*MU* OPIOD RECEPTOR: A GATEWAY TO DRUG ADDICTION

BY

AJAYI ABIGAIL ITUNUOLUWA

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BY DR D.A, ADEKOMI

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CERTIFICATION

This is to certify that this is an original seminar carried out by Ajayi Abigail Itunuoluwa, with matriculation number ANA/2016/0018, in the Department of Anatomy, Faculty of Basic Medical Sciences, Osun State University, Osogbo, Osun, Nigeria.

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Supervisor

Dr. D.A Adekomi Date

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Head of Department Date

Dr D.A Adekomi

DEDICATION

This seminar work is dedicated to GOD ALMIGHTY my creator, my source of understanding and for making this seminar work a huge success.

To my beloved parents Barrister S.J.B Ajayi and Mrs E.M Ajayi for their support and mutual understanding throughout the end of the course. I love you so much.

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**TABLE OF CONTENT**

TITLE………………………………………………………………………………

CERTIFICATION………………………………………………………………….

DEDICATION………………………………………………………………………

ACKNOWLODGEMENT………………………………………………………....

CHAPTER ONE…………………………………………………………………....

INTRODUCTION…………………………………………………………………….

* 1. OPIOD RECEPTORS…………………………………………………………….
  2. *MU* OPIODRECEPTOR………………………………………………………………
  3. LOCATION OF *MU* OPIOID RECEPTOR……………………………………..
  4. ACTIVATION OF *MU* OPIOD RECEPTOR…………………………………………………..
  5. DEACTIVATION OF *MU* OPIOD RECEPTOR……………………………………………….

CHAPTER TWO………………………………………………………………………………

2.1 EPIDEMIOLOGY OF ADDICTION…………………………………………………..

2.2 MOLECULAR ADAPTATIONS TO MU RECEPTOR ACTIVATION IN VIVO……………….

2.3 MU RECEPTOR ACTIVATED NEURAL CIRCUITS………………………………………

2.4 NOVEL APPROACHES TO STUDY MU RECEPTOR…………………………………………..

CHAPTER THREE……………………………………………………………………………………

3.1 NEUROBIOLOGY OF ADDICTION………………………………………………………

3.2 ADDICTION AND THE NEURON…………………………………………………………

3.3 PHARMACOKINETICS OF ADDICTION…………………………………………………….

CHAPTER FOUR……………………………………………………………………………………...

4.1 NEUROBIOLOGICAL DISORDERS FROM ADDICTION…………………………………

4.2 PHARMACOLOGICAL APPROACHES TO TREAT ADDICTION………………………..

4.3 EFFECTS OF DRUG INTERACTION ON MU RECEPTORS………………………………..

4.4 OTHER APPROACGES TO TREAT ADDICTION…………………………………………..

CHAPTER FIVE…………………………………………………………………………………….

5.1 CONCLUSION…………………………………………………………………………………

REFERENCES………………………………………………………………………………………

**CHAPTER ONE**

1. **Introduction**

Drug addiction is a chronic relapsing disorder that results from gradual adaptations of the brain to repeated drug exposure. The current understanding of this complex phenomenon is that neurons responding to natural reinforces such as food, sex, and social interactions are abnormally stimulated, leading to strong deregulations of brain reward pathways (Koob and Moal 1997) and aberrant learning processes (Robbins and Everitt 1999). Addiction has many faces, including initiation and maintenance of drug consumption, withdrawal episodes, protracted abstinence, and relapse. Animal models for different aspects of drug-seeking behaviors have been successfully developed, and efforts are made to comprehend the transition between drug use and drug abuse (Ahmed *et al*., 2002).The brain circuits of addiction involve reward pathways, in association with stress, obsessive-compulsive, and habit-forming systems (Gerrits *et al*., 2003). And molecular adaptations to chronic drug use are being actively examined in this broad neural network. Many neurotransmitter systems are recruited during these processes, with dopaminergic systems being important and the most frequently studied (Gerrits *et al*., 2003).

The endogenous opioid system is also a major player in addiction. Because the opioid system plays a central part in modulating mood and wellbeing, it is believed that modifications of endogenous opioids participate in the development of drug abuse. In addition, the opioid system could also influence drug craving and relapse by altering stress physiology. Both pharmacological and genetic experimental manipulations of the opioid system support these views and demonstrate that endogenous opioids influence reinforcement and adaptations to many drugs of abuse (Gerrits *et al*., 2003). The opioid system consists of three G protein-coupled receptors, *mu*, delta, and kappa, which are stimulated by a family of endogenous opioid peptides (Kieffer 1995). Opioid receptors can also be activated exogenously by alkaloid opiates, the prototype of which is morphine. The finding that morphine’s analgesic and addictive properties are abolished in mice lacking the *mu* opioid receptor has unambiguously demonstrated that *mu* receptors mediate both the therapeutic and the adverse activities of this compound (Matthes *et al*., 1996). Importantly, a series of studies has shown that the reinforcing properties of alcohol, cannabinoids, and nicotine each of which acts at a different receptor are also strongly diminished in these mutant mice (Kieffer *et al*., 2002). The genetic approach therefore highlights *mu* receptors as convergent molecular switches, which mediate reinforcement following direct (morphine) or indirect activation. Beyond the rewarding aspect of drug consumption, pharmacological studies have also suggested a role for this receptor in the maintenance of drug use, as well as craving and relapse (Gerrits *et al*., 2003). As a consequence, expanding the basic understanding of *mu* receptor function should greatly help to further our knowledge of the general mechanisms that underlie addiction.

Opioid addiction is a long-lasting disorder that can cause major health, social, and economic problems. Opioids are a class of drugs that act in the nervous system to produce feelings of pleasure and pain relief. Some opioids are legally prescribed by healthcare providers to manage severe and chronic pain. Commonly prescribed opioids include oxycodone, fentanyl, buprenorphine, methadone, oxymorphone, hydrocodone, codeine, and morphine. Some other opioids, such as heroin, are illegal drugs of abuse (Bonci *et al*., 2003).

Opioid addiction is characterized by a powerful, compulsive urge to use opioid drugs, even when they are no longer required medically (Bonci *et al*., 2003). Opioids have a high potential for causing addiction in some people, even when the medications are prescribed appropriately and taken as directed. Many prescription opioids are misused or diverted to others. Individuals who become addicted may prioritize getting and using these drugs over other activities in their daily lives, often negatively impacting their professional and personal relationships. It is unknown why some people are more likely to become addicted than others.

Opioids change the chemistry of the brain and lead to drug tolerance, which means that over time the dose needs to be increased to achieve the same effect. Taking opioids over a long period of time produces dependence, such that when people stop taking the drug, they have physical and psychological symptoms of withdrawal (such as muscle cramping, diarrhea, and anxiety). Dependence is not the same thing as addiction; although everyone who takes opioids for an extended period will become dependent, only a small percentage also experience the compulsive, continuing need for the drug that characterizes addiction (Kieffer 1995).

Opioid addiction can cause life threatening health problems, including the risk of overdose. Which occurs when high doses of opioids cause breathing to slow or stop, leading to unconsciousness and death if the overdose is not treated immediately, Both legal and illegal opioids carry a risk of overdose if an individual takes too much of the drug, or if opioids are combined with other drugs (particularly tranquilizers called benzodiazepines).

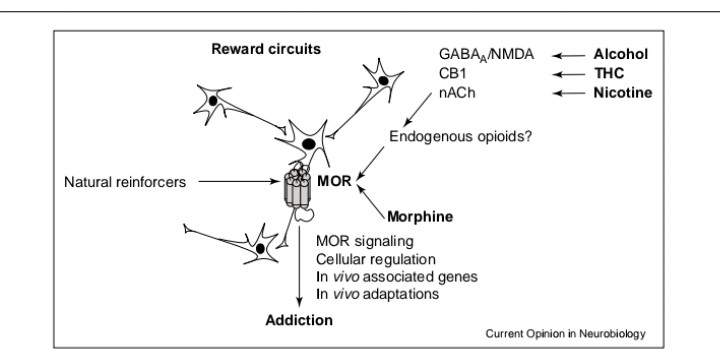


Figure 1: Schematic diagram showing the distribution of mu opioid receptor (MOR) during the reward circuits.

**1.1 Opioid**

Opioids, sometimes called narcotics, are medications prescribed by doctors to treat persistent or severe pain. They are used by people with chronic headaches and backaches, by patients recovering from surgery or experiencing severe pain associated with cancer, and by adults and children who have gotten hurt playing sports or who have been seriously injured in falls, auto accidents or other incidents (Bolanos *et al*., 2003).

**1.2 *Mu* opioid receptor**

The *mu*-opioid receptors (MOR) are a class of opioid receptors with a high affinity for enkephalins and beta-endorphin, but a low affinity for dynorphins. They are also referred to as *μ*(*mu*)-opioid peptide (MOP) receptors. The prototypical *μ*-opioid receptor agonist is morphine, the primary psychoactive alkaloid in opium. It is an inhibitory G-protein coupled receptor that activates the Gi alpha subunit, inhibiting adenylate cyclase activity, lowering cAMP levels (Bolanos *et al*., 2003).

**1.3 Location of *mu* opioid receptor**

The *μ*-opioid receptors exist mostly presynaptically in the periaqueductal gray region, and in the superficial dorsal horn of the spinal cord (specifically the substantia gelatinosa of Rolando). Other areas where they have been located include the external plexiform layer of the olfactory bulb, the nucleus accumbens, in several layers of the cerebral cortex, and in some of the nuclei of the amygdala, as well as the nucleus of the solitary tract. Some MORs is also found in the intestinal tract. Activation of these receptors inhibits peristaltic action which causes constipation, a major side effect of *μ* agonists (WHO 2009).

**1.4 Activation of *mu* opioid receptor**

*Mu* opioid receptor (MOR) can mediate acute changes in neuronal excitability via suppression of presynaptic release of GABA. Activation of the MOR leads to different effects on dendritic spines depending upon the agonist, and may be an example of functional selectivity at the *μ*-receptor. (Schwabe *et al*., 2011) The pathophysiological roles of these two distinct mechanisms remain to be clarified. Perhaps, both might be involved in opioid addiction and opioid-induced deficits in cognition (Schwabe *et al*., 2011).

Activation of the *μ*-opioid receptor by an agonist such as morphine causes analgesia, sedation, slightly reduced blood pressure, itching, nausea, euphoria, decreased respiration, meiosis (constricted pupils), and decreased bowel motility often leading to constipation. Some of these effects, such as analgesia, sedation, euphoria, itching and decreased respiration, tend to lessen with continued use as tolerance develops. Meiosis and reduced bowel motility tend to persist; little tolerance develops to these effects.

The canonical MOR1 isoform is responsible for morphine-induced analgesia, whereas the alternatively spliced MOR1D isoform (through heterodimerization with the gastrin-releasing peptide receptor) is required for morphine-induced itching (Schwabe *et al*., 2011).

**1.5 Deactivation of *mu* opioid receptor**

As with other G protein-coupled receptors, signaling by the *μ*-opioid receptor is terminated through several different mechanisms, which are up regulated with chronic use, leading to rapid tachyphylaxis (Schwabe *et al*., 2011). The most important regulatory proteins for the MOR are the β-arrestinsarrestin beta 1 and arrestin beta 2 (Schwabe *et al*., 2011).

Long-term or high-dose use of opioids may also lead to additional mechanisms of tolerance becoming involved. This includes down regulation of *mu* opioid receptor (MOR) gene expression, so the number of receptors presented on the cell surface is actually reduced, as opposed to the more short-term desensitization induced by β-arrestins or RGS proteins. Another long-term adaptation to opioid use can be up regulation of glutamate and other pathways in the brain which can exert an opioid-opposing effect, to reduce the effects of opioid drugs by altering downstream pathways, regardless of *mu* opioid receptor (MOR) activation (Kessler *et al*., 2005).

**CHAPTER** **TWO**

1. **Epidemiology of addiction**

Although often previously associated with physiological tolerance and withdrawal effects, the term “addiction” has achieved a broader definition (Brewer *et al.,* 2008). Among many researchers and clinicians, “addiction” has come to refer to a disorder in which an individual becomes intensely preoccupied with a behavior that at first provides a desired or appetitive effect. The appetitive effect generally is equated with changes in firing in the mesolimbic dopaminergic system, but there are numerous brain neurotransmission and hormonal systems involved, including mu opioid, serotonin, norepinephrine, anandamide and the hypothalamic-pituitary axis (HPA), among others; associated with subjective reports of arousal, pleasure, or fantasy (Potenza *et al.,* 2008). The addictive behavior occurs with several pattern variations (e.g. bingeing or sustained preoccupation), but always repeatedly, involving a great deal of time thinking about and engaging in the behavior, which operates beyond the need to remove intense anxiety common in compulsive disorders (Brewer and Potenza 2008; Marks, 1990).

An addiction disorder also involves loss of ability to choose freely whether to stop or continue the behavior (loss of control) and leads to experience of behavior-related adverse consequences (Schneider and Irons 2001). In other words, the person becomes unable to reliably predict when the behavior will occur, how long it will go on, when it will stop, or what other behaviors may become associated with the addictive behavior. As a consequence, other activities are given up or, if continued, are no longer experienced as being as enjoyable as they once were. Further negative consequences of the addictive behavior may include interference with performance of life roles (e.g. job, social activities, or hobbies), impairment of social relationships, criminal activity and legal problems, involvement in dangerous situations, physical injury and impairment, financial loss, or emotional trauma. Although many drug and nondrug addictions do not appear to produce obvious physical dependence (i.e., physiological-based tolerance and withdrawal effects), they do create a subjective need for increased involvement in the behavior to achieve satiation and abrupt termination of the behavior often leads to symptoms such as depression, intense anxiety, hopelessness, helplessness and irritability. (Therme and Griffiths 2006; Hausenblas and Down 2002).

**2.1 Regulation of *mu* receptor signaling in neuron: an agonist dependent process:**

Opioid agonists binding at *mu* receptors modulate intracellular effectors through inhibitory Go/Gi proteins. Receptor signaling, in turn, is readily terminated by several cellular regulatory processes that include phosphorylation, desensitization, endocytosis, and down regulation. An important observation from signaling and trafficking studies in transfected cells is that *mu* receptor activation and subsequent regulations are strongly agonist-dependent. Therefore, the agonist–receptor complex, rather than the receptor itself, determines the ultimate physiological effects of the ligand. Responses to peptide opioids (DAMGO [(D-Ala2, N-Me-Phe4, Gly5 -ol)-enkephalin], enkephalins) and alkaloid-type compounds (morphine, fentanyl, methadone) have been examined to find a relationship between agonist efficacy and agonist-induced regulatory processes (Zastrow *et al.,* 2003). Although correlations do not appear straightforward, it is currently accepted that opioid peptide signaling is efficiently blunted by the different regulatory mechanisms, whereas morphine signaling induces low levels of *mu* receptor regulation. The impact of agonist-induced *mu* receptor regulation on long-term in *vivo* adaptations is a matter of debate (Littleton 2001; Kieffer and Evans 2002). A recent hypothesis is that *mu* receptor regulation could protect neurons from overstimulation and prevent counter adaptations that eventually lead to dependence. One approach used to explore this hypothesis in *vivo* was the simultaneous administration of *mu* agonists with distinct efficacy and regulatory profiles. The co-administration of a sub effective dose of DAMGO together with morphine reduced tolerance to morphine analgesia, and was accompanied by enhanced receptor internalization in spinal cord neurons (He *et al*., 2002). Two recent studies have examined whether or not this agonist combination would similarly enhance *mu* receptor desensitization in the locus coeruleus. In these neurons, however, morphine did not efficiently desensitize G protein-coupled inwardly rectifying potassium channel (GIRK) currents either with or without the co-application of the low dose of DAMGO (Blanchet *et al*., 2003; Bailey *et al*., 2003). In addition, in Bailey’s study (Bailey *et al*., 2003) sub effective DAMGO could neither facilitate desensitization of the morphine-induced guinea pig ileum twitch inhibition nor trigger morphine-induced internalization of the *mu* receptor in transfected human embryonic kidney (HEK) cells (Bailey *et al*., 2003). Thus, the benefit of *mu* agonist cocktails in minimizing long-term adaptations remains controversial. At present, the question of whether or not regulatory properties of *mu* agonists are predictive of abuse liability is a growing topic of attention. The lack of morphine-induced *mu* receptor internalization, proposed to be responsible for cellular adaptations relevant to addiction, has been widely observed in heterologous systems. It is crucial to examine whether or not morphine also poorly induces endocytosis in brain neurons expressing endogenous *mu* receptors. In many *mu*-expressing brain regions (Keith *et al., 1998*), including the locus coeruleus (Bockstaele and Commons 2001), treatment of animals with morphine failed to induce *mu* receptor endocytosis, which is consistent with in vitro studies. In rat nucleus accumbens neurons, however, acute morphine administration unexpectedly produced an intracellular redistribution of *mu* receptors in dendrites. In the same neurons, morphine was ineffective in cell bodies as previously observed in other systems (Haberstock *et al., 2003*). This study shows that trafficking of *mu* receptors following morphine binding depends on which subcellular compartment within the neuron is involved, and is therefore more complex than was anticipated from studies in transfected cells.

