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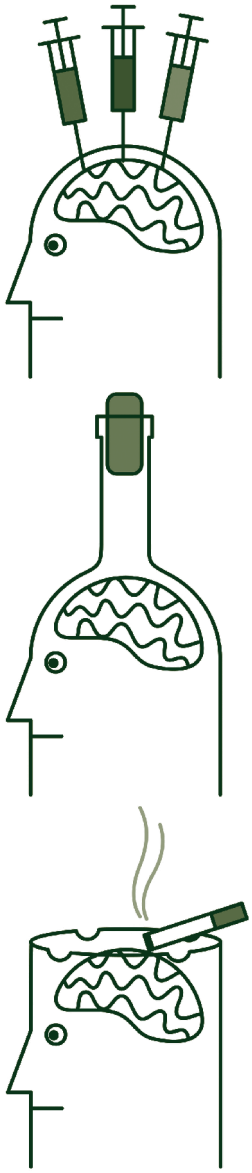

EDITORIAL

A Call to Arms: The Role of the Psychiatry Resident in the Current Opioid Epidemic

Rachel Katz, M.D.

On February 2, 2016, the White House released an update to the President's annual budget, proposing $1.1 billion in additional funding to address the growing epidemic of prescription opiate and heroin abuse in the United States. This revision of the 2010 National Drug Control Strategy and 2011 Prescription Drug Abuse Prevention Plan pledged improved access to medication-assisted treatment, addiction research, prescriber training and expanded prevention efforts for an illness to which the Centers for Disease Control and Prevention attributes greater annual mortality than motor vehicle accidents (1). Even as top government agencies fight to stem the tide of opiate abuse, overdoses, and deaths, the stigma of addiction persists—among the general population, those who represent us in government, and even our colleagues in medicine—resulting in inadequate access to what is now the standard of care for opiate use disorders: detoxification then multimodal treatment programs that include long-term opiate replacement medication (2). Reluctance to accept opiate replacement and harm-reduction practices as the new standard perpetuates inadequate care practices, despite compelling data that detoxification-only and abstinence-only approaches result in high rates of relapse and overdose (2–4).

The numbers of opioid users, overdoses, and deaths continue to escalate, with an alarming transition rate to heroin (now often laced with fentanyl at unpredictable potencies), despite legislative measures increasing prescriber oversight and limiting opioid availability (4). As psychiatrists, we have a unique role to play in this public health crisis.

We must provide care that is supported by the literature rather than public or political opinion.

ADVOCATE WITHIN YOUR TRAINING PROGRAM

Request training in naloxone kit prescribing and counseling, and prescribe them to appropriate patients and their families (5). Obtain a Drug Enforcement Agency "X" license to prescribe buprenorphine/naloxone and be familiar with the practice. Seek to care for patients with comorbid substance and psychiatric disorders to better appreciate their accompanying diagnostic challenges and complex care needs. Request education on the ever-evolving legislative changes regarding opiates and other substances of abuse. Stay up to date with the literature linking substance use and chronic psychiatric illness (6).

ADVOCATE WITHIN YOUR COMMUNITY

Encourage local governments to approve over-the-counter access to naloxone emergency kits (5). Be a proponent of the harm-reduction model: abstinence-only programs are often inadequate and can perpetuate stigma (2, 3). Emphasize the need to treat rather than incarcerate. Support the enforcement of prescription monitoring programs and mandated reviews by prescribers (5, 6). Volunteer to speak publicly to provide evidence-based information and combat stereotypes.

ADVOCATE WITHIN YOUR MEDICAL SYSTEM

Assess whether your hospital is equipped to host a needle exchange program or will accept unused medications (6). Seek out opportunities to collaborate with medical and surgical training programs to provide education about the treatment of patients with comorbid substance use disorders. Emphasize the importance of frequent reviews of prescription monitoring programs and the dangers of haphazard prescribing practices (5, 6).

During the last opiate epidemic of the 1880s, largely considered iatrogenic, physicians played a considerable role in limiting access to opiates, advocating for more appropriate prescribing practices, increased police involvement, and eventually the passage of the Harrison Act of 1915, which mandated monitoring and documentation of prescriptions from medical sources (2). We must prepare ourselves for the influx of patients who will need our care. We must provide care that is supported by the literature rather than public or political opinion. We can help curb this epidemic, like our predecessors before us.

In this issue of the Residents' Journal, our authors have addressed topics highly relevant to the care of this complex and stigmatized population. We hope you find the articles a valuable read.

Dr. Katz is a third-year resident in the Department of Psychiatry, Yale University, New Haven, Conn, and the Guest Editor for this issue of the *Residents' Journal*.

Starting in July, she will serve as Senior Deputy Editor.

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ARTICLE

Nicotine Replacement Therapy

Lee Flowers, M.D., M.P.H.

According to the Centers for Disease Control and Prevention, tobacco use is the leading preventable cause of death in the United States (1). The average lifespan of smokers is reduced by more than 10 years compared to individuals who have never smoked (2). Smoking cessation by age 40 reduces mortality by about 90% and cessation by age 60 reduces the loss by 40% (2). Some studies have found improvements in symptoms of depression and anxiety from smoking cessation with effect sizes comparable to those for antidepressants (3). The prevalence and mortality of smoking is so great among individuals with major psychiatric disorders that it is estimated that one-half of patients diagnosed with schizophrenia, bipolar disorder, and major depressive disorder will die of a tobacco-related illness (4). There is evidence that smoking cessation promotes abstinence from other substances in those with more than one substance use disorder (5, 6). As alcohol and tobacco together produce more than additive risks for cancer, treating tobacco and alcohol use together in particular can be more helpful than treating each in isolation (5).

Despite the high impact on health outcomes, there is a major discrepancy between the low rate of clinicians treating tobacco use disorder and the availability of effective treatment (7). Despite efficacy of treatment, up to two-thirds of smokers attempting to quit do not use any evidence-based treatment (8). Psychiatrists have the under-recognized opportunity and obligation to provide patients lifesaving and life-improving treatments for tobacco use disorder that are safe, effective, affordable, and often well received. Patients should be aware that under the Affordable Care Act, they are covered for smoking cessation treatment with no cost sharing. With the exception of unchanged plans grandfathered in before March 2010, health insurance providers are required to cover at least two tobacco cessation attempts annually, including four counseling sessions and 90 days of Food and Drug Administration (FDA)-approved smoking cessation medications (9). Nicotine replacement therapy products come in five forms: gum, inhalers, lozenges, nasal sprays, and transdermal patches (see Table 1). As applied in the present article, nicotine replacement therapy does not refer to smoked tobacco products, smokeless tobacco, or electronic cigarettes.

