16 - 13 Impulsivity, Compulsivity, and Addiction

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1 Impulsivity, Compulsivity, and Addiction What Are Impulsivity and Compulsivity? 538 Neurocircuitry and the Impulsive–Compulsive Disorders 539 The Dopamine Theory of Addiction: The Mesolimbic Dopamine Circuit as the Final Common Pathway of Reward 542 Substance Addictions 544 Stimulants 544 Nicotine 547 Alcohol 553 Sedative Hypnotics 556 Gamma-Hydroxybutyrate (GHB) 559 Opiates or Opioids? 559 Cannabis 563 Hallucinogens 567 Empathogens 569 Dissociatives 569 Abuse Your Way to Abstinence? 571 “Therapeutic” Dissociation, Hallucinations, and Empathy? 574 Behavioral Addictions 575 Binge Eating Disorder 575 Other Behavioral Addictions 575 Obsessive–Compulsive and Related Disorders 576 Impulse Control Disorders 577 Summary 578 Impulsivity and compulsivity are symptoms that cut across many psychiatric disorders. Some conditions with impulsivity as a prominent feature have already been discussed, including mania (Chapter 4); attention deficit hyperactivity disorder (ADHD; Chapter 11), and agitation in dementia (Chapter 12). Several other disorders in which impulsivity and/or compulsivity are core features are discussed in this chapter. Full clinical descriptions and formal criteria for how to diagnose the numerous known diagnostic entities discussed here should be obtained by consulting standard diagnostic and reference sources. Here we emphasize what is known or hypothesized about the brain circuits and neurotransmitters mediating impulsivity and compulsivity, and how engaging neurotransmitters at various nodes in impulsivity/compulsivity networks can result in successful psychopharmacological treatments. WHAT ARE IMPULSIVITY AND COMPULSIVITY? Impulsivity can be defined as a predisposition towards rapid, unplanned reactions to internal or external stimuli, with diminished regard for the negative consequences of these reactions. In contrast, compulsivity is defined as the performance of repetitive and dysfunctionally impairing behavior that has no adaptive function. Compulsive behavior is performed in a habitual or stereotypical fashion, either according to rigid rules or as a means of avoiding perceived negative consequences. These two symptom constructs can perhaps be best differentiated by how they both fail to control responses: impulsivity as the inability to stop initiating actions, and compulsivity as the inability to terminate ongoing actions. These constructs have thus been viewed historically as diametrically opposed, with impulsivity being associated with risk seeking and compulsivity with harm avoidance. Currently the emphasis is on the fact that both share different forms of cognitive inflexibility leading to a profound feeling of lack of control. More precisely,

impulsivity is action without forethought; the lack of reflection on the consequences of one's behavior; the inability to postpone reward with preference for immediate reward over more beneficial but delayed reward; a failure of motor inhibition, often choosing risky behavior; or (less scientifically) lacking the will power not to give in to temptations and provocative stimuli from the environment. On the other hand, compulsivity is action inappropriate to the situation but which nevertheless persists, and which often results in undesirable consequences. In fact, compulsions are characterized by the curious inability to adapt behavior after negative feedback. Habits are a type of compulsion, and can be seen as responses triggered by environmental stimuli, regardless

of the current desirability of the consequences of that response. Whereas goal-directed behavior is mediated by knowledge of and desire for its consequences, habits are controlled by external stimuli through stimulus–response associations that are stamped into brain circuits through behavioral repetition and formed after considerable training, can be automatically triggered by stimuli, and are defined by their insensitivity to their outcomes. Given that goal-directed actions are relatively cognitively demanding, for daily routines, it can be adaptive to rely on habits that can be performed with minimal conscious awareness. However, habits can also represent severely maladaptive perseveration of behaviors as components of various impulsive–compulsive disorders (see Table 13-1). Another way to look at addiction is as a habit much like the behavior of a Pavlovian dog! That is, drug seeking and drug taking behaviors can be viewed as conditioned responses to the conditioned stimuli of being around people or places or items associated with drugs, or having craving and withdrawal. When addicted, drug seeking and taking are automatic, thoughtless, conditioned responses that occur in an almost reflexive fashion to conditioned stimuli, just as Pavlov's dogs developed mouth-watering in response to a bell associated with food. When such stimulus–response conditioning runs amok in addiction, it does not perform an adaptive purpose of sparing cognitive efforts from doing routine tasks. Instead, the "habit" of drug addiction has become a perverse form of learning, almost as though one has learned how to have a psychiatric disorder! NEUROCIRCUITRY AND THE IMPULSIVE–COMPULSIVE DISORDERS Impulsivity and compulsivity are thought to be mediated by neuroanatomically and neurochemically distinct, but in many ways parallel, components of cortico-subcortical circuitry (Figures 13-1 and 13-2). When these networks are dysfunctional, they hypothetically result in "lack of control" of thoughts and behaviors. Simply put, impulsivity and compulsivity are both symptoms that result from the brain having a hard time saying "no." Why can't impulses and compulsions be stopped in various psychiatric disorders? An over-simplified explanation was discussed in Chapter 12 and illustrated in Figures 12-43 and 12-44, showing either too much "bottom-up" limbic emotional drive or too little "topdown" cortical inhibition of these drives. In Alzheimer disease, for example, impulsivity resulting in agitation Chapter 13: Impulsivity, Compulsivity, and Addiction is thought to be due principally to neurodegeneration of top-down controls (see Chapter 12 and Figures 12-45B and 12-46B). In ADHD, impulsivity, especially motor impulsivity, is thought to be due to neurodevelopmentally delayed or absent top-down Table 13-1 Impulsive–compulsive disorders Substance addictions Cannabis Nicotine Alcohol Opioids Stimulants Hallucinogens Empathogens Dissociatives Behavioral addictions Binge eating disorder Gambling disorder Internet gaming disorder Obsessive–compulsive related disorders Obsessive–compulsive disorder Body dysmorphic disorder Trichotillomania Skin picking Hoarding Shopping Hypochondriasis Somatization Impulse control disorders Agitation in Alzheimer disease Motor and behavioral impulsivity in ADHD Mood disorders Provocative behaviors in mania Disruptive mood dysregulation disorder Pyromania Kleptomania Paraphilias Hypersexual disorder Autism spectrum disorders Tourette syndrome and

tic disorders Stereotyped movement disorders Borderline personality disorder Self harm and parasuicidal behaviors Conduct disorder Antisocial personality disorder Oppositional defiant disorder Intermittent explosive disorder Aggression and violence: impulsive psychotic psychopathic 539

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Impulsivity and Reward ventral Figure 13-1 Circuitry of impulsivity and reward. The "bottomup" circuit that drives impulsivity is a loop with projections from the ventral striatum to the thalamus, from the thalamus to the ventromedial prefrontal cortex (VMPFC) and the anterior cingulate cortex (ACC), and from the VMPFC/ACC back to the ventral striatum. This circuit is usually modulated "top-down" from the prefrontal cortex. If this top-down response inhibition system is inadequate or is overcome by activity from the ventral striatum, impulsive behaviors may result. cortical controls (see Chapter 11 and Figures 11-17 through 11-21). In a wide variety of other disorders discussed below, the problem may lie anywhere within two parallel cortico-striatal circuits, namely at two striatal nodes (one impulsive and the other compulsive), which drive these behaviors, or at two corresponding prefrontal cortical nodes, which restrain them (Figures 13-1 and 13-2). Overlap between these two parallel networks exists such that a problem in the impulsive circuit can end up as a problem in the compulsive circuit and vice versa, leading to the concept of "impulsive– compulsive disorders," all of which have this symptom domain as one of their core features. Such psychiatric conditions incorporate a wide range of disorders, from obsessive–compulsive disorder (OCD) to addictions, and far beyond (Table 13-1). Although there are many other important symptom domains in these various conditions that distinguish one from another, all can be associated with disordered impulsivity and/or compulsivity, and this is the shared domain of their psychopathology that is discussed here. Neuroanatomically, impulsivity is thus seen as regulated by an action–outcome ventrally dependent learning system (Figure 13-1) whereas compulsivity Compulsivity and Motor Response Inhibition dorsal Figure 13-2 Circuitry of compulsivity and motor response inhibition. The "bottom-up" circuit that drives compulsivity is a loop with projections from the dorsal striatum to the thalamus, from the thalamus to the orbitofrontal cortex (OFC), and from the OFC back to the dorsal striatum. This habit circuit can be modulated "top-down" from the OFC. If this top-down response inhibition system is inadequate or is overcome by activity from the dorsal striatum, compulsive behaviors may result. is hypothesized to be controlled by a habit system that is dorsal (Figure 13-2). That is, many behaviors start out as impulses mediated by the ventral loop, which reacts to reward and motivation (Figure 131). Over time, however, the locus of control for these behaviors migrates dorsally (Figure 13-2) due to a cascade of neuroadaptations and neuroplasticity that engage a dorsal "habit system" by means of which an impulsive act eventually becomes compulsive (Figures 13-2 and 13-3). This naturally occurring process can have adaptive value in everyday life, freeing the brain to spend its efforts on novel, cognitively demanding activities. However, when it runs hypothetically amok in a myriad of psychiatric disorders (Table 13-1), the goal is to stop or reverse this spiral of information from the impulsive neuronal loop to the compulsive "habit" loop. Unfortunately, there are relatively few highly effective treatments for impulsive–compulsive disorders today. We have discussed effective treatments for ADHD in Chapter 11 and for agitation in Alzheimer disease in Chapter 12. Here we review the hypothetically shared neurobiology of many other impulsive–compulsive disorders and discuss what treatments are available for some of these conditions.

Chapter 13: Impulsivity, Compulsivity, and Addiction ACC VMPFC thalamus thalamus ventral striatum OFC IMPULSIVITY impulsive violence ADHD mania intermittent explosive disorder kleptomania pyromania autism spectrum Tourette syndrome body dysmorphic disorder skin picking trichotillomania OCD somatization gambling internet paraphilias hypersexual drug addiction gambling obesity/ binge eating compulsive shopping hypochondriasis borderline personality disorder antisocial behavior COMPULSIVITY dorsal striatum Figure 13-3 Impulsive–compulsive disorder construct. Impulsivity and compulsivity are seen in a wide variety of psychiatric disorders. Impulsivity can be thought of as the inability to stop the initiation of actions and involves a brain circuit centered on the ventral striatum and linked to the thalamus, to the ventromedial prefrontal cortex (VMPFC), and to the anterior cingulate cortex (ACC). Compulsivity can be thought of as the inability to terminate ongoing actions and hypothetically involves a brain circuit centered on the dorsal striatum and linked to the thalamus and orbitofrontal cortex (OFC). Impulsive acts such as drug use, gambling, and over-eating can eventually become compulsive due to neuroplastic changes that engage the dorsal habit system and theoretically cause impulses in the ventral loop to migrate to the dorsal loop.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY circuit discussed in Chapter 4 on psychosis and hypothesized to be overly active in psychosis, mediating the positive symptoms of schizophrenia and also motivation and reward (see Figures 4-14 through 4-16). Some even consider the mesolimbic dopamine pathway to be the “pathway of hedonic pleasure” of the brain and dopamine to be the “neurotransmitter of hedonic pleasure.” According to this notion, there are many natural ways to trigger your mesolimbic dopamine neurons to release dopamine, ranging from intellectual accomplishments, to athletic victories, to enjoying a good symphony, to experiencing an orgasm. These are sometimes called “natural highs” (Figure 13-4). The Dopamine Theory of Addiction: The Mesolimbic Dopamine Circuit as the Final Common Pathway of Reward A leading theory of addiction for over 40 years has been the dopamine theory, proposing that the final common pathway of reinforcement and reward in the brain for anything pleasurable is the mesolimbic dopamine pathway (Figure 13-4). This theory is a bit of an oversimplification and perhaps most applicable to drugs that cause the greatest effects upon dopamine release, especially stimulants and nicotine, but less so for marijuana and opioids. The mesolimbic dopamine pathway is familiar to readers as it is the same brain VTA nucleus accumbens YES! YES! Reward: DA mesolimbic pathway Natural Highs Substance-Induced Highs Behaviorally Induced Highs Figure 13-4 Dopamine is central to reward. Dopamine (DA), and specifically the mesolimbic pathway from the ventral tegmental area (VTA) to the nucleus accumbens, has long been recognized as a major player in the regulation of reinforcement and reward. Naturally rewarding activities, such as achieving major accomplishments, can cause fast and robust increases in DA in the mesolimbic pathway. Drugs of abuse also cause DA release in the mesolimbic pathway, and can often increase DA in a manner that is more explosive and pleasurable than that which occurs naturally.