Finally, intriguing cellular consequences of chronic morphine treatment have been described recently. In one study, prolonged morphine treatment produced recruitment of intracellular delta receptors to the cell surface in dendrites of rat spinal cord neurons, an effect mediated by *mu* receptors and whose mechanism remains to be elucidated (Cahill *et al*., 2001; Morinville *et al*., 2003). In another study, basal signaling of *mu* receptors was enhanced in the brain of mice chronically treated with morphine, a phenomenon that might contribute to the establishment of dependence in these animals (Wang *et al*., 2004).

**2.2 Molecular adaptations to *mu* receptor activation in *vivo*: genetic approaches:**

Among *mu* agonists, morphine is most relevant both in terms of clinical use (pain treatment) and in abuse potential (heroin addiction). Morphine essentially activates *mu* receptors in *vivo*, and the effects of chronic morphine exposure in whole animals reflect the consequences of repeated *mu* receptor activation in the nervous system.

The analysis of morphine responses in about 30 genetically modified animals has recently revealed many partners of *mu* receptor signaling in *vivo*. The inactivation of many genes encoding neurotransmitters and their receptors disrupts morphine conditioned place preference or self-administration, two paradigms testing reinforcing properties of morphine. These systems therefore exhibit ‘pro-opioid’ activity, possibly acting in conjunction with *mu* receptor signaling to produce morphine reinforcement. Interestingly, several of these pro-opioid genes (D2 [dopamine D2 receptor], NK1 [neurokinin-1 receptor], CB1 [cannabinoid 1 receptor], M5 [muscarinic M5 acetylcholine receptor]) also participate in the development of morphine dependence, suggesting a broad recruitment of these transmitter systems in several aspects of addictive behaviors. Some pro-opioid genes (aCGRP [calcitonin gene-related peptide], KOR. [kappa opioid receptor]) Contribute to physical dependence but not to reward, as a result of temporal and spatial dissociation of the two phenomena. The inactivation of other genes results in enhanced morphine effects, and thus, these genes display an ‘anti-opioid’ activity which normally opposes morphine action in wild type mice. Consistent with the pharmacology, CCK2 (cholecystokinin 2 receptor) and OFQ/N (orphanin FQ/nociceptin) systems belong to this category. Gene products known to desensitize G protein signaling in vitro (RGS9 [regulator of G protein signaling 9], b-arrestin 2) also counteract some morphine responses in *vivo*. Interestingly, the dopamine transporter DAT differentially modulates reward and withdrawal. Signaling effectors otherwise display pro-opioid (PKCg [protein kinase C g isoform], CREB [cAMP responsive element binding protein]), anti-opioid (ERK1; extracellular signal regulated kinase 1), or no (nNOS; neuronal nitric oxide synthase) activity. At present, data from genetically modified mice have essentially addressed the role of genes already known to influence addictive behaviors from the pharmacological perspective. It is likely that a broad ‘morphine screen’ of available mouse mutants would reveal unexpected genes that contribute to adaptations to drugs of abuse, and be informative in terms of gene discovery for addiction research.

Identifying neural sites of gene activity is crucial in our understanding of addiction. The constitutive knockout approach provides no clues as to regional gene activity, and, furthermore, compensations could take place during development and account for the observed phenotypes. While strategies for the site-specific knockout of candidate genes are being developed, alternative approaches have provided fascinating results. Recent examples are data showing the modulation of morphine reward and withdrawal following either neurotoxic methods or local gene expression. The selective ablation of cholinergic neurons in the nucleus accumbens of mice, using immunotoxin-mediated cell targeting, led to increased morphine reinforcement as well as increased aversion to morphine withdrawal. Combined with experiments using acetylcholinesterase inhibitors, the data suggest that enhancement of acetylcholine in this brain region hampers the development of addiction (Hikida *et al*., 2003). Neurons expressing NK1 receptors were selectively destroyed by local treatments with the neurotoxic substance P–saporin conjugate in several mouse brain areas.

Morphine conditioned place preference was reduced when amygdala, but not striatal neurons, were lesioned, which suggests that NK1-bearing neurons of the amygdala are involved in morphine reward (Bolanos *et al*., 2003). Viral-mediated overexpression of PLCg1 (phospholipase C g 1) in the rat ventral tegmental area (VTA) increased morphine reward when gene transfer was made in the rostral ventral tegmental area (VTA) and produced morphine aversion when the injection site was the caudal ventral tegmental area (VTA). These findings define two distinct regions of the ventral tegmental area (VTA) that regulate the motivational properties of morphine in opposite directions (Zachariou *et al*., 2003). Viral gene transfer was also used to rescue RGS9 gene expression in selected brain areas of RGS9 knockout mice. The increased morphine conditioned place preference of the knockout animals was reversed by RGS9 expression in nucleus accumbens, but not caudate putamen, highlighting the contribution of a limited population of RGS9 proteins in the regulation of morphine reward (Zachariou *et al*., 2003).

Gene rescue on a knockout background was also achieved by electroporation in a mouse brain in *vivo*. The local re-expression of the GluRe1 (NMDA receptor e1 subunit) subunit of the N-Methyl-D-aspartate (NMDA) receptor in the nucleus accumbens partially reversed the attenuate morphine withdrawal syndrome of the GluRe1 knockout mice. Morphine analgesic tolerance was otherwise rescued in other brain areas, demonstrating spatial dissociation of distinct long-term adaptations to morphine (Inoue *et al*., 2003).

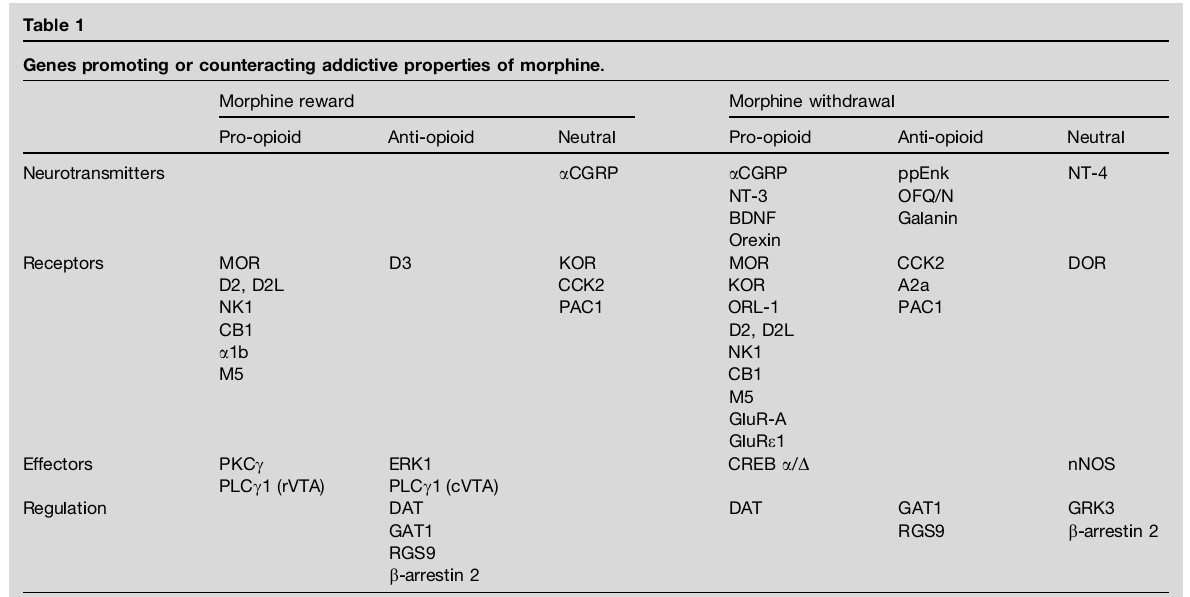
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Table 1: This table summarizes data from gene over expression (PLCg1, GAT1), gene knock out or a combination of both (gelanin, GluRe1, RGS9) in mice (Bohn *et* *al*., 2003).

**2.3 *Mu* receptor-activated neural circuits: functional maping**

*Mu* receptors are broadly expressed in all brain areas belonging to the circuits of addiction (Figure 2). These include mesolimbic dopaminergic neurons, which originate from the ventral tegmental area (VTA) and project to the nucleus accumbens. These neurons have been widely studied in the past few years. The nucleus accumbens itself is part of a complex network that includes prefrontal cortical areas, hippocampus, and basal forebrain structures known as the extended amygdala. The extended amygdala is formed by a continuum between the shell of the nucleus accumbens, the bed nucleus of the striaterminalis and the central nucleus of the amygdala, and is becoming the focus of much interest in drug abuse research (Koob 2003). Other brain areas important in adaptations to drugs of abuse include the locus coeruleus, the hypothalamus, and some brainstem nuclei. Many functional mapping studies conducted following acute or chronic morphine administration have shown neural activation of all these structures. Low doses of naloxone administered to morphine dependent rats produced place aversion without somatic signs of withdrawal, and this treatment specifically increased c-fos activity in areas of the extended amygdala (Gracy *et al*., 2001; Frenois *et al*., 2002). In a sensitization study, morphine-abstinent rats were re-exposed to the drug in a place conditioning paradigm. The animals showed potentiated morphine reinforcement that was associated with enhanced c-fos expression in the extended amygdala as well as the cingulate cortex, the core of the nucleus accumbens, and the basolateral nucleus of the amygdala (Harris *et* *al*., 2003). In another functional mapping study, constant or escalating doses of morphine led to the development of either sensitization or tolerance, two conditions in which mitogen activated protein kinase (MAPK) activation patterns differed markedly, particularly in the basolateral amygdala. Changes in morphine induced MAPK phosphorylation were attenuated along the two chronic morphine regimes (tolerance) in most brain areas, except in the central nucleus in the amygdala (Eitan *et al*., 2003). CRE-LacZ reporter mice, in which the LacZ gene encoding b-galactosidase is under the control of cAMP response element-consensus sequence, represent another useful approach for the functional mapping of morphine, induced neuronal activation (Shaw-Lutchman *et al*., 2012) and it is likely that similar strategies will be developed in the future.

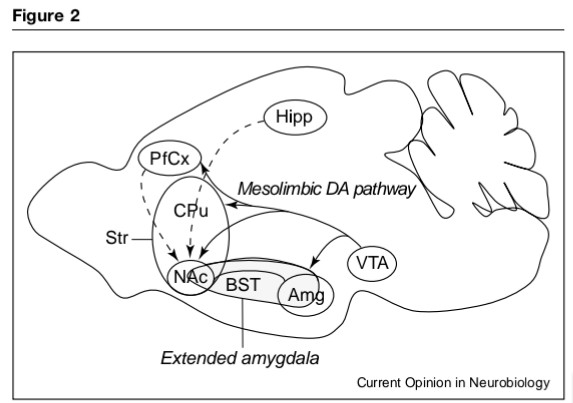


Figure 2: Schematicrepresentationofbrainareasunderstudyinaddictionresearch (Nestler *et* *al*., 2004).

**2.4 Novel approaches to study *mu* receptor signaling and molecular adaptation to morphine in *vivo***

To complement candidate gene approaches several screening methods are now being developed to better understand the consequences of *mu* receptor activation. The yeast two-hybrid system has identified proteins that physically interact with the carboxy-termini of *mu* receptors and regulate distinct aspects of *mu* receptor activity at the cellular level. Phospholipase D2 was found to associate with the *mu* receptor in the plasma membrane of transfected HEK cells, and accelerated agonist-induced internalization (Koch *et al*., 2003). Filamin A, a cytoskeletal protein known to bind to several membrane proteins, appeared necessary for normal *mu* receptor trafficking in a study comparing filamin-expressing versus filamin-deficient melanoma cells (Onoprishvili *et al*., 2003). By contrast, periplakin, another cytolinker protein, did not alter *mu* receptor internalization in transfected HEK cells but reduced coupling to the G protein through interaction with helix VIII of the receptor (Feng *et al*., 2003). Proteins that interact with intracellular domains of other G protein-coupled receptors are being discovered, such as GASP (G protein-coupled receptor associated sorting protein), which interacts with delta rather than *mu* receptors (Whistler *et al*., 2002). Whether or not GASP homologs (Simonin *et al*., 2004) regulate *mu* receptor signaling in *vivo* is an open question. At present, only heterologous systems have been used to study the putative *mu* receptor partners, and the biological relevance of these interactions remains to be established. Differential gene expression experiments have identified several gene families whose transcription is regulated following treatment with drugs of abuse (Pollock 2002). The drugs that have been used in these studies are mainly psych stimulants; studies with morphine are still limited. Acute morphine administration modified transcription of 45 genes (down-regulation) and nine genes (up-regulation) belonging mostly to mitochondrial and cytoskeletal gene families in the medial striatum of mice (Loguinov *et* *al*., 2001). In the rat frontal cortex, chronic morphine exposure upregulated a set of 14 genes including many heat-shock proteins, whereas naloxone-precipitated withdrawal induced 18 genes that essentially encoded transcription factors (Ammon *et al*., 2003). In a series of interesting studies that compared self- versus forced-heroin administration in rats (Jacobs *et al*., 2003), 25 genes were down regulated in the shell of the nucleus accumbens in active but not passive drug consumption (Jacobs *et al*., 2002). Among these, 18 genes were also up-regulated in the core of the nucleus accumbens irrespective of the administration mode (Jacobs *et al*., 2004). Together therefore, the two studies reveal genes involved either in the cognitive aspect of voluntary drug use (shell) or in the general plasticity consecutive to heroin pharmacological effects (core). In fact, surprisingly few novel genes have emerged from these initial studies, and these approaches await further refinement of brain dissection methods, combined with parallel proteomic screens and extensive target validation.

**CHAPTER THREE**

**3.1 Neurobiology of addiction**

Addiction neurobiology is superbly situated to benefit from many neuroscience advances. Advanced imaging that reflects neuronal activity and neurochemistry in humans and experimental animals provides substantial insights into meso-scale brain changes that are highly relevant for addictions. Addiction researchers’ early adoption of optogenetic and chemogenetic approaches has provided elegant support for and refinement of hypotheses about roles for specific circuits in addiction-related behaviors and physiology.

Much progress in the neurobiology of addiction can be placed into a heuristic three-stage addiction cycle framework: binge or intoxication, withdrawal or negative affect, and preoccupation or anticipation. This framework is supported by multiple neuroadaptations in three corresponding domains: (1) increased incentive salience (2) decreased brain reward and increased stress, and (3) compromised executive function; and in three major neurocircuits: basal ganglia, extended amygdala, and prefrontal cortex. The focus in the neurobiology of addiction has changed with emphasis on the mechanisms of acute reward in the binge or intoxication stage broadened to include neuroadaptations that are consequent to drug exposure. These include mechanisms driving incentive salience, compulsive habits, deficits in reward and recruitment of stress during the withdrawal or negative affect stage, and modulation of executive function systems and mnemonic systems (and being modulated by mnemonic processes) in the preoccupation/anticipation stages of substance use disorders.