MECHANISM OF ACTION AND PHARMACOKINETICS

Nicotine acts as a full agonist on nicotinic acetylcholine receptors in the autonomic ganglia and CNS. It has stimulant properties and enhances rewarding effects by increasing downstream release of dopamine in the ventral tegmentum of the midbrain (10). Additionally, nicotine's desensitization of a6b2 nAChRs on cholinergic interneurons of the striatum slows dopamine depletion and enhances the contrast between dopamine release evoked by phasic and tonic firing of dopaminergic nerves in the striatum, leading to increased reward salience (11). Both positive reinforcement (e.g., heightened vigilance, improved mood, and weight loss) and negative reinforcement (alleviation of withdrawal symptoms, e.g., anxiety, irritability, impaired concentration, and increased appetite) mediate nicotine addiction (12). The pharmacokinetics of nicotine peak and fall quickly, contributing to their addictive potential. Nicotinic acetylcholine receptors become desensitized when nicotine levels in the brain are high and then resensitize, leading to withdrawal effects, as nicotine levels fall. Slower release nicotine delivery mechanisms are therefore less reinforcing both because nicotinic acetylcholine receptors cannot rapidly resensitize and because the user has less control in titrating the dose to receive a rewarding effect when desired (12). Furthermore, nicotine replacement therapy lacks additional potentially addictive compounds, such as menthol and acetaldehyde condensation products, which inhibit dopamine metabolism through monoamine oxidase inhibition (2, 10).

Nicotine inhaled from cigarette smoke is easily absorbed over the large surface area of the lungs and is transported directly to the brain via the pulmonary venous system in 10–20 seconds (13). Nicotine levels reaching the brain fall quickly as nicotine is redistributed in the body, largely to skeletal muscle (12, 13). Nicotine replacement therapies from gum, lozenges, inhalers, and nasal sprays are absorbed through oral or nasal mucosa and go into systemic venous circulation. These forms cause nicotine levels to peak on the order of minutes, while transdermal patches release nicotine even more gradually with peak concentrations within hours after application (13). Swallowed nicotine is absorbed poorly in the acidic stomach environment (2). Some is absorbed in the small bowel and is carried into the portal venous circulation where it undergoes first-pass hepatic metabolism, resulting in low (30%–40%) bioavailability. Ingestion of nicotine replacement therapy by swallowing gum or lozenges is therefore not recommended, but rather through buccal absorption. Elimination of nicotine is highly variable from person to person, with an average half-life of approximately 2 hours, primarily by CYP2A6 (10, 13). Nicotine has varying addictive potential depend-

TABLE 1. Nicotine Replacement Therapy Types, Dosage Guidance, and Precautions and Side Effects

Type	Dosage Guidance	Precautions and Side Effects
All types	Variable by form Informed by individual clinical factors	Use with caution within 2 weeks of myocardial infarction, in patients with serious arrhythmias, and in patients with unstable angina pectoris. Nicotine replacement therapy does not have an established favorable benefit/risk balance in pregnant or breastfeeding patients.
Gum	2-mg or 4-mg per piece 4-mg gum is for patients smoking ≥25 cigarettes daily Use at least one piece every 1–2 hours as needed up to 12 weeks. Maximum: 24 pieces per day	Mouth soreness, hiccups, dyspepsia, and jaw ache. Usually mild and transient and often can be alleviated with improved chewing technique.
Inhaler	A cartridge delivers 4 mg of nicotine over approximately 80 inhalations Recommended dosage is 6–16 cartridges/day Recommended duration up to 6 months, with taper over in the final 3 months	Local irritation in the mouth and throat, coughing, rhinitis. Usually mild and declines with use.
Lozenges	2-mg or 4-mg per piece 4-mg lozenge is recommended for patients who smoke their first cigarette within 30 minutes of waking Use at least nine lozenges per day in the first 6 weeks and up to 12 weeks Maximum: 20 per day	Nausea, hiccups, and heartburn. A 4-mg lozenge is associated with increased headache and coughing.
Nasal spray	0.5-mg dose delivered to each nostril (1 mg total) Start at 1–2 doses per hour, increasing until symptom relief Recommended range of 8–40 doses per day for 3–6 months	Nasal irritation (≥90%), nasal congestion, and sometimes transient changes in smell and taste. Not to be used in patients with severe reactive airway disease. Highest dependence potential of nicotine replacement therapies. A total of 15%–20% of patients report using beyond the recommended period and 5% above the recommended dose.
Transdermal patch	7-, 14-, and 21-mg doses Individualize dose by previous experience with patch and amount smoked (one cigarette often yields roughly 1 mg nicotine)	Local skin reactions (up to 50%), usually self-limited. Insomnia and/or vivid dreams.

ing on the mechanism by which it is administered (10, 13). The FDA recognizes that nicotine delivered via gum, lozenges, and patches has little potential for abuse or dependence and has approved these forms for over-the-counter sale (14). The pharmacokinetics of inhalers and nasal sprays may make them more habit-forming than other nicotine replacement therapies but less so than smoking (13). Nicotine replacement therapies assist with smoking cessation by stabilizing nicotine levels in the blood, thereby reducing both the positive and negative reinforcing effects of faster-acting nicotine delivery mechanisms such as cigarettes.

DRUG-DRUG INTERACTIONS

Nicotine has direct interactions with some drugs and also may indirectly affect hepatic metabolism of other drugs insofar as it offsets smoking, which induces hepatic enzymes. A randomized controlled study of 10 patients demonstrated that nicotine potentiates the effect of adenosine and that tachycardia is more likely to occur when both agents are combined (15). Cimetidine has been demonstrated to slow the elimination of nicotine, resulting in greater effect duration for the same dose (16). Cigarette smoke contains polycyclic aromatic hydrocarbons that are strong inducers of the hepatic enzymes CYP1A1, CYP1A2, and 2E1 (17, 18). Smoking tobacco accordingly decreases the serum levels of medications such as clozapine, olanzapine, imipramine, fluvoxamine, caffeine, theophylline, tacrine, propranolol, flecainaide, pentazocine, and erlotinib. However, nicotine itself is not responsible for these interactions. Clinicians must monitor levels and side effects of these medications closely if the patient's smoking habits change, as levels can increase significantly with smoking cessation and nicotine replacement therapy.