Chapter 13: Impulsivity, Compulsivity, and Addiction amphetamine (dopamine itself) (Figure 13-5). Thus, the idea formed that all drugs of abuse – as well as many maladaptive behaviors such as gambling, binge eating, using the internet – have a final common pathway of causing pleasure. This happens by provoking dopamine release in the mesolimbic pathway in a manner often The inputs to the mesolimbic pathway that mediate these natural highs include a most incredible “pharmacy” of naturally occurring substances, ranging from the brain’s own morphine/heroin (endorphins), to the brain’s own marijuana (anandamide), to the brain’s own nicotine

(acetylcholine), to the brain's own cocaine and Figure 13-5 Neurotransmitter regulation of mesolimbic reward. The mesolimbic dopamine pathway is modulated by many naturally occurring substances in the brain in order to deliver normal reinforcement to adaptive behaviors (such as eating, drinking, sex) and thus to produce "natural highs," such as feelings of joy or accomplishment. These neurotransmitter inputs to the reward system include the brain's own morphine/heroin (endorphins), the brain's own cannabis/marijuana (endocannabinoids such as anandamide), the brain's own nicotine (acetylcholine [ACh]), and the brain's own cocaine/amphetamine (dopamine [DA] itself), among others. The numerous psychotropic drugs of abuse that occur in nature bypass the brain's own neurotransmitters and directly stimulate the brain's receptors in the reward system, causing dopamine release and a consequent "artificial high." Thus, alcohol, opioids, stimulants, marijuana, benzodiazepines, sedative hypnotics, hallucinogens, and nicotine all affect this mesolimbic dopaminergic system. endorphin VTA raphe DA endocannabinoid endocannabinoid GABA Neurotransmitter Regulation of Mesolimbic Reward 5HT 5HT ACh ACh GABA GABA endorphin Glu Glu PPT/LDT arcuate nucleus PFC amygdala hippocampus nucleus accumbens endocannabinoid endocannabinoid

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY more explosive and pleasurable than that which occurs naturally. In this formulation, drugs bypass the brain's own neurotransmitters and directly stimulate the brain's own receptors for these same drugs, causing dopamine to be released. Since the brain already uses neurotransmitters that resemble drugs of abuse, it is not necessary to earn your reward naturally since you can get a much more intense reward in the short run and upon demand from a drug of abuse than you can from a natural high with the brain's natural system. However, unlike a natural high, a drug-induced reward can start the diabolical cascade of neuroadaptation into habit formation. SUBSTANCE ADDICTIONS Addiction is a horrible disease. What starts out as fun and increased dopamine release in the ventral striatum with enhanced anterior cingulate cortex (ACC) activity and reward ends up with the locus of control in the habit circuit as a mindless, automatic, and powerful compulsive drive to obtain drugs that is basically irresistible. Since it is not presently known what treatment mechanisms might suppress the wicked habit circuit that has commandeered behavioral control in the addict, treatments for addiction are few and far between and often not very effective. What is needed are treatments capable of wresting control back from the habit circuit and returning it to voluntary control, perhaps by neuroplasticity reverse-migrating control from dorsal back to ventral, where things began before addiction was present. Once addicted, the brain is no longer rewarded principally by the drug itself, but as well by anticipation of the drug and its reward. This generates compulsive drug-seeking behaviors which are themselves rewarding. That is, some studies suggest that dopamine neurons terminating in the ventral striatum (Figure 13-1) actually stop responding to the primary reinforcer (i.e., taking the drug, eating the food, doing the gambling) and instead dopamine neurons terminating in the dorsal striatum (Figure 13-2) begin to respond to the conditioned stimuli (i.e., handling the heroin syringe, feeling the crack pipe in your hand, entering the casino) before the drug is even taken! Since drug seeking and drug taking become the main motivational drives when addicted, this explains why the addicted subject is aroused and motivated when seeking to procure drugs, but is withdrawn and apathetic when exposed to non-drug-related activities. When drug abuse reaches this stage of compulsivity, it is clearly a maladaptive perseveration of behavior – a habit and a Pavlovian conditioned response, and not any longer being simply naughty or giving in to temptation. Stimulants Stimulants as therapeutic agents have been discussed in Chapter 11 covering the treatment of ADHD. For optimized treatment of ADHD, stimulant dosing is carefully

controlled to deliver constant drug levels within a defined therapeutic range (see Chapter 11 and Figure 11-34). Theoretically, this amplifies tonic release of dopamine (Figure 11-33) to optimize pro-cognitive ADHD therapeutic effects. On the other hand, these very same stimulants can also be used as drugs of abuse by changing the dose and the route of administration to amplify phasic dopamine stimulation and thus their reinforcing effects (Figure 11-35). Although therapeutic actions of stimulants are thought to be directed at the prefrontal cortex to enhance both norepinephrine and dopamine neurotransmission there, at moderate levels of dopamine transporter (DAT) and norepinephrine transporter (NET) occupancy (Figure 11-26), the reinforcing effects and abuse of stimulants occur when DATs in the mesolimbic reward circuit are suddenly blasted and massively blocked (Figure 13-6). The speed with which a stimulant enters the brain dictates the degree of the subjective “high” (Figure 137). This was also discussed in Chapter 11 as one of the properties of the “mysterious DAT.” This sensitivity of the DAT to the way in which it is engaged likely explains why stimulants when abused are often not ingested orally but instead are smoked, inhaled, snorted, or injected so they can enter the brain in a sudden explosive manner, to maximize their reinforcing nature. Oral absorption reduces reinforcing properties of stimulants because speed of entry to the brain is considerably slowed by the process of gastrointestinal absorption. Cocaine is not even active orally so users have learned over the years to take it intranasally so that drug rapidly enters the brain directly, bypassing the liver, and thus can have a more rapid onset than even with intravenous administration. The most rapid and robust way to deliver drugs to the brain is to smoke those that are compatible with this route of administration, as this avoids first-pass metabolism through the liver and is somewhat akin to giving the drug by intra-arterial/intra-carotid bolus via immediate absorption across the massive surface area of the lung. The faster the drug’s entry into brain, the stronger are its reinforcing effects (Figure 13-7), probably because this

 stereotyped behavior. At even higher repetitive doses, stimulants can induce paranoia and hallucinations resembling schizophrenia (see Chapter 4 and Figures 4-14 through 4-16) as well as hypertension, tachycardia, ventricular irritability, hyperthermia, and respiratory depression. In overdose, stimulants can cause acute heart failure, stroke, and seizures. Over time, stimulant abuse can be progressive (Figure 13-8). Initial doses of stimulants that cause pleasurable phasic dopamine firing (Figure 13-8A) give leave to reward conditioning and addiction with chronic use, causing craving between stimulant doses and residual tonic dopamine firing with a lack of pleasurable phasic dopamine firing (Figure 138B). Now addicted, higher and higher doses of stimulants are needed in order to achieve the pleasurable highs of form of drug delivery triggers phasic dopamine firing, the type associated with reward (see Chapter 11 for discussion and Figure 11-35). Amphetamine, methamphetamine, and cocaine are all inhibitors of the DAT and the NET. Cocaine also inhibits the serotonin transporter (SERT) and is also a local anesthetic, which Freud himself exploited to help dull the pain of his tongue cancer. He may have also exploited the second property of the drug, which is to produce euphoria, reduce fatigue, and create a sense of mental acuity due to inhibition of dopamine reuptake at the DAT, at least for a while, until drug-induced reward is replaced by drug-induced compulsivity. High doses of stimulants can cause tremor, emotional lability, restlessness, irritability, panic, and repetitive, Figure 13-6 Stimulant actions on the mesolimbic dopamine circuit. The reinforcing effects and abuse potential of stimulants occurs when dopamine transporters (DATs) in the mesolimbic reward circuit are blocked, causing a phasic increase in dopamine (DA) in the nucleus accumbens. VTA raphe DA endocannabinoid stimulants endocannabinoid GABA

Stimulant Actions on the Mesolimbic Dopamine Circuit 5HT 5HT ACh ACh GABA GABA endorphin Glu Glu PPT/LDT arcuate nucleus PFC amygdala hippocampus nucleus accumbens endocannabinoid endocannabinoid endorphin YES! substance-induced high DA 5HT 545

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Atypical Stimulants "Bath salts" are a form of stimulant. Their name derives from efforts to disguise these abusable stimulants as common Epsom salts used in baths, with similar packaging as white or colorful powders, granules, or crystal forms but quite different chemically! Bath salts are often labelled "not for human consumption" in a further attempt to be mistaken for Epsom salts and thus circumventing drug prohibition laws. Bath salts, however, are not for bathing, but are synthetic stimulants that commonly include the active ingredient methylenedioxypyrovalerone (MDPV) and may also contain mephedrone or methylone. They are phasic dopamine firing (Figure 13-8C). Unfortunately, the higher the high, the lower the low, and between stimulant doses, the individual experiences not only the absence of a high, but also withdrawal symptoms such as sleepiness and anhedonia (Figure 13-8D). The effort to combat withdrawal coupled with habit formation leads to compulsive use and ultimately dangerous behavior in order to secure drug supplies (Figure 13-8E). Finally, there may be enduring if not irreversible changes in dopamine neurons, including long-lasting depletions of dopamine levels and axonal degeneration, a state that clinically and pathologically is appropriately called "burnout" (Figure 13-8F). Figure 13-7 Dopamine, pharmacokinetics, and reinforcing effects. Acute drug use causes dopamine release in the striatum. However, the reinforcing effects of the drug are largely determined not only by the presence of dopamine, but also by the rate at which dopamine increases in the brain, which in turn is dictated by the speed at which the drug enters and leaves the brain. This is likely because abrupt and large increases in dopamine (such as those caused by drugs of abuse) mimic the phasic dopamine firing associated with conveying information about reward and saliency. As shown here, the self-reported high associated with intravenous (IV) cocaine use correlates with both the rate and extent of dopamine transporter (DAT) blockade. The rate of drug uptake is subject to the route of administration, with intravenous administration and inhalation producing the fastest drug uptake, followed by snorting. In addition, different drugs of abuse have different "reward values" (i.e., different rates at which they increase dopamine) based on their individual mechanisms of action. 0 40 80 120 DAT blockade Dopamine, Pharmacokinetics, and Reinforcing Effects Cocaine (IV) % of Peak Self-reported high 20 Time (minutes) 50 546

Chapter 13: Impulsivity, Compulsivity, and Addiction Treatment of Stimulant Addiction Unfortunately, there are currently no approved drug treatments for stimulant addicts, as many dopaminelinked and serotonin-linked therapeutics have failed. In the future, there may be a cocaine vaccine that removes the drug before it reaches the brain so there are no more reinforcing effects that accompany drug ingestion. Nicotine How common is smoking in clinical psychopharmacology practices? Some estimates are that more than half of all cigarettes are consumed by patients with a concurrent psychiatric disorder, and that smoking is the most common comorbidity among seriously mentally ill patients. Other estimates are that about 16–20% of the general population (in the US) smoke, about 25% of people who regularly see general physicians smoke, but that 40–50% of patients in a psychopharmacology practice smoke, including 60–85% of patients also called "plant food" and like other stimulants can have reinforcing effects but also cause agitation, paranoia, hallucinations, suicidality, and chest pain. Some would consider inhalants as atypical types of stimulants since they are thought to be direct releasers of dopamine in the nucleus accumbens. Inhaling fumes – called "huffing" – of substances such as toluene found

in paint thinner, felt-tip markers, glue, various aerosol sprays, and even freon found in air conditioners, can cause a feeling similar to alcohol intoxication, with dizziness, lightheadedness, and disinhibition; it can also cause impaired judgment and possibly hallucinations. Long-term huffing can cause depression, weight loss, and brain damage. Huffing can also be dangerous in the short term, as it can cause sudden death due to cardiac arrest, aspiration, or suffocation. Freon in particular can cause these effects and can also freeze the lungs, making it extremely dangerous. Substances that are huffed do not show up on drug tests. Figure 13-8 Progression of stimulant abuse. (A) Initial doses of stimulants such as methamphetamine and cocaine cause pleasurable phasic dopamine firing. (B) With chronic use, reward conditioning causes craving between stimulant doses and residual tonic dopamine firing with a lack of pleasurable phasic dopamine firing. (C) In this addicted state, higher and higher doses of stimulants are needed in order to achieve the pleasurable highs of phasic dopamine firing. (D) Unfortunately, the higher the high, the lower the low, and between stimulant doses, the individual experiences not only the absence of a high, but also withdrawal symptoms such as sleepiness and anhedonia. (E) The effort to combat withdrawal can lead to compulsive use and impulsive, dangerous behavior in order to secure the stimulant. (F) Finally, there may be enduring if not irreversible changes in dopamine neurons, including long-lasting depletions of dopamine levels and axonal degeneration, a state that clinically and pathologically is appropriately called “burn-out.” time DA firing cocaine amphetamine Progression of Stimulant Abuse postsynaptic A B fun craving “where’s my dopamine?” reverse tolerance/ addicted “brainwashed” compulsive use marathon sex paranoia HIV violence anhedonia sleepiness withdrawal enduring cognitive loss “burn-out” C D E F amphetamine cocaine amphetamine cocaine

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY with ADHD, schizophrenia, and bipolar disorder. Unfortunately, histories of current smoking are often not carefully taken or recorded as one of the diagnoses for smokers in mental health practices and only about 10% of smokers report being offered treatment pro-actively by psychopharmacologists and other clinicians even though somewhat effective treatments are available. Nicotine acts directly upon nicotinic cholinergic receptors in mesolimbic reward circuits to release dopamine (Figure 13-9). Cholinergic neurons and the neurotransmitter acetylcholine (ACh) are discussed in Chapter 12 and illustrated in Figures 12-24 through 12-32. Nicotinic receptors are specifically illustrated in Figure 12-28. There are several subtypes of nicotinic receptors present in brain. The α7 nicotinic receptor on postsynaptic prefrontal cortex neurons may be linked to the pro-cognitive and mentally alerting actions of nicotine, but not to addictive actions. It is the α4β2 subtype discussed here and illustrated in Figure 13-9 that is thought to be most relevant to smoking and nicotine addiction. That is, nicotine’s actions at α4β2 nicotinic postsynaptic receptors directly on dopamine neurons in the ventral tegmental area (VTA) are those that are theoretically linked to addiction (Figure 13-9). Nicotine also indirectly activates dopamine release from the VTA by activating nicotinic presynaptic receptors on glutamate neurons, causing glutamate release, which in turn causes dopamine release (Figure 13-9). Nicotine also appears to desensitize α4β2 postsynaptic receptors on inhibitory GABAergic interneurons in the VTA, indirectly leading to dopamine release in the nucleus accumbens by disinhibiting dopaminergic mesolimbic neurons (Figure 13-9). The α4β2 nicotinic receptors adapt to the chronic intermittent pulsatile delivery of nicotine in a way that leads to addiction (Figure 13-10). Initially these receptors in the resting state are opened by delivery of nicotine, which in turns leads to dopamine release and reinforcement, pleasure, and reward (Figure 13-10A). By the time the cigarette is finished, these receptors become desensitized, so that they