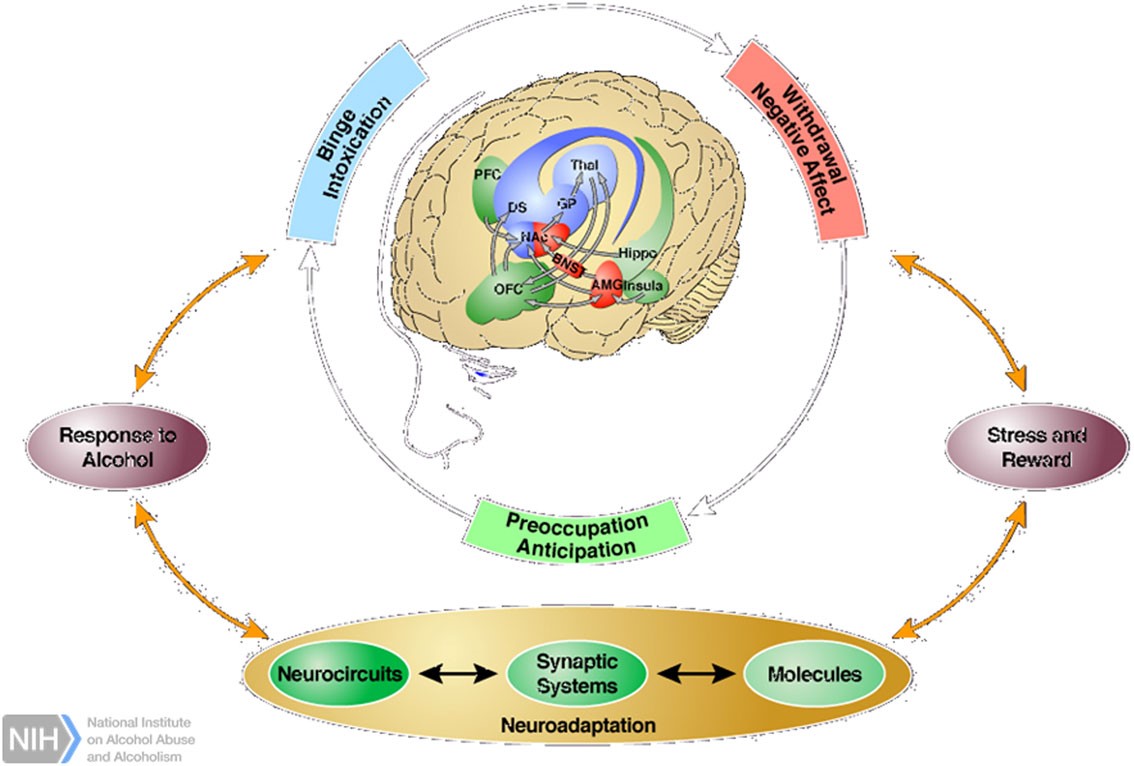


Figure 1: Conceptual framework for neurobiological bases of the transition to substance use disorders.

**3.1.1 The role of dopamine in addiction**

Addictive drugs are inherently rewarding. They highjack the brain’s dopamine system to increase dopamine levels in the nucleus accumbens, a key focal point for reward neurocircuitry in the brainwhile dopamine is critical for the rewarding effects of drugs, its role in substance use disorders is still evolving. Nearly 20 years ago, Nora Volkow (National Institute on Drug Abuse, National Institutes of Health) showed via positron emission tomography imaging that higher dopamine levels correspond with a more intense high in healthy volunteers given intravenous methylphenidate(MPH), a central nervous stimulant also known as Ritalin. There was considerable variability in dopamine levels across subjects; some individuals experienced neither increased dopamine levels nor “high.” Administration of oral MPH, which takes longer to enter the brain, resulted in no high with slower increases in dopamine levels (Volkow *et al*., 2001)

Since the rate of dopamine increase plays a factor in whether a drug will produce a rewarding effect, the different properties and effects of dopamine receptors in the brain are likely to play significant roles. The prefrontal cortex contains both dopamine D1 and D2 receptors. D2 receptors have an approximately 10- to 100-fold greater affinity for dopamine than D1 receptors and are therefore activated at lower dopamine concentrations. Under normal circumstances, the prefrontal cortex receives a low level, stable flow of dopamine owing to relatively slow, tonic firing of dopamine neurons in the ventral tegmental area (VTA) that project to the cortex. However, in response to an unexpected event, such as an extraordinary reward or very aversive event, dopamine neurons fire much more quickly. This phasic firing results in an abrupt, yet transient, increase in dopamine. The high levels of dopamine achieved during phasic firing are able to activate D1 receptors and are thought to be required for dopamine’s full rewarding effects (Grace 2000; Baik 2013).Drugs of abuse, particularly psycho stimulants, mimic the high dopamine concentrations produced by phasic firing and thus activate both D1 and D2 receptors (Volkow and Morales 2015).

D1 receptors stimulate both reward, via pathways modulating the striatum and cortex, and conditioning and memory mechanisms that involve the amygdala, medial orbitofrontal cortex (OFC), and hippocampus. The conditioning or memory processes critical to addiction allows individuals to automatically associate a stimulus with a reward or punishment. Perhaps paradoxically, several studies have shown that addictive drugs fail to increase dopamine release in addicted individuals compared with non-addicted controls. MPH did not significantly increase dopamine levels among active (Volkow *et al*., 2014)or detoxified cocaine addicts (Volkow *et al*., 1997).Cocaine users also reported less of a high from MPH than controls (Volkow *et al*., 1997).However, among active addicts shown a video to produce craving, increased dopamine was observed in the dorsal striatum. The magnitude of this dopamine increase was associated with the extent of drug craving (volkow *et al*., 2014).These data suggest that in addiction there is thus a switch from the drug itself initiating dopamine release to drug cues and stimuli initiating dopamine release. This shift from reward to conditioning involves dopamine phasic firing leading to drug cravings and compulsive drug use in response to drug and other conditioned cues (Volkow *et al*., 2011).

Normally, D2 receptors modulate the effects of D1 receptors via the striatal indirect pathway (Volkow and Morales 2015); however, several studies have shown that addicted subjects have lower expression of dopamine D2 receptors (Volkow *et al*., 2002).Reductions in D2 receptors among addicted subjects are associated with decreased activity in the OFC, anterior cingulate gyrus, and dorsolateral prefrontal cortex areas of the brain involved in emotion regulation and decision making. Because impairments in the orbitofrontal and anterior cingulate cortices are associated with compulsive behaviors, impaired dopamine signaling in these areas in addicted subjects may be partially responsible for their compulsive behavior and impulsivity (Volkow *et al*., 2011).In animal studies, increased dopamine D2 receptor expression in the nucleus accumbens reduced drug consumption in models of both alcohol and cocaine dependence (Thanos *et al*., 2001; Thanos *et al*., 2004).In humans, a recent study in methamphetamine users demonstrated that regular aerobic exercise can up regulate striatal dopamine D2 and D3 receptors; whether this results in reduced cravings and drug use remains to be seen (Robertson *et al*., 2016).

**3.1.2 The dark side of addiction: stress neurocircuitry/mechanisms underlying addiction**

The role of corticotrophin releasing factor and dynorphin in the dark side of addictionthe brain’s stress and reward systems are intricately linked. Moderate forms of stress, such as skydiving, can also activate the reward system. Excessive activation of the reward system, as in the case of excessive drug use, can also engage the brain’s stress system. As individuals who have become dependent on drugs lose normal function of aspects of their reward systems, they can gain activation of their stress system as well.

George Koob (National Institute on Alcohol Abuse and Alcoholism) described his longstanding fascination with understanding the connections between stress and addiction and how they contribute to a powerful additional source of motivation in addiction: negative reinforcement. Here, Koob argues that the driving force for negative reinforcement (where removal of an aversive stimulus, drug withdrawal, increases the probability of drug seeking and taking) is the negative emotional state of withdrawal mediated by stress-related neurotransmitters, particularly corticotropin-releasing factor (CRF) and dynorphin. He emphasized that there are also many other stress-related neurotransmitters up- or down regulated in addiction that warrant further study (Koob 2008).

During acute stress, the peptide CRF is activated in the extended amygdala during withdrawal from abused substances that include alcohol (Merol *et al*., 1995), cocaine (Richter and Weiss 1999), cannabinoids (Rodr´ıguez *et al*., 1997),opioids (Weiss *et al*., 2001),and nicotine (George *et al*., 2007).CRF antagonists decrease withdrawal-induced anxiety like responses in animals (Overstreet and Breese 2004),decrease the escalation associated with extended access to drugs of abuse, and decrease alcohol intake in alcohol dependent rats while having no effect on alcohol intake in nondependent rats (Koob *et al*., 2001).

These dynamic changes in extra hypothalamic CRF may begin with the initial hormonal response of increased release of glucocorticoids driven by hypothalamic CRF. However, during periods of chronic stress, high levels of glucocorticoids decrease CRF levels in the hypothalamic periventricular nucleus while increasing CRF levels in the amygdala (Koob *et al*., 2001). A similar effect has been seen in drug-dependent animals (Roberto *et al*., 2010).Compulsive-like drug taking thus increases CRF levels in the amygdala, prefrontal cortex, and VTA, contributing to stress like responses and negative emotional states, which provide the motivation for sustaining compulsive like drug taking via negative reinforcement. Similar to CRF antagonists, glucocorticoid antagonists reduced alcohol consumption in alcohol dependent animals, but not in nondependent controls (Vendruscolo *et al*., 2012).A recent human laboratory study in non-treatment-seeking individuals with alcohol addiction demonstrated that the glucocorticoid antagonist mifepristone reduced craving and drinking compared with placebo (Vendruscolo *et al*., 2015).

Dynorphin is a kappa opioid whose expression can be modulated by activation of dopamine or opioid receptors (Nestler 2001).Unlike other opioids, kappa opioids induce feelings of dysphoria. Compulsive drug taking increases dynorphin levels in the nucleus accumbens and amygdala, contributing to a dysphonic-like state. High levels of dynorphin signal through a negative feedback loop to turn off dopamine production, and kappa opioid agonists decrease extracellular dopamine levels in the nucleus accumbens.The kappa antagonist nor-binaltorphimine (nor-BNI) decreases excessive drinking in alcohol-dependent rats while having no effect in nondependent animals, similar to CRF and glucocorticoid antagonists (Walker *et al*., 2011).Injecting nor-BNI into dynorphin-expressing areas of the nucleus accumbens blocks withdrawal-induced increases in alcohol administration in rats (Nealey *et al*., 2011).Thus, from a conceptual perspective, Koob emphasized that these stress-driven negative emotional states create an additional source of motivation for drug seeking involving negative reinforcement. Termed “the dark side of addiction,” this source of motivation is becoming increasingly recognized as contributing to the deaths of despair involving opioids and alcohol.

**3.1.3 Drug cue–induced neuroplasticity**

Insights into the physiological processes behind the overwhelming drive in individuals with addiction to seek out a drug and forgo other competing choices were discussed by Peter W. Kalivas (Medical University of South Carolina). When an individual with addiction encounters an external cue or stimulus associated with a drug, such as a call from a friend to meet them at a bar or, in the case of a laboratory animal, a light associated with a drug-delivering lever, cells in the nucleus accumbens are activated, resulting in a cue-specific engram that results in drug-seeking behavior. In individuals without addiction, competing thoughts or cues can alter that response. However, drug cues leave behind long-term potentiation of activity of the nucleus accumbens that blunts the effects of competing stimuli (Gipson *et al*., 2013).

Michael Scofield (Medical University of South Carolina) described the mechanism behind this over potentiation. Normally, when a cue comes to the prefrontal cortex, glutamate is released into the nucleus accumbens, activating a small percentage of neurons, resulting in a stimulus-specific memory trace or engram. Excess glutamate is removed from the synaptic cleft by transporters including GLT-1, a glutamate transporter found on astroglial cells. However, on the basis of animal models of drug addiction, the hypothesis is that GLT-1 is down regulated, and there are fewer astroglial cells in the synaptic left (Scofield *et al.*, 2016).Thus, drug cues cause accumulation of glutamate in the synaptic left; subsequent activation of mGluR5, a receptor found on interneurons that express neuronal nitric oxide synthase; release of nitric oxide into the extracellular space; nitrosylation; and activation of matrix metalloproteases (MMPs), especially MMP9, that cause local degradation of the extracellular matrix. This cascade of events provides transient plasticity that contributes to drug-seeking behavior. In withdrawn animals, drug cues result in significant increases in MMP9. Inhibiting MMP9 inhibits drug-seeking behavior in response to drug-associated cues.MMP activity also creates an RGD-binding ligand that activates integrins on spiny neurons, resulting in an increase in spine head diameter and expression of AMPA receptors (Wiggins *et al*., 2011).

Down regulation of GLT-1 can be found with administration of several classes of addictive substances to animals, including cocaine,nicotine,heroin,and alcohol (Sari *et al*., 2011).An a*cc*umulation of glutamate has been observed in animal models of cocaine,nicotine,alcohol,and methamphetamine addictions (Parsegian, and R.E. 2014).Drugs that enhance GLT-1 function, including *N*-acetylcysteine (NAC), ceftriaxone, and propentofylline, have shown positive results in animal models of addiction to cocaine,nicotine,and alcohol (Sari *et al*., 2011)use disorders. NAC has also shown improved behavior in human disorders characterized by intrusive thoughts, such as pathological gambling,trichotillomania,obsessive compulsive disorder (OCD) (Afshar *et al*., 2012)and depression,though there are failures to show improvements in pediatric trichotillomaniaor methamphetamine addiction(Grant *et al*., 2010).In a recent double-blind, place to controlled trial of NAC in veterans with posttraumatic stress disorder (PTSD) and substance abuse, NAC reduced cravings by week 8. This effect persisted for 4 weeks after stopping NAC. Subjects also reported improvements in CAPS scores of PTSD symptoms and CAPS intrusive thoughts score (Back *et al*., 2016).

**3.1.4 The role of serotonin in anxiety and addiction**

Increasing synaptic serotonin levels through the use of selective serotonin reuptake inhibitors (SSRIs), such as ProzacR (fluoxetine) and ZoloftR (sertraline), is a common strategy to relieve anxiety and depression, but the role of serotonin in the brain is complicated (Thibaut 2017). First, one of the primary sources of serotonin, the dorsal raphe, projects to areas of the brain involved in impulsivity, reward, stress, anxiety, and feeding. Second, there are many types of serotonin receptors, which can have different effects on behavior. Thomas L. Kash (University of North Carolina School of Medicine) discussed the role of serotonin in increasing anxiety.

Several lines of evidence suggest that increased activation of at least some serotoninergic systems can be highly aversive. SSRI treatment can lead to anxiety, panic, and suicidal ideation in some patients (Pfizer 2018).Serotonin has also been shown to play a role in alcohol-induced anxiety. In individuals with AUD, the serotonin agonist metachlorophenylpiperazine has been shown to induce cravings (Umhau *et al*., 2011).SSRI treatment has been shown to increase anxiety and alcohol consumption in some individuals with AUD (Kranzler *et al*., 2012).

Work from Kash’s laboratory has helped to elucidate the neural networks underlying the role of serotonin in alcohol-induced anxiety. In a mouse model of alcohol dependence in which mice were exposed to alcohol vapor and evaluated 24 h after withdrawal, mice displayed increased anxiety related behavior.This effect is dependent on serotonin, since injecting the mice with a serotonin receptor antagonist reduced these behaviors (Marcinkiewcz *et al*., 2015). At a neural level, alcohol induced hyper excitability in both the dorsal raphe, a key source of the serotonin projections to the forebrain, and the bed nucleus of the stria terminals (BNST), part of the extended amygdala located between the nucleus accumbens and central amygdala and well known for its role in aversive behaviors.

