Clark MS, Dobbs T, Galli R, Sherman J, Cox R. Top 10 facts you need to know about synthetic cannabinoids: not so nice spice. *The American Journal of Medicine* 2016; 129(3): 240-4.
157. Kersey RD, Elliot DL, Goldberg L, Kanayama G, Leone JE, Pavlovich M, Pope HG. National Athletic Trainers' Association Position Statement: Anabolic-Androgenic Steroids. Journal of Athletic Training 2012; 47(5):567-588.

158. Kiluk BD, Nich C, Babuscio T, Carroll KM. Quality versus quantity: acquisition of coping skills following computerized cognitive-behavioral therapy for substance use disorders. Addiction 2010; 105(12):2120-2127.
159. Kim SJ, Marsch LA, Guarino H, Acosta MC, Aponte-Melendez Y. Predictors of outcome from computer-based treatment for substance use disorders: results from a randomized clinical trial. *Drug Alcohol Depend* 2015; 157: 174-8.
160. King BA, Alam S, Promoff G, Arrazola R, Dube SR. Awareness and ever use of electronic cigarettes among U.S. adults, 2011-2011. *Nicotine Tob Res* 2013; 15(9): 1623-7.
161. Kleber HD & Smith Connery H. (2007). *Guideline Watch (April 2007): Practice Guideline for the Treatment of Patients With Substance Use Disorders, 2nd Edition*. FOCUS: The Journal of Lifelong Learning in psychiatry V(2):1-4, Spring 2007.
162. Kleber HD, Dupont RL. Physicians and medical marijuana. *Am J Psychiatry* 2012; 16996).
163. Koegelenberg CFN, Noor F, Bateman ED, van Zyl-Smit RN, Bruning A, O'Brien JA, Smith C, Abdool-Gaffar MS, Emanuel S, Esterhuizen TM, Irusen EM. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *JAMA* 2014; 312(2): 155-161.
164. Kowalczyk WJ, Phillips KA, Jobes ML, Kennedy AP, Ghitza UE, Agage Da, Schmittner JP, Epstein DH, Preston KL. Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessment. *Am J Psychiatry* 2015; 172(8): 760-767.
165. Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. Addiction 2011; 106(3):574-580.
166. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc Interval Screening In methadone Treatment. Ann Intern Med. 2009; 150: 387-395.
167. Kranzler HR, Armeli S, Tennen H, Covault J, Feinn R, Arias AJ, Pettinati H, Oncken C. A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset and 5-HTTLPR genotype. J Clin Psychopharmacol 2011; 31(1):22-30.
168. Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, Gelernter J, Pond T, Oncken C, Kampman KM. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry 2014; 171(4): 445-52.
169. Kraus ML, Alford DP, Kotz MM, Levounis P, Mandell TW, Meyer M, Salsitz EA, Wetterau N, Wyatt SA. Statement of the American Society of Addiction Medicine Consensus Panel on the use of buprenorphine in office-based treatment of opioid addiction. J Addict Med 2011; 5(4):254-263.
170. Kriston L, Holzel L, Weiser AK, Berner MM, Harter M. Meta-analysis: Are 3 Questions Enough to Detect Unhealthy Alcohol Use? Ann Intern Med. Vol 149, No. 12, 2008.
171. Laino C. Extended-Release Naltrexone Reduces Opioid Use. Medscape Medical News. Accessed website on December 6, 2010 http://www.medscape.com/viewarticle/722907_print
172. Laniado-Laborin R. Smoking Cessation Intervention: An Evidence-Based Approach. Postgraduate Medicine, Volume 122, Issue 2, March 2010.
173. Lee J, Kresina TF, Campopiano M, Lubran R, Clark HW. Use of pharmacotherapies in the treatment of alcohol use disorders and opioid dependence in primary care. *BioMed Res Int* 2015.
174. Leggio L. Understanding and Treating Alcohol Craving and Dependence: Recent Pharmacological and Neuroendocrinological Findings. Alcohol and Alcoholism Vol. 44, No. 4, pp. 341-352, 2009.
175. Levin FR, Mariani JJ, Brooks DJ, Pavlicova M, Cheng W, Nunes E. Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend 2011; 116(1-3):142-150.