cannot function temporarily, and thus cannot react either to acetylcholine or nicotine (Figure 13-10A). In terms of obtaining any further reward, you might as well stop smoking at this point. An interesting question to ask is: how long does it take for the nicotinic receptors to desensitize? The answer seems to be: about as long as it takes to inhale all the puffs of a standard cigarette and burn it down to a butt. Thus, it is probably not an accident that cigarettes are the length that they are. Shorter does not maximize the pleasure. Longer is a waste since by then the receptors are all desensitized anyway (Figure 13-10A). The problem for the smoker is that when the receptors resensitize to their resting state, this initiates craving and withdrawal due to the lack of release of further dopamine (Figure 13-10A). Another interesting question is: how long does it take to resensitize nicotinic receptors? The answer seems to be: about the length of time that smokers take between cigarettes. For the average one-pack-per-day smoker, awake for 16 hours, that would be about 45 minutes, possibly explaining why there are 20 cigarettes in a pack (i.e., enough for an average smoker to keep his or her nicotinic receptors completely desensitized all day long). Putting nicotinic receptors out of business by desensitizing them causes neurons to attempt to overcome this lack of functioning receptors by upregulating the number of receptors (Figure 13-10B). That, however, is futile, since nicotine just desensitizes all of them the next time a cigarette is smoked (Figure 13-10C). Furthermore, this upregulation is self-defeating because it serves to amplify the craving that occurs when the extra receptors are resensitizing to their resting state (Figure 13-10C). From a receptor point of view, at first the goal of smoking is to desensitize all nicotinic α4β2 receptors and get the maximum dopamine release. Eventually, however, the goal is mostly to prevent craving. Positron emission tomography (PET) scans of α4β2 nicotinic receptors in human smokers confirm that nicotinic receptors are exposed to just about enough nicotine for just about long enough from each cigarette to accomplish this. Craving seems to be initiated at the first sign of nicotinic receptor resensitization. Thus, the bad thing about receptor resensitization is craving. The good thing from an addicted smoker’s point of view is that as the receptors resensitize, they are available to release more dopamine and cause pleasure or suppress craving and withdrawal again. Treatment of Nicotine Addiction Treating nicotine dependence is not easy. There is evidence that nicotine addiction begins with the first cigarette, with the first dose showing signs of lasting a month in experimental animals (e.g., activation of the anterior cingulate cortex for this long after a single dose). Craving begins within a month of repeated administration. Perhaps even more troublesome is the finding that the “diabolical learning” of dorsal to ventral

Chapter 13: Impulsivity, Compulsivity, and Addiction VTA Detail of Nicotine Actions 4 2 ß ACh nicotine DA Glu GABA VTA DA neuron PFC Glu neuron GABA interneuron nicotine indirectly activates DA release nicotine directly activates DA release nicotine desensitizes PPT/LDT ACh neuron α α Figure 13-9 Actions of nicotine. Nicotine directly causes dopamine (DA) release in the nucleus accumbens by binding to α4β2 nicotinic postsynaptic receptors on dopamine neurons in the ventral tegmental area (VTA). In addition, nicotine binds to α7 nicotinic presynaptic receptors on glutamate (Glu) neurons in the VTA, stimulating glutamate release that in turn leads to dopamine release in the nucleus accumbens. Nicotine also seems to desensitize α4β2 postsynaptic receptors on GABA interneurons in the VTA; the reduction of GABA neurotransmission disinhibits mesolimbic dopamine neurons and thus is a third mechanism for enhancing dopamine release in the nucleus accumbens.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 13-10 Reinforcement and α4β2 nicotinic receptors. (A) In the resting state α4β2 nicotinic receptors are closed (left). Nicotine administration,

as by smoking a cigarette, causes the receptor to open, which in turn leads to dopamine release (middle). Longterm stimulation of these receptors leads to their desensitization, such that they temporarily can no longer react to nicotine (or to acetylcholine); this occurs in approximately the same length of time it takes to finish a single cigarette (right). As the receptors resensitize (return to resting state), they initiate craving and withdrawal due to the lack of release of further dopamine. (B) With chronic desensitization, α4β2 receptors upregulate to compensate. (C) If one continues smoking, however, the repeated administration of nicotine continues to lead to desensitization of all of these α4β2 receptors and thus the upregulation does no good. In fact, the upregulation can lead to amplified craving as the extra receptors resensitize to their resting state. resting cigarette upregulated cigarette finished desensitized chronically desensitized initiation of craving A B C open

- DA releases upregulated, resting open, DA release cigarette cigarette finished desensitized enhanced craving drug-seeking behavior impulsive choices reward sensitivity Addiction and 4ß2 α 4ß2 α 4ß2 α Reinforcement and Nicotinic Receptors Adaptation of Nicotinic Receptors

migration of control from impulsive to compulsive circuits may be very, very long-lasting once exposure to nicotine is stopped. Some evidence even suggests that these changes last a lifetime, with a form of “molecular memory” to nicotine, even in long-term abstinent former smokers. One of the first successful agents proven to be effective for treating nicotine addiction is nicotine itself, but in a route of administration other than smoking: gums, lozenges, nasal sprays, inhalers, and transdermal patches. Delivering nicotine by these other routes does not attain the high levels nor the pulsatile blasts that are delivered to the brain by smoking, so they are not very reinforcing, just as discussed for delivery of stimulants above and illustrated in Figure 13-7. However, these alternative forms of nicotine delivery can help to reduce craving due to a steady amount of nicotine that is delivered and presumably desensitizing an important number of resensitizing and craving nicotinic receptors. Another treatment for nicotine dependence is varenicline, a selective α4β2 nicotinic acetylcholine receptor partial agonist (Figures 13-11 and 13-12). Figure 13-11 contrasts the effects of nicotinic partial agonists (NPAs) with nicotinic full agonists and with nicotinic antagonists on the cation channel associated with nicotinic cholinergic receptors. Nicotinic full agonists include acetylcholine, which is very short-acting, and nicotine, which is very long-acting. They open the channel fully and frequently (Figure 13-11, left). By contrast, nicotinic antagonists stabilize the channel in the closed state, but do not desensitize these receptors (Figure 13-11, right). NPAs stabilize nicotinic receptors in Molecular Actions of a Nicotinic Partial Agonist (NPA) acetylcholine nicotinic partial agonist nicotinic antagonist nicotinic partial agonist (NPA): stabilizes channel in less frequently open state, nicotinic full agonist: channel frequently open not desensitized Chapter 13: Impulsivity, Compulsivity, and Addiction an intermediate state that is not desensitized and where the channel opens less frequently than with a full agonist, but more frequently than with an antagonist (Figure 1311, middle). How addicting is tobacco and how well do NPAs work to achieve cessation of smoking? About two-thirds of smokers want to quit, one-third try, but only 2–3% succeed long term. Of all the substances of abuse, some surveys show that tobacco has the highest probability of making you dependent when you have tried a substance at least once. It could be argued, therefore, that nicotine might be the most addicting substance known. The good news is that the NPA varenicline triples or quadruples the 1-month, 6-month, and 1-year quit rates compared to placebo; the bad news is that this means only about 10% of smokers

who have taken varenicline are still abstinent a year later. Many of these patients are prescribed varenicline for only 12 weeks, which might be far too short a period of time for maximal effectiveness. Another approach to the treatment of smoking cessation is to try to reduce the craving that occurs during abstinence by boosting dopamine with the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion (see Chapter 7 and Figures 7-34 through 7-36). The idea is to give back some of the dopamine downstream to the craving postsynaptic D2 receptors in the nucleus accumbens while they are readjusting to the lack of getting their dopamine "fix" from the recent withdrawal of nicotine (Figure 13-13). Thus, while smoking, dopamine is happily released in the nucleus accumbens because of the actions of nicotine on α4β2 Figure 13-11 Molecular actions of a nicotinic partial agonist (NPA). Full agonists at α4β2 receptors, such as acetylcholine and nicotine, cause the channels to open frequently (left). In contrast, antagonists at these receptors stabilize them in a closed state, such that they do not become desensitized (right). Nicotinic partial agonists (NPAs) stabilize the channels in an intermediate state, causing them to open less frequently than a full agonist but more frequently than an antagonist (middle). nicotinic antagonist: stabilizes channel in closed state, not desensitized 551

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 13-12 Varenicline actions on reward circuits. Varenicline is a nicotinic partial agonist (NPA) selective for the α4β2 receptor subtype. When varenicline binds to α4β2 nicotinic receptors – located on dopamine (DA) neurons, glutamate (Glu) neurons, and GABA interneurons in the ventral tegmental area (VTA) – it stabilizes the channels in an intermediate state, with less frequent opening than would occur if nicotine were bound, but more frequent than if a nicotinic antagonist were bound. Thus, it can reduce the dopaminergic reward that would occur if a patient did smoke (by competing with nicotine) but also reduce withdrawal symptoms by stimulating at least some neurotransmission. VTA Varenicline Actions on Reward Circuits VTA DA neuron PFC Glu neuron GABA interneuron varenicline varenicline PPT/LDT ACh neuron 4 2 ß ACh varenicline DA Glu GABA α α

receptors on the VTA dopamine neuron (shown in Figure 13-13A). During smoking cessation, resensitized nicotinic receptors no longer receiving nicotine are craving due to an absence of dopamine release in the nucleus accumbens (where is my dopamine?) (Figure 13-13B). When the NDRI bupropion is administered, theoretically a bit of dopamine is now released in the nucleus accumbens, making the craving less but usually not eliminating it (Figure 13-13C). How effective is bupropion in smoking cessation? Quit rates for bupropion are about half that of the NPA varenicline. Quit rates for nicotine in alternative routes of administration such as transdermal patches are similar to those of bupropion. Novel approaches to treating nicotine addiction include the investigation of nicotine vaccines and other directacting nicotinic cholinergic agents. Mechanism of Action of Bupropion in Smoking Cessation ACh neuron ACh DA DA neuron nicotine A ACh neuron DA neuron B ACh neuron DA neuron C Chapter 13: Impulsivity, Compulsivity, and Addiction Alcohol The famous artist Vincent van Gogh reportedly drank ruinously, some speculating that he self-medicated his bipolar disorder this way, a notion reinforced by his explanation, "If the storm within gets too loud, I take a glass too much to stun myself." Alcohol may stun but it does not treat psychiatric disorders adaptively long term. Unfortunately, many alcoholics who have comorbid psychiatric disorders continue to selfmedicate with alcohol rather than seeking treatment with a more appropriate psychopharmacological agent. In addition to frequent comorbidity with psychiatric disorders, it is estimated that 85% of alcoholics also smoke. Many alcoholics abuse additional drugs as well, including benzodiazepines, marijuana, opioids, and others. Figure 13-13

Mechanism of action of bupropion in smoking cessation. (A) A regular smoker delivers reliable nicotine (circle), releasing dopamine (DA) in the limbic area at frequent intervals, which is rewarding to the limbic dopamine D2 receptors on the right. (B) However, during attempts at smoking cessation, dopamine will be cut off when nicotine no longer releases it from the mesolimbic neurons. This upsets the postsynaptic D2 limbic receptors and leads to craving and what some call a “nicotine fit.” (C) A therapeutic approach to diminishing craving during the early stages of smoking cessation is to deliver a bit of dopamine itself by blocking dopamine reuptake directly at the nerve terminal with bupropion. Although not as powerful as nicotine, it does take the edge off and can make abstinence more tolerable. where's my dopamine?? NDRI 553

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Although we are still struggling to understand how alcohol actually exerts its psychotropic actions, an overly simplified view of alcohol’s mechanism of action is that it enhances inhibition at GABA (γ-aminobutyric acid) synapses and reduces excitation at glutamate synapses. Alcohol actions at GABA synapses hypothetically enhance GABA release via blocking presynaptic GABAB receptors and also by positively allosterically modulating postsynaptic GABAA receptors, especially those containing δ subunits that are responsive to neuroactive steroids but not to benzodiazepines (Figures 13-14 and Possible Binding Sites for Sedative Hypnotic Drugs chloride channel GABA binding site benzodiazepine binding site α ß γ α ß α1, α2, α3, α5 subtypes benzodiazepine receptors: A chloride channel GABA binding site ß α4,6 α4,6

ß subtypes (α4, α6)

benzodiazepine receptors: B 13-15). Non-benzodiazepine-sensitive GABAA receptors containing δ subunits are discussed in Chapter 7 and illustrated in Figure 7-56. Alcohol also hypothetically acts at presynaptic metabotropic glutamate receptors (mGluRs) and presynaptic voltage-sensitive calcium channels (VSCCs) to inhibit glutamate release (Figure 13-15). mGluRs are introduced in Chapter 4 and illustrated in Figures 4-23 and 4-24. VSCCs and their role in glutamate release are introduced in Chapter 3 and illustrated in Figures 3-22 through 3-24. Alcohol may also reduce the actions of glutamate at postsynaptic NMDA Figure 13-14 Binding sites for sedative hypnotic drugs. (A) Benzodiazepines and barbiturates both act as positive allosteric modulators at GABAA receptors, but at different binding sites from each other. Benzodiazepines do not act at all GABAA receptors; rather, they are selective for the α1, α2, α3, and α5 subtypes of receptors that also contain γ but not δ subunits. (B) General anesthetics, alcohol, and neuroactive steroids may bind to other types of GABAA receptors, particularly those containing δ subunits. barbiturate binding site neuroactive steroid binding site ? alcohol binding site general anesthetics

Chapter 13: Impulsivity, Compulsivity, and Addiction Figure 13-15 Actions of alcohol in the ventral tegmental area (VTA). Alcohol hypothetically enhances inhibition at GABA synapses by binding at both GABAA and GABAB receptors, and hypothetically reduces excitation at glutamate synapses by acting at postsynaptic metabotropic glutamate (mGluR) receptors and presynaptic voltage-sensitive calcium channels (VSCCs). Alcohol may also reduce the actions of glutamate at postsynaptic NMDA receptors and postsynaptic mGluR receptors. In addition, alcohol’s reinforcing effects may be mediated by actions at opioid synapses within the VTA. Stimulation of μ-opioid receptors there causes dopamine release in the nucleus accumbens. Alcohol may either directly act upon μ receptors or cause release of endogenous opioids such as enkephalin. VTA Detail of Alcohol Actions in the VTA DA Glu endorphin GABA A receptor -opioid receptor GABA B receptor