INDICATIONS AND EFFICACY

The United States Public Health Service recommends the use of nicotine replacement therapy, bupropion, varenicline, or a combination for all patients attempting to quit smoking, except when medically contraindicated or for populations in which insufficient evidence for efficacy exists (pregnant women, adolescents, and smokeless tobacco users) (7). Nicotine replacement therapy increases the success rate of smoking quit attempts by 50%–80% and demonstrates similar efficacy to bupropion and varenicline (19–21). Combination treatment with both nicotine replacement therapy and bupropion is more effective than monotherapy with either (19). The most effec-

tive type of therapy is a combination of the transdermal patch and a faster-acting form, such as the lozenge or gum, for breakthrough cravings (12, 21). Although varenicline is more effective than any single form of nicotine replacement therapy, combination nicotine treatment can be equally effective (20). Additionally, nicotine replacement therapy-assisted smoking reduction has the benefit of promoting abstinence among smokers who are not ready to quit at the time therapy is started (22, 23).

Optimal clinical strategies for nicotine replacement therapy are subject to ongoing study and development. Evidence supporting the role of nicotine replacement therapy in adolescent and pregnant smokers is sparse, and different countries have conflicting recommendations on its use (8). Studies comparing nicotine replacement therapy regimens beginning 2 or 4 weeks before a quit attempt with therapy beginning at smoking cessation yield conflicting results and deserve further research (8, 19). Extended duration or maintenance treatment and high-dose nicotine replacement therapy (e.g., 42 mg daily transdermal vs. 21 mg daily transdermal) applied to study populations have only weak evidence of benefit (8). This does not mean that individual patients cannot benefit from these strategies. Some smokers do benefit from maintenance treatment with therapy, and long-term use is believed to be safe (13, 21). If decreasing intensity of nicotine cravings and diminishing medication adherence explain nonsuperiority of extended treatment in study populations, select patients with sustained cravings who can adhere to a prolonged therapy regimen might still benefit from extended treatment (8). The degree of nicotine dependence likely mediates optimal dosing for individual patients. Ongoing research may help guide individualized therapy regimens by phenotypes of nicotine dependence and nicotine metabolism and by genetic markers of nicotine metabolism, nicotine receptors, and dopamine receptors (8). New delivery mechanisms being developed include a nicotine inhalator, nicotine cannon, nicotine pouch, and rapid delivery gum, as well as an oral spray, all of which appear to control nicotine withdrawal at least as well as currently available therapies. Early evidence is mixed regarding the superiority versus equality of oral spray compared with standard therapy in maintaining abstinence from tobacco (8).

KEY POINTS/CLINICAL PEARLS

- Cigarettes differ greatly from nicotine replacement therapy in addictive potential, morbidity, mortality, and drug-drug interactions. Nicotine replacement therapy is much safer, less addictive, and less prone to medication interactions than cigarettes.
- A combination of a long-acting nicotine patch along with lozenge or gum is more effective than a single form of nicotine replacement therapy.
- Pharmacotherapy for smoking cessation, including but not limited to nicotine replacement therapy, should be offered to all smokers except those with contraindications.
- Nicotine replacement therapy should be approached with caution in pregnant or breastfeeding patients or within 2 weeks of myocardial infarction.

Nicotine replacement therapy can be used to alleviate the discomfort of nicotine withdrawal for individuals who are unable to smoke (e.g., while hospitalized). The importance of such symptomatic care is underlined by data showing that smokers with schizophrenia experiencing nicotine withdrawal in a psychiatric emergency department setting demonstrated less agitation when treated with therapy (24).

ADVERSE EFFECTS

Cigarette smoking is known to precipitate acute cardiac events by at least three mechanisms, one of which involves nicotine. Nicotine's hemodynamic effects include increasing heart rate and blood pressure and constricting coronary arteries, increasing myocardial work while decreasing blood flow to the myocardium. Unrelated to nicotine, cigarettes produce a hypercoagulable state, and carbon monoxide in smoke decreases oxygen delivery to the heart (25). Chronic use of nicotine replacement products in nonsmokers should theoretically increase the risk of acute cardiac events but to a much lesser degree than tobacco. No effect of increased risk of acute cardiac events is actually seen when nicotine replacement therapy is used by smokers. This is due to the following reasons: the hemodynamic effects of nicotine have a relatively flat dose-response relationship; cigarettes deliver nicotine more rapidly than gum or patches, resulting in more intense hemodynamic effects; and nicotine obtained from nicotine replacement products typically decreases nicotine intake from smoking even in people instructed to smoke ad libitum on nicotine replacement therapy (25). In the Lung Health Study, a multicenter trial following 5,887 middle-aged smokers over 5 years, two-thirds of participants had treatment for smoking cessation that often included nicotine gum. Smokers who quit with assistance from nicotine gum had fewer hospital admissions for cardiovascular events than either continuing smokers or those who quit without nicotine gum (26). Multiple clinical trials have failed to demonstrate increased risk of cardiovascular events with transdermal nicotine patches in current smokers with known cardiovascular disease (25).

Smokeless tobacco is associated with increased risk of pregnant women delivering infants that are small for gestational age and apnea in newborns, both of which might be mediated by effects of nicotine (2). Several studies have examined adverse effects of nicotine replacement products used for smoking cessation in pregnant smokers. No statistically significant differences were found between cohorts regarding outcomes such as preterm birth, placental abruption, or birth weight. Of five studies that compared birth weights and rates of preterm delivery, three found no differences in average birth weight and two found risk of higher-average birth

weight with nicotine replacement therapy, one of which also found decreased incidence of low birth weight and preterm delivery with therapy (27). For pregnancy, transdermal nicotine is classified as FDA Category D, and shorter-acting therapies are classified as FDA Category C. Nicotine concentrates in breast milk, with a 2.9:1 ratio with maternal serum (28). Risks to breastfeeding infants are not well known (29).

Precaution should be taken for patients less than 18 years old, those with serious or worsening angina, those with myocardial infarction in the past 2 weeks, or those with serious arrhythmia. Nicotine gum and lozenges may cause hiccups, cough, and dyspepsia. Nicotine gum may also cause mouth/jaw soreness. With incorrect chewing technique, lightheadedness and nausea/vomiting may occur (21). Both lozenges and patches can cause sleep disturbances, and patches also may precipitate local skin reactions (19). Nasal sprays can cause tearing, sneezing, and rhinitis. All forms of nicotine replacement therapy have the potential to trigger headaches (21).

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ARTICLE

Heavy-Drinking Smokers: Pathophysiology and Pharmacologic Treatment Options

Michael Mirbaba, M.D., M.A., Ph.D.