176. Liang J, Olsen RW. Alcohol use disorders and current pharmacological therapies: the role of GABA receptors. *Acta Pharmacologica Sinica* 2014; 35:981-993.
177. Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, Rosenthal RN, Beebe KL. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA. 2010 October 13; 304(14).
178. Magellan Healthcare 2016. Medication Assisted Treatment: Taking Aim at America's Hidden Epidemic. Assessed online at http://magellanhealthinsights.com/resources/.
179. Magellan Healthcare 2016. Evidence-based Practices in Drug and Alcohol Treatment and Recovery. Assessed online at http://magellanhealthinsights.com/resources/
180. Mann C, Frieden T, Hyde PS, Volkow ND, Koob GF. Informational Bulletin: Medication assisted treatment for substance use disorders. Center for Medicaid and CHIP Services, Centers for Disease Control and Prevention, Substance Abuse and Mental Health Services Administration, National Institute on Drug Abuse, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health 2014.
181. Mannelli P. Smoking thwarts positive outcomes in opioid addiction. Presented at the American Society of Addiction Medicine 43rd Annual Medical-Scientific Conference on April 20, 2012.
182. Marchand KI, Oviedo-Joekes E, Guh D, Brissette S, Marsh DC, Schechter MT. Client satisfaction among participants in a randomized trial comparing oral methadone and injectable diacetylmorphine for long-term opioid-dependency. BMC Health Serv Res 2011; 11:174.
183. Marsch AL, Bickel WK, Badger GJ, Stothart ME, Quesnel KJ, Stanger C, Brooklyn J. Comparison of Pharmacological Treatments for Opioid-Dependent Adolescents. Arch Gen Psychiatry/Vol 62, October 2005.
184. Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, Fiellin DA. Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy and Association with Addiction. 16 January 2007 Annals of Internal Medicine Volume 146 Number 2.
185. Martell BA, Orson FM, Polin J, Mitchell E, Rossen RD, Gardner T, Kosten TR. Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone-Maintained Patients. Arch Gen Psychiatry/Vol. 66 (No.10), October 2009.
186. Martin JA, Campbell A, Killip T, Kotz M, Krantz MJ, Kreek MJ, McCarroll BA, Mehta D, Payte JT, Stimmel B, Taylor T, Haigney MCP, Wilford BB. QT screening in methadone maintenance treatment: report of a SAMHSA expert panel. J Addict Dis 2011; 4:283-306.
187. Martinez D, Narendran R, Foltin RW, Slifstein M, Hwang D, Broft A, Huang Y, Cooper TB, Fischman MW, Kleber HD, Laruelle M. Amphetamine-Induced Dopamine Release: Markedly Blunted in Cocaine Dependence and Predictive of the Choice to Self-Administer Cocaine. Am J Psychiatry 164:4, April 2007.
188. Mauger S, Fraser R, Gill K. Utilizing buprenorphine-naloxone to treat illicit and prescription-opioid dependence. *Neuropsychiatr Dis Treat* 2014; 10:587-598.
189. *Medical Marijuana Pros and Cons: 23 Legal medical marijuana states and DC: laws, fees, and possession limits.* Accessed on November 10, 2014 online at http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.
190. Medscape. New Deadly Class of Synthetic Hallucinogens Mimics LSD. Accessed December 29 2014 at http://www.medscape.com/viewarticle/836297.
191. Miller SC, Baktash SH, Webb TS, Whitehead CR, Maynard C, Wells TS, Otte CN, Gore RK. Risk for addiction-related disorders following mild traumatic brain injury in a large cohort of active-duty U.S. airman. *Am J Psychiatry* 2013; 170: 383-390.
192. Mills KL, Teeson M, Ross J, Peters L. Trauma, PTSD, and Substance Use Disorder: Findings From the Australian National Survey of Mental Health and Well-Being. Am J Psychiatry 2006; 163: 651-658.

193. Mooney ME, Herin DV, Specker S, Babb D, Levin FR, Grabowski J. Pilot study of the effects of lisdexamfetamine on cocaine use: a randomized, double-blind, placebo controlled trial. *Drug Alcohol Depend* 2015; 153: 94-103.
194. Moore BA, Barry DT, Sullivan LE, O'Connor PG, Cutter CJ, Schottenfeld RS, Fiellin DA. Counseling and directly observed medication for primary care buprenorphine/naloxone maintenance: a pilot study. J Addict Med 2012; 6(3): 205-11.