NMDA receptor mGluR receptor GABA VTA DA neuron PFC Glu neuron GABA interneuron alcohol alcohol alcohol VSCC alcohol arcuate nucleus opioid neuron μ ß

 (N-methyl-D-aspartate) receptors and at postsynaptic mGluR receptors (Figure 13-15). Alcohol's reinforcing effects are theoretically mediated not only by its effects at GABA and glutamate synapses, causing downstream dopamine release in the mesolimbic pathway, but also by actions at opioid synapses within mesolimbic reward circuitry (Figure 13-15). Opioid neurons arise in the arcuate nucleus and project to the VTA, synapsing on both glutamate and GABA neurons. The net result of alcohol actions on opioid synapses is thought to be the release of dopamine in the nucleus acccumbens (Figure 13-15). Alcohol may do this by either directly acting upon μ-opioid receptors or by releasing endogenous opioids such as β-endorphin. Treatment of Alcoholism The actions of alcohol on opioid synapses create the rationale for blocking μ-opioid receptors with antagonists such as naltrexone or nalmefene (Figure 13-16). Naltrexone and nalmefene (approved outside the US) are μ-opioid antagonists that hypothetically block the euphoria and "high" of heavy drinking. This theory is supported by clinical trials that show that naltrexone given either orally or by a 30-day-long acting injection reduces days of heavy drinking (defined as five or more drinks per day for a man and four or more for a woman) and also increases the chances of attaining complete abstinence from alcohol. If you drink when you take an opioid antagonist, the opioids released by alcohol do not lead to pleasure, so why bother drinking? Some patients may also say, why bother taking the opioid antagonist, of course, and relapse back into drinking alcohol. Thus, a long-acting injection may be preferable but, unfortunately, hardly any of this is prescribed. Acamprosate is a derivative of the amino acid taurine and interacts with both the glutamate system to inhibit it, and with the GABA system to enhance it, a bit like a form of "artificial alcohol" (compare Figure 13-15 with Figure 13-17). Thus, when alcohol is taken chronically and then withdrawn, the adaptive changes that it hypothetically causes in both the glutamate system and the GABA system create a state of glutamate overexcitement and even excitotoxicity as well as GABA deficiency. To the extent that acamprosate can substitute for alcohol in patients during withdrawal, the actions of acamprosate mitigate the glutamate hyperactivity and the GABA deficiency (Figure 13-17). This occurs because acamprosate appears to have direct blocking actions on certain glutamate receptors, particularly mGluR receptors (specifically mGlu5 and perhaps mGlu2). One way or another, acamprosate apparently reduces the glutamate release associated with alcohol withdrawal (Figure 1317). Actions, if any, at NMDA receptors may be indirect, as are actions at GABA systems, both of which may be secondary downstream effects from acamprosate's actions on mGluR receptors (Figure 13-17). Although approved, acamprosate is not prescribed very often. Disulfiram is the classic drug for treating alcoholism. It is an irreversible inhibitor of the liver enzyme aldehyde dehydrogenase that normally metabolizes alcohol. When alcohol is ingested in the presence of disulfiram, alcohol's metabolism is inhibited and the result is the build-up of toxic levels of acetaldehyde. This creates an aversive experience with flushing, nausea, vomiting, and hypotension, hopefully conditioning the patient to a negative rather than positive response to drinking. Obviously, compliance is a problem with this agent, and its aversive reactions are occasionally dangerous. Use of disulfiram was greater in the past and is not prescribed very often today. Unapproved agents that may be effective in treating alcoholism include the anticonvulsant topiramate and the 5HT3 antagonist ondansetron. Several other agents are used "off-label," especially in Europe. The subject of how to treat alcohol abuse and dependence is obviously complex, and any psychopharmacological treatment for alcoholism is more effective when integrated with appropriate psychopharmacological treatment of comorbid

psychiatric disorders, as well as with structured therapies such as 12-step programs, a topic which is beyond the scope of this text. Sedative Hypnotics Sedative hypnotics include barbiturates and related agents such as ethchlorvynol and ethinamate, chloral hydrate and derivatives, and piperidinedione derivatives such as glutethimide and methyprylon. Experts often include alcohol, benzodiazepines, (discussed in Chapter 8), and Z-drug hypnotics (discussed in Chapter 10) in this class as well. The mechanism of action of sedative hypnotics is basically thought to be the same as those described in Chapter 7 (on drugs for depression), Chapter 8 (on drugs for anxiety), and Chapter 10 (on drugs for insomnia) and illustrated in Figure 13-14, namely as positive allosteric modulators (PAMs) of either benzodiazepine-sensitive (Figure 13-14A) or benzodiazepine-insensitive (Figure 13-14B) GABAA receptors, or both. Barbiturates are much less safe in overdose than benzodiazepines, cause

Chapter 13: Impulsivity, Compulsivity, and Addiction VTA Actions of μ-Opioid Antagonists Reducing the Reward of Drinking nalmefene/ naltrexone nalmefene/ naltrexone DA Glu GABA A receptor -opioid receptor GABA B receptor NMDA receptor mGluR receptor GABA VTA DA neuron PFC Glu neuron GABA interneuron VSCC arcuate nucleus opioid neuron μ -opioid antagonist μ endorphin ß Figure 13-16 Actions of μ-opioid antagonists in the ventral tegmental area (VTA). Opioid neurons form synapses in the VTA with GABAergic interneurons and with presynaptic nerve terminals of glutamate (Glu) neurons. Alcohol either acts directly upon μ-opioid receptors or causes release of endogenous opioids such as enkephalin; in either case, the result is increased dopamine (DA) release to the nucleus accumbens. Mu-opioid receptor antagonists such as naltrexone or nalmefene block the pleasurable effects of alcohol mediated by μ-opioid receptors.

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 13-17 Actions of acamprosate in the ventral tegmental area (VTA). When alcohol is taken chronically and then withdrawn, the adaptive changes that it causes in both the glutamate system and the GABA system create a state of glutamate overexcitation as well as GABA deficiency. Acamprosate seems to reduce the glutamate release associated with alcohol withdrawal, presumably by blocking metabotropic glutamate receptors (mGluRs). VTA Actions of Acamprosate: Reducing Excessive Glutamate Release to Relieve Alcohol Withdrawal DA Glu endorphin GABA A receptor -opioid receptor GABA B receptor NMDA receptor mGluR receptor GABA VTA DA neuron PFC Glu neuron GABA interneuron VSCC acamprosate acamprosate arcuate nucleus opioid neuron μ ß

dependence more frequently, are abused more frequently, and produce much more dangerous withdrawal reactions. Because of this they are rarely prescribed today as sedative hypnotics or anxiolytics. Gamma-Hydroxybutyrate (GHB) This agent is discussed in Chapter 10 as a treatment for narcolepsy/cataplexy. It is sometimes also abused by individuals wanting to get high or by predators to intoxicate their dates (GHB is one of the "date rape" drugs; see further discussion in Chapter 10). The mechanism of action of GHB is as an agonist at its own GHB receptors and at GABAB receptors (illustrated in Figure 10-68). Opiates or Opioids? While subtle, the distinction between opioids and opiates is significant. An opiate is a drug naturally derived from the flowering opium poppy plant. Examples of opiates include heroin and its derivatives morphine and codeine. On the other hand, the term opioid is a broader term that includes opiates and refers to any substance, natural or synthetic, that binds to the brain's opioid receptors – the parts of the brain responsible for controlling pain, reward, and addictive behaviors. Some examples of synthetic opioids include the prescription painkillers hydrocodone (Vicodin) and oxycodone (OxyContin), as

well as fentanyl and methadone. Endogenous Opioid Neurotransmitter System There are three parallel opioid systems, each with its own neurotransmitter and receptor. Neurons that release β-endorphin – sometimes referred to as the “brain’s own Endogenous Opioid Neurotransmitters E E POMC proenkephalin prodynorphin enkephalin -endorphin ß δ κ μ Chapter 13: Impulsivity, Compulsivity, and Addiction morphine” – synapse with postsynaptic sites containing μ-opioid receptors; neurons that release enkephalin synapse with postsynaptic δ-opioid receptors; neurons that release dynorphin synapse with postsynaptic κ-opioid receptors (Figure 13-18). All three opioid peptides are derived from precursor proteins called pro-opiomelanocortin (POMC), proenkephalin, and prodynorphin, respectively (Figure 13-18). Parts of these precursor proteins are cleaved off to form endorphins or enkephalins or dynorphins, then stored in opioid neurons, to be released during neurotransmission to mediate endogenous opioid actions. Opioid Addiction Although illicit opioids derived from poppies have been known for their addictive properties for centuries, it has taken a recent sobering epidemic of opioid abuse with devastating effects on contemporary lives and society for us to recognize the powerful destructive potential of oral opioids prescribed legally for pain relief. Recent surveys suggest that the US consumes 85% of the world’s legal and illegal supply of opioids. In the US every year, over 60 million people fill at least one prescription for an opioid, 20% of them use their opioids in a manner that was not prescribed, another 20% report sharing pills, and over 2 million become iatrogenically addicted. As the need for higher and higher dosing exceeds the pills that can be obtained from prescribers or from the street, many patients resort to the more affordable street heroin inhaled or injected to “chase the dragon” of opioid addiction. Street supplies of heroin are increasingly laced with fentanyl which is 100 times more potent than morphine. Fentanyl derivatives like the elephant Figure 13-18 Endogenous opioid neurotransmitters. Endogenous opioids are peptides derived from precursor proteins called POMC (proopiomelanocortin), proenkephalin, and prodynorphin. Parts of these precursor proteins are cleaved off to form endorphins, enkephalins, or dynorphin, which are then stored in opioid neurons and released during neurotransmission to mediate reinforcement and pleasure. Neurons that release endorphin synapse with sites containing μ-opioid receptors, those that release enkephalin synapse with sites containing δ-opioid receptors, and those that release dynorphin synapse with sites containing κ-opioid receptors. E dynorphin 559

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY tranquilizer carfentanil are 10,000 times more potent than morphine. In fact, fentanyl and derivatives are so powerful that they are unable to be reversed by opioid antagonists such as naloxone, and thus an estimated one-third of 60,000 annual US overdose deaths from opioids are caused by fentanyl and derivatives. A very sad outcome from what may have started as legitimate treatment of acute pain. This recent epidemic of opioid addiction has also dashed the fallacy that oral controlled-release formulations reduce addiction liability. The ongoing and sweeping contagion triggered by oral painrelieving opioids of all types has taught us, somewhat surprisingly, that opioids may not be highly effective analgesics in the long run, but only in the short run, losing their analgesic effectiveness within days to weeks as tolerance, dependence, and addiction take hold. Thus, prescription opioids are being increasingly limited in amount and in time, both to reduce dependence in patients with pain and to prevent diversion of their opioids to others. At and above pain-relieving doses, opioids induce euphoria, a powerful reinforcing property. There is less dopamine release with opioids than with stimulants in the mesolimbic pleasure center, but certainly not less pleasure, so it is not entirely clear how the “high” of opioids is fully mediated. Likely, the impulsive ventral circuit begins its pleasurable reinforcing work early in the use of an opioid. Opioids induce a very intense but brief euphoria,

sometimes called a “rush,” followed by a profound sense of tranquility, which may last several hours, followed in turn by drowsiness (“nodding”), mood swings, mental clouding, apathy, and slowed motor movements. In overdose, these same opioids act as depressants of respiration, and can also induce coma. The acute actions of opioids other than fentanyl and derivatives can be reversed by synthetic opioid antagonists, such as naloxone, which compete as antagonists at μ-opioid receptors if given soon enough and in sufficient dosage. The opioid antagonists can also precipitate a withdrawal syndrome in opioid-dependent persons. When taken chronically, opioids readily cause both tolerance and dependence because adaptation of opioid receptors occurs quite readily. This adaptation hypothetically correlates with the migration of behavioral control from ventral circuits to dorsal habit circuits. The first sign of this is the need of the patient to take a higher and higher dose of opioid in order to relieve pain or to induce the desired euphoria. Eventually, there may be little room between the dose that causes euphoria and that which produces toxic effects of an overdose. Another sign that dependence has occurred and that opioid receptors have adapted is the development of a withdrawal syndrome once the chronically administered opioid wears off. The opioid withdrawal syndrome is characterized by the patient feeling dysphoria, craving another dose of opioid, being irritable, and having signs of autonomic hyperactivity such as tachycardia, tremor, and sweating. Pilo-erection (“goose-bumps”) is often associated with opioid withdrawal, especially when the drug is stopped suddenly (“cold turkey”). This is so subjectively horrible that the opioid abuser will often stop at nothing in order to get another dose of opioid to relieve symptoms of withdrawal. Thus, what may have begun as a quest for pain relief or euphoria may end up as a quest to avoid withdrawal. Treatment of Opioid Addiction Treatment of opioid addiction begins with managing withdrawal. Running out of money and drug supply as well as being incarcerated can be forms of forced withdrawal, but a gentler version is to reduce or even avoid withdrawal symptoms. One way to do this is to substitute a prescribed opioid at known dose and avoid intravenous administration. There are two options: methadone or buprenorphine. Methadone is a full agonist at μ-opioid receptors and can suppress withdrawal symptoms completely given orally and usually administered daily at a clinic. Buprenorphine is a μ-opioid partial agonist that has less powerful agonist effects, yet can suppress withdrawal symptoms especially when mild withdrawal has already begun after stopping abused opioids. Buprenorphine is administered sublingually as it is not well absorbed if swallowed. It can also be prescribed in a several-day supply and taken as an outpatient instead of returning daily to a clinic. Buprenorphine is usually combined with naloxone. Naloxone is not absorbed orally or sublingually, yet prevents intravenous abuse, since naloxone is active by injection. The injection of the combination of buprenorphine and naloxone results in no high and may even precipitate withdrawal, so prevents diversion for intravenous abuse of the sublingual preparation. Buprenorphine can also be administered as an implantable 6-month formulation or as a 1-month depot injection. Although tapering off methadone or buprenorphine directly to a state of opioid abstinence is theoretically