Optogenetic stimulation of serotonin from the dorsal raphe to the BNST also increased anxiety-like behaviors and fear learning in mice. Animals were placed into a chamber where they received a small shock in response to a tone. Stimulating serotonin release optogenetically during the tone resulted in increased freezing behavior, suggesting that serotonin can increase fear recall (data unpublished). A similar study from researchers at Columbia University showed that increasing serotonin levels by injecting fluoxetine into the BNST also enhances fear learning (Burghardt *et al*., 2007).There is a population of serotonin-responsive neurons in the BNST, which express both CRF and the serotonin 5HT2C receptor. Upon activation, these neurons inhibit neurons that project into the ventral tegmental area (VTA) and lateral hypothalamus, thus inhibiting reward-promoting outputs and driving aversive states. Silencing CRF neurons in the BNST blocks the effects of fluoxetine in enhancing fear memory and anxiety (Marcinkiewcz *et al*., 2016).

**3.1.5 Effects of addictive drugs on the developing brain: adolescents and young adults**

Diana Fishbein (Pennsylvania State University) described adolescence as a period of significant, rapid brain development during which the adolescent brain provides increased addiction-related risks. The last region of the brain to develop is the frontal cortex, responsible for executive functions that include impulse control, risk determination, evaluation of consequences, and decision making. During adolescence and into the early 20s, there are significant changes in both gray and white matter in the frontal cortex, including continued myelination, gray matter thinning, and pruning of excess connections established earlier in development(Bava *et al*., 2010).The prefrontal cortex also serves to modulate the activities of noncortical systems, such as regulating emotional circuit activity in the limbic system. Imaging studies have revealed that the dopaminergic connectivity to the frontal cortex is weaker in children than in adults. As the prefrontal cortex matures during adolescence, there is a linear increase in inhibitory control. However, there is also an increased activity in the nucleus accumbens, which increases reward sensitivity.These differences are likely to contribute to the greater risk-taking behavior, novelty seeking, and impulsivity that can be observed in adolescence.

Because their brains are still developing, adolescents are thus more likely to both engage in risk-taking behaviors, including drug self-administration, and display enhanced vulnerability to the effects of drugs and alcohol. Large epidemiological studies show that adolescents and young adults are more likely to start using drugs than older adults. Adolescents are also more likely to transition from experimenting with drugs to develop substance use disorders (Galvan *et al*., 2006).In the National Longitudinal Alcohol Epidemiologic Survey, 45% of people who began drinking before the age of 14 grew up to ultimately have an AUD, compared with 10% of people who began drinking after the age of 21.The more recent National Epidemiologic Survey on Alcohol and Related Conditions showed that those who started drinking at an early age were more likely to experience alcohol dependence within 10 years of beginning drinking (Hingson *et al*., 2006).

**3.1.6 The effects of alcohol on brain development**

Alcohol use among adolescents has been associated with differences in and/or changes in brain structure and function (Lisdahl *et al*., 2013).Fifteen- and 16-year-olds enrolled in an alcohol treatment program showed about a 10% deficiency in memory compared with nondrinking, matched controls as well as differences in cerebellar, hippocampal, and prefrontal cortex volume and white matter quality.

Susan Tapert (University of California, San Diego) described work on the Youth at Risk Study to elucidate how adolescents who use drugs and alcohol differ from those who do not. In this longitudinal study of 300 middle scholars who had not started drinking at the time of study entry, 40% remained nondrinkers, 30% drank modestly or moderately, and 30% had become heavy drinkers when studied 4 years later. Adolescents who began drinking during the follow-up period performed worse on several measures of neurocognition compared with those who did not start drinking. Girls who started drinking showed greater impairment in memory tests; boys did worse on tests of visual attention (Squeglia *et al*., 2009).Extreme binge drinking was associated with poorer performance on several measures of verbal learning and memory compared with subjects who engaged in little or no binge drinking (Nguyen *et al*., 2016).

Several differences in brain structure and activity were also observed. Adolescents who initiate heavy drinking showed accelerated reduction of gray matter volumes, particularly in temporal and lateral frontal areas, and attenuated growth in white matter. Structural MRI data also reveal greater reductions in brain volume in the left temporal lobe, caudate, thalamus, and brain stem (Squeglia *et al*., 2015).

Functional MRI studies reveal that teens who become heavy drinkers display lower levels of brain activity during visual working memory tasks even before they start drinking, without any deficit in performance (Squeglia *et al*., 2012).This suggests that they are not as cognitively involved in the non-rewarding task as those who do not become drinkers. After they become drinkers, however, their brain activity increases during these tasks, likely indicating that their brains are working harder to do the same task than their nondrinking counterparts.

Lindsey Squeglia (Medical University of South Carolina) described baseline characteristics that predicted future heavy drinking. Demographic variables, including male gender and higher socioeconomic status, were associated with higher risk of becoming a heavy drinker, as were behaviors that included conduct disorders. In addition, several neuropsychological and imaging characteristics differed at baseline in future heavy drinkers. Subjects who began drinking had pre-existing smaller volumes in the inferior frontal cortex, cingulate, and cerebellum. They also had thinner cortex in several brain regions and showed less brain activity during a working memory task. A predictive model consisting of 38 variables demographic, behavioral, neuropsychiatric, and imaging could predict future heavy drinking with 74% accuracy. Understanding the risk factors for heavy drinking among teens can help pediatricians and counselors (Squeglia *et al*., 2017).

Functional MRI studies have also shed light on the role that the media and advertising may play in substance use initiation. A group of 15- to 18year-olds composed of heavy binge drinkers and moderate, nonbinge drinkers was shown a series of advertisements for alcoholic and nonalcoholic products. Heavy drinkers showed greater brain activation when looking at the alcohol ads compared with nonalcoholic ads. Conversely, the nonbinge drinkers showed no difference in brain activation for the two types of ads (Tapert *et al*., 2003).Abstaining from alcohol for 5 weeks was able to attenuate this response, suggesting that the response may be reversible.

Two large-scale, longitudinal studies are underway to better understand the effects of alcohol and/or other abused substances on neurodevelopment in adolescents. The National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) has recruited over 800 adolescents from ages 12 to 21, many of them at risk of substance use, among five sites in the United States by 2016. Subjects are being followed up annually with neuroimaging and neurophysiological testing (Brown *et al*., 2015).A second, larger study, the Adolescent Brain Cognitive Development (ABCD), is following over 11,000 9 to 10-year-olds for 10 years in 19 sites around the United States. Enrollment of the study began in 2016, and as of early 2018, over 11,000 participants have been enrolled, with baseline data available to researchers for 4500 participants (Volkow *et al*., 2018).

**3.1.7 Inuteroexposure to cannabis**

Yasmin Hurd (Icahn School of Medicine at Mount Sinai Hospital) noted that cannabis use is relatively common among pregnant women. In a retrospective study of newborn drug testing in the United States, nearly 20% of fetuses tested positive for THC (Wood *et al*., 2014).The long-term implications of this exposure are unclear. In postmortem brain samples of human fetuses, Hurd showed that exposure to cannabis inuterowas associated with lower levels of the dopamine D2 receptor in the amygdala and nucleus accumbens. Lower expression correlated with more maternal smoking.Similar expression patterns are observed in animal models, which last into adulthood (DiNieri *et al*., 2011).

Perhaps most strikingly, cannabis use may even affect future generations even without direct exposure. In rats, exposure to cannabis during adolescence has epigenetic and behavioral effects in unexposed offspring and later generations. Offspring of parents exposed to THC were more likely to self-administer heroin and had changes in DNA methylation in genes associated with synaptic plasticity, psychiatric disorders, and neurodevelopment (Szutorisz *et al*., 2014).

**3.1.8 Effects of marijuana on the adolescent brain**

In 2015, daily marijuana use (6%) surpassed daily cigarette use (5.5%) among high school seniors. At the same time, the perception of risk and harm associated with marijuana among high scholars fell to an all-time low (29%) (Johnston *et al*., 2018).Understanding the effects of marijuana on this vulnerable population will continue to be important as legalization efforts continue across the country.

While several studies have compared the effects of marijuana use on brain structure and function in smokers versus nonsmokers, few have looked at whether the age at which a person starts smoking cannabis comes into play. Staci Gruber (McLean Hospital, Harvard Medical School) investigated whether the age of onset of marijuana use affects neurocognitive performance, brain function, and brain structure. In MRI studies, late onset smokers had activation patterns that were more similar to control, nonsmokers than to early-onset smokers. Adolescents who began smoking earlier (before 16 years of age) smoked nearly twice as often and more than 2.5 times as much as those who began smoking later. Earlier age of onset was also associated with poorer performance on measures of executive function than late age of onset (Gruber *et al*., 2012).

Marijuana users also exhibit differences from controls in brain volume, mass, and shape. There are regional differences in cerebral cortical thickness compared with nonusers and differences in density and in gyrification, a measure of the folding of the cortex in the gray matter that has been related to poor performance on intentional tasks. Among early-onset smokers, significant reductions in white matter integrity have been observed by diffusion tensor imaging compared with images from late onset smokers and nonsmokers. This difference in white matter integrity was associated with higher self-reported impulsivity among early-onset smokers, but not among late-onset smokers or nonsmoking controls (Gruber *et al*., 2014),although the causality of this relationship is not fully understood.

Susan Weiss also noted both the importance of determining the effects of marijuana on the developing brain, given its increasing prevalence and availability to adolescents, and the lack of consistency in the field. For example, a large longitudinal study in New Zealand reported that persistent cannabis use was associated with a decline in IQ (Meier *et al*., 2012);however, twin studies failed to observe this connection (Verweij *et al*., 2013).Studies of the effects of marijuana on brain structure are also mixed.Gaps in knowledge include whether the effects of marijuana are reversible with abstinence; how varying doses, strains, and potency of cannabis affect outcomes; whether there are gender-specific effects; and how the age of onset influences cannabis effects.

**3.1.9 Electronic cigarettes and adolescents**

Thomas Eissen berg (Virginia Commonwealth University) noted that according to National Youth Tobacco Surveys, while cigarette use has declined among high scholars (Jamal *et al*., 2017),e-cigarette use has been steadily increasing.E-cigarettes are now the most popular tobacco product among U.S. adolescents with 16% of high scholars reporting recent e-cigarette use (Singh *et al*., 2016).E-cigarettes represent a constantly evolving class of devices for which there are currently few standards and only emerging regulation; several FDA-announced regulations are being challenged by e-cigarette companies (Wheeler *et al*., 2018).

Eissen berg expressed concern that e-cigarettes are being marketed to young consumers with flavors like blue cotton candy, apple jack, and hard candy. Advertisements geared toward young adults focus on low nicotine products, which may function as gateway products. These devices deliver nicotine poorly, giving new users opportunities and chances to try products and experiencing some positive reinforcement without the acute nicotine toxicity that they might experience with more potent products (Duke *et al*., 2016).

E-cigarettes are often marketed as a safer alternative to cigarettes, with a focus on reduced risk of lung cancer. However, Olusegun Owotomo (University of Texas at Austin) stressed that nicotine addiction is an important health risk of e-cigarettes. He showed that among a nationally representative sample of 8th and 10th graders from the Monitoring the Future Study, adolescent e-cigarette users endorsed a number of attitudes, perceptions, and characteristics that are risk factors for cigarette smoking compared with nonusers (Owotomo *et al*., 2018).

The variability between products in relation to construction, power, and components in the e-liquid makes it difficult to study e-cigarettes as a class. In addition, e-cigarette liquid usually contains flavorants intended for consumption that have not been tested for inhalation safety. Finally, the presence of other potentially toxic compounds, such as aerosolized propylene glycol or formaldehyde, depends on the type of device and liquid used. Unsurprisingly, there are few data on the long-term health effects of e-cigarettes. Indeed, such data will likely be difficult to gather given the variability not only between devices but also between users.

Commercial e-cigarette products vary widely with respect to how much nicotine they deliver, with some devices delivering more nicotine than a conventional combustible cigarette. Factors such as construction, battery power, the liquid used, and user behavior can significantly affect the amount of nicotine that is delivered to the smoker (Yan and D’Ruiz. 2015).Increasing the battery wattage by a factor of two can quadruple the amount of nicotine delivered (Talih *et al*., 2015).Level of experience can also affect nicotine delivery. Cigarette smokers trying e-cigarettes for the first time were not as efficient as experienced e-cigarette smokers. Experienced smokers take drags that are twice as long as those of new smokers, keeping the heating element activated for longer time periods and delivering more nicotine (Spindle *et al*., 2015).

**3.2 Addiction and neurons**

Any drug has multiple targets and this also concerns those targeted to the central nervous system (CNS). It is common in the literature that either the agent or its target is always emphasized as prevailingly important depending on research interests (Kodirov 2006). However, conclusive effects are not always observed for classical agents, except perhaps for acetylcholine (Bogomolets 1970). The complexity of targets and the interrelationship among pathologies (Chaves *et al*., 2015; Stowie *et al*., 2015)make the brain even more complex. Although there is a reward center – area tegmentalis ventralis in CNS, neurons and their neurotransmitters are influenced by addictive substances in several other regions and also contribute to the underlying addictive behaviors (Briun *et al*., 2001).

The ventral tegmental area (VTA) in turn may not only process and weigh the reward expectancy, but as recognized earlier by electrical stimulation with electrodes, this nucleus may contribute to the ‘expression of unpleasant emotion’ (Magoun *et al*., 2000). The center of emotions thereafter was established to be the amygdala, but the importance of this region meanwhile is almost replaced by the frontal or prefrontal cortex – PFC. Moreover, the anxiety is not represented by the amygdala alone, but lateral septum – LS may also be involved (Thomas *et al*., 2013). Many syndromes comprise changes in electrical properties of neuronal membranes that is either small (depolarization) or with more impact (spikes). Although neural cells in CNS of animal have similar electrical properties in the form of spikes (either spontaneous or triggered), only neurons of humans are able and will respond to ‘clench your hand to make a fist!’ (Raeva *et al*., 2006).

Human beings have multiple choices when it concerns addictive substances ranging from the traditionally accepted to those prohibited ones. These are alcohol, amphetamine, cocaine, marijuana, tobacco and in lesser extent other popular drugs. All these agents are also the subject of ongoing research. The targeted research in endogenous cannabinoids (eCB) field started with the discovery of arachidonylethanolamide – AEA (Devane *et al*., 2000). The biological actions of eCBs target the binding to the type 1 and 2 cannabinoid receptors (CB1R and CB2R). The native ligands of eCBs are derivatives of arachidonic acid. The CB1R is mainly expressed in the CNS while CB2R in peripheral tissues. The eCBs also participate in reward mechanism/cascade of the brain The AEA known as ‘anandamide’ was for the first time identified in the vas deferens of mice. The electrically evoked twitch response is blocked by this ligand, similar to those of psychotropic cannabinoids (Devane *et al*., 2000). The anandamide is an endogenous cannabimimetic eicosanoid and this name derives from the Sanskrit word ananda meaning ‘bliss’. The marijuana Cannabis sativa (Linnaeus 1753) effects are mimicked by anandamide in the brain’s reward circuits. Addicted individuals may want to quit but the addiction trace will not cease easily. Earlier on the severity of withdrawal effects of addictive drugs was recognized and correlations with EEG patterns are documented (Logar *et al*., 2001).

Among all addictive drugs only activity of eCBs and receptors can be distinctly demonstrated by a designated electrophysiological paradigm – depolarization-induced suppression of excitation (DSE) and inhibition (DSI) in many brain regions (Kodirov *et al*., 2010). Note that these phenomena were known before and could predict the exact machinery, since ‘DSI is due to somato dendritic exocytosis of a retrograde messenger, and that this exocytosis is highly sensitive to [Ca2+] (Glitsch e*t al*., 2000) in Purkinje neurons.

The aim of this work is not to review all existing studies (which is not possible anymore), but rather to exemplify the duality of the effects of substances and that there are no distinct neurons that are solely prone to addiction.