195. Moore THM, Zummit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G. Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review. www.thelancet.com Vol. 370 July 28, 2007.
196. Morbidity and Mortality Weekly Report: Calls to poison centers for exposures to electronic cigarettes – United States, September 2010-February 2014. Accessed online on November 10, 2014 at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6313a4.htm.
197. Morgan PR, Pace-Schott E, Pittman B, Stickgold R, Malison RT. Normalizing Effects of Modafinil on Sleep in Chronic Cocaine Users. Am J Psychiatry 2010; 167: 331-340.
198. Morgenstern J, Neighbors CJ, Kuerbis A, Riordam A, Blanchard KA, McVeigh KH, Morgan TJ, McCrady B. Improving 24-Month Abstinence and Employment Outcomes for Substance-Dependent Women Receiving Temporary Assistance for Needy Families With Intensive Case Management. American Journal of Public Health. February 2009, Vol. 99, No. 2.
199. Muhuri PK, Gfroerer JC, Davies MC. SAMHSA. Center for Behavioral Health Statistics and Quality(CBHSQ). *Data Review. Associations of nonmedical pain reliever use and initiation of heroin use in the United States*. Rockville MD 2014.
200. Najavits LM, Kivlahan, Kosten T. A national survey of clinicians' views of evidence-based therapies for PTSD and substance abuse. Addiction Res Theor 2011; 19(2):138-147.
201. National Conference of State Legislatures 7/20/16. State Medical Marijuana Laws. Accessed online at http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx.
202. National Drug Early Warning System (NDEWS) 2015. Fentanyl and fentanyl analogs. Accessed online at https://ndews.umd.edu/featuredcontent/1403.
203. National Institute of Health. News Release: Prevalence of marijuana use among U.S. adults doubles over past decade. Accessed online on November 10, 2016 at https://www.nih.gov/news-events/news-releases/prevalence-marijuana-use-among-us-adults-doubles-over-past-decade.
204. National Institute on Drug Abuse: the Science of Drug Abuse & Addiction. Accessed online on December 29 2014 at http://www.drugabuse.gov/drugs-abuse/bath-salts-synthetic-cathinones.
205. National Institute on Drug Abuse: "Flakka." Accessed online at https://www.drugabuse.gov/emerging-trends/flakka-alpha-pvp.
206. Naudet F, Palpacuer C, Boussageon R, Laviolle B. Evaluation in alcohol use disorders-insights from the nalmefene experience. *BMC Medicine* 2016; 14:119.
207. Nelson L. Hallucinogen in 'magic mushrooms' helps longtime smokers quit in Hopkins trial. *Hopkins Medicine* 2014. Accessed online on November 10, 2014 at http://hub.jhu.edu/2014/09/11/magic-mushrooms-smoking.
208. Neumann AM, Blondell RD, Azadfard M, Nathan G, Homish GG. Primary care patient characteristics associated with completion of 6-month buprenorphine treatment. *Addict Behav* 2013; 38(11): 2724-8.
209. Newton TF, Garza RDL, Brown G, Kosten TR, Mahoney JJ, Haile CN. Noradrenergic α_1 receptor antagonist treatment attenuates positive subjective effects of cocaine in humans: a randomized trial. PLoS One 2012; 7(2) e30854. Accessed website on November 5, 2012 at http://www.ncbi.nlm.nih.gov/pubmed?term=noradrenergic%20receptor%20antagonist%20treatment%20attenuates%20positive%20subjective%20effects%20of%20cocaine%20in%20humans%3A%20a%20randomized%20trial.

210. Ngo HTTT, Tait RJ, Hulse GK. Comparing Drug-Related Hospital Morbidity Following Heroin Dependence Treatment With Methadone Maintenance or Naltrexone Implantation. Arch Gen Psychiatry/Vol 65(No.4), Apr 2008.
211. Nia Ab, Medrano B, Perkel C, Galynker I, Hurd YL. Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis. *J Psychopharm* 2016.
212. NIDA InfoFacts. National Institute on Drug Abuse National Institutes of Health U. Department of Health and Human Services. January 2010.