possible, it is rarely successful long term. Of those opioid addicts who enter residential rehabilitation and treatment for 30–90 days off all drugs, some analyses suggest relapse back into opioid abuse as high as 60–80% within a month and 90–95% by 3 months. The drive to reinstitute street opioids coming from the addict’s habit circuit – especially if re-exposed to the environmental cues linked to previous opioid abuse such as the people, places, and paraphernalia associated with prior opioid abuse – is akin to putting oneself in the situation where bells for Pavlov’s dogs are ringing loud and clear. Involuntary, mindless, and powerful habit drives then take over reflexively,

bypassing voluntary will power, no longer able to suppress drug seeking and drug taking. This outcome results whether the opioid addict is trying to stop methadone, buprenorphine, or street opioids. How can this dismal outcome be avoided? First of all, it is important to recognize that the intensity and duration of withdrawal from most drugs including opioids are linked to drug half-life, with short-half-life full agonists such as morphine or heroin producing much more intense and short-lasting withdrawal symptoms than either long-acting methadone, which has a less intense but much longer duration withdrawal, or buprenorphine, the withdrawal of which is both less intense and shorter (Figure 13-19). Second of all, the Comparative Severity and Duration of Opioid Withdrawal morphine Severity of Withdrawal buprenorphine 5 Days since opioid Chapter 13: Impulsivity, Compulsivity, and Addiction intensity but not the duration of withdrawal of both methadone (Figure 13-20) and buprenorphine (Figure 13-21) can be reduced by the addition of an α2A agonist. Both clonidine and lofexidine are α2-adrenergic agonists that reduce signs of autonomic hyperactivity during withdrawal and aid in the detoxification process. And finally, in an attempt to enhance successful long-term abstinence, opioid addicts may be transitioned not to abstinence but to maintenance on a long-acting injectable opioid antagonist like naltrexone. In the short run, naltrexone shortens the withdrawal time of an α2 agonist administered either with methadone (Figure 13-20) or with buprenorphine (Figure 13-21). The advantages of giving naltrexone long term are having the drug present at therapeutic levels all day long, in contrast to administering naltrexone orally (Figure 1322). Furthermore, with naltrexone monthly injections the opioid-abstinent person now only has to make a decision to take medication once every 30 days instead of 30 times in 30 days. Even better, an impulsive patient cannot readily stop his/her injectable naltrexone in order to relapse. Agonist substitution treatments like methadone or buprenorphine – often called medication-assisted therapy (MAT) – are most successful in the setting of a structured maintenance treatment program that includes random urine drug screening and intensive Figure 13-19 Comparative severity and duration of opioid withdrawal.

Following abrupt discontinuation, the time to onset of peak withdrawal symptoms and the duration of symptoms are dependent on the half-life of the drug involved. With morphine (and heroin) withdrawal, symptoms peak within 36–72 hours and last for 7–10 days. With methadone withdrawal, symptoms are less severe and peak at 72–96 hours, but can last for 14 days or more. With buprenorphine withdrawal, symptoms peak after a few days and are less severe than with morphine/heroin; the duration of symptoms is similar to morphine/heroin. methadone 15 561

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Severity and Duration of Withdrawal After Methadone Discontinuation Severity of Withdrawal lofexidine alone lofexidine+ naltrexone 5 Days since last methadone dose Severity and Duration of Withdrawal After Buprenorphine Discontinuation Severity of Withdrawal lofexidine alone lofexidine+ naltrexone 7 3 Days since last buprenorphine dose psychological, medical, and vocational services. The same is true for those on long-acting naltrexone injections. Unfortunately, only a minority of opioid addicts enter treatment, only a minority of those in treatment receive MAT, and almost none of them Figure 13-20 Severity and duration of withdrawal after methadone discontinuation. With abrupt discontinuation of methadone, withdrawal symptoms peak at 72–96 hours but can last for 14 days or more. The intensity, but not the duration, of withdrawal symptoms can be reduced by adding an α2-adrenergic agonist such as lofexidine or clonidine. Specifically, these agents can relieve autonomic symptoms. Adding both an α2-adrenergic agonist and a μ-opioid receptor antagonist such as naltrexone can reduce the severity as well as the duration of withdrawal symptoms. abrupt

discontinuation of methadone Figure 13-21 Severity and duration of withdrawal after buprenorphine discontinuation. With abrupt discontinuation of buprenorphine, withdrawal symptoms peak at around 72 hours and last for about a week. The intensity, but not the duration, of withdrawal symptoms can be reduced by adding an α2-adrenergic agonist such as lofexidine or clonidine. Specifically, these agents can relieve autonomic symptoms. Adding both an α2-adrenergic agonist and a μ-opioid receptor antagonist such as naltrexone can reduce the severity as well as the duration of withdrawal symptoms. abrupt discontinuation of buprenorphine receive injectable naltrexone. Whether this is because of philosophical differences of various treatment facilities, economic incentives, or therapeutic nihilism is unknown but it seems that the currently available best treatments are insufficiently prescribed.

Naltrexone: Oral vs. Long-Acting Injectable Naltrexone Mean Plasma Levels (ng/mL) 20 10 0 5 20 Time (Days) Cannabis You can indeed get stoned without inhaling (see endocannabinoids released in Figure 13-5)! The brain makes its own cannabis-like neurotransmitters – anandamide and 2-arachidonoylglycerol (2-AG) (Figures 13-23 and 13-24). So does the body. These neurotransmitters and their receptors cannabinoid 1 and 2 (CB1 and CB2) make up the “endocannabinoid” system – the endogenous cannabinoid system (Figure 13-23). In the brain, release of classic neurotransmitters can stimulate the synthesis of endocannabinoids from precursors stored in postsynaptic lipid membranes (Figure 13-24A). Upon release of these endocannabinoids into the synapse, they travel retrograde to presynaptic CB1 receptors and “talk back” to the presynaptic neuron where they can inhibit the release of the classic neurotransmitter (Figure 13-24B). Retrograde neurotransmission was introduced in Chapter 1 and illustrated in Figure 1-5. Both CB1 receptors and CB2 receptors are localized in brain, with CB1 receptors present in greater density. Both receptors bind both endocannabinoids, 2-AG with high efficacy and anandamide with low efficacy (Figure 13-23). CB2 receptors are also in the periphery, mostly on immune cells, and also bind the same two endocannabinoids (Figure 13-23). Cannabis is a mixture of hundreds of chemicals and over 100 alkaloid cannabinoids. The most important of these are tetrahydrocannabinol (THC) and cannabidiol (CBD) (Figure 13-25). THC interacts with CB1 and CB2 receptors and has psychoactive properties. CBD is an isomer of THC and relatively inactive at CB1 Chapter 13: Impulsivity, Compulsivity, and Addiction Figure 13-22 Naltrexone formulations.

The μ-opioid receptor antagonist naltrexone is available in both an oral formulation and as a once-monthly intramuscular (IM) injection. With oral naltrexone, one experiences fluctuating, dose-dependent plasma concentrations. In addition, one must decide daily whether or not to continue treatment. With the monthly injection, one experiences increased and consistent plasma concentrations and only has to make the decision to take medication once every 30 days. naltrexone 380 mg IM injection oral naltrexone 50 mg 25 and CB2 receptors (Figure 13-25). CBD does not have psychoactive properties and its mechanism of action is really unknown (Figure 13-25). Cannabis comes in various mixtures of THC and CBD (Figure 13-26). Higher CBD content has a lower risk of hallucinations, delusions, and memory impairment (Figure 13-26). Pure CBD might even be antipsychotic and anxiolytic (Figure 13-26). Over time, cannabis has become more potent in terms of more THC and less CBD, with resultant higher risk of hallucinations, delusions, anxiety, and memory impairment (Figure 13-26). It is not currently possible to identify in advance those vulnerable to psychosis or to the precipitation of schizophrenia by cannabis. Nevertheless, an influential recent study concluded that if nobody smoked highpotency cannabis, 12% of all cases of first-episode psychosis across Europe would be prevented, rising to 32% in London and 50% in

Amsterdam. Cannabis can also exacerbate psychosis in patients who already have a psychotic illness. In usual intoxicating doses for most persons without risk for psychosis, cannabis produces a sense of well-being, relaxation, a sense of friendliness, a loss of temporal awareness, including confusing the past with the present, slowing of thought processes, impairment of short-term memory, and a feeling of achieving special insights. At high doses, cannabis can induce panic, toxic delirium as well as psychosis, especially in the vulnerable. One complication of longterm cannabis use is the “amotivational syndrome” in frequent users. This syndrome is seen predominantly in heavy daily cannabis users and is characterized 563

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY agent whereas medical marijuana is an unprocessed plant containing 500 chemicals with 100+ cannabinoids. Prescription drugs require a consistent, well-defined pharmacokinetic profile, and safety and efficacy data from double-blind, placebo-controlled, randomized clinical trials, as well as warnings for all potential side effects. However, medical marijuana contains compounds that vary from plant to plant, with residual impurities such as pesticides and fungal contaminants, and dosing which is not well regulated. Even so, there have been a myriad of studies of medical marijuana, and these have been recently reviewed by a panel of experts who report various benefits and risks for which there is a range of evidence, from substantial evidence, to moderate evidence, to limited evidence (Table 13-2), to insufficient evidence (Table 13-3). by the emergence of decreased drive and ambition, thus “amotivational.” It is also associated with other socially and occupationally impairing symptoms, including a shortened attention span, poor judgment, easy distractibility, impaired communication skills, introversion, and diminished effectiveness in interpersonal situations. Personal habits may deteriorate, and there may be a loss of insight, and even feelings of depersonalization. Recent years have led to a search for potential therapeutic uses of cannabis in general and for THC and CBD in particular. The problem with “medical marijuana” is that it is not a prescription option that can be developed according to the standards of prescription medication. Those standards require consistent, pure, well-defined chemical formulation of the therapeutic Figure 13-23 The endocannabinoid system: receptors and ligands. There are two main types of cannabinoid (CB) receptors. CB1 receptors are the most abundant and are present at neuron terminals throughout the central and peripheral nervous systems. CB2 receptors are not expressed as widely in the brain, although they are present in glial cells and in the brainstem. Instead, CB2 receptors are primarily found in immune cells, where they modulate cell migration and cytokine release. Of the multiple endogenous cannabinoids, the best understood are anandamide and 2-arachidonoylglycerol (2-AG). Anandamide is a low-efficacy agonist at CB1 receptors and a very low-efficacy agonist at CB2 receptors. 2-AG is a high-efficacy agonist at both CB1 and CB2 receptors. CB1 CB = cannabinoid 2-AG = 2-arachidonoylglycerol anandamide central and peripheral neuron terminals immune cells 2-AG: high-efficacy agonist anandamide: low-efficacy agonist CB1 CB2 CB2 2-AG: high-efficacy agonist anandamide: very low-efficacy agonist The Endocannabinoid System: Receptors and Ligands

Chapter 13: Impulsivity, Compulsivity, and Addiction Figure 13-24 The endocannabinoid system: retrograde neurotransmission. (A) Precursors to the endocannabinoids are stored in the lipid membrane of the postsynaptic neuron. When that neuron is activated, either via depolarization or the presence of a neurotransmitter binding to a G-protein-coupled receptor, this triggers an enzymatic reaction to form and release the endocannabinoid. (B) The endocannabinoid then binds to a presynaptic cannabinoid receptor, causing the inhibition of neurotransmitter release. This form

of neurotransmission is known as retrograde neurotransmission. classic neurotransmission A B retrograde neurotransmission endocannabinoid released CB1 CB1 The Endocannabinoid System: Retrograde Neurotransmission Tetrahydrocannabinol (THC) vs. Cannabidiol (CBD) CBD THC isomer of THC psychoactive anxiogenic Potential Therapeutic Properties? • Anti-inflammatory • Euphoria • “Opiate type pain relief” Potential Therapeutic Properties? • Neuropathic pain relief • Anti-inflammatory • Patient-specific NOT psychoactive anxiolytic anticonvulsant O O H H H H H H O O Figure 13-25 Tetrahydrocannabinol (THC) vs. cannabidiol (CBD). There are two well-known and relatively well-studied exogenous cannabinoids: (1) tetrahydrocannabinol (THC), which is considered psychoactive and binds as a partial agonist at CB1 and CB2 receptors, causing inhibition of neurotransmitter release; and (2) cannabidiol (CBD), which is not considered psychoactive and for which the binding at CB receptors is not entirely clear, although it does seem to interact with other neurotransmitter systems, such as the serotonin system.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Table 13-2 Areas where there is a range of benefits and risks of cannabis Associated with benefits to: Associated with risk of: Substantial evidence Chronic pain Chemotherapy-induced nausea Spasticity in multiple sclerosis (patient-reported) Respiratory symptoms Motor vehicle crashes Lower birth weight Psychosis Moderate evidence Sleep in obstructive sleep apnea, fibromyalgia, chronic pain, and multiple sclerosis Airway dynamics Forced vital capacity Cognition in psychosis Overdose injuries in pediatric population Impaired learning, memory, and attention Increased (hypo)mania in bipolar disorder Depressive disorders Suicidality and suicide completion Social anxiety disorder Development of substance use disorder for other substances Limited evidence Increasing appetite/decreasing weight loss in HIV/AIDS Spasticity in multiple sclerosis (clinician-reported) Tourette syndrome Anxiety PTSD Testicular cancer Acute myocardial infarction Ischemic stroke of subarachnoid hemorrhage Prediabetes Chronic obstructive pulmonary disease Pregnancy complications Infant admission to neonatal intensive care Impaired academic achievement Increased unemployment Impaired social functioning Increased positive symptoms in schizophrenia Bipolar disorder Anxiety disorders (other than social anxiety disorder) Increased severity of PTSD symptoms THC vs. CBD: Psychiatric Effects Cannabis with Low CBD Content Cannabis with High CBD Content CBD Alone Psychosis symptoms Psychotic disorder Cognition Anxiety Higher risk of hallucinations and delusions Earlier age of onset Higher risk of acute memory impairment Anxiogenic Increased amygdalar activity Lower risk of hallucinations and delusions Later age of onset Lower risk of acute memory impairment Possible antipsychotic effects Anxiolytic Reduced amygdalar activity Figure 13-26 THC vs. CBD: psychiatric effects. Each strain of cannabis may contain a different combination of the 60–100 known cannabinoids. Cannabis with THC and low CBD content may carry higher risk of psychotic symptoms, memory impairment, and anxiety. Cannabis with THC and high CBD content may have lower risk of psychotic symptoms, memory impairment, and anxiety. Pure CBD has been studied for its potential use as an antipsychotic agent or anxiolytic.