**3.2.1 Ventral tegmental area (VTA) DA neurons**

Neurons of ventral tegmental area (VTA) are of two major subtypes – DA (dopamine) and GABAergic. These two types of cells as constituents of the ‘ventral tegmental area microcircuit model challenges the classical view that GABA neurons exclusively reduce dopamine neuron firing and bursting’ (Morozova *et al*., 2016). DA and GABAergic cells are distinguished by both action and membrane potential (AP and MP) properties as the former exhibits robust sag that is absent in the latter (Koyama *et al*., 2006). VTA DA neurons express HCN and Kv – voltage dependent K+ channels similar to other excitable cells (Kodirov *et al*., 2004) and their tails are inhibited by 20 μM DA (Akopian *et al*., 1996). The amplitude and density of IA is higher in DA vs. GABAergic neurons, but the conductance of channels are comparable (Koyama *et al*., 2006). The respective values of the recovery from inactivation also differ and are ~50 vs. 300 ms in young rats. There are also SK channels in VTA DA neurons and their outward K+ currents are decreased by 15 μM NMDA (Paul *et al*., 2003)revealing the complex nature of neurons and all elements of their membrane. This is also substantiated by their spiking with common basic properties yet distinct rates and modes.

There is no a strict area division between the ventral tegmental area (VTA) and SNc – substantia nigra pars compacta nuclei and DA neurons resemble to a greater extent each other with common electrophysiological hallmarks. DA neurons of SNc have a depolarized RMP – resting membrane potential and in order to repolarize to −60 mV a negative current of ~65 pA is injected (Vandecasteele *et al*., 2008). Upon the hyperpolarizing steps of −90 pA these neurons exhibit sag with maximal amplitude of ~20 mV during 1 s. No gap junction response was observed among the pairs of DA neurons, but there was either a train of APs or a single spike-evoked hyperpolarization (SEH) that was heterogeneous in terms of amplitudes. As expected the neurotransmitter between DA neurons is dopamine, however perhaps not alone, since neither 300 μM Cd2+ (targets Cav – voltage dependent Ca2+ channels) nor could the antagonist of type 2 dopamine receptor (D2R) raclopride at 1 μM obliterate the SEH. When MP is held at −75 mV (by −95 pA) 50 μM ZD7288 does not alter evoked APs waveforms and rates in neuron 1 and related SEH in postsynaptic cells held at −80 mV (−220 pA). Interestingly, ‘once cell2 had been depolarized at −60 mV, ZD7288 became effective and abolished the SEH’ (Vandecasteele *et al*., 2008). This is indeed an important result, but the MP of 2nd cell is devoted to be −85 mV and also considerably less current was injected (−90 vs. −220 pA). Similarly it is confusing why the MP of active neuron was changed to −90 mV that now was achieved by only −20 pA when under control conditions −95 pA was necessary to hold MP at −75 mV. Therefore, perhaps not effects of ZD7288, but the appearance of SEH is voltage dependent as also revealed by authors. Since these are similar DA neurons holding the MP at identical −60 mV would be comprehensive as it is shown during recording of sag and its abolishment in the same 2nd cell. Consistently, the rebound action potential – RAP – is obliterated by ZD7288 (Vandecasteele *et al*., 2008). Note that as highlighted the ZD7288 exerts heterogeneous effects on neurons (Kodirov *et al*., 2014).

Transition into the bursting mode perhaps could be considered as readout of addictive neurons (Kodirov *et al*., 2016). VTA DA neurons respond to a synthetic cannabinoid receptor agonist WIN55, 212-2 at 1 mg/kg with an increased spontaneous bursting that is quantitatively similar to the effects of 0.125 mg/kg SM-11 [21]. When the concentration of SM-11 were 2 or 4 fold higher, then the bursting rate was considerably decreased compared to basal values hinting at tonic release of eCB. These effects of both compounds were similarly reflected on numbers of spikes within a burst (SWB). Caution: it is not a comparison between WIN and SM-11 but SM-11 was concurrently applied with WIN in order to antagonize the effects of the CB1 agonist. Therefore, SM-11 was proposed as a new CB1 antagonist. Stimulation of nucleus accumbens – NAc evoked an antidromic spike in ventral tegmental area (VTA) DA neuron that had an identical phenotype and similar amplitude to spontaneous ones. The stimulus was ineffective when a neuron experienced a recent spontaneous spike and hence there was a refractory period which presumably is more than 10 ms and perhaps ~40 ms based on the latency of the evoked spike. WIN increased the basal spontaneous frequency from ~3 to 5 Hz. The spike frequency in VTA DA neurons of male rats is similar to those of mice (~3 Hz) of the same gender at P60 [22]. Voluntary drinking in these adolescent males did not alter spike rates. Units of summarized values are not clear, since baseline rates are shown obviously in Hz and effects of ethanol at 10, 20 50 mM refers to percentage changes (data most probably is presented as a ratio). Independent what an actual unit of the value of −0.4 is, the frequency was decreased at 10 mM ethanol in naïve males, while increased (9.5) in drinkers. What is the difference between the WT and TH-GFP+ mice? The rate in the former ranged between 1 and 12 Hz, while in the latter from 1 to 13 Hz. The rate of spikes decreased at P120 to 2.5 Hz in naïve males. The polarity of effects at 10 mM ethanol was identical to that of P60, but those of 20 and 50 mM were not significant. Comparisons as to age are not entirely adequate as data of P60 comprises the maximum of n = 42, while those of P120 n = 11, as well as to concentration dependencies, since it was not perhaps always a cumulative application of all three. Also the criteria of 1–12 Hz did not apply to adults.

In adults rats the rate of spikes in ventral tegmental area (VTA) DA neurons is ~3 Hz in vivo and LSD – lysergic acid diethylamide decreases the number of bursts and SWB starting only at 30 μg/kg while it obliterates at 120 (De Gregorio *et al*., 2016). Spontaneous spikes are not always observed in ventral tegmental area (VTA) DA neurons and bursting is even seldom (Shinba *et al*., 2000). The particular feature of SWB concerns the gradual decrease of amplitude of each subsequent spike.

Since ventral tegmental area (VTA) in rodents and monkeys has no clear borders as a nucleus unlike the amygdala, hippocampus and septum, defining DA neurons would be always ‘somewhat misleading’ by any criteria (Avegno *et al*., 2016). Therefore, also previous studies in rats observed heterogeneities in spike properties and when possible have classified them as type 1 or 2 (Shinba *et al*., 2000). The latter has considered those triggering antidromic spikes (in response to electrical stimulation) with a latency of ~13 ms as VTA DA neuron – type 1.

As revealed by fast-scan cyclic voltammetry (FSCV) the dopamine concentration in NAc is ~ 17 nM (Danjo *et al*., 2016). When the state of in excitability of DA VTA neurons was achieved by 10 s (not 20 s as stated) stimulation accompanied by a ~1 nA inward current, it declined to ~10 nM and upon the cessation of stimuli it gradually returned back to the baseline. Although, also WT VTA were infected with an adeno-associated viral construct encoding Arch-eGFP, only in TH-Cre mice the above-mentioned effects were observed, since AAV was Cre inducible. Tyrosine hydroxylase – TH targets only neurons releasing catecholamines ‘either into the circulation or locally to brain regions as a response to stress’ (Kodirov *et al*., 2011) and which ‘comprise epinephrine (adrenaline – A), norepinephrine (noradrenalin – NA), and dopamine (DA)’(Kodirov *et al*., 2012).

In WT mice the content of DA has slightly increased to ~ 20 nM (Danjo *et al*., 2016) that perhaps comprises basal variations. However, the electrophysiology of APs is not very convincing, since the stimulation paradigm is considerably short (~0.5 vs. 10 s). Moreover, since the inter spike interval was on average ~500 ms, what if the stimulation occurs within it, i.e. between the two spontaneous APs? Strictly speaking then ‘spikes / second’ is not correct. Note that the DA content in response to evoked release by electrical stimulus is higher and reaches ~55 nM in TH-Cre. During the Cre-inducible inhibition the peak concentration was ~30 nM. The latter hints that the silencing might be effective only toward the baseline neuronal activities. This procedure increased the number of for expressing neurons in basolateral amygdala (BLA) from ~55 to 105 per 1 mm2 in TH-Cre mice. Effects were not restricted to only stimulated sides in BLA and the septum in contrast to the hypothalamus. Significant for expression is observed in the lateral nuclei of septum (LS) compared to WT mice. No apparent changes are seen in the medial septum (MS) of both groups of mice.

Dopamine has an effect whether direct (via dedicated receptors) or indirect and is not unique to mammals, but universal to all animals (Barbas *et al*., 2006). DA receptor expression in HEK293 cells is accompanied by an increase in cAMP. The EC50 of DA was 35 nM while that of apomorphine 552 nM. The 37% of amino acid sequence of type 1 dopamine receptors (D1R) were identical in human and mollusks.

**3.3 Pharmacokinetics of addiction**

There is now little doubt that the development of addiction to drugs of abuse is, in part, a function of predisposing factors in an individual’s genome as well as factors associated with childhood and adolescent development (Nestler 2001). As much as drugs of abuse have profound pharmacological consequences on neuronal physiology, it is clear that while these drug actions are necessary, they are not sufficient for the development of addiction. When one compares the widespread recreational use of addictive drugs and the substantially fewer individuals meeting DMS-IV criteria for substance abuse disorder (Nestler 2001), it is apparent that drug pharmacology is only one factor in a multifactorial gene-environment pharmacologic disorder. The search for the factors producing addiction and, more specifically, those factors that mediate the transition from recreational to compulsive (addicted) drug use has preceded at all levels of investigation, from gene polymorphisms to sociological interventions (Nestler 2001). Exploring the factors causing addiction has primarily involved examining addicts for neurobiological and genetic differences from comparison subjects lacking a substance abuse disorder who are matched according to a variety of other biological, diagnostic, and sociological criteria. In this issue of the Journal, three research reports reflect different aspects of this research tactic. The article by Little et al. is indicative of perhaps the most traditional approach (Nestler 2001). As in many studies, postmortem tissue obtained from the caudate of cocaine addicts and matched comparison subjects was compared for protein content or function. This is an extension of many previous investigations that have hypothesized neuroadaptations in the proteins associated with the pharmacodynamics action of cocaine on dopamine transmission (Nestler 2001), pointing toward nigrostriatal dopamine depletion or perhaps a lesion in the caudate of addicts. Little et al. employ an arguably more definitive measure: the immunoreactive level of the central vesicular monoamine transporter protein (VMAT2) was used to verify that cocaine addicts have less of this critical enzyme for concentrating dopamine in synaptic vesicles (Nestler 2001). The authors recognize this as a pharmacological effect of heavy cocaine abuse and make no speculations as to whether this alteration is related to a predisposition for addiction or is even a marker of compulsive versus recreational cocaine use. However, as the authors note, it is likely that the down-regulation of VMAT2 is associated with high levels of recent drug use (Nestler 2001), since animal studies that do not involve the levels of drug administration typically observed in severe cocaine addicts do not show enduring alterations in the basal levels of any metric of dopamine transmission. The authors did, however, find hints of a predisposing or associated factor in that the capacity of cocaine to reduce VMAT2 was potentially more profound in addicts with associated mood disorder (Nestler 2001). Nonetheless, the research tactic of examining postmortem brain tissue for proteins directly associated with the pharmacological effects of the drug, while likely to yield drug-mediated differences, cannot assess the role of the neurobiological adaptation as a predisposing factor or even as an important factor in maintaining addiction (Nestler 2001).

A primary reason for this lack of certainty can be found in the animal literature, where drug-induced changes in protein expression or function have been shown to depend on the time of sampling and to vary during drug administration and withdrawal (Nestler 2001). The general inability of postmortem studies in addicts to determine the length of abstinence or to sample at different points in the sequel of drug taking, withdrawal, and craving severely limits the capacity to interpret the relationship between the pharmacodynamics of the drug and factors that predispose to or maintain addiction (Nestler 2001).

A second paper in this issue of the Journal by (Wall *et al*., 2001) is indicative of a widely used and potentially more profitable approach toward identifying predisposing factors in alcohol addiction. These authors studied a population of Native North American Indians to examine alcohol and aldehyde dehydrogenase polymorphisms as pharmacokinetic predisposing factors in alcoholismet (Higuchi *et al*., 1995). Reminiscent of previous studies that have established that polymorphisms in one aldehyde dehydrogenase gene contribute strongly to reduced alcohol consumption and addiction in Asian populations (Higuchi *et al*., 1995), these authors demonstrate that polymorphisms in one of the alcohol dehydrogenase genes is a predisposing factor in alcoholism in Native Americans. Not only does this information link a specific enzyme to alcohol dependence, but it confirms the utility of examining discrete populations with high levels of addiction as a mechanism for identifying important but relative uncommon polymorphisms (Higuchi *et al*., 1995).

Although it is tempting to generalize findings between addictive substances, pharmacokinetic predispositions will not generally cross between drug classes where different catabolic or bio activating enzymes are involved. In contrast (Higuchi *et al*., 1995), another research tactic has emerged over the last few years that can potentially identify common predisposing factors between different addictive substances (Higuchi *et al*., 1995). This tactic is based upon a deepening reservoir of neurophysiological knowledge regarding the functional brain circuits that mediate the physiological and pathological acquisition of environmental reinforcement, ranging from food and sex to gambling and addictive drugs (Garavan *et al*., 2000). The most relevant information in this regard has emerged from increasingly sophisticated neuroimaging studies that point directly to the importance of interconnections between prefrontal and allocortical limbic brain regions and subcortical motor systems in addiction to all drugs of abuse examined (Garavan *et al*., 2000). The third paper in this issue of the journalcombines this neurophysiological database with cognitive testing to probe whether poor performance in a decision-making task may be a shared trait between a population of adolescents known to be prone to developing addiction and adults meeting criteria for substance abuse disorder. Ernst et al. discovered that adolescents with externalizing behavioral disorders, including ADHD and conduct disorder, and adult addicts both performed poorly on aspects of repeated testing with the Gambling Task. On the basis of this finding (Garavan *et al*., 2000), it is possible that a shared neurophysiological dysfunction may exist between drug addicts and adolescents with externalizing behavioral disorders, and poses the possibility that this may be a predisposing cognitive characteristic. While the authors identify many appropriate caveats to accepting this conclusion, the data point to important future studies that could combine neuroimaging with decision-making performance in the Gambling Task between these two populations (Garavan *et al*., 2000). Such cognitive probes of neural circuitry combined with populations vulnerable to addictive disorders constitutes an experimental design that might reveal common circuitry dysfunctions that can begin to define a common pathological basis of predisposition to addiction. The potential for distinctions in brain circuitry to underlie predispositions in vulnerable populations stands in contrast to the pharmacokinetic or pharmacodynamics properties of individual drugs (Garavan *et al*., 2000).

**CHAPTER FOUR**

**4.1 NEUROBIOLOGICAL DISORDERS FROM ADDICTIONS**

# 4.1.1 OVERALL NEUROCIRCUITRY OF ADDICTION

In summary, three neurobiological circuits have been identified that have heuristic value for the study of the neurobiological changes associated with the development and persistence of drug dependence. The acute reinforcing effects of drugs of abuse that comprise the binge or intoxicationstage most likely involve actions with an emphasis on the reward system and inputs from the ventral tegmental area and arcuate nucleus of the hypothalamus. In contrast, the symptoms of acute withdrawal important for addiction, such as negative effect and increased anxiety associated with the withdrawal or negativeaffectstage, most likely involve decreases in function of the extended amygdala system but also a recruitment of brain stress neurocircuitry therein. The craving stage or preoccupation or anticipation stage involves key afferent projections to the nucleus accumbens and amygdala, specifically the prefrontal cortex (for drug-induced reinstatement) and the basolateral amygdala (for cue-induced reinstatement). Compulsive drug-seeking behavior is hypothesized to be perpetuated by ventral striatal-ventral pallidal-thalamic-cortical loops.