Heavy-drinking smokers are a sizeable population with comorbid alcohol and tobacco use disorders requiring specific treatments tailored to both disorders. Heavy-drinking smokers are defined as women who drink >7 alcoholic beverages per week and >3 drinks on one occasion and men who drink >14 alcoholic beverages per week and >4 drinks on one occasion at least once weekly (in the past 30 days) and smoke at least 10 cigarettes daily (1). Though not formally recognized in DSM-5, heavy-drinking smokers are a distinct subpopulation identified in research studies, amounting to more than 6 million people in the United States who suffer greater risks of negative health consequences than those with either an alcohol use disorder or tobacco use disorder alone (2). Increased morbidity and mortality in heavy-drinking smokers are in part attributable to cardiopulmonary disease, malignancies, and hepatic disease. It is not surprising that alcohol and tobacco are the most commonly used legal substances of abuse given their widespread availability and lengthy market presence. Interestingly, use of either substance predisposes to use of the other: drinkers who have five or more drinks per week are 2.4 times more likely to smoke than those who have less than five drinks per year; smokers are three times more likely to engage in hazardous drinking than nonsmokers; during drinking episodes, abstinent smokers are five times more likely to have a tobacco relapse (3). In view of the staggering statistics that patients with mental illness consume 38% of all alcohol and 40% of all cigarettes and the fact that these substances cost society an estimated $550 billion annually, psychiatrists should be familiar with heavy-drinking smokers to provide evidence-based treatments (4).

PATHOPHYSIOLOGY

Although the mechanism of the comorbidity between alcohol and tobacco use disorders remains unclear, there are shared genetic risk factors (polymorphisms), pharmacologic (cross-sensitization) and psychological (conditioning) changes, and common pathophysiology within mesolimbic dopaminergic, nicotinic, and opioid pathways that may contribute (5, 6). The role of nicotinic acetylcholine receptors (nAChRs) is of particular interest in understanding the co-use of alcohol and nicotine, as nAChRs are where both substances are believed to interact.

nAChRs are ligand-gated ion channels that are highly prevalent throughout the CNS and consist of several subtypes with varying functions modulating excitatory neurotransmission. Research has focused primarily on two specific subtypes of nAChRs, α4β2 and α7, which are the most common subtypes. Nicotine binds the α4β2 subtype with higher affinity than the α7 subtype and causes the channels to open, leading to an influx of calcium and sodium ions that subsequently depolarize the neuron. Nicotine has a wide range of pharmacologic effects beyond its nAChR agonism, as it also causes release of dopamine, serotonin, norepinephrine, GABA, glutamate, and endogenous opioids, all of which have been implicated in its addictive potential. With chronic nicotine exposure, nAChRs become desensitized to its excitatory effects, particularly the α4β2 subtype whose expression increases over time (7).

Beyond alcohol's well-known agonist effects at GABA-A receptors and glutamatergic antagonism, it also exhibits agonism at α4β2 and antagonism at α7 nAChRs, the latter of which appears to be involved in protecting neurons from alcohol's toxicity (8). Alcohol's effects specifically on the α4β2 subtype may decrease the nicotine-induced desensitization of α4β2 nAChRs, thereby enhancing excitatory neurotransmission, which could in part contribute to the co-use of alcohol and nicotine. Furthermore, chronic use of alcohol has been shown not only to produce tolerance at GABA-A receptors, but it also alters the prevalence of nAChRs, and in doing so produces cross-tolerance to nicotine. Likewise, chronic nicotine exposure has been known to produce cross-tolerance to alcohol in animal models (9). Both of these processes may be mediated by genetic factors related to the expression of certain polymorphisms of the α4 and α7 nAChR subunits, which could explain individual differences in sensitivity to the effects of alcohol and nicotine (9). More recent research has shown that alcohol and nicotine co-use enhances ventral tegmental area glutamatergic AMPA receptor function via agonism at α6 nAChRs (10). This results in increased excitatory neurotransmission within mesolimbic dopamine pathways critical to addiction pathophysiology. Despite these putative mechanisms, pathophysiologic interactions between alcohol and nicotine at nAChRs and other key receptors are likely more complex and not entirely understood at this time.

PHARMACOTHERAPIES

There are no Food and Drug Administration (FDA)-approved pharmacother-

TABLE 1. Potential Pharmacotherapies for Heavy-Drinking Smokers

Medication	Dosage	Mechanism of Action	Common Side Effects	Contraindications/Cautions
Oral naltrexone	50 mg daily Maximum: 200 mg daily	Mu-opioid receptor antagonism with kappa-opioid receptor partial agonism Blocks rewarding effects of alcohol and nicotine in the nucleus accumbens	Nausea, vomiting, headache, anorexia, fatigue, sedation, insomnia, anxiety, apathy, anhedonia, opioid withdrawal, dose-dependent hepatotoxicity	Requires naloxone challenge/opioid abstinence Hepatic or renal impairment Depression, suicidal ideation
Injectable extended-release naltrexone	380 mg (IM) every 4 weeks	Same as oral naltrexone	Injection site reactions, plus all others listed above for oral naltrexone	Same as oral naltrexone
Varenicline	1 mg twice daily for up to 14 weeks	Partial agonism of multiple nAChRs, including α4β2 and α6β2 Believed to reduce the ability of nicotine and alcohol to activate mesolimbic pathways	Nausea, vomiting, insomnia, headache, abnormal dreams, somnolence, xerostomia, constipation, diarrhea, flatulence, dysgeusia, dyspepsia, appetite changes, hostility, agitation, depression, suicidal ideation	Renal impairment Psychiatric disorders or history Seizure disorder or risk Cardiovascular disease Alcohol use Patients <18 years old Safe in stable cardiovascular disease
Topiramate	200–300 mg daily Maximum: 400 mg daily	Antagonism of AMPA/kainate glutamatergic receptors Antagonism of voltage-dependent sodium channels Agonism of GABA-A receptors Inhibition of carbonic anhydrase	Nausea, diarrhea, somnolence, fatigue, cognitive impairment, dizziness, ataxia, anorexia, weight loss, paresthesias, nasopharyngitis, diplopia, glaucoma, metabolic acidosis, nephrolithiasis, depression, anxiety, suicidal ideation	Hepatic or renal impairment Depression, suicidal ideation Pregnancy Acute myopia and secondary angle closure glaucoma Hyperthermia Hyperammonemia Encephalopathy

apies tailored to heavy-drinking smokers. Despite expert consensus that both disorders should be treated simultaneously, many heavy-drinking smokers receiving treatment for their alcohol use disorder are not offered treatment for their tobacco use disorder, even though up to 80% are interested in smoking cessation and effective tobacco use disorder treatments are easy to provide (11). This occurs in spite of the fact that tobacco use is the leading preventable cause of death in the United States, according to the Centers for Disease Control and Prevention (12). Furthermore, there is evidence that continued tobacco use represents a substantial risk for alcohol relapse and increases the likelihood of having an alcohol use disorder 3 years after treatment (odds ratio=2.30) (13). By providing interventions targeting both disorders, chances of successful treatment outcomes may improve.