213. NIDA InfoFacts: Heroin. National Institute on Drug Abuse. Accessed website on September 29, 2010 http://www.drugabuse.gov/infofacts/heroin.html
214. NIDA. National Institute on Drug Abuse. Monitoring the Future. Data Tables and Figures 2011. Bethesda MD, NIDA, NIH, DHHS. Accessed on October 26, 2012 at http://monitoringthefuture.org/data/11data/pr11t1.pdf
215. Nides M, Oncken C, Gonzales D, Rennard S, Watshy E, Anziano R, Reeves KR. Smoking Cessation with Varenicline, a Selective α4β2Nicotinic Receptor Partial Agonist. Arch Intern Med. 2006; 166: 1561-1568.
216. O'Brien CP. Anticraving medication for Relapse Prevention: A Possible New Class of Psychoactive Medications. Am J Psychiatry 2005; 162: 1423-1431.
217. O'Malley SS, Cooney JL, Krishnan-Sarin S, Dubin JA, McKee SA, Cooney NL, Blakeslee A, Meandzija B, Romano-Dahlgard D, Wu R, Makuch R, Jatlow P. A Controlled Trial of Naltrexone Augmentation of Nicotine Replacement Therapy for Smoking Cessation. Arch Intern Med. 2006; 166: 667-674.
218. Office of National Drug Control Policy: Office of Public Affairs February 11, 2014. Fact Sheet: Opioid Abuse in the United States. Accessed online on November 10, 2014 at http://www.whitehouse.gov/sites/default/files/ondcp/Fact_Sheets/opioids_fact_sheet.pdf.
219. Olsen Y, Sharfstein JM. Chronic Pain, Addiction, and Zohydro. *N Engl J Med* 2014; 370(22): 2061-3.
220. Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Feinn R, Kranzler HR. Nicotine Gum for Pregnant Smokers: A Randomized Controlled Trial. Obstet Gynecol. 2008 October; 112(4): 859-867.
221. Ostacher MJ, Perlis RH, Nierenberg AA, Calabrese J, Stange JP, Salloum I, Weiss RD, Sachs GS for the STEP-BD Investigators. Impact of Substance Use Disorders on Recovery From Episodes of Depression in Bipolar Disorder Patients: Prospective Data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 167:3, March 2010.
222. Oviedo-Joekes E, Brissette S, Marsh DC, Lauzon P, Guh D, Anis A, Schechter MT. Diacetylmorphine versus Methadone for the Treatment of Opioid Addiction. N Engl J Med 2009; 361:777-86.
223. Oviedo-Joekes E, Guh D, Brissette S, Marchand K, Marsh D, Chettiar J, Nosyk B, Krausz M, Anis A, Schechter MT. Effectiveness of diacetylmorphine versus methadone for the treatment of opioid dependence in women. Drug Alcohol Depend 2010 111(1-2):50-7.
224. Oviedo-Joekes E, Guh D, Brissette S, Marsh DC, Nosyk B, Krausz M, Anis A, Schechter MT. Double-blind injectable hydromorphone versus diacetylmorphine for the treatment of opioid dependence: a pilot study. J Subst Abuse Treat 2010; 38(4):408-11.
225. Paille F and Martini H. Nalmefene: a new approach to the treatment of alcohol dependence. *Subst Abuse Rehabil* 2014; 5: 87-94.
226. Paparrigopoulos T, Tzavellas E, Karaiskos D, Kourlaba G, Liappas I. Treatment of alcohol dependence with low-dose topiramate: an open-label controlled study. BMC Psychiatry 2011; 11:41.
227. Paulozzi LJ, Opioid Analgesics Involvement in Drug Abuse Deaths in American Metropolitan Areas. American Journal of Public Health. October 2006, Vol. 96. No. 10.

228. Penetar DM, Toto LH, Lee DYW, Lukas SE. A single dose of kudzu extract reduces alcohol consumption in a binge drinking paradigm. *Drug Alcohol Depend* 2016.
229. Pettinati HM, O'Brien CP, Dundon WD. Current status of co-occurring mood and substance use disorders: a new therapeutic target. *Am J Psychiatry* 2013; 170: 23-30.
230. Pettinati HM, Oslin DW, Kampman KM, Dundon WD, Xie H, Gallis TL, Dackis CA, O'Brien CP. A Double-Blind, Placebo-Controlled Trial Combining Sertraline and Naltrexone for Treating Co-Occurring Depression and Alcohol Dependence. Am J Psychiatry 167:6, June 2010.