# 4.1.2 MOLECULAR AND CELLULAR TARGETS WITHIN THE BRAIN CIRCUITS ASSOCIATED WITH ADDICTION

However, parallel to the neuroplasticity of the neurocircuitry are the molecular changes that occur in these same structures. Chronic exposure to opiates and cocaine leads to activation of cyclic adenosine monophosphate response-element binding protein (CREB) in the nucleus accumbens and central nucleus of the amygdala (Shaw-Lutchman *et al*., 2002; Edwards *et al*., 2007). CREB can be phosphorylated by protein kinase A and by protein kinase regulated by growth factors, putting it at a point of convergence for several intracellular messenger pathways that can regulate gene expression. Activation of CREB in the nucleus accumbens with psych stimulant drugs is linked to the motivational symptoms of psych stimulant withdrawal, such as dysphoria, possibly through the induction of the opioid peptide dynorphin, which binds to opioid receptors and has been hypothesized to represent a mechanism of motivational tolerance and dependence (Nestler *et al*., 2005). Repeated CREB activation drives dynorphin expression in the nucleus accumbens, which in turn decreases dopaminergic activity and may activate other brain stress systems, all of which can contribute to negative emotional states. Extracellular signal-regulated kinase (ERK) is another key element of intracellular signaling that is considered a key component in the plasticity associated with repeated administration of cocaine, specifically behavioral sensitization, cocaine reward, and time-dependent increases in cocaine seeking after withdrawal (i.e., incubation effect) (Lu *et al*., 2006, Li *et al*., 2008).

Another molecular target for regulating the plasticity that leads to addiction is dysregulation of cysteine-glutamate exchange, which is hypothesized to drive pathological glutamate signaling related to several components of the addiction cycle. Repeated administration of cocaine blunts cysteine-glutamate exchange, leading to reduced basal and increased cocaine-induced glutamate in the nucleus accumbens that persists for at least three weeks after the last cocaine treatment (Baker *et al*., 2003). Most compelling is the observation that treatment with *N*-acetylcysteine, by activating cysteine-glutamate exchange, prevented cocaine-induced escalation and behavioral sensitization, restored the ability to induce long-term potentiation and long term depression in the nucleus accumbens, and blunted reinstatement in animals and conditioned reactivity to drug cues in humans ( Madayag *et al*., 2007; LaRowe *et al*., 2007; Moussawi *et al*., 2009)

Finally, CREB and other intracellular messengers can activate transcription factors, which can change gene expression and produce long-term changes in protein expression, and, as a result, neuronal function. Although acute administration of drugs of abuse can cause rapid (within hours) activation of members of the Fos protein family, such as c-fos, FosB, Fra-1, and Fra-2 in the nucleus accumbens, other transcription factors and isoforms of FosB (i.e., a highly stable form of FosB) have been shown to accumulate over longer periods of time (days) with repeated drug administration **(**Nestler *et al*., 2005). Animals with activated FosB have exaggerated sensitivity to the rewarding effects of drugs of abuse, and FosB has been hypothesized to act as a sustained molecular “switch” that helps initiate and maintain a state of addiction (McClung *et al*., 2004). Whether (and how) such transcription factors influence the function of the brain stress systems, such as CRF, dynorphin, neuropeptide Y, and the others described above, remains to be further explored.

**Drug craving**

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| --- | --- |
| Drug craving | “Drug craving is the desire for the previously experienced effects of a psychoactive substance. This desire can become compelling and can increase in the presence of both internal and external cues, particularly with perceived substance availability. It is characterized by an increased likelihood of drug-seeking behavior and, in humans, of drug-related thoughts.” (United Nations International Drug Control Programme, 1992) |
| Craving Type-1 | Induced by stimuli that have been paired with drug self-administration such as environmental cues  Termed conditioned positive reinforcement in experimental psychology  Animal model: Cue-induced reinstatement where a cue previously paired with access to a drug reinstates responding for a lever that has been extinguished |
| Craving Type-2 | State of protracted abstinence in drug dependent individual’s weeks after acute withdrawal.  Conceptualized as a state change characterized by anxiety and dysphoria.  Animal model: Residual hypersensitivity to states of stress and environmental stressors that lead to relapse to drug seeking behavior |

**4.2 PHARMACOLOGICAL APPROACHES TO TREAT ADDICTION**

# 4.2.1 Nicotine

## **Neurobiology**

When inhaled, nicotine rapidly crosses into the brain where it binds to nicotine acetylcholine receptors (nAChR), ligand-gated ion channels that open upon nicotine binding. The a4b2\* nAChR is the most abundant nAChR type found in mammalian brains and is thought to be the primary mediator of nicotine dependence (Maskos *et al*., 2005; Picciotto *et al*., 1998). Stimulation of nAChRs results in the release of multiple neurotransmitters, dopamine being the most important in mediating the addictive properties of nicotine (Benowitz 2008). Additionally, nicotine directly augments the release of glutamate and, with chronic administration, inhibits the release of GABA both synergistically enhancing dopamine release. With chronic smoking, the activity of brain monoamine oxidase (MAO, an enzyme responsible for metabolizing monoamines such as dopamine, norepinephrine, and serotonin) is reduced, thus even further increasing these neurotransmitters in the brain.

**Treatment Approaches**

**Withdrawal/Abstinence/Initiation**

Nicotine withdrawal is characterized by increased appetite, poor concentration, insomnia, irritability, reduced heart rate, anxiety, and low mood (Benowitz 2008). With repeated nicotine exposure, nAChRs become upregulated in the brain in response to nicotine-induced receptor desensitization (Benowitz 2008). Current thinking suggests that craving and withdrawal symptoms occur when previously desensitized receptors regain their functionality in the absence of smoking, such as after a night of sleep. This is supported by research showing that typical daily smokers maintain levels of nicotine enough for near saturation of the brain receptors (Benowitz 2008; Brody *et* *al*., 2006). Also contributing to low rates of success at quitting, a relative dopamine depletion, and subsequent feeling of general anhedonia, occurs upon nicotine cessation. Conditioned behaviors (pairing of the pharmacologic actions of a drug with specific behaviors) also promote continued smoking even when the majority of nAChRs are saturated and desensitized (Balfour 2004; Benowitz 2008).

**Nicotine Replacement Therapies**

Nicotine replacement therapies (NRT) were the first proven effective medications for the treatment of nicotine dependence and remain a mainstay and first-line pharmacotherapy in the treatment of nicotine withdrawal symptoms. NRTs come in the form of gum, patch, lozenge, sublingual tablet (not available in the United States), nasal spray, and inhaler. Analyses comparing the effectiveness of different preparations do not demonstrably support one form over another (Buchhalter *et* *al*., 2008). Novel approaches using NRT utilize unique delivery systems. Currently, three new formulations are being researched: the straw, nicotine drops, and a pulmonary inhaler (delivery mechanism different than currently available inhalers). To conceptualize the nicotine straw, tiny nicotine beads are attached inside and swallowed while consuming a beverage. With the straw and drops, nicotine is absorbed via the intestine rather than bucally, as with the gum or lozenge. Safety and pharmacokinetic studies are limited by potential drug–beverage interactions (Buchhalter *et* *al*., 2008; D’Orlando and Fox 2004; Westman *et* *al*., 2001). Research on pulmonary inhalers is spurred by the promise of delivering nicotine to the lungs in a manner similar to inhaled cigarettes, thus allowing for rapid reduction in withdrawal symptoms as well as mimicking more closely the behavioral and sensory aspects of smoking. Current inhalers deliver nicotine bucally only to the mouth and throat. Drawbacks include technical challenges to engineering such a device as well as potential abuse liability. While NRTs have aided many people worldwide to quit smoking, they do not meet the needs of all smokers and have limited utility in long-term relapse prevention.

**Nicotinic Receptor Antagonists/Partial Agonists**

Mecamylamine is a nicotine antagonist with antihypertensive effects. It does not appear to trigger withdrawal (Eissenberg *et* *al*., 1996) and may help with smoking cessation by reducing craving, negative affect, and appetite (Buchhalter *et* *al*., 2008; Rose *et* *al*., 1998). Randomized controlled trials (RCT) evaluating mecamylamine and the nicotine patch together have yielded conflicting results on its utility in enhancing cessation rates (Glover *et* *al*., 2007; Rose *et* *al*., 1994, 1998).

Varenecline, a partial agonist of the a4b2 and full agonist of the a7 nACh receptors, has become an additional first-line option for smoking cessation pharmacotherapy (Fiore *et* *al*., 2008; Hays and Ebbert 2008). Varenecline (marketed as Chantix) gained Food and Drug Administration (FDA) approval in 2006 after several RCTs demonstrated its efficacy and safety tolerability (Gonzales *et* *al*., 2006; Jorenby *et* *al*., 2006; Nides *et* *al*., 2006; Oncken *et* *al*., 2006). Varenecline binds to the a4b2 nACh receptor triggering partial stimulation – and subsequent release of dopamine in the brain reward center – while simultaneously and competitively inhibiting nicotine delivered by cigarettes (Hays and Ebbert 2008). Varenecline is typically dosed 1 mg twice daily. This dosing is achieved after an upward taper over a week’s period prior to an individual’s quit smoking date. Six months of therapy has been shown superior to 12 weeks in achieving abstinence (Tonstad *et* *al*., 2006).

**Antidepressants**

It has long been recognized that individuals with depression suffer disproportionately from nicotine dependence, that cessation may precipitate symptoms of depression or a major depressive episode, and that nicotine may have antidepressant properties (Hughes *et* *al*., 2007). These observations provide rationale for research using antidepressants in the treatment of nicotine dependence. Studied antidepressants include: bupropion, nortriptyline, reboxetine, venlafaxine, fluoxetine, paroxetine, meclobromide, and selegiline. Currently, only bupropion and nortriptyline show clear efficacy in smoking cessation (approximately doubling the quit rate) and only bupropion is FDA approved for use in both nicotine dependence and depression.

Bupropion has both adrenergic and dopaminergic actions and appears to antagonize the nicotinic acetylcholinergic receptor (Hughes *et* *al*., 2007). Smokers interested in quitting are encouraged to begin bupropion 1 week prior to a set quit date, similar to varenecline. The dose is typically tapered from 150 mg daily to 150 mg twice daily over 3 days and maintained for at least 7 weeks.

Nortriptyline is considered second-line treatment in smoking cessation. According to the U.S. Surgeon General’s report, it is generally started 10–28 days before a quit attempt at a dose of 25 mg daily, increasing gradually to a target dose of 75– 100 mg per day and continuing for 12 weeks or up to 6 months (Fiore *et* *al*., 2008).

Despite the high comorbidity with major depression, selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, paroxetine, and sertraline, have generally provided disappointing results for smoking cessation. One large multicenter, placebo-controlled trial showed improved short-term abstinence rates in individuals taking fluoxetine compared to placebo; however, this effect was lost at 6-month follow-up (Hughes *et* *al*., 2007; Niaura *et* *al*., 2002). Venlafaxine, an inhibitor of both serotonin and norepinephrine, was studied in combination with NRT and showed no main effect of treatment on abstinence. Post hoc analysis, however, demonstrated some limited efficacy among light smokers both at the end of treatment and at 1-year follow up (Cinciripini *et* *al*., 2005). Reboxetine, currently available only in Europe, is a selective norepinephrine uptake inhibitor that also inhibits nAChR activity. While no human trials have been published for smoking cessation, reboxetine is known to decrease nicotine self-administration in animals, and thus warrants continued investigation into its utility (Foulds *et* *al*., 2006; Rauhut *et* *al*., 2002).

Meclobomide and selegiline, two monoamine oxidase inhibitors (MAOI), have also been evaluated as potential treatments (George and Weinberger 2008). Meclobomide is a reversible MAO-A inhibitor not currently available for use in the United States. The sole study evaluating efficacy in smokers showed a statistically significant improvement in self-reported abstinence rates; however, only trend significance was found in verified cotinine plasma levels (Berlin *et* *al*., 1995). Selegiline, an irreversible inhibitor of MAO-B available for use as an antidepressant and treatment for Parkinson’s disease in the U.S., has shown more promise for smoking cessation. In one trial, smokers treated with selegiline combined with NRT showed double the abstinence rates at 1-year follow-up (25 vs. 11%) compared with smokers given placebo with NRT. This effect, however, was not powered to show statistical significance (Biberman *et* *al*., 2003). Additionally, besides inhibiting MAO-B, a recent study demonstrated selegiline as also an inhibitor of CYP2A6, the enzyme primarily responsible for nicotine metabolism. Thus, there are two potential mechanisms by which selegiline may aid in smoking cessation (Siu and Tyndale 2008).

In summary, some, but not all, antidepressants have demonstrated efficacy in the treatment of nicotine dependence.

**Central Adrenergic Agonists**

Central a2-adrenergic agonists, such as clonidine and lofexidine, decrease noradrenergic cell firing and subsequent neurotransmitter release, thus reducing overall noradrenergic activity (Carter 1997). It is hypothesized that these agents prevent the sympathetic overload accompanying various drug withdrawal states and have been found to reduce various symptoms of opiate, alcohol, and cannabis withdrawal (Baumgartner and Rowen 1987; Gossop 1988; Hart *et* *al*., 2008). A multitrial metaanalysis of clonidine’s effectiveness upon smoking cessation at 12-week follow-up found small but significant benefit of use. The authors noted potential study biases, however, and warned that side effects may limit clonidine’s effectiveness (Gourlay *et* *al*., 2004). Clonidine, though not FDA approved, is considered a second-line therapy and is typically dosed 0.10 mg twice daily oral or 0.10 mg day1 transdermal, increasing by 0.10 mg day1 per week if needed (Fiore *et* *al*., 2008).

**Immunotherapy**

Interest in immunotherapy for the treatment of substance use disorders is emerging. The majority of currently available pharmacotherapies act centrally in the brain to block the rewarding properties of or reduce withdrawal symptoms from drugs of abuse. Yet, what if the drug could be neutralized peripherally before ever reaching the brain? This is the basic premise upon which the development of nicotine vaccines lies. Currently, all vaccinations for nicotine in the pipeline are conjugates, meaning nicotine is linked to a carrier protein capable of mounting an immune response. To date, three companies have begun clinical trials of their antinicotine vaccines (Cerny and Cerny 2008). Two studies have demonstrated efficacy as long as a sufficient antibody level is achieved (Cornuz *et* *al*., 2008; Hatsukami *et* *al*., 2005; Maurer and Bachmann 2007).

**Other Medications**

Naltrexone and nalmefene, two opioid antagonists, have been evaluated as potential treatments for nicotine dependence. While naltrexone is currently FDA approved for treatment of alcohol dependence, two studies failed to demonstrate its efficacy in treating nicotine withdrawal symptoms or promoting smoking cessation (Buchhalter *et* *al*., 2008). More recently, however, pretreatment with naltrexone prior to cessation was found to be more helpful among individuals with higher levels of depressive symptomatology (Walsh *et* *al*., 2008). This point highlights an emerging understanding among researchers and clinicians that no single treatment will be a panacea for addiction. Rather, treatments will need to be tailored to the specific characteristics of individuals in order to maximize effectiveness.

Rimonabant is a cannabinoid-1 (CB1) antagonist temporarily approved (and most recently suspended due to psychiatric side effects) for use in Europe in the treatment of obesity (Buchhalter *et* *al*., 2008). Rimonabant may aid smoking cessation by activating and restoring balance to the endocannabinoid system and, in particular, addressing concerns regarding post cessation weight gain. A meta-analysis of three trials (n ¼ 1567) indicate dosing of 20 mg daily conferred a 1½-fold increase in odds of quitting but its effect on maintaining abstinence remains inconclusive (Cahill and Ussher 2007).

GABAergic neurons provide inhibitory input to the dopaminergic neurons projecting from the Ventral Tegmental Area (VTA) to the NAc. Thus, medications affecting GABA neurotransmission may confer benefits for addiction treatment by modulating the dopaminergic tone in these brain regions integral to the reward process. To date, research on vigabatrin, baclofen, gabapentin, and tiagabine (all GABA-related medications) has been minimal in smoking cessation and the few trials available have not shown demonstrable efficacy (Buchhalter *et* *al*., 2008; Cousins *et* *al*., 2001; Sofuoglu *et* *al*., 2005; White *et* *al*., 2005).

**Relapse Prevention**

Relapse to smoking following a period of cessation appears to be the rule, rather than the exception. At this time, no pharmacotherapy is indicated for long-term use. However, a 2009 meta-analysis of behavioral and pharmacologic relapse prevention interventions concluded that extended treatment with varenecline – but not bupropion – may aid in relapse prevention (Hajek *et* *al*., 2009; Tonstad *et* *al*., 2006). Additionally, the authors noted that additional studies with extended use of NRT are warranted.