Naltrexone

Of the four FDA-approved pharmacotherapies for alcohol use disorder, only oral naltrexone has been shown to decrease smoking while decreasing alcohol use in recent clinical studies (14). Beyond blunting the rewarding and reinforcing properties of each substance, decreased tobacco use may also be a consequence of naltrexone acting to concomitantly decrease alcohol use, which in turn leads to less tobacco use, given their correlated co-use. Although there are no clinical studies investigating the effect of injectable extended-release naltrexone on smoking cessation in heavy-drinking smokers, it is not unreasonable to infer similar outcomes given their identical mechanisms of action. In fact, injectable extended-release naltrexone may have further advantages of improved treatment retention (see Table 1).

Varenicline

Varenicline monotherapy has also been shown to decrease alcohol use and cravings in heavy-drinking smokers while decreasing smoking rates (15). This is hypothesized to be the result of varenicline's partial agonism at multiple nAChRs, most notably the α4β2 subtype. Partial agonism at α4β2 nAChRs appears to blunt the effects of alcohol and nicotine on mesolimbic pathways. Specifically, varenicline's partial agonism at α4β2 nAChRs likely decreases alcohol's ability to activate α4β2 nAChRs, as any increased presence of activating ligands, such as alcohol, leads to competitive antagonistic effects from varenicline at this subunit. Moreover, recent research has identified that varenicline's α6β2 partial agonism decreases the α6 nAChR activation induced by co-use of alcohol and nicotine, which in turn decreases AMPA receptor activation within the ventral tegmental area (10). By reducing the agonist effects of alcohol and nicotine on both α4β2 and α6 nAChRs, varenicline may indirectly decrease dopamine release within the nucleus accumbens when the substances are co-used, thereby reducing the rewarding and reinforcing properties of each (see Table 1).

Varenicline Plus Naltrexone

Given these putative effects of alcohol and nicotine on the endogenous opioid system and nAChRs, the combination of varenicline plus naltrexone is an appealing treatment for heavy-drinking smokers, since it targets two distinct but overlapping pathways that contribute to addiction pathophysiology. In a recent short-term clinical study involving heavy-drinking smokers, varenicline plus low-dose naltrexone (25 mg/day) acted synergistically to decrease use

of both alcohol and tobacco more than placebo or either medication alone (16). These promising results require replication before consensus agreement on this particular combination pharmacotherapy. Of note, although the FDA issued a black box warning for varenicline regarding increased risks of adverse neuropsychiatric events, such as depression, suicidal ideation/behaviors, and suicide in patients with or without preexisting psychiatric conditions, subsequent analyses have not found any evidence of these increased risks (17).

Topiramate

Beyond targeting the endogenous opioid system and nAChRs, there is growing evidence that off-label use of topiramate decreases both alcohol and tobacco use (18, 19). Topiramate has also been shown to decrease use of both substances in heavy-drinking smokers (20, 21). Topiramate acts by blocking AMPA/kainate glutamatergic receptors and facilitating GABA-A neurotransmission, the former of which may reduce the AMPA-mediated ventral tegmental area activation by alcohol and nicotine co-use (10). Though tolerability of topiramate represents a significant drawback, it offers another promising monotherapy for heavy-drinking smokers (see Table 1).

POTENTIAL PHARMACOTHERAPIES

Potential treatments that have yet to be studied in heavy-drinking smokers include the combination of varenicline plus oral naltrexone plus nicotine replacement therapy, varenicline plus injectable extended-release naltrexone with or without nicotine replacement therapy, varenicline plus topiramate with or without nicotine replacement therapy, and bupropion sustained release plus injectable extended-release naltrexone, acamprosate, or disulfiram with or without nicotine replacement therapy (see Table 1).

CONCLUSIONS

Tobacco use disorder is the leading preventable cause of death in the United States, and alcohol use disorder follows closely behind. Heavy-drinking smokers suffer from both conditions and are at risk for disproportionately more frequent negative health consequences. Furthermore, these disorders cost society hundreds of billions of dollars annually in health care expenditures and lost productivity. Currently, there are no FDA-approved pharmacotherapies for heavy-drinking smokers, but treatment of both disorders simultaneously has been shown to improve health outcomes for both disorders. Of the available FDA-approved pharmacotherapies for alcohol and tobacco use disorders, both varenicline and oral naltrexone independently decrease both alcohol and tobacco use as monotherapies. In combination, a recent study demonstrated promising results for enhanced efficacy compared to either medication alone in reducing both alcohol and tobacco use. This may result from synergistic mechanisms of action targeting two different foci of addiction pathophysiology: the mesolimbic endogenous opioid system and neuronal nAChRs. Off-label use of topiramate represents another promising monotherapy for heavy-drinking smokers, as it has also been shown to decrease use of alcohol and tobacco in heavy-drinking smokers. More clinical research is warranted to validate these findings and elucidate other potential pharmacotherapies to treat this sizeable population.

Dr. Mirbaba is a fourth-year resident at UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles.

KEY POINTS/CLINICAL PEARLS

- Heavy-drinking smokers are a sizeable population who face more frequent adverse health consequences than those with either alcohol use disorder or tobacco use disorder alone.
- Treatments targeting both alcohol and tobacco use disorders are necessary to improve health outcomes, but there are currently no FDA-approved treatments for heavy-drinking smokers.
- Combination pharmacotherapies for alcohol and tobacco use disorders targeting different foci of addiction pathophysiology, such as varenicline plus oral naltrexone, or off-label use of topiramate monotherapy, may improve treatment outcomes for heavy-drinking smokers, but further studies are warranted.

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The AJP-Residents' Journal would like to thank all applicants.

COMMENTARY

Adolescents "Dabbing" With Marijuana: A Novel Mechanism for Smoking Highly Concentrated Tetrahydrocannabinol

Katrina Furey, M.D.