231. Poling J, Oliveto A, Petry N, Sofuoglu M, Gonsai K, Gonzalez G, Martell B, Kosten TR. Six-Month Trial of Bupropion with Contingency Management for Cocaine Dependence in a Methadone-Maintained Population. Arch Gen Psychiatry/Vol. 63, Feb 2006.
232. Practice Parameter for the Assessment and Treatment of Children and Adolescents with Substance Use Disorders. J. Am. Acad. Child Adolesc. Psychiatry, 44:6, June 2005.
233. Prescription Drug Abuse. Topics in Brief. National Institute on Drug Abuse. March 2008.
234. ProCon. 28 Legal medical marijuana states and DC. Accessed online at http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.
235. ProCon.Org 2012. Accessed website on November 9, 2012 at http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.
236. ProCon.Org 2014. Accessed online n November 10, 2014 at http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.
237. Ray LA, Hutchison KE. Effects of Naltrexone on Alcohol Sensitivity and Genetic Moderators of Medication Response. Arch Gen Psychiatry/Vol. 64 (No.9), Sept 2007.
238. Rech MA, Donahey E, Dziedzic JMC, Oh L, Greenhalgh E. New drugs of abuse. *Pharmacotherapy* 2015; 35(2): 189-197.
239. Recovery Research Institute 2015. Retrain the Brain: Effects on Neural Alcohol Cue Reactivity. Accessed online at http://www.recoveryanswers.org/pressrelease/retrain-the-brain-effects-on-neural-alcohol-cue-reactivity/.
240. Reece AS. Review. Chronic toxicology of cannabis. Clinical Toxicology (2009) 47, 517-524.
241. Regulatory Affairs Professionals Society, 2016. Accessed online at http://www.raps.org/Regulatory-Focus/News/2016/02/24/24400/OTC-Opioid-Overdose-Antidote-Why-is-it-not-FDA-Approved/.
242. Reid HH and Ledgerwood DM. Depressive symptoms affect changes in nicotine withdrawal and smoking urges throughout smoking cessation treatment; preliminary results. *Addiction Research & Theory* 2016; 2491): 48-53.
243. Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings. U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration Office of Applied Studies.
244. Riggs PD, Mikulich-Gilbertson SK, Davies RD, Lohman M, Klein C, Stover SK. A Randomized Controlled Trial of Fluoxetine and Cognitive Behavioral Therapy in Adolescents with Major Depression, Behavior Problems, and Substance Use Disorders. Arch Pediatr Adolesc Med/Vol. 161 (No. 22), November 2007.
245. Rigotti NA, Munafo MR, Stead LF. Smoking Cessation Interventions for Hospitalized Smokers. Arch Intern Med. 2008; 168(18): 1950-1960.
246. Rigotti NA, Pipe AL. Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and Safety of Varenicline for Smoking Cessation in Patients with Cardiovascular Disease. A Randomized Trial. Circulation. 2010; 121:221-229.
247. Rose JE, Behm FM. Adapting smoking cessation treatment according to initial response to precessation nicotine patch. *Am J Psychiatry* 2013; 170:860-867.
248. Rubio G, Jimenez-Arriero MA, Martinez I, Ponce G, Palomo T. Efficacy of Physician-delivered Brief Counseling Intervention for Binge Drinkers. The American Journal of Medicine, Vol 123, No 1, January 2010.

249. Rupprecht LE, Donny EC, Sved AF. Obese smokers as a potential subpopulation of risk in tobacco reduction policy. *Yale Journal of Biology and Medicine* 2015; 88: 289-94.
250. SAMHSA 2015. Clinical use of extended-release injectable naltrexone in the treatment of opioid use disorder: a brief guide. Accessed online at http://store.samhsa.gov/product/Clinical-Use-of-Extended-Release-Injectable-Naltrexone-in-the-Treatment-of-Opioid-Use-Disorder-A-Brief-Guide/SMA14-4892R.
251. SAMHSA. 2015 National survey on drug use and health: summary of the effects of the 2015 NSDUH questionnaire redesign: implications for data users. Accessed online on November 10, 2010 at http://www.samhsa.gov/data/sites/default/files/NSDUH-TrendBreak-2015.pdf.