Chapter 13: Impulsivity, Compulsivity, and Addiction Hallucinogens It can be a challenge to categorize the various substances that cause not only occasional hallucinations, but more commonly, non-ordinary psychological states and altered states of consciousness. The terminology for these substances is ever evolving and more descriptive than scientific. Here we will use the category hallucinogen to imply three classes of However, both pure THC and pure CBD have been FDA approved according to traditional drug standards for various indications (Table 13-4). Whether some of those areas where some degree of benefit and safety has been described for cannabis

(see Table 13-2) will eventually lead to formal FDA approval of pure compounds for any of those indications is currently under investigation. Table 13-4 Approved uses for THC and CBD Active ingredient Formulation Approval(s) Schedule Dronabinol Synthetic THC Oral capsule or solution Chemo-induced nausea and vomiting (US) Appetite boost in AIDS wasting syndrome (US) III Nabilone Synthetic THC analogue Oral capsule Chemo-induced nausea and vomiting (US) II (due to its potency) Nabiximols Purified ~1:1 THC and CBD Spray Spasticity caused by multiple sclerosis (UK, Canada, Europe, Australia, New Zealand, Israel) Pain in multiple sclerosis and in cancer (Canada, Israel) N/A Epidiolex CBD purified from marijuana Oral solution Seizures associated with two rare and severe forms of epilepsy, Lennox– Gastaut syndrome and Dravet syndrome, in patients 2 years of age and older (US) Not a controlled substance Table 13-3 Areas where there is insufficient evidence for benefits or risks of cannabis Associated with benefits to: Associated with risk of: Insufficient evidence Dementia Intraocular pressure associated with glaucoma Depression in chronic pain or multiple sclerosis Cancer Anorexia nervosa Irritable bowel syndrome Epilepsy Spasticity in spinal cord injury Amyotrophic lateral sclerosis Huntington's disease Parkinson’s disease Dystonia Addiction Psychosis Lung, head, and neck cancers Esophageal cancer Prostate and cervical cancer Certain leukemias Asthma Liver fibrosis or hepatic disease in individuals with Hepatitis C Adverse immune cell response Adverse effects on immune status in HIV Oral human papilloma virus All-cause mortality Occupational accidents/injuries Death from overdose Later outcomes to offspring (e.g., sudden infant death syndrome, academic achievement, later substance abuse) Worsening of negative symptoms in schizophrenia

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY agents that act, at least in part, as agonists at 5HT2A receptors (Figure 13-27). These are: • tryptamines (such as psilocybin) • ergolines (such as lysergic acid diethylamide [LSD]) • phenethylamines (such as mescaline) Hallucinogens are not selective for 5HT2A receptors alone, and their actions at other serotonin receptor subtypes may contribute to their mind-altering states (see Chapter 7 and Figure 7-88). Psilocybin (4-diphosphoryloxy-N,N-dimethyltryptamine) is a prototypical hallucinogen that is derived from hallucinogenic mushrooms. It is both an active drug and a prodrug for another hallucinogen called psilocin (N,N-dimethyltryptamine or DMT). Together, psilocybin, psilocin, and the other tryptamines, ergolines, and phenethylamines in this category act not only at 5HT2A receptors, but also at 5HT2B, 5HT7, 5HT1D, 5HT1E, 5HT2C, 5HT6, and even more serotonin receptor subtypes (see Figure 7-88). Some evidence suggests that 5HT2A antagonists, but not D2 dopamine antagonists, can reverse the action of hallucinogens in humans, supporting the predominant mechanism of action of hallucinogens as being agonists at 5HT2A receptors (Figure 13-27). Hallucinogens can produce incredible tolerance, sometimes after a single dose. Desensitization of 5HT2A receptors is hypothesized to underlie this rapid clinical and pharmacological tolerance. Another unique dimension of hallucinogen use is the production of “flashbacks,” namely the spontaneous recurrence of some of the symptoms of intoxication that lasts from a few seconds to several hours but in the absence of recent administration of the hallucinogen, mostly reported with LSD. This occurs days to months after the last drug experience, and can apparently be precipitated by a number of environmental stimuli. The psychopharmacological mechanism underlying flashbacks is unknown but its phenomenology suggests the possibility of a neurochemical adaptation of the serotonin system and its receptors, related to reverse tolerance that is incredibly long-lasting. Alternatively, flashbacks could be a form of emotional conditioning embedded in the amygdala and then triggered when a later emotional experience that one has when one is not taking a hallucinogen nevertheless reminds one of experiences that occurred when intoxicated with a

hallucinogen. This could precipitate a whole cascade of feelings that occurred while intoxicated with a hallucinogen. This is analogous to the types of re-experiencing flashbacks that occur without drugs in patients with posttraumatic stress disorder Mechanism of Hallucinogens at 5HT2A Receptors 5HT neuron psilocybin LSD mescaline 5HT2A 5HT2A 5HT2A Figure 13-27 Mechanism of hallucinogens at 5HT2A receptors. The primary action of hallucinogenic drugs such as psilocybin, lysergic acid diethylamide (LSD), and mescaline is agonism at 5HT2A receptors. These hallucinogens may have additional actions at other serotonin receptors. (PTSD) and is why hallucinogenic and empathogenic drugs are now being cautiously used for therapeutic purposes in PTSD (see below). The state of hallucinogenic intoxication, sometimes called a “trip,” is associated with changes in sensory experiences, including visual illusions and sometimes hallucinations. Actually, hallucinogens often don’t cause hallucinations (the apparent perception of something that is not actually present), but are much more likely to cause illusions (distortions of sensory experiences that are present). These experiences are produced with a clear level of consciousness and a lack of confusion and may be both psychedelic and psychotomimetic. Psychedelic is the term for the subjective experience that,

due to heightened sensory awareness, one’s mind is being expanded or that one is in union with mankind or the universe and having some sort of a religious experience. Psychotomimetic means that the experience mimics a state of psychosis, but the resemblance between a trip and psychosis is superficial at best. The stimulants cocaine and amphetamine (see discussion in Chapter 4 and also the discussion above for stimulants in this chapter) and the club drug phencyclidine (PCP; discussed in Chapter 4 and also below) much more genuinely mimic psychosis than do hallucinogens. Instead, hallucinogen intoxication includes visual illusions; visual “trails,” where the image smears into streaks of its image as it moves across a visual trail; macropsia and micropsia; emotional and mood lability; subjective slowing of time; the sense that colors are heard and sounds are seen; intensification of sound perception; depersonalization and derealization; yet retaining a state of full wakefulness and alertness. Other changes may include impaired judgment, fear of losing one’s mind, anxiety, nausea, tachycardia, increased blood pressure, and increased body temperature. Not surprisingly, hallucinogen intoxication can cause what is perceived as a panic attack, often called a “bad trip.” As intoxication escalates, one can experience an acute confusional state called delirium, where the abuser is disoriented and agitated. This can evolve further uncommonly into frank psychosis with delusions and paranoia. Empathogens Another category of psychoactive drug is called an empathogen or an entactogen. Empathogens produce an altered state of consciousness described as experiences of emotional communion, oneness, relatedness, emotional openness – that is, empathy or sympathy. The prototype empathogen is MDMA (3,4-methylenedioxymethamphetamine). MDMA is a synthetic amphetamine derivative that acts more selectively on serotonin transporters (SERTs) than upon dopamine transporters (DATs) and norepinephrine transporters (NETs), whereas amphetamine itself acts more selectively on DATs and NETs than on SERTs. Amphetamine’s primary actions on both dopamine and norepinephrine synapses are explained in Chapter 11 and illustrated in Figure 11-32. For its more important serotonin actions, MDMA targets the SERT as a competitive inhibitor and pseudosubstrate (Figure 13-28, upper left), binding at the same site where serotonin binds to this transporter, thus Chapter 13: Impulsivity, Compulsivity, and Addiction inhibiting serotonin reuptake (Figure 13-28, upper left). At psychoactive doses, following competitive inhibition of the SERT (Figure 13-28, upper left), MDMA is actually transported as a hitch-hiker into the presynaptic serotonin terminal. Once there in sufficient quantities, MDMA is also a competitive inhibitor of the vesicular monoamine transporter

(VMAT) for serotonin (Figure 12-28, upper right). Once MDMA hitch-hikes another ride into synaptic vesicles, it displaces the serotonin there, causing serotonin release from synaptic vesicles into the cytoplasm presynaptically (Figure 12-28, lower left) and then from the presynaptic cytoplasm into the synapse to act at serotonin receptors (Figure 12-28, lower right). Once in the synapse, the serotonin can play upon any serotonin receptors that are there, but the evidence suggests that this is mostly upon 5HT2A receptors, just like the hallucinogens. However, given that the clinical state after MDMA differs somewhat from the clinical state after hallucinogens, the pattern of action at serotonin receptors likely differs somewhat. Both human and animal studies show that MDMA actions can be blocked by selective serotonin reuptake inhibitors (SSRIs), supporting the notion that MDMA gets into the presynaptic neuron to release serotonin aboard the SERT. Although there is certainly overlap between the experiences of the so-called hallucinogen psilocybin and the so-called empathogen MDMA, some of the differences are more culturally bound than scientific. The subjective effects of MDMA emphasized by users include a sense of well-being, elevated mood, euphoria, a feeling of closeness with others, and increased sociability. MDMA can produce a complex subjective state, sometimes referred to as “Ecstasy,” which is also what users call MDMA itself. It is also called “Molly,” presumably slang for “molecular.” MDMA was initially popular in the nightclub scene and at all-night dance parties (“raves”) where dehydration and overheating from too much dancing in enclosed spaces led to some deaths from hyperthermia. Some MDMA users report experiencing visual hallucinations, pseudo-hallucinations/illusions, synesthesia, facilitated recollections or imagination, and altered perception of time and space. Others who take MDMA can have unpleasant mania-like experiences, anxious derealization, thought disorders, or fears of loss of thought and body control. Dissociatives Dissociatives are the NMDA (N-methyl-D-aspartate) receptor antagonists phencyclidine (PCP) and ketamine. 569

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY or painful procedures, this is considered a form of anesthesia called dissociative anesthesia in which the patient does not necessarily lose consciousness. The patient, however, does experience a sense of conscious dissociation in which they are disconnected from the environment and from their body and they experience a lack of continuity between thoughts, memories, surroundings, actions, and identity. This dissociative state can be associated with hallucinations, feelings of sensory deprivation, and a dream-like state or trance. Both act at the same site on NMDA receptors (discussed in Chapter 4 and illustrated in Figures 4-1, 4-29B, 4-30 through 4-33, and Table 4-1). These agents were both originally developed as anesthetics because they cause a dissociative state characterized by catalepsy, amnesia, and analgesia. In this state patients experience distorted perceptions of sight and sound, and feelings of detachment – dissociation – from their environment. Signals from the brain to the conscious mind and to the body seem to be blocked. If deep enough for surgery Figure 13-28 Mechanism of MDMA at serotonin synapses. MDMA is a synthetic amphetamine derivative that acts more selectively on the serotonin transporter (SERT) than on the dopamine transporter (DAT). MDMA is a competitive inhibitor and pseudosubstrate at SERTs, thus both blocking serotonin from binding (1) and itself being taken up into the serotonin terminal via SERTs (2). MDMA is also a competitive inhibitor of vesicular monoamine transporters (VMATs) and can be packaged into vesicles (3). At high levels, MDMA will lead to the displacement of serotonin from the vesicles into the terminal (4). Furthermore, once a critical threshold of serotonin has been reached, serotonin will be expelled from the terminal via two mechanisms: the opening of channels to allow for a massive dumping of serotonin into the synapse (5) and the reversal of SERTs (6). 1 = competitive inhibition 2 = SERT transport of MDMA Mechanism of MDMA at Serotonin Synapses 3 = VMAT

transport of MDMA 5 = high 5HT opens channel and spills out 6 = high 5HT reverse transports 5HT out 4 = MDMA displacement of serotonin 2 3 4 4 4 6 5 VMAT serotonin MDMA