While complete abstinence from drugs of abuse, particularly illicit ones, remains the preferred goal of treatment, there nonetheless remains interest in helping individuals reduce consumption of licit substances either as an intermediate goal to abstinence or in lieu of abstinence altogether. This approach undergirds interest in pharmacotherapies targeting the cytochrome P450 (CYP) system. Nicotine is primarily metabolized into cotinine via this system and genetic variations in the allele coding for the CYP2A6 enzyme have been linked to differences in nicotine metabolism and smoking behaviors (Schoedel *et* *al*., 2004; Tyndale and Sellers 2002). Certain ethnic groups with higher rates of slow nicotine metabolism have been shown to take in less nicotine per cigarette with reduced risk of lung cancer (Benowitz *et* *al*., 1999, 2002). Thus, inhibiting CYP2A6 may reduce nicotine intake among smokers, and thereby reduce adverse consequences. At this time, given the current socio-political climate and known serious health consequences to even low rate smoking, harm reduction approaches tend to be less well supported than abstinence approaches to treating nicotine dependence.

# 4.2.2 Alcohol

## **Neurobiology**

Alcohol, like all drugs of abuse, increases the release of dopamine in the brain’s mesocorticolimbic system (Weiss *et* *al*., 1993). However, unlike stimulants, which directly increase dopamine, alcohol’s mechanism of action is believed to work through indirect effects on modulating neurotransmitters. For example, acute alcohol administration leads to inhibition of GABA in the VTA and NAc that, in turn, disinhibits the dopaminergic neurons found there. Chronic alcohol use sensitizes the system and leads to relative dopamine deficiency (Koob and Le Moal 2001; Petrakis 2006). Alcohol directly influences the GABAA receptor complex, but it is plausible that its effects on the GABA receptors are modulated via other GABA mechanisms as well (Krystal *et* *al*., 2006; Petrakis *et* *al*., 2001).

The glutamate receptors include the N-methyl-D-aspartate (NMDA) receptors, the a-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) receptors, and kainate receptors (Dingledine *et* *al*., 1999). The NMDA glutamate receptor plays a central role in the neuropharmacological effects of alcohol (Tsai *et* *al*., 1995). Alcohol is an NMDA receptor antagonist (Hoffman *et* *al*., 1989) and it has been hypothesized that the changes in the NMDA receptor or its function may underlie the neurobiological changes associated with alcohol dependence, withdrawal, and related behavioral phenomena such as “craving” (Davis and Wu 2001).

The endogenous opioid system has also been implicated in the rewarding effects of alcohol. Alcohol modulates release of opioid neuropeptides, and this effect is more striking in animals bred for alcohol preference (Froehlich 1997). Moreover, human studies have shown central deficiencies of endorphins in alcohol-dependent individuals (Genazzani *et* *al*., 1982).

In animal studies, serotonergic function has consistently been associated with the regulation of alcohol intake. Specifically, a central serotonergic deficiency correlates with high alcohol intake. In contrast, human studies have not reliably detected abnormal serotonergic function in alcohol-dependent individuals (Petrakis et al. 1999, 2001; Roy and Linnoila 1989). Nonetheless, recent evidence is emerging implicating serotonin dysregulation in a subset of individuals with alcohol dependence, highlighting the notion that alcohol dependence is likely a heterogeneous disorder (Johnson *et* *al*., 2000; Johnson 2000).

**Treatment approaches**

**Withdrawal/Abstinence**

Alcohol withdrawal is characterized by a wide range of symptoms from mild autonomic instability, tremor, nausea, and psychiatric distress (including anxiety, insomnia, psychomotor agitation, and dysphoria) to more severe cases with accompanying hallucinations, delirium tremens, seizures, and even death. The presence of withdrawal symptoms is influenced by both the frequency and quantity of drinking (Petrakis 2006). The goals of an optimal pharmacologic treatment for alcohol withdrawal include: (1) treating immediate symptoms, (2) preventing complications, and (3) initiating long-term preventive therapy (Ait-Daoud *et* *al*., 2006).

**Benzodiazepines and Barbiturates**

Benzodiazepines and barbiturates are cross-tolerant at the GABAA receptor and benzodiazepines, in particular, have been the mainstay of pharmacologic treatment of alcohol withdrawal up to the present (Petrakis 2006). These medications, however, have significant limitations including their abuse potential, pharmacologic interaction with alcohol, and their cognitive and psychomotor side effects (AitDaoud *et* *al*., 2006). Additionally, there is some evidence that their use may increase the risk of relapse, particularly in individuals with genetic predisposition to alcohol and comorbid anxiety and personality disorders (Longo *et* *al*., 2002; Malcolm *et* *al*., 2002). Given these concerns, interest remains in developing additional therapies for alcohol withdrawal in particular, genetically driven treatments that may provide more specificity and compliance.

**Nonbenzodiazepine GABA Modulators**

Carbamazepine and valproate, both commonly used anticonvulsants, have been evaluated in the treatment of alcohol withdrawal and found to be safe alternatives to benzodiazepines with several significant advantages including reduced adverse side effects, no demonstrable abuse potential, and no potentiation of alcohol’s cognitive and psychomotor effects (Ait-Daoud *et* *al*., 2006; Longo *et* *al*., 2002; Malcolm *et* *al*., 2001, 2002). Although not completely understood mechanistically, these medications may suppress “kindling” via facilitation of GABA neurotransmission and subsequent suppression of excitatory glutamatergic transmission (Ait-Daoud *et* *al*., 2006; Hillemacher *et* *al*., 2006; Petrakis 2006). The “kindling hypothesis” proposes that heavy alcohol use with repeated withdrawal episodes is associated with neuronal changes and increasingly severe alcohol withdrawal symptoms (Brown *et* *al*., 1988).

Gabapentin, an anticonvulsant with structural similarity to GABA, garnered initial interest when clinical cases and open-label trials indicated it might have particular efficacy in reducing generalized tonic-clonic seizures associated with alcohol withdrawal (Bonnet *et* *al*., 2003; Myrick and Anton 1998; Rustembegovic *et* *al*., 2004). However, a 2003 controlled study of gabapentin 400 mg qid compared to placebo found no differences in the frequency or severity of withdrawal symptoms (Ait-Daoud *et* *al*., 2006; Bonnet *et* *al*., 2003). Additionally, a recent doubleblind RCT found the anticonvulsants gabapentin and valproic acid to be no better than placebo for mild to moderate withdrawal symptoms, preventing relapse, or reducing depressive symptoms (Trevisan *et* *al*., 2008).

Baclofen is a GABAB receptor agonist approved for the treatment of spasticity. Consistent with preclinical, case reports, and open-label studies (Addolorato *et* *al*., 2002, 2003; Colombo *et* *al*., 2000), a 2006 randomized single-blind study compared baclofen to diazepam in patients needing alcohol detoxification. Both medications significantly decreased alcohol withdrawal symptoms with no significant between-medication differences (Addolorato *et* *al*., 2006; Leggio *et* *al*., 2008).

**Other Medications**

Though most detoxification strategies in current clinical use exert effects via the GABAergic system, there is theoretical evidence to support the use of glutamatergic agents, such as topiramate, in treating alcohol withdrawal. A 2005 in-patient study demonstrated that topiramate 50 mg daily (N ¼ 25) was as efficacious as lorazepam up to 4 mg daily (N ¼ 27) in treating alcohol withdrawal, and allowed for simple transition to out-patient care on the same regimen without the potential for abuse or the increased risk of relapse commonly seen in alcoholics treated with benzodiazepines (Choi *et* *al*., 2005).

**Relapse Prevention**

As with smoking, relapse is common among alcohol-dependent individuals with up to 25–50% of treated individuals returning to alcohol use in the 2 years post treatment and vulnerability to relapse persisting for years (Kalivas and Volkow 2005). Research suggests that drug relapse is a complex phenomenon moderated by both biological and environmental factors (Koob and Le Moal 2001; Sinha *et* *al*., 2003). Historically, research into the pharmacotherapy of drug addiction has focused on modulating dopamine function. Yet, direct dopaminergic agents have yielded disappointing results in preventing relapse despite the plausible hypothesis that agonists would decrease drug intake/drinking by mimicking alcohol properties and antagonists could interfere with alcohol’s pleasurable effects (Petrakis 2006). Instead, more recent evidence has emerged that once addicted, the final common pathway for drug-seeking behavior is the glutamatergic projection from the prefrontal cortex to the accumbens (Gass and Olive 2008; Kalivas and Volkow 2005). Thus, pharmacotherapies targeting this system may provide novel approaches for relapse prevention.

**Glutamate Modulators**

Acamprosate, FDA approved in 2004 for use in alcohol-dependent individuals, is believed to exert its effect through antagonism of NMDA glutamate receptors. Clinically, it may help patients achieve abstinence by reducing distress and interfering with the processes of reward and conditioning (Mason 2001; Petrakis 2006; Weinstein *et* *al*., 2003). Acamprosate obtained FDA approval largely on the basis of European studies, as the multisite US trial did not find an overall effect. Post-hoc analysis of this US trial, however, suggested therapeutic benefit in a subgroup of individuals with a goal of abstinence (Mason *et* *al*., 2006) and a large meta-analysis of 20 studies confirmed this finding (Mann *et* *al*., 2004). Still, a recent large, multisite, clinical trial conducted in the US did not demonstrate acamprosate’s superiority to placebo on percent days abstinent or return to heavy drinking (Anton *et* *al*., 2006), though complete abstinence was not measured. The typical acamprosate dosing is two 333mg tablets three times daily.

Other glutamatergic medications under investigation include memantine and topiramate. Clinical trials with memantine, an NMDA antagonist currently approved for use in Alzheimer’s disease, are ongoing, though a preliminary double-blind pilot study yielded negative results compared to placebo (Evans *et* *al*., 2007).

Topiramate has demonstrated more positive results in clinical trials and is one of the most promising new medications for alcohol dependence. A double-blind RCT of 150 alcohol-dependent individuals treated with either 300 mg daily of topiramate or placebo found improvement in multiple clinical outcome domains, including measures of drinking and overall quality of life and well-being ratings (Johnson *et* *al*., 2003, 2004; Ma *et* *al*., 2006). A subsequent 14-week multisite trial of 371 men and women replicated the findings of improved drinking outcomes. (Johnson *et* *al*., 2007) In fact, the effect size for topiramate is larger than for any other medication to treat alcohol dependence, including that of naltrexone. However, topiramate’s utility is somewhat compromised by the side effect burden. This same trial reported retention rates among those randomized were 61.2% for the topiramate group and 76.6% for the placebo group (p < 0.001).

**Serotonergic Modulators**

Preclinical studies in animals support the notion that selective serotonin reuptake inhibitors (SSRIs) suppress ethanol consumption (Boyce-Rustay *et* *al*., 2006; Gill *et* *al*., 1988) and that medication effects diminish when they are discontinued (Johnson 2008; Murphy *et* *al*., 1988). Despite this, clinical trials using SSRIs have generally yielded disappointing results (Gorelick and Paredes 1992; Kabel and Petty 1996; Kranzler *et* *al*., 1995). More recently, there has been renewed understanding in how differing serotonergic agents might produce different results depending on the particular subtype of alcoholism an individual has (Johnson *et* *al*., 2000; Johnson 2000). Using Cloninger’s classification scheme,(Cloninger 1987) Type I alcoholics are characterized by later age of onset, greater anxiety and guilt, and lower familial loading for alcohol dependence. In contrast, Cloninger Type-2 alcoholics demonstrate an early age of onset (before 25), greater antisocial and impulsive traits, and high familial loading. Solid evidence exists supporting the notion of serotonergic dysfunction in Type-2 compared with Type-1 alcoholism (Ballenger et al. 1979; Fils-Aime et al. 1996; Johnson et al. 2000; Virkkunen and Linnoila 1990). Despite this, research has not shown benefit of SSRIs in this earlyonset typology. Instead, surprisingly two studies have demonstrated improved drinking outcomes among Type-1 late-onset individuals when treated with SSRIs (Dundon *et* *al*., 2004; Pettinati *et* *al*., 2000).

Recent decades have generated an explosion of knowledge in serotonin receptor subtypes and functions and this knowledge is being applied to the addiction research field. The serotonin-1 (5-HT1) partial receptor agonist, buspirone, for example, has been examined for its efficacy in reducing ethanol consumption. Buspirone is FDA approved for the treatment of generalized anxiety disorder. While buspirone has not shown efficacy among alcohol-dependent individuals without comorbidity, there might be benefit among alcohol-dependent individuals with a comorbid anxiety disorder (Malec *et* *al*., 1996). Ondansetron is a serotonin-3 (5-HT3) antagonist that has shown more promise, particularly for individuals with Type-2, early-onset, alcoholism. Two studies (combined n = 361) demonstrated ondansetron was superior to placebo in drinking outcomes, including fewer drinks per day and drinks per drinking day, and found these benefits augmented in early- versus late-onset alcoholism (Johnson *et* *al*., 2000; Kranzler *et* *al*., 2003). This line of research reiterates an emerging theme in addiction research: dependence syndromes are likely heterogeneous, thus requiring individualized therapies to optimize outcomes.

**Other Medications**

Disulfiram exerts its effect through inhibition of alcohol dehydrogenase, an enzyme responsible for metabolizing alcohol’s primary metabolite, acetaldehyde. In large quantities, acetaldehyde is toxic to humans. Disulfiram has been used in the treatment of alcohol dependence since the 1940s, is FDA approved, and works as an aversive therapy. Once taken, it will prevent further metabolism of acetaldehyde and the individual will experience flushing, sweating, headache, nausea, and vomiting. Association of these symptoms with drinking discourages alcohol intake. Because of the risk of the disulfiram–alcohol interaction, individuals using disulfiram should be highly motivated to quit drinking (Johnson, 2008). However, disulfiram is limited in patient acceptability. There are also some reports of disulfiraminduced psychosis. Although such reports were generally found in early literature where higher doses of disulfiram were used, nevertheless, disulfiram should be used with caution in patients who are vulnerable to develop psychosis. It has since been recognized that disulfiram affects dopamine beta-hydroxylase centrally and may be the mechanism by which this side effect is produced. Additionally, this mechanism has been hypothesized to contribute to its potential to treat cocaine dependence (discussed later). A typical daily dose of disulfiram is 250 mg daily. Care should be taken to ensure an individual has not consumed alcohol within 12 h of dosing (Antabuse, 2001)

Finally, there is some preliminary evidence that baclofen, a GABAB receptor agonist, reduces cravings and may have a place in relapse prevention (Addolorato *et* *al*., 2002, 2006; Leggio *et* *al*., 2008).

# 4.2.3 Cannabis

## **Neurobiology**

For years, conventional wisdom held that marijuana (Cannabis sativa) was not truly addictive; however, several recent discoveries have disproved this assumption. First, it is now known that D9-tetrahydrocannabinol (D9-THC), the main psychoactive ingredient of marijuana, activates the mesocorticolimbic system, the same system responsible for the reinforcing properties of all drugs of abuse (Nordstrom and Levin 2007; Tanda and Goldberg 2003; Tanda *et* *al*., 1997). Second, a withdrawal syndrome consisting of irritability, anxiety, depressed mood, decreased appetite, sleep difficulty, and physical discomfort has now been validated and well characterized (Budney *et* *al*., 2007; Nordstrom and Levin 2007). D9-THC acts primarily through the endocannabinoid system in the brain. This system modulates diverse physiologic functions including motor function, memory, motivation and drive, pain, and emotion (Clapper *et* *al*., 2008; Piomelli 2003; Xie *et* *al*., 2007) and is widely distributed throughout the brain. While understanding of the neurobiology has lagged behind other prototypical drugs of abuse, the field has accelerated substantially since the identification and cloning of the first cannabinoid receptor subtype, CB1, in 1990 (Matsuda *et* *al*., 1990). CB1 is one of the most abundant neuromodulatory receptors in the brain and is expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia. It is believed that D9-THC acts in humans primarily via presynaptic CB1 receptor activation (Huestis *et* *al*., 2001; Maldonado *et* *al*., 2006; Tanda and Goldberg 2003; Van Sickle *et* *al*., 2005; Wilson and Nicoll 2002).