252. SAMHSA. Incorporating alcohol pharmacotherapies into medical practice: a review of the literature. Update: Treatment Improvement Protocol (Tip) 49. Accessed online on November 21, 2012 at http://kap.samhsa.gov/products/manuals/tips/pdf/TIP49_LitRev_Update_January_2012.pdf.
253. SAMHSA. Key substance use and mental health indicators in the United States: results from the 2015 National Survey on Drug Use and Health. Accessed online on November 10, 2016 at http://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf.
254. SAMHSA. National Institute on Alcohol Abuse and Alcoholism. Medication for the Treatment of Alcohol Use Disorder: A Brief Guide 2015. Accessed online at http://store.samhsa.gov/shin/content/SMA15-4907/SMA15-4907.pdf.
255. SAMHSA. Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings (NSDUH Series H-44). HHS Publication No. (SMA) 12-4713. Rockville, MD.
256. SAMHSA. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality September 4, 2014. *The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings*. Rockville, MD 2014.
257. SAMHSA. Substance Abuse and Mental Health Services Administration. *Results from the 2013 national survey on drug use and health: summary of national findings*. NSDUH Series H-48, HHS Publication No. (SMA) 13-4864. Rockville MD 2014.
258. Saylor K, Williams DW, Schuh KJ, Wietecha L, Greenbaum M. Effects of atomoxetine on self-reported high-risk behaviors and health-related quality of life in adolescents with ADHD. Curr Med Res Opin 2010; 26(9).
259. Schaub MP, Wenger A, Berg O, Beck T, stark L, Buehler E, Haug S. A web-based self-help intervention with and without chat counseling to reduce cannabis use in problematic cannabis users: three-arm randomized controlled trial. *Journal of Medical Internet Research* 2015; 17(10): e232.
260. Schnoll RA, Martinez E, Tatum KL, Glass M, Bernath A, Ferris D, Reynolds P. Increased self-efficacy to quit and perceived control over withdrawal symptoms predict smoking cessation following nicotine dependence treatment. Addict Behav 2011; 36(1-2):144-147.
261. Schnoll RA, Patterson F, Wileyto P, Heitjan DF, Shields AE, Asch DA, Lerman C. Effectiveness of Extended-Duration Transdermal Nicotine Therapy. A Randomized Trial. Ann Intern Med. 2010; 152: 144-51.
262. Schuckit MA. Treatment of opioid-use disorders. *The New England Journal of Medicine* 2016; 375(4): 357-368.
263. Schuler MS, Puttaiah S, Mojtabai R, Crum RM. Perceived barriers to treatment for alcohol problems: a latent class analysis. *Psychiatric Services* 2015; 66(11): 1221-1228.
264. Schwartz RP, Highfield DA, Jaffe JH, Brady JV, Bulter CB, Rouse CO, Callaman JM, O'Grady KE, Battjes RJ. A Randomized Controlled Trial of Interim Methadone Maintenance. Arch Gen Psychiatry/ Vol 63, Jan 2006.

265. Schwartz RP, Kelly SM, O'Grady KE, Gandhi D, Jaffe JH. Interim methadone treatment compared to standard methadone treatment: 4-month findings. J Subst Abuse Treat 2011: 41(1):21-29.
266. Seamon MJ. Medical Marijuana: An Evolving Landscape. Accessed website on July 7, 2010 www.medscape.com/viewarticle/716940
267. Secades-Villa R, Olfson M, Okuda M, Velasquez N, Pérez-Fuentes G, Liu S, Blanco C. Trends in the prevalence of tobacco use in the United States, 1991-1992 to 2004-2005. *Psychiatr Serv* 2013; 64(5): 458-65.
268. Shi Y. Smoking cessation among people seeking mental health treatment. *Psychiatr Serv* 2014 65(8): 957-960.
269. Silins E, Horwood LJ, Patton GC, Fergusson DM, Olsson CA, Hutchinson DM, Spry E, Toumbourou JW, Degenhardt L, Swift W, Coffey C, Tait RJ, Letcher P, Copeland J, Mattick RP. Young adult sequelae of adolescent cannabis use: an integrative analysis. *Lancet Psychiatry* 2014; 1: 286-93.