The legalization of marijuana and decriminalization of its possession across America has likely contributed to the public's view of marijuana as a relatively safe drug (1, 2). Marijuana is still the most widely abused drug among adolescents (1). Yet, public health campaigns depicting the harms associated with adolescent marijuana use, such as increased rates of psychosis in teenagers with a predisposition for schizophrenia and a dose-dependent increase in rates of suicide attempts, have not kept pace with legalization (1). Although epidemiologic data are sparse and inconsistent, there is evidence that the rates of youth marijuana abuse increase postlegalization (1, 3). Given peer pressure and access to drugs in this population, novel mechanisms for ingestion, like dabbing, may be used earlier and more frequently by adolescents.

Dabbing is a mode of marijuana ingestion in which individuals inhale a highly concentrated form of tetrahydrocannabinol (THC) from vaporized butane hash oil (colloquially called dabs, earwax, budder, shatter) created via butane extraction (3). Dabs contain THC concentrations up to 23%–80%, compared to the 3%–6% seen in traditionally smoked cannabis (2, 4, 5). Up to 40% of the THC can be inhaled, based on controlled experiments (4). Recreational users can synthesize dabs at home through a process known as blasting, with directions easily found via Internet search (2, 3).

Dabbing brings up several safety concerns, primarily dangers inherent to blasting, potential contamination of homemade dabs, and an increased risk of addiction and psychosis associated with the highly concentrated THC vapors (2, 4–6). The safety of at-home blasting has been compared to that of home methamphetamine labs due to butane's highly flammable and volatile nature (3). Blasting has resulted in several documented cases of fires, explosions, and severe burns (3).

Because of this growing trend, increasing numbers of patients will likely present to emergency room settings with acute marijuana wax intoxication.

Advocates of dabbing argue that this preparation of THC eliminates dangerous bacteria, mold, fungi, and other toxic compounds found in traditionally smoked cannabis (3). However, a recent study examining 57 dab concentrates available for consumption in the California medical cannabis market found that 80% were contaminated by considerable amounts of residual solvent, most commonly isopentane, and less frequently pesticides, like paclobutrazol and bifenthrin (4).

In 2014, Loflin and Earleywine (2) reported that 357 surveyed dab users, ranging from 18–71 years of age, preferred dabbing over smoking traditional cannabis due to the potency of dabs. The high was described by users as "stronger" and "qualitatively different." However, the authors also found that dabbing was associated with statistically significant increases in subjective withdrawal and tolerance symptoms, suggesting that dabbing could have a greater addictive potential than traditional smoking (2, 3).

Because of this growing trend, increasing numbers of patients will likely present to emergency room settings with acute marijuana wax intoxication. At least one case of butane hash oil-induced psychosis that did not respond to an antipsychotic has been reported in the literature (5). It is unclear whether dabbing-induced psychosis is transient or could lead to chronic psychotic illness in vulnerable patients. Because dabs can be easily made at home following online tutorials and most adults would not recognize these small, waxy resins as marijuana, adolescents may be at particularly high risk of experimenting with dabbing and subsequently experiencing its negative consequences.

Dr. Furey is a second-year resident in the Department of Psychiatry, Yale-New Haven Hospital, New Haven, Conn.

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COMMENTARY

Ayahuasca: Friend or Foe?

Gerard I. Fernando, M.D.

Ayahuasca is an entheogenic brew that is used as a medicinal sacrament and for ritualistic purposes among religious groups in South America. In the last decade, people from all walks of life, usually in their 20s and 30s, from North America and Europe have started to seek access to the substance. Many have traveled to South America, notably Brazil and Peru, to participate in the ayahuasca ritual.

Once consumed, it induces hallucinations and spiritual experiences that are thought to be due to increased introspection. Effects begin about 30 minutes after consumption and can last up to 8 hours. Ayahuasca can contain the Banisteriopsis caapi vine alone, which contains monoamine oxidase A (MAO-A)-inhibiting beta-carbolines, but is often combined with Chacruna (Psychotria viridis) or Chagropanga leaves, which have high concentrations of the psychedelic compound N, N-dimethyltryptamine (DMT) (1). Alone, DMT is made inactive by intestinal MAO-A metabolism; therefore, it is combined with a monoamine oxidase inhibitor to allow absorption of the active substance. Once it crosses the blood-brain barrier, DMT acts as a 5-HT1A/2A/2C agonist and a mGluR2 agonist. There is increased blood flow to the frontal and paralimbic brain areas after ingestion, specifically bilateral activation of the anterior insula/inferior frontal gyrus, anterior cingulate/medial frontal gyrus in the right hemisphere, and amygdala/parahippocampal gyrus in the left hemisphere (2). These areas have previously been implicated in somatic awareness and emotional arousal. Compared with the better studied psychedelic lysergic acid diethylamide (LSD), the experience with ayahuasca is described as more intense, with people sometimes losing touch with their physical surroundings. Ayahuasca also causes vomiting (unlike LSD), which is considered to be an important part of the ritual.

> Our patients may become interested in ingesting ayahuasca in hopes of treating their psychiatric conditions.

An explanation for the increase in popularity may be due to a recent spike in media coverage of ayahuasca. Celebrities—from the singer Sting to the actress Lindsay Lohan—along with major media outlets, such as the New York Times and Huffington Post, are singing the praises of ayahuasca, which may be contributing to the increase in its use and perceived safety. Furthermore, ayahuasca may show promise in the treatment of several psychiatric disorders. Studies have shown its effectiveness in treating depression (3) and addiction (4) in humans, although these were observational and limited in significance. In a CNN documentary hosted by journalist Lisa Ling, increasing use of the psychedelic in veteran populations was exposed. Ling followed veterans to South America, where they ingested ayahuasca in hopes of treating their PTSD symptoms. While popular culture has supported its expanding use, it can lead to significant medical complications, such as serotonin syndrome and death. An increasing number of deaths after intoxication have been reported and suspected to be the result of serotonin syndrome, as many of the affected individuals were medicated with selective serotonin reuptake inhibitors prior to taking ayahuasca (5).

Due to an explosion of media coverage, our patients may become interested in ingesting ayahuasca in hopes of treating their psychiatric conditions. Warning them of the possible dangers, particularly serotonin syndrome, could potentially save their lives.

Dr. Fernando is a fourth-year resident at Harvard South Shore, VA Boston Healthcare System, Psychiatry, Brockton, Mass.

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HISTORY IN PSYCHIATRY

Opium Use in 19th-Century Britain: The Roots of Moralism in Shaping Drug Legislation

Stephanie V. Ng, M.D.