At higher doses, PCP and ketamine have general depressant effects and produce sedation, respiratory depression, analgesia, anesthesia, and ataxia, as well as cognitive and memory impairment and amnesia. PCP proved to be totally unacceptable for use as an anesthetic because it induces a powerful and unique psychotomimetic/hallucinatory experience very similar to schizophrenia, often when emerging from a state of anesthesia (see Chapter 4 and Figures 4-1, 4-30 through 4-33, and Table 4-1). The NMDA receptor hypoactivity that is caused by PCP has thus become a model for the same neurotransmitter abnormalities postulated to underlie schizophrenia. PCP also causes intense analgesia, amnesia, delirium, stimulant as well as depressant actions, staggering gait, slurred speech, and a unique form of nystagmus (i.e., vertical nystagmus). Higher degrees of intoxication of PCP can cause catatonia (excitement alternating with stupor and catalepsy), hallucinations, delusions, paranoia, disorientation, and lack of judgment. Overdose can include coma, extremely high temperature, seizures, and muscle breakdown (rhabdomyolysis). PCP's structurally related and mechanism-related analogue ketamine is still used as a dissociative anesthetic, especially in children, and causes far less of the psychotomimetic/hallucinatory experience than that seen after PCP administration. It is also used in veterinary medicine as an animal tranquilizer. Some people abuse ketamine, one of the "club drugs" that is sometimes called "special K." At subanesthetic doses, dissociatives alter many of the same cognitive and perceptual processes affected by other hallucinogenic drugs such as mescaline, LSD, and psilocybin; hence they are also considered hallucinogenic and psychedelic. However, hallucinations are far less common with ketamine at the subanesthetic doses used to treat depression, and at these doses the most significant subjective differences between dissociatives and the hallucinogens (such as LSD, psilocybin, and mescaline) are the dissociative effects of ketamine, including: depersonalization, the feeling of being unreal, disconnected from one's self, or unable to control one's actions; and derealization, the feeling that the outside world is unreal or that one is dreaming. Given as a subanesthetic infusion or as a nasal spray, ketamine and its enantiomer esketamine are discussed as breakthrough rapid-onset novel therapies for treatmentresistant depression in Chapter 7 and illustrated in Chapter 13: Impulsivity, Compulsivity, and Addiction Figures 7-59 to 7-63. These agents are also in trials for rapidly eliminating suicidal thoughts and some studies pairing ketamine/esketamine with psychotherapy sessions for various conditions have also begun to appear. The feelings of dissociation can hypothetically be used to shape psychotherapeutic outcomes as discussed below. Abuse Your Way to Abstinence? Essentially all of our current treatments for substance addiction target the "liking" and "wanting" of drugs, i.e., the first phase of addiction driven by impulsively seeking reward (Figure 13-29A). They all do this by blocking acute receptor actions (i.e., of nicotine, alcohol, or opioids; there are no approved treatments for stimulants). However, none of the currently approved treatments for substance abuse are able to block the migration of control from ventral to dorsal (Figures 13-1 and 13-2) and from impulsivity to compulsivity (Figure 13-29A). This is because we do not know the mechanism of this neuronal adaptation, so we cannot (yet) block it. Even more importantly, addicted patients are not often treated during the impulsivity phase when they are still developing addiction and when receptor blocking actions of drugs might be most useful to prevent stimulus-response conditioning. Instead, those with substance addiction almost always seek treatment during the compulsivity phase of their illness, once stimulus-response conditioning has already occurred and the habit circuit is firmly in control. Unfortunately, we are currently unable to reverse this phenomenon

pharmacologically, but only by long-term abstinence, hoping for reversal of stimulus-response conditioning over time. Staying abstinent long enough for this to occur while in the grips of addiction is the problem for any effective treatment, of course. On the other hand, there are anecdotal reports that combining psychopharmacological treatments that can block the drug of abuse with extinction of the reward by further abusing that drug can facilitate reversal of the drug habit. What?? How can further abuse of a drug lead to non-abuse of the drug? This novel concept comes from observations that when addicted patients are becoming abstinent, they often have “slips” and “cheat” along the way. They “fall off the wagon” – or any number of other expressions for re-using again – because the nature of recovery is to relapse. If you are a horseback rider you are likely familiar with the expression “you are not a rider until you have fallen off a horse seven times.” That is because the nature of riding – unfortunately – is to fall, 571

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 13-29A Maladaptations of the reward pathway. Left: Under normal conditions, if a salient stimulus causes a favorable outcome this behavior will be encoded as a pleasurable reward. The learning of this pleasurable reward is called “liking” and is an opioiddependent process. The knowledge and anticipation of this pleasurable reward is called “wanting” and is a dopamine-dependent process. Center: An increase in “wanting” is thought to underlie impulsivity, such that the drive for the pleasurable reward outweighs the outcome and the behavior is repeated without forethought. Repetition of the impulsive behavior doesn’t happen all the time, and the absence of the behavior can lead to a stronger desire, or anticipation, for the reward. It is this cycle of binge–abstinence–anticipation that can lead to compulsivity. Right: When a behavior becomes compulsive, the reward no longer matters and the behavior is strictly driven by the stimulus. It is through this mechanism that habits develop. Maladaptations of the Reward Pathway Can Shift Behavior from Normal to Impulsive to Compulsive Normal Impulsivity Compulsivity Salient Stimulus Favorable Outcome “Liking” Opioids Binge Absence Anticipation “Wanting” Dopamine Habits Learning Knowing & Anticipating Pleasurable Reward Salient Stimulus Outcome Pleasurable Reward Stimulus Pleasurable Reward Figure 13-29B Reversing habit learning. Since drug abuse is a form of learned behavior, it is theoretically possible to induce pharmacological extinction. In the case of alcohol or opioid dependence, this can theoretically be achieved by administering a μ-opioid antagonist at the same time that alcohol or opioid use occurs (rather than during abstinence). This prevents any enjoyment or euphoria associated with taking the substance. If this approach is successful short term and repeated over and again, it begins the process of extinction or habit reversal. Eventually, the conditioned response of consuming alcohol or taking an opioid in response to conditioned stimuli (withdrawal and environmental cues) becomes extinguished. Theoretically, the brain is “relearning” to disassociate alcohol or opioid use from past triggers and control returns to circuits of voluntary actions and away from involuntary habit circuits. Reversing Habit Learning and the Potential of Long-Acting Injectable Naltrexone Normal Impulsivity Compulsivity Salient Stimulus Favorable Outcome “Liking” Opioids Binge Absence Anticipation “Wanting” Dopamine Habits Learning Knowing & Anticipating Pleasurable Reward Salient Stimulus Outcome Pleasurable Reward Stimulus Administration of the long-acting injectable naltrexone may in fact enhance this process of habit extinction

especially when you are learning. Similarly, the nature of recovery is to relapse, and indeed maybe seven times or more before becoming truly abstinent. The novel concept explained here takes advantage of this inevitability of multiple relapses to reverse the habit circuit by learning that

relapse is no longer rewarding. Drink Your Way to Sobriety This idea uses the brain's own mechanisms of neuroplasticity, learning, and migration of control in the impulsive–compulsive circuitry to induce pharmacological extinction. Since drug abuse is a form of learned behavior, patients with alcoholism experience enhanced reinforcement (via the opioid system) when they drink (discussed above and illustrated in Figures 1315 and 13-16). Contrary to earlier beliefs, detoxification and alcohol deprivation do not stop alcohol craving, but instead increase subsequent alcohol drinking. Recovered alcoholics will often mention that many years following their last drink they still get a burst of craving just driving past their favorite bar, a vestige of their incompletely extinguished alcohol habit. So, the idea is to give alcohol to an active alcoholic and have the patient experience the lack of enjoyment, the lack of euphoria, and the loss of craving that drinking normally produces and that heavy drinking in particular produces. The program involves taking an oral opioid antagonist (e.g., naltrexone or nalmefene) approximately 1 hour prior to consuming alcohol. When the alcohol no longer produces the desired effects because of the opioid antagonist, the alcohol is no longer reinforcing. If this approach is successful short term, and repeated over and again, it begins the process of extinction. The patient slowly learns that they cannot "drink over" their opioid antagonist and drinking is no longer rewarding. Or at least the reward is greatly blunted and the habit of alcohol consumption eventually becomes at least partially extinguished, making eventual abstinence easier to attain, at least in theory. Blocking the reinforcing properties of alcohol weakens the mindless automatic responses to cues in the environment to drink. The theory goes that if drinking is not reinforcing, drinking will abate. Rather like the conditioned Pavlovian dog whose mouth waters at the sound of the bell, but when food is no longer associated with the bell, sooner or later the involuntary mouth-watering is extinguished and the bell now causes no mouth-watering. Sometimes called the Sinclair method and championed at first in Scandinavia, this therapeutic intervention for alcoholism has been tested in many Chapter 13: Impulsivity, Compulsivity, and Addiction clinical studies with good reported success. Interesting here is the observation that opioid antagonists are particularly effective when paired with drinking, but relatively ineffective when given during abstinence. This fits with the notion that to reverse the "habit" of drinking, extinction learning must take place where the reward of abusing alcohol is unpaired with taking alcohol (Figure 13-29B). This can also be done when attempting (and failing) to "drink over" a long-acting injection of naltrexone. Unfortunately, very little opioid antagonist therapy is prescribed for alcohol use disorder. One reason for this might be that opioid antagonist treatment is most effective in reducing heavy drinking, and not necessarily as effective in promoting complete abstinence. Inject Your Way to Heroin Abstinence Scandinavian and other investigators have also noted that individuals with opioid use disorder act similarly to those with alcohol use disorder in response to opioid antagonist treatment. That is, individuals dependent on opioids who attempt to "inject over" long-acting naltrexone with an illicit street opioid find that the opioid is no longer reinforcing. The more times one tries but fails to get high, the faster they develop extinction of their habit, learning that injections are associated with reward (Figure 13-29B). The learned behavior of reinforcement from opioids is now slowly reversed as the act of injecting an opioid is not rewarding. Eventually, the conditioned response of taking an opioid in response to conditioned stimuli (withdrawal and environmental cues) becomes extinguished (Figure 13-29B). Theoretically, the brain is "relearning" to disassociate opioid use from past triggers and control returns to circuits of voluntary actions and away from involuntary habit circuits. Unfortunately, very little opioid antagonist treatment is prescribed for opioid addicts. Smoke Your Way to Quitting This same phenomenon of "cheating" assisting the development of abstinence due to behavioral and pharmacological extinction has been seen in smoking cessation

treatment as well. Many smokers who take treatments to stop smoking nevertheless simultaneously smoke. Thus, such patients “smoke over” their nicotine patch or bupropion and are able to quell craving and allow their habit to perpetuate in the face of treatment. However, with the nicotinic partial agonist varenicline, they cannot “smoke over” this treatment since it has higher affinity for nicotinic receptors than nicotine itself and the result is a lack of reinforcement from the cheating 573

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY while taking varenicline. If smoking on varenicline is no longer reinforcing and this is repeated again and again, as for alcohol and opioids, smoking becomes extinguished as a conditioned response as the brain “unlearns” the habit of smoking (Figure 13-29B). “Therapeutic” Dissociation, Hallucinations, and Empathy? The ability of dissociative agents, hallucinogens, and empathogens to produce mystical-like experiences has been utilized within ancient cultures and indigenous populations for religious and healing purposes for centuries. In the modern era, these same agents are starting to be used in a process called “dissociationassisted psychotherapy” to produce these same experiences in a controlled setting with a psychotherapist. The idea is that mystical states with feelings of oceanic boundlessness, internal unity, external unity, sacredness, “noetic” insights, transcendence of time and space, deeply felt positive mood, and ineffability can be guided with psychotherapy to potentially “heal” some of the most treatment-resistant disorders in psychiatry. These are early days for this approach, and the parameters that might lead to successful outcome are still being defined. Some of the variables are “set,” “setting,” and “cast.” That is, what is the “mind-set” of the patient; what is the “setting” or environment, including sounds of the room where this experience occurs; and who are the “cast,” including therapist and any others that are present. Preparation variables to be clarified include having established a trusting relationship between the patient and therapist in advance, explaining to the patient what to expect, and selection of drug, dose, and accompanying psychotherapy. Few of these variables are well established yet. Most of these approaches to date have used ketamine, psilocybin, or MDMA to induce the dissociative or mystical-like psychological state in a therapist’s office, while conducting psychotherapy for up to several hours. Psychotherapies studied include nondirectedness/self-directedness, mindfulness-based behavioral modification, motivational enhancement therapy, and others. Ketamine-Assisted Psychotherapy Use of ketamine and esketamine without psychotherapy for treatment-resistant depression has been discussed in Chapter 7 and illustrated in Figures 7-59 to 7-62. Investigators are now evaluating subanesthetic infusions of ketamine for treating the craving and abuse of a wide range of substances including cocaine, nicotine, and alcohol, with some success. One of the ideas behind the use of ketamine is to promote prefrontal neural plasticity (see Figures 7-61 and 7-62) to reverse drug-related ventral to dorsal migration of neuronal control discussed extensively in this chapter (see Figure 13-29A), and to facilitate this with guidance from a psychotherapist. Psilocybin-Assisted Psychotherapy Originally utilized for the treatment of anxiety related to late-stage cancer, psilocybin use has been expanded to the treatment of other resistant anxiety disorders and notably to treatment-resistant depression, with some promising preliminary results. Psilocybin is also under investigation in OCD, pain, various addictions, sexual dysfunction, cluster headaches, mild traumatic brain injury, and many more conditions. It is not known whether the psychological state induced by psilocybin or the pharmacology of psilocybin is responsible for any therapeutic effects, or whether the differences between these variables and those induced by either ketamine or MDMA play a role in which patients, with which disorders, might respond. Any role of 5HT2A receptors in triggering potentially favorable neuroplastic changes analogous to those seen with ketamine

remains to be determined. MDMA-Assisted Psychotherapy The idea here is that an empathic state induced by MDMA may be even better than a mystical state induced by psilocybin or a dissociative state induced by ketamine, in that it renders the patient more amenable to exploring painful memories. MDMA has been mostly studied in PTSD, attempting to reduce traumatic memories and the symptoms they trigger. First-line treatment of PTSD is exposure therapy (fear extinction), but there are many patients for whom repeated exposure to the traumatic memory is either unsuccessful or too painful. Extinction of fearful memories was discussed in Chapter 8 on anxiety disorders and illustrated in Figures 8-21 and 8-22. MDMA can potentially provide a safe psychological state where there can be self-directed exploration of painful traumatic memories in the presence of a therapist, in order to contextualize them and thus reduce them. In Chapter 8, the process of reconsolidation of traumatic memories was also discussed and illustrated in Figure 8-21 and 8-22. In this formulation, emotional memories are thought to be amenable to weakening or even erasure at the time they are re-experienced. The notion is that re-experiencing the traumatic memory in a safe psychological state induced by MDMA, and accompanied