270. Sittambalam CD, Vij R, Ferguson RP. Buprenorphine outpatient outcomes project: can Suboxone be a viable outpatient option for heroin addiction? *J Comm Hosp Intern Med Perspect* 2014. Accessed online on January 12, 2014 at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3992357/pdf/JCHIMP-4-22902.pdf.
271. Smith SS, McCarthy DE, Japuntich SJ, Christiansen B, Piper ME, Jorenby DE, Fraser DL, Fiore MC, Baker TM, Jackson TC. Comparative Effectiveness of 5 Smoking Cessation Pharmacotherapies in Primary Care Clinics. Arch Intern Med. 2009; 169 (22): 2148-2155.
272. Smokeless Tobacco and Cancer: Questions and Answers. National Cancer Institute Fact Sheet. Accessed website on June 30, 2010 http://www.cancer.gov/cancertopics/factsheet/Tobacco/smokeless.
273. Song H, Li J, Lu C, Kang L, Xie L, Zhang Y, Zhou X, Zhong S. Tetrodotoxin alleviates acute heroin withdrawal syndrome: a multicentre, randomized, double-blind, placebo-controlled study. Clin Exp Pharmacol Physiol 2011; 38(8):510-4.
274. Soyka m. Nalmefene for the treatment of alcohol use disorders: recent data and clinical potential. *Expert Opinion on Pharmacotherapy* 2016.
275. Spoth R, Guyll Mx, Chungyeol. Universal Intervention as a Protective Shield Against Exposure to Substance Use: Long-Term Outcomes and Public Health Significance. American Journal of Public Health November 2009, Vol 99, No. 11.
276. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioral interventions for smoking cessation (Review). The Cochrane Library 2016.
277. Steinberg MB, Greenhaus S, Schmelzer AC, Bover MT, Foulds J, Hoover DR, Carson JL. Triple-Combination Pharmacotherapy for Medically Ill Smokers. Ann Intern Med. 2009; 1500:447-454.
278. Studts JS, Burris JL, Kearns DK, Worth CT, Sorrell CL. Evidence-based tobacco cessation treatment by dental hygienist. J Dent Hyg 2011; 85(1):13-21.
279. Subramaniam GA, Warden D, Minhajuddin A, Fishman MJ, Stitzer ML, Adinoff B, Trivedi M, Weiss R, Potter J, Poole S, Woody GE. Predictors of abstinence: National Institute of Drug Abuse multisite buprenorphine/naloxone treatment trial in opioid-dependent youth. J Am Acad Child Adolesc Psychiatry 2011; 50(11): 1120-8.
280. Tait R, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical Toxicology* 2016; 54(1): 1-13.
281. Timko C, Schultz NR, Cucciare MA, Vittorio BA, Garrison-Diehn CG. Retention in medication-assisted treatment for opiate dependence: a systematic review. *Journal of Addictive Diseases* 2016; 35(1):22-35.

282. The American College of Obstetricians and Gynecologists. At-Risk Drinking and Illicit Drug Use: Ethical Issues in Obstetric and Gynecologic Practice. ACOG Committee Opinion Number 422, December 2008.
283. The American College of Obstetricians and Gynecologists. Committee Opinion Number 538 October 2012. Accessed on October 25, 2012 at http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Health_Care_for_Underserved_Women/Nonmedical_Use_of_Prescription_Drugs.
284. The Medical Letter 2015. Bunavail: another buprenorphine/naloxone formulation for opioid dependence. Accessed online at http://secure.medicalletter.org/TML-article-1461c.
285. The U.SA. Department of Justice. The dangers and consequences of marijuana abuse. Accessed online on November 10, 2014 at http://getsmartaboutdrugs.com/sites/getsmartaboutdrugs.com/files/publications/The_Dangers_and_Consequences_of_Marijuana_AbuseMay2014.pdf.
286. Thomas CP, Fullerton CA, Kim M, Montejano L, Lyman, DR. Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv* 2014; 65(2): 158-70.
287. U.S. Dept. of Health and Human Services. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Accessed online at https://addiction.surgeongeneral.gov/surgeon-generals-report.pdf.
288. Volkow ND, Baler RD, Compton Wm, Weiss SRB. Adverse health effects of marijuana use. *N Engl J Med* 2014; 371(9): 2219-2227.
289. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies-Tackling the opioid overdose epidemic. *N Engl J Med* 2014; 370(22): 2064-65.
290. Volkow ND, Wang GJ, Begleiter H, Porjesz B, Fowler JS, Telang F, Wong C, Yeming M, Logan J, Goldstein R, Alexoff D, Thanos PK. High Levels of Dopamine D_2 Receptors in Unaffected Members of Alcoholic Families. Arch Gen Psychiatry/ Vol. 63, Sep 2006.
291. VolKraft WK, Gibson E, Dysart K, Damle VS, LaRusso JL, Greenspan JS, Moody DE, Kaltenback K, Ehrlich ME. Sublingual Buprenorphine for Treatment of the Neonatal Abstinence Syndrome: A Randomized Trial. Pediatrics. 2008 September; 122(3): e601-e607.
292. Watkins KE, Hunter SB, Hepner KA, Paddock SM, Cruz EDL, Zhou AJ, Gilmore J. An effectiveness trial of group cognitive behavioral therapy for patients with persistent depressive symptoms in substance abuse treatment. Arch Gen Psychiatry 2011; 68(6):577-584.
293. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MCP. QT-Interval Effects of Methadone, Levomethaldyl, and Buprenorphine in a Randomized Trial. Arch Intern Med. 2007; 167 (22): 2469-2475.
294. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MN, Haller KL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, Ling W. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence. Arch Gen Psychiatry; 68(12):1238-46.
295. Westover AN, McBride S, Haley RW. Stroke in Young Adults Who Abuse Amphetamine or Cocaine. Arch Gen Psychiatry/Vol. 64, April 2007.
296. Whittaker R, Dorey E, Bramley D, Bullen C, Denny S, Elley CR, Maddison R, McRobbie H, Parag V, Rodgers A, Salmon P. A theory-based messaging mobile phone intervention for smoking cessation: randomized controlled trial. J Med Internet Res 2011; 13(10):e10.
297. Wiers CE, Steizel C, Gladwin TE, Park SQ, Pawelczack s, Gawron CK, Stuke H, Heinz A, Wiers RW, Rinck M, Lindenmeuyer J, Walter H, Bermpohl F. Effects of cognitive bias modification training on neural alcohol cue reactivity in alcohol dependence. *Am J Psychiatry* 2015; 172:4: 335-343.
298. Williams AR and Bisaga A. From AIDS to opioids – how to combat an epidemic. *NEJM* 2016; 375(9): 813-815.

299. Williams JM, Steinberg ML, Zimmermann MH, Gandhi KK, Stipelman B, Budsock PD, Ziedonis DM. Comparison of two intensities of tobacco dependence counseling in schizophrenia and schizoaffective disorder. J Subst Abuse Treat 2010;38(4): 384-393.
300. Wilson CR, Harris SK, Sherritt L, Lawrence N, Glotzer D. Parental Alcohol Screening in Pediatric Practices. Pediatrics Volume 122, Number 5, November 2008.
301. Winickoff JP, Healey EA, Regan S, Park ER, Cole C, Friebely J, Rigotti. Using the postpartum hospital stay to address mother's and father's smoking: the NEWS study. Pediatrics 2010; 125; 518-525.
302. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, Patkar A, Publicker M, McCain K, Potter JS, Forman R, Vetter V, McNicholas L, Blaine J, Lynch KG, Fudala P. Extended vs. Short-term Buprenorphine-Naloxone for Treatment of Opioid-Addicted Youth: A Randomized Trial. *JAMA* 2008 November 5, 300(17): 2003-2011.
303. Young-Wolff KC, Kline-Simon AH, Das S, Mordecai DJ, Miller-Rosales C, Weisner C. Smoking trends among adults with behavioral health conditions in integrated healthcare: a retrospective cohort study. *Psychiatric Services* 2016; 67(9): 996-1003.
304. Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan A, Tsui T, Aguilera JA, Advani S, Alexander LEC, Brumund KT, Wang-Rodriguez JW, Ongkeko WM. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. *Oral Oncology* 2016; 52: 58-655.
305. Ziedonis D, Das S, Tonelli M. Smoking and mental illness: strategies to increase screening, assessment, and treatment. *Focus* 2015; 13(3):290-305.