The topic of addiction in psychiatry remains contentious, riddled with moral arguments that skew public sentiment and policy. Since the 1970s, when a "War on Drugs" was declared, U.S. discourse has veered between portraying addicted individuals as morally bankrupt criminals or victims of biology and environment.

The history of opium use in 19th-century Britain illustrates how sociopolitical factors shaped this epidemic and those like it. Public opinion about addiction, as evidenced by the opium epidemic, has been strongly influenced by professional, social, and geopolitical interests.

Prior to the 1868 Pharmacy Act, which restricted the sale of opium to pharmacists, opium was widely available, typically purchased at the grocer (1). Opium's uses were manifold, from toothaches and bruises to cough and diarrhea. The working class used it as a stimulant prior to going to work, and mothers found laudanum (a form of opium) useful for quieting babies. Medical discussion during this time had little to do with opium's addictive potential. Instead, medical experts addressed opium's role in limiting life expectancy and in accidental poisoning, as well as the lack of product purity in the market (2).

Eventual restriction of opiate use in the mid-1800s was influenced by a number of factors, including professional self-interest, class and racial tension, and various international pressures. As a professional group interested in safeguarding its role as gatekeepers to medicines, pharmacists advocated for the 1868 Pharmacy Act, which limited opium's point of sale to specific vendors. Doctors, invested in their role as prescribers, started discouraging self-medication with opium.

Class and racial tensions also contributed to growing public concern—while opium was "respectable" for the middle class to use, its spread to the working class caused concerns about opium abuse contributing to their "degeneracy"(3). Later, public sentiment and xenophobia were stirred as opium became associated with Chinese opium dens; in particular, white women were thought to be at risk of being corrupted by foreigners (3).

International political and economic pressures also played a role. The 1874 Society for the Suppression of the Opium Trade was created specifically to campaign against Britain's involvement in the opium trade with China; in the process, they became a forceful voice describing opium's addictive nature. Wartime concerns that narcotics were corrupting the character of military men fueled the passage of the 1916 Defense of the Realm Act. This was a precursor to the 1920 Dangerous Drugs Act, which penalized opium and its derivatives other than for "legitimate" medical use (2).

Within a century, societal and cultural factors shaped an evolving public perception of opiates. At the beginning of the 19th century, it was considered a syrup innocuous enough for babies. By the end, it was viewed as an immoral, addictive drug to be tightly regulated. This illustrates how societal and cultural factors can drive policy and medical management. In the United States, our drug policy debates remain colored by morality-based rhetoric. It behooves us, especially as psychiatrists working to address the problem individually and systematically, to consider the myriad factors influencing our status quo.

Dr. Ng is a second-year resident in the Department of Psychiatry, Yale University, New Haven, Conn.

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BOOK FORUM

Drinking: A Love Story

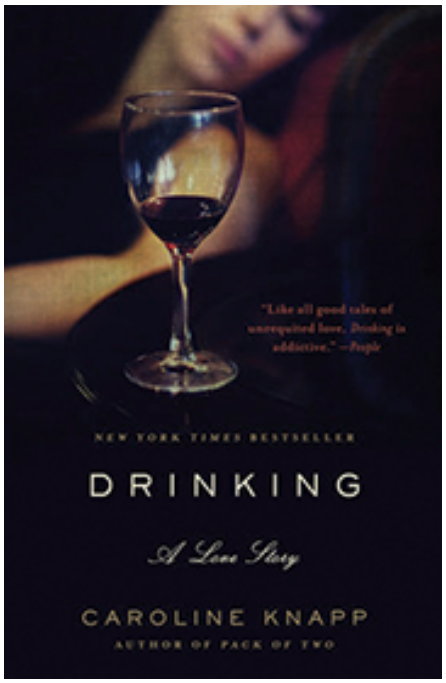
Reviewed by C. T. Flinton, M.D.

Alcohol-related disorders constitute a behavioral health epidemic. According to the 2014 National Survey on Drug Use and Health, 6.8% of Americans over the age of 18 suffer from alcohol use disorders (1). Unfortunately, only about 8.9% of these Americans will receive specialized treatment (1).

Patients in remission from alcohol use disorders carry high relapse risk and may pose significant challenges for even the most seasoned provider. Understanding the patient experience can be vital to developing rapport and formulating an appropriate treatment plan for such complex patients. With this goal, Caroline Knapp's memoir, *Drinking: A Love Story*, may have no equal.

In Knapp's words, "an addict is someone who seeks physical solutions to emotional or spiritual problems" (p. 58). She describes a powerlessness experienced by the active alcoholic, a kind of passive self-loathing. Personifying alcohol, Knapp underscores its ability to act as a companion and, in turn, temporarily reduce the experience of social isolation in intoxicated moments. This kind of validation is—by definition—transient; dependence on this external approval fuels a cycle in which the addict will "surrender [the] sense of self" (p. 91). Knapp describes that as her alcohol dependence progressed, denial and the construction of alternative identities offered comforting defenses: "we hide from others (and often from ourselves) the truth about our real selves" (p. 16). She laments that many alcohol abusers employ this denial to avoid substance abuse treatment for years.

Knapp bravely narrates the troubling progression of alcoholism from her teen years to her eventual sobriety in her mid-thirties. In chapters with titles such as "Love," "Sex," "Addiction," and "Denial," she provides a compelling depiction of her relationship with alcohol and how it invaded every aspect of her life. She imparts decades of wisdom from her observations of her fellow Alcoholics Anonymous members. She also draws upon experiences in therapy and with her father, a Harvard-trained psychoanalyst, to examine the dynamics underlying her romance with alcohol; she suggests understanding of alcohol both as a mechanism to cope with intolerable affect and a transitional object (2) in a way that resonates with laypeople and physicians alike.



by Caroline Knapp. New York, Random House, 1997, 304 pp., $16.00 (paper).

After a series of tragic events, Knapp credits her own desperation as the driving force for recovery. Nevertheless, she admits that even after years of sobriety, at the site of a wine glass, "my pulse still quickens and I find myself watching it wistfully, the way you might look at a photograph of someone you loved deeply and painfully and then lost," (p. 105).

Drinking: A Love Story artfully explains the power of a patient's attraction and struggle through a harmful relationship with alcohol. It provides valuable insight into the denial and resistance a provider may encounter when treating alcohol use disorders. Knapp's well-crafted prose presents an enjoyable read as an excellent, easy-to-access guide to the psychological and emotional experience of alcoholism for any behavioral health provider.

Dr. Flinton is a second-year resident in the National Capital Consortium Psychiatry Program, Walter Reed National Military Medical Center, Bethesda, Md.