by a trusted and experienced therapist, can facilitate the blocking or weakening of reconsolidation of painful emotional memories. BEHAVIORAL ADDICTIONS Binge Eating Disorder Can you become addicted to food? Can your brain circuits make you eat it? Although “food addiction” is not yet accepted as a formal diagnosis, binge eating disorder (BED) is now a formal DSM diagnosis. When external stimuli are triggers for maladaptive eating habits that are performed despite apparent satiety and adverse health consequences, this defines a compulsion and a habit, with the formation of aberrant eating behaviors in a manner that parallels drug addiction. Compulsive eating in BED and bulimia can be mirrored by compulsive rejection of food as in anorexia nervosa. BED is characterized by loss of control for eating, much as substance abuse has loss of control over seeking and taking a substance. For formal diagnostic criteria and clinical descriptions of BED as well as differentiation from the related disorder bulimia nervosa, the reader is referred to standard reference books. Here, we address the construct of BED as falling within the category of an impulsive–compulsive disorder. Briefly, BED is defined as having recurrent episodes of binge eating, with binges being eaten in a discrete period of time, an amount of food larger than most people would eat in a similar amount of time under similar circumstances. What was once perhaps pleasurable eating to satisfy hunger and appetite has now become mindless, compulsive eating, out of control, and associated with marked distress. Not everyone with BED is obese and not everyone with obesity has BED even though about half of people with BED are obese. BED is the most common eating disorder but is commonly undiagnosed. Many clinicians do not inquire about this even if the patient is obese, perhaps because of fear that asking will be taken as offensive by the patient. It is a reality that most BED patients coming to a healthcare professional have a comorbid psychiatric condition, and are usually seeking treatment for that rather than for binge eating. In fact, 80% of patients with BED meet the criteria for a mood disorder, anxiety disorder, other substance abuse disorder, or ADHD. One thing for a clinician to remember is to ask about binge eating in patients with any of these conditions because treatment is available and the long-term complications of obesity are serious (discussed in Chapter 5 on drugs for psychosis). In fact, the D-amphetamine Chapter 13: Impulsivity, Compulsivity, and Addiction precursor lisdexamfetamine discussed in Chapter 11 on ADHD and illustrated in Figure 11-31 is the only currently approved treatment for BED. Several agents with limited efficacy and side effects used off-label include topiramate, several drugs used to treat depression, and naltrexone. BED is another condition that belongs in the addictive disorders group and amongst the impulsive–compulsive

disorders as it, too, is hypothesized to be linked to abnormalities in cortical striatal circuitry where impulsivity (Figure 13-1) leads to compulsivity (Figure 13-2). The mechanism of D-amphetamine reversing binge eating symptoms may not be due to suppressing appetite since appetite no longer really drives binge eating disorder when it becomes compulsive. Instead, it is known that stimulants induce neuroplasticity particularly in the striatum. Hypothetically, promotion of striatal neuroplasticity could help reverse food-related behaviors that have had their control migrate from ventral to dorsal control when impulsive eating became compulsive. As for most impulsive–compulsive disorders, most studies adding various psychotherapies to drug treatment of BED report enhancement of efficacy. Other Behavioral Addictions Although behaviors such as gambling and too much internet gaming have many parallels to BED and to substance abuse disorders, these are not yet generally recognized formally as behavioral “addictions.” Internet addiction can involve an inability to stop the behavior, tolerance, withdrawal, and relief when reinitiating the behavior. Many experts believe gambling disorder should be classified along with drug addiction and BED as a nonsubstance abuse/behavioral addiction disorder. Gambling disorder is characterized by repeated unsuccessful efforts to stop despite adverse consequences, tolerance (gambling higher and higher dollar amounts), psychological withdrawal when not gambling, and relief when reinitiating gambling. Gambling has been observed after treatment with dopamine agonists and partial agonists, suggesting that stimulating the mesolimbic dopamine reward system can induce gambling in some patients. The neurobiology and treatment of other behavioral disorders listed in Table 13-1 are all under investigation as possible impulsive to compulsive and thus ventral to dorsal shifts of control of the abnormal or undesired behavior. The hope is that therapies useful for one of the impulsive–compulsive disorders might be helpful across the spectrum of other disorders in this group. 575

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY OBSESSIVE–COMPULSIVE AND RELATED DISORDERS Obsessive–compulsive disorder (OCD) was once classified as an anxiety disorder (Figure 13-30) but is now placed in its own category by some diagnostic systems such as the DSM-5. In OCD, many patients experience an intense urge to perform stereotypic, ritualistic acts despite having full insight into how senseless and excessive these behaviors are, and having no real desire for the outcome of these actions. The most common types of compulsions are checking and cleaning. For OCD, a general propensity towards habit may be expressed solely as avoidance, deriving from the comorbid anxiety reported. In the context of high anxiety, superstitious avoidance responses may offer relief, which reinforces the behavior. Stress and anxiety may enhance the formation of habits, whether positively or negatively motivated. However, as the habit becomes progressively compulsive, the experience of relief may no longer be the driving force and instead the behavior comes under external control as a conditioned response. Excessive inflexible behaviors are often thought to be carried out in order to neutralize anxiety or distress evoked by particular obsessions. Paradoxically, although OCD patients feel compelled to perform these behaviors, they are often aware that they are more disruptive than helpful. So why do they do them? Rather than conceptualizing compulsive behaviors as goal-directed to reduce anxiety (Figure 13-30), these rituals might be better understood as habits provoked mindlessly from a stimulus in the environment. This is OCD anxiety/ fear about obsessions/ compulsions worry/ obsession why some diagnostic systems no longer categorize OCD as an anxiety disorder. The compulsive habits provoked by environmental stimuli in OCD are hypothetically the same phenomenon within the same neurocircuits as described throughout this chapter for addiction. So, are OCD patients addicted to their obsessions and to their compulsions? Certainly, that is one way to look at OCD

symptoms. OCD patients have demonstrated lack of efficient information processing in their orbitofrontal cortex (Figure 13-2) and lack of cognitive flexibility, and thus cannot inhibit their compulsive responses/habits. Just like drug addicts. Such hypothesized habit learning in OCD – called addiction when applied to drugs, gambling, and binge eating – can be reduced or reversed in OCD with exposure and response prevention, involving graded exposure to anxiety-provoking stimuli/ situations, and prevention of the associated avoidance compulsions. This type of cognitive behavioral therapy is thought to have its therapeutic effect by breaking the pattern of compulsive avoidance that confers dominant control to the external environment (such that the sight of a door elicits checking) and also maintains inappropriate anxiety. Instead of considering compulsions as behavioral reactions to abnormal obsessions, the reverse may be true: obsessions in OCD may in fact be post hoc rationalizations of otherwise inexplicable compulsive urges. Unfortunately, this same type of cognitive behavioral therapy has often proven less effective in drug and behavioral addictions. If successful, cognitive behavioral therapy reverses Figure 13-30 Obsessive–compulsive disorder (OCD). The symptoms typically associated with OCD are shown here and include obsessions that are intrusive and unwanted and that cause marked anxiety or distress, as well as compulsions that are aimed at preventing or suppressing the distress related to the obsessive thoughts. Compulsions can be repetitive behaviors (e.g., handwashing, checking) or mental acts (e.g., praying, counting). compulsions

habits in OCD as it therapeutically helps to migrate the neurocircuit of control of OCD behaviors from dorsal back to ventral, where it belongs. Some other form of doing this same thing may be the key to developing robust treatments for addictions, most of which have little or no highly effective therapeutic drugs or interventions. First-line drug treatment of OCD today is one of the SSRIs, although their efficacy is modest and half of patients treated with these agents show poor responses. Behavioral treatments such as exposure therapy with response prevention often have greater efficacy than serotonergic treatments. It seems as if serotonergic therapies suppress abnormal neurocircuitry, whereas exposure therapy may actually reverse abnormal neurocircuitry because symptoms continue to be improved after stopping exposure therapy but not after stopping SSRIs. Although second-line treatments with one of the tricyclic antidepressants with serotonergic properties, clomipramine, with serotonin–norepinephrine reuptake inhibitors (SNRIs) or with monoamine oxidase inhibitors (MAOIs) are all worthy of consideration, the best pharmacological option for a patient who has failed several SSRIs is often to consider very high doses with an SSRI or augmentation of an SSRI with a serotonin–dopamine blocker. The mechanisms of action of all of these agents are covered in detail in Chapter 5 and 7. Augmentation of an SSRI with a benzodiazepine, lithium, or buspirone can also be considered. Repetitive transcranial magnetic stimulation (rTMS) is an approved treatment for OCD. Experimental treatments for OCD include deep brain stimulation, or even stereotactic ablation of the impulsive–compulsive pathways shown in Figures 13-1 and 13-2, for the most resistant of cases. Conditions related to OCD may respond somewhat to SSRIs, including hoarding, compulsive shopping, skin picking, and body dysmorphic disorder, but not especially trichotillomania (compulsive hair pulling). No agent is officially approved for any of these conditions (Table 13-1). Body dysmorphic disorder for example is preoccupation with perceived defects or flaws in appearance that cause repetitive behavior like looking in the mirror, grooming, reassurance seeking. Preoccupation with health, body function, and pain exist in hypochondriasis and somatization disorders and some experts consider these types of obsessions. It is clear that more robust treatments with a different mechanism of action are needed for the group of obsessive–compulsive related disorders. Chapter 13: Impulsivity,

Compulsivity, and Addiction IMPULSE CONTROL DISORDERS A large variety of disorders that have lack of control of impulsivity are listed in Table 13-1. How many of these disorders can be conceptualized within the impulsive–compulsive spectrum, with abnormalities of cortico-striatal circuitry, remains to be shown, but the descriptive parallels between the impulsive symptoms of these various and sundry conditions gives face validity to this notion. Since the impulsivity of none of these conditions has an approved treatment, we are left with the hope that interventions that work in one of the impulsive–compulsive disorders may be effective across the spectrum of disorders that share this same dimension of psychopathology. However, this remains to be proven and has the risk of oversimplifying some very complex and very different disorders (Table 13-1). One general principle being tested and that may apply across the waterfront of these many and varied disorders is that interventions that can stop the frequent repetition of short-term rewarding impulsive behaviors may hopefully act to prevent converting them into long-term habits that lead to poor functional outcomes. Aggression and violence have long been controversial issues in psychiatry. Experts categorize violence as psychotic, impulsive, or psychopathic, with the most common being impulsive (Figure 13-31). Perhaps somewhat surprisingly, the least frequent type of violent act is one due to cold, calculated psychopathy. Psychopathic violence seems to be the most lethal and the least responsive to treatment. Approximately 20% of violent acts are of the psychotic variety and require standard if not aggressive treatment for the underlying psychotic illness. The most frequent type of violent act is impulsive, especially in institutional settings and especially in patients with underlying psychotic illnesses (Figure 13-31). Each type of aggression may be attributable to dysfunction in distinct neural circuits, with impulsive violence being linked to the same problems of balancing top-down inhibition with bottom-up emotional drives, as discussed in Chapter 12 on agitation in dementia and illustrated in Figures 12-43 and 12-44. Impulsive violence can occur in psychotic disorders of many types, including drug-induced psychosis, schizophrenia, and bipolar mania, as well as in borderline personality disorder and other impulsive–compulsive disorders (Table 13-1). Treatment of the underlying condition, often with drugs for psychosis (discussed in Chapter 5), 577

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY The Heterogeneity of Violence Psychotic - 20% Psychopathic - 17% Impulsive - 63% Figure 13-31 Heterogeneity of violence. Violence is categorized as psychotic, impulsive, or psychopathic. The most common form is impulsive and the least common is psychopathic. Approximately 20% of violent acts are of the psychotic variety. can be helpful. Aggression and violence in such disorders can be considered examples of the imbalance between top-down “stop” signals, and bottom-up drives and “go” signals, as already discussed in dementia (Figures 12-43 and 12-44) and in several other impulsive–compulsive disorders (Table 13-1). Impulsive aggression can be considered a type of addictive behavior when it becomes increasingly compulsive, rather than manipulative and planned, and a habit that must be extinguished with behavioral interventions rather than with purely psychopharmacological approaches SUMMARY We have discussed the current conceptualization of impulsivity and compulsivity as dimensions of psychopathology that cut across many psychiatric disorders. Rewarding behaviors and addiction to drugs hypothetically share the same underlying circuitry. These disorders are characterized at first by impulsivity – defined as behaviors that are difficult to prevent because short-term reward is chosen over long-term gain. Such impulsivity is hypothetically mapped onto a prefrontal ventral striatal reward circuit. Impulsivity can transition to compulsivity – defined as an originally rewarding behavior becoming a habit that is difficult to stop because it reduces tension and withdrawal effects. Compulsivity is hypothetically mapped onto a prefrontal dorsal motor response inhibition circuit. Failure of the balance between top-down

inhibition and bottom-up drives is the common underlying neurobiological mechanism of impulsivity and its transition to compulsivity. Both drugs and behaviors can be associated with impulsivity/compulsivity and are dimensions of psychopathology for a wide range of drug addictions and psychiatric disorders. The chapter discusses the psychopharmacology of reward and the brain circuitry that regulates reward. We have attempted to explain the psychopharmacological mechanisms of actions of various drugs of abuse, from nicotine to alcohol, and also opioids, stimulants, sedative hypnotics, cannabis, hallucinogens, empathogens, and dissociative drugs. In the case of nicotine and alcohol, various novel psychopharmacological treatments are discussed, including the α4β2 selective nicotine partial agonist (NPA) varenicline for smoking cessation, opioid replacement therapies for opioid addiction, and opioid antagonists for both alcohol and opioid addiction. Use of habit extinction in treatment of addiction is explored as is the evolving use of dissociative/hallucinogen-assisted psychotherapy for treatment-resistant conditions. Binge eating disorder is discussed as the prototypical behavioral addiction, and its treatment with stimulants. Impulsive violence is mentioned as a possible form of impulsive–compulsive disorder as well.