The views expressed in this book review are those of the author and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.

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Residents' Resources

Here we highlight upcoming national opportunities for medical students and trainees to be recognized for their hard work, dedication, and scholarship.

**To contribute to the Residents' Resources feature, contact the incoming Deputy Editor, Oliver Glass, M.D. (glassol@ecu.edu).*

JULY DEADLINES

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
Student Mental Health Fellowship **Deadline: July 1, 2016**	Stanford University Medical Center	This is a 1-year fellowship for a psychiatric physician starting July 1, 2016, that provides specialized psychiatric training in student mental health at both the Stanford Hospital and Clinic and the student mental health center at Stanford University. Successful applicant will receive the Stanford resident salary and benefits commensurate with the years of training.	Must be Board-eligible in psychiatry.	Amy Poon, M.D. (aspoon@stanford.edu) or Alan Louie, M.D. (louiemd@stanford.edu)	psychiatry.stanford.edu
Trainee Travel Award **Deadline: July 1, 2016**	APM	To encourage psychosomatic fellows, residents, and medical students to join APM, attend the Annual Meeting. A limited number of monetary awards are given to help offset the cost of attending the Annual Meeting (APM Council determines the dollar amount and number of awards.)	Medical students, residents, and fellows.	http://www.apm.org/awards/trainee-travel.shtml	http://www.apm.org/awards/trainee-travel.shtml
American Academy of Child and Adolescent Psychiatry (AACAP) Educational Outreach Program for General Psychiatry Residents (former Travel Grant Program) **Deadline: July 13, 2016**	AACAP	Provides the opportunity for general psychiatry residents to receive a formal overview to the field of child and adolescent psychiatry, establish child and adolescent psychiatrists as mentors, and experience the AACAP Annual Meeting in New York, Oct. 24–Oct. 29, 2016.	General psychiatry residents who are AACAP members or have pending AACAP membership.	AACAP Assistant Director of Training and Education **e-mail:** training@aacap.org **phone:** 202-587-9663	http://www.aacap.org/AACAP/Awards/Resident_and_ECP_Awards/AACAP_Educational_Outreach_Program_for_General_Psychiatry_Residents.aspx
AACAP Educational Outreach Program for Child and Adolescent Psychiatry (CAP) Residents (former Travel Grant Program) **Deadline: July 13, 2016**	AACAP	Provides the opportunity for CAP residents to receive a formal overview to the field of child and adolescent psychiatry, establish child and adolescent psychiatrists as mentors, and experience the AACAP Annual Meeting in New York, Oct. 24–Oct. 29, 2016.	Child and adolescent psychiatry fellows who are AACAP members or have pending AACAP membership.	AACAP Assistant Director of Training and Education **e-mail:** training@aacap.org **phone:** 202-587-9663	http://www.aacap.org/AACAP/Awards/Resident_and_ECP_Awards/AACAP_Educational_Outreach_Program_for_CAP_Residents.aspx

AUGUST DEADLINES

Fellowship/Award and Deadline	Organization	Brief Description	Eligibility	Contact	Website
The PRITE Fellowship Program **Nomination Deadline: August 15, 2016**	The American College of Psychiatrists	PRITE Fellows participate in the question writing process by developing an assigned number of questions and then editing and referencing exam items. PRITE Fellows must be able to attend the 4-day July meeting of the PRITE Editorial Board where all travel-related costs will be covered by the College.	The nominee must be a current PGY-II or -III in general psychiatry or a first-year child fellow on Aug. 15, 2016. The recipient must be able to attend the entire meeting of the PRITE Editorial Board during each of the 2 years after being named a Fellow. Specific meeting dates are posted on the website as soon as they have been confirmed.	Kathryn Delk, Program Manager **e-mail:** Kathryn@ACPsych.org **phone:** 312-938-8840 ext. #14	https://www.acpsych.org/resident-fellowships/the-prite-fellowship-program/application-process
The Laughlin Fellowship **Nomination Deadline: August 15, 2016**	The American College of Psychiatrists	Laughlin Fellows are chosen from an elite pool of applicants deemed likely to make a significant contribution to the field of psychiatry. They participate in all educational and social functions held during the Annual Meeting, making valuable contacts with their peers and College members.	The nominee must be a current PGY-3, PGY-4, or PGY-5 resident in general psychiatry or a resident in child, addiction, forensic, geriatric, or psychosomatic psychiatry as of August 15, 2016	**e-mail**: Angel@ACPsych.org **phone**: 312-938-8840	https://www.acpsych.org/resident-fellowships/the-laughlin-fellowship-program

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2. **History of Psychiatry:** Provides a historical perspective on a topic relevant to psychiatry. Limited to 500 words and five references.
3. **Treatment in Psychiatry:** This article type begins with a brief, common clinical vignette and involves a description of the evaluation and management of a clinical scenario that house officers frequently encounter. This article type should also include 2-4 multiple choice questions based on the article's content. Limited to 1,500 words, 15 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
4. **Clinical Case Conference:** A presentation and discussion of an unusual clinical event. Limited to 1,250 words, 10 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
5. **Original Research:** Reports of novel observations and research. Limited to 1,250 words, 10 references, and two figures. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
6. **Review Article:** A clinically relevant review focused on educating the resident physician. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
7. **Drug Review:** A review of a pharmacological agent that highlights mechanism of action, efficacy, side-effects and drug-interactions. Limited to 1,500 words, 20 references, and one figure. This article type should also include a table of Key Points/Clinical Pearls with 3–4 teaching points.
8. **Letters to the Editor:** Limited to 250 words (including 3 references) and three authors. Comments on articles published in *The Residents' Journal* will be considered for publication if received within 1 month of publication of the original article.
9. **Book Review:** Limited to 500 words and 3 references.

Abstracts: Articles should not include an abstract.

Upcoming Themes

Please note that we will consider articles outside of the theme.

Social Media and Psychiatry
If you have a submission related to this theme, contact the Section Editor Spencer Hansen, M.D. (shansen3@tulane.edu)

Psychiatry in the General Hospital
If you have a submission related to this theme, contact the Section Editor Kamalika Roy, M.D. (Kroy@med.wayne.edu)

Suicide Risk and Prevention
If you have a submission related to this theme, contact the Section Editor Katherine Pier, M.D. (Katherine.Pier@mssm.edu)

*If you are interested in serving as a **Guest Section Editor** for the *Residents' Journal*, please send your CV, and include your ideas for topics, to Katherine Pier, M.D., incoming Editor-in-Chief (katherine.pier@mssm.edu).