Two endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), have been identified as important neurotransmitters for the endocannabinoid system. These neurotransmitters are thought to be deactivated via a two-step process. First, the endocannabinoids are taken up into neurons via as-yet-unidentified protein transporters and second, are hydrolyzed intracellularly by specific hydrolases. Current research into novel pharmacotherapies for cannabis dependence includes CB1 receptor agonist/antagonists and inhibitors of endocannabinoid degradation. Additional therapeutic options will depend upon further characterization and understanding of the cannabinoid system.

## **Treatment Approaches**

## **Withdrawal/Abstinence Initiation**

Cannabis withdrawal is now a well-recognized clinical entity with symptoms including insomnia, irritability, appetite suppression, anxiety, restlessness, and low mood (Budney and Hughes 2006; Budney *et* *al*., 2004). Unlike nicotine and alcohol, there are currently no FDA-approved medications for the treatment of any aspect of cannabis dependence including withdrawal, relapse prevention, or harm reduction. Research in this area, however, is burgeoning (Nordstrom and Levin 2007).

**Cannabinoid Receptor Agonists**

Oral D9-THC, also known as dronabinol, has shown great promise in treating withdrawal symptoms. In a human laboratory study, dronabinol, compared with placebo, was shown to improve sleep, maintain appetite, and decrease anxiety and craving; it had no effect on irritability or social withdrawal (Haney *et* *al*., 2004). Several later out-patient studies – performed among nontreatment-seeking individuals – again demonstrated dronabinol’s efficacy in reducing withdrawal symptoms, with higher dosages producing greater suppression of symptoms (Budney *et* *al*., 2007; Haney *et* *al*., 2008). Significantly, intoxicating effects were not observed (Elkashef *et* *al*., 2008).

**Central Adrenergic Agonists**

As with nicotine and alcohol withdrawal, preclinical data demonstrates cannabis withdrawal is associated with noradrenergic hyperactivity (Lichtman *et* *al*., 2001) and blocking this over activity may help alleviate various symptoms of cannabis withdrawal (Hart 2005). A recent small (n ¼ 8) in-patient study among nontreatment-seeking male regular marijuana users compared the efficacy of four different dosing regimens upon withdrawal symptoms and relapse prevention: placebo, oral D9-THC only, oral lofexidine (central a2-receptor agonist), and finally, a combination of both oral D9-THS and lofexidine. Oral D9-THC reversed some withdrawal symptoms but did not decrease marijuana relapse, while lofexidine did not robustly attenuate withdrawal but did decrease marijuana relapse. The combination treatment produced the most robust improvement in withdrawal symptomatology and relapse prevention (Haney *et* *al*., 2008).

**Mood Stabilizers and Antidepressants**

There is some preclinical data suggesting a role for lithium in attenuating cannabis withdrawal. Lithium was found to dose-dependently prevent symptoms of cannabinoid withdrawal in rats. The investigators speculated that this action was not due to lithium’s mood stabilizing effects – as valproic acid, another mood stabilizer, did not attenuate symptoms – but rather a result of lithium’s enhancement of oxytocin activity in the central nervous system (CNS). This hypothesis was based on the fact that oxytocin administration mimicked lithium’s effect upon withdrawal, and pretreatment with an oxytocin antagonist blocked lithium’s action (Cui *et* *al*., 2001). A recent small open-label in-patient study among treatment-seeking individuals found some benefit of lithium in alleviating withdrawal symptoms (Winstock *et* *al*., 2009).

Consistent with the preclinical finding in rats that valproic acid did not reduce withdrawal symptoms (Cui *et* *al*., 2001), a study in humans evaluating divalproex effects on marijuana withdrawal found it actually worsened mood and cognitive performance (Haney *et* *al*., 2004). Published trials on bupropion, like divalproex, found it worsened symptoms during withdrawal as well (Haney *et* *al*., 2001). It may be that a medication with stimulant side effects, such as bupropion, is ill-suited for cannabis withdrawal symptoms. As such, nefazodone, an antidepressant thought to exert its action by antagonizing the serotonin 5-HT2a receptor with sedative and anxiolytic effects, has been studied. During withdrawal, nefazodone reduced anxiety and muscle pain, but had limited effect on other withdrawal symptoms (Elkashef *et* *al*., 2008; Haney *et* *al*., 2003).

**Relapse Prevention**

**CB1 Antagonists**

Rimonabant, the first specific CB1 receptor antagonist discovered, has been shown to block dysfunctional craving of food and drugs and is currently undergoing study in the treatment of obesity, smoking cessation and alcohol abuse (Howlett *et* *al*., 2004; Xie *et* *al*., 2007). As might be expected given its mechanism of action, pretreatment with rimonabant has been shown to decrease marijuana drug effect in a dose-dependent fashion (Huestis *et* *al*., 2001). At this time, however, and despite its promise, there is a paucity of clinical evidence to promote use in relapse prevention (Elkashef *et* *al*., 2008). Additionally, there is concern for psychiatric side effects which prompted Europe to suspend its approval of rimonabant for obesity treatment.

**Opioid Antagonists**

Early preclinical work in animals suggested opioid antagonists block the reinforcing effects of cannabinoids (Kaymakcalan *et* *al*., 1977; Navarro *et* *al*., 1998). This discovery laid the groundwork for trials in humans. Disappointingly, however, such trials have not demonstrated effectiveness in blocking the subjective effects of cannabis (Wachtel and de Wit 2000). Rather, a small study (n ¼ 9) among regular marijuana smokers actually found naltrexone pretreatment increased the subjective effects of oral D9-THC (Haney et al. 2003).

**Anandamide Deactivation Inhibitors**

After reuptake into neurons and glia, anandamide, one of the two known endogenous cannabinoids, is hydrolyzed by the activity of fatty-acid amide hydrolase (FAAH) (Desarnaud *et* *al*., 1995). Some current preclinical research utilizing FAAH inhibitors to enhance anandamide signaling in the brain has shown the ability to potentiate stress-coping behaviors, oppose the anhedonic effects of stress, and promote normal positive responses to pleasurable stimuli in rodents (Clapper *et* *al*., 2008). No studies have been conducted in humans.

**Other Medications**

Buspirone, an anxiolytic with serotonergic actions, has shown preliminary promise for use in marijuana-dependent individuals. A 12-week open-label trial used flexible dosing of buspirone up to a maximum of 60 mg day1. The participants had used marijuana for an average of 13 years. The median follow-up time was 23 days. Statistically significant reductions in frequency and duration of craving and degree of irritability were found. Additionally, there was a nearly 80% reduction in use observed during the study. The authors conclude a placebo-controlled trial is warranted (McRae *et* *al*., 2006).

As with its use in treating withdrawal symptoms, a 14-week placebocontrolled trial of divalproex observed no group difference on any outcome measure – retention, psychological measures of outcomes, or urine analyses (Levin *et* *al*., 2004). Other studies, ongoing or recently completed, are evaluating efficacy of the antiparkinson drug, selegiline, antidepressants (venlafaxine, fluoxetine, atomoxetine), GABAergic medications (gabapentin and baclofen), and the cannabinoid agonist, dronabinol, in treating marijuana dependence (Health 2008).

# 4.2.4 Stimulants

## **Neurobiology**

While all drugs of abuse ultimately exert their actions on the VTA-NAc reward pathway, stimulants such as cocaine and methamphetamine do so directly. By inhibiting dopamine reuptake from the synaptic cleft via binding to dopamine transporters (DAT), cocaine increases synaptic dopamine availability. Like cocaine, methamphetamine elevates dopamine concentrations at the extracellular level by inhibiting dopamine reuptake at the DAT and actually promotes dopamine release from the presynaptic neuron. Methamphetamine is taken up into the intracellular space and may produce toxicity as dopamine accumulates and undergoes oxidation (Carboni *et* *al*., 2001; Davidson *et* *al*., 2001). Additionally, stimulants block norepinephrine and serotonin transporters. Glutamate and GABA neurons have also shown importance in the neurobiology of stimulant addiction (Kalivas 2007).

While there are no current FDA-approved pharmacotherapies for treating stimulant dependence, hundreds of published trials exist evaluating medications for potential to aid in the initiation of abstinence and/or prevent relapse. Medications targeting various transmitter systems implicated in addiction generally, and stimulants specifically, including dopamine, glutamate, and GABA, have been investigated.

## **Cocaine Treatment Approaches**

Cocaine withdrawal syndrome, while not life threatening – as is alcohol and sedative/hypnotic withdrawal – nor as medically uncomfortable as opiate withdrawal, nonetheless, describes a cluster of symptoms including intense cocaine craving, sleep disturbances, fatigue, anhedonia, apathy, dysphoria, carbohydrate craving, anxiety, and decreased activity level (Brower *et* *al*., 1988; Cottler *et* *al*., 1993; Kampman *et* *al*., 1998). Moreover, the presence of severe withdrawal symptoms has predictive validity for poorer outcomes, highlighting the clinical utility of ameliorating cocaine withdrawal symptoms (Kampman *et* *al*., 2001; Sofuoglu *et* *al*., 2006). While many agents investigated for use in cocaine dependence have targeted these symptoms, the majority of trials have focused on relapse prevention. Many medications have been identified because of their mechanism of action and so, for purposes of this review, they will be grouped this way. These include medications primarily modulating dopamine, adrenergic blockers, and medications affecting GABA and glutamate. Other medications, including acetylcholine receptor agents and immunotherapies, have also been evaluated.

**Dopaminergic Agents**

Bupropion represents a novel class of antidepressant with dopaminergic and adrenergic – but little serotonergic – effects. As such, its side effect profile differs from other antidepressants with diminished weight gain and sexual dysfunction (Stahl *et* *al*., 2004). Given bupropion’s actions upon dopaminergic and noradrenergic systems, bupropion was hypothesized to have efficacy for treating cocaine withdrawal. However, while a small (n ¼ 10) laboratory study found benefit in self-reported effects (Oliveto *et* *al*., 2001), randomized controlled trials (RCT) have not consistently supported these findings. Three double blind, placebo-controlled trials have been published using bupropion for cocaine dependence, two of which were conducted in methadone-maintained cocaine-dependent individuals. The first found no group differences between bupropion and placebo on primary outcome measures. A post-hoc analysis of individuals with high depression ratings, however, revealed a significant reduction in cocaine-positive urines among bupropion compared to placebo-treated individuals, suggesting bupropion may be more effective in individuals with comorbid depression (Margolin *et* *al*., 1995). The second study combined bupropion with contingency management (CM) (n ¼ 106) and reported more positive results in support of bupropion treatment (Poling *et* *al*., 2006). Adding to the inconsistencies, however, the third RCT found no better outcomes on any primary measure when comparing bupropion with placebo (both combined with cognitive behavioral therapy) (Shoptaw *et* *al*., 2008). Thus, these results indicate that bupropion may be effective particularly in conjunction with certain psychosocial treatments, or for a subgroup of patients with comorbid psychiatric disorders (Levin *et* *al*., 2002; Margolin *et* *al*., 1995).

Amantadine is an antiviral agent with low abuse potential used primarily for the treatment of Parkinson’s disease and extra pyramidal symptoms (Burgyone *et* *al*., 2004; Uitti *et* *al*., 1996). Its actions promote the release and inhibit the reuptake of dopamine. Additionally, amantadine antagonizes the glutamatergic NMDA receptor as well as cholinergic receptors (Vamvakides 1991; Wenk *et* *al*., 1995). Preclinical studies have suggested amantadine may decrease cocaine withdrawal symptoms (King *et* *al*., 1994). RCTs have been inconsistent. Some studies have found no effect of amantadine (Alterman *et* *al*., 1992; Kampman *et* *al*., 1996; Weddington *et* *al*., 1989). In contrast, two double-blind RCT found amantadine was associated with decreased cocaine cravings, greater study retention among participants, better global ratings of outcomes, and superior outcomes on urine screens compared with placebo (Kampman *et* *al*., 2000; Shoptaw *et* *al*., 2002). The latter included individuals with severe cocaine withdrawal symptoms. Disappointingly, however, a replication study was conducted that did not confirm these findings (Kampman *et* *al*., 2006).

Bromocriptine is a dopamine agonist with high affinity for the D2 dopaminergic receptor and partial agonism at the D1 receptor. It is used for treatment of hyperprolactinemic disorders, Parkinson’s disease, and acromegaly (Gorska 2000; Jackson *et* *al*., 1988). Laboratory studies have found no effect of bromocriptine in the subjective response to cocaine (Kumor *et* *al*., 1989; Preston et al. 1990b). Two double-blind, placebo-controlled RCTs did not find bromocriptine better than placebo in treatment retention, cocaine positive urine samples, or craving (Gorelick and Wilkins 2006; Handelsman *et* *al*., 1997).

Disulfiram is used in the treatment of alcoholism because it inhibits the enzyme aldehyde dehydrogenase. Disulfiram also inhibits the enzyme dopamine beta hydroxylase, which converts dopamine to noradrenaline, leading to an increase in dopamine concentration (Suh *et* *al*., 2006). Although disulfiram was first tested for cocaine dependence because of the high comorbidity between cocaine dependence and alcohol dependence (Carroll *et* *al*., 1998), its efficacy for cocaine dependence has been confirmed in nonalcohol-dependent individuals. Disulfiram has been found to promote cocaine abstinence within buprenorphine (George *et* *al*., 2000) and methadone-maintained opioid individuals (Petrakis *et* *al*., 2000). In the largest clinical trial to date (n ¼ 121), disulfiram in combination with two types of psychotherapy, was found more effective than placebo in reducing cocaine use even in the nonalcoholic patients (Carroll *et* *al*., 2004). Its use, however, has been limited by concerns about safety. Laboratory studies performed with controlled conditions have shown disulfiram increases plasma cocaine levels and decreases clearance. While no significant cardiovascular effects were found in two trials of disulfiram combined with intravenous or smoked cocaine, a study evaluating the cardiovascular response to intranasal cocaine combined with disulfiram demonstrated a significant increase in systolic and diastolic blood pressure and heart rate (Baker *et* *al*., 2007; Hameedi *et* *al*., 1995; McCance-Katz *et* *al*., 1998). As such, safety concerns due to the possible interaction effects with cocaine and with alcohol in clinical populations may limit its utility in clinical practice.

Other investigators have tested the efficacy of agonist replacement medications such as methylphenidate, dextroamphetamine, and oral cocaine in the treatment of cocaine addiction and found them to be generally effective. While sustained release methylphenidate was found to decrease cocaine use among cocaine dependent patients with comorbid attention deficit hyperactivity disorder (ADHD) symptoms (Levin *et* *al*., 2007), the immediate-release form was not found to be effective in a similar sample (Schubiner *et* *al*., 2002). Additionally, sustained-release dextroamphetamine has been demonstrated to decrease cocaine use when compared with placebo (Grabowski *et* *al*., 2004; Shearer *et* *al*., 2003). Oral cocaine has been shown to decrease cocaine cravings and relapse in a caseseries of coca-paste smokers (Llosa 1994) as well as decrease the subjective and physiological responses to intravenous cocaine administration (Walsh *et* *al*., 2000). Although it is plausible that medications with slow release formulations have diminished abuse potential compared to immediate release forms, abuse liability, nonetheless, is of great concern when proposing agonist pharmacotherapies for the treatment of cocaine addiction.

**4.3 EFFECT OF DRUG INTERACTION ON *MU* RECEPTORS**

In 1994, oral naltrexone, an antagonist at the *mu*-opioid receptor, was FDA approved for use in the treatment of alcohol dependence based on two relatively small studies (total n ¼ 167) demonstrating a modest but significant effect on maintaining abstinence rates and reducing relapse for 12 weeks in recently abstinent alcoholics (Johnson 2008; O’Malley *et* *al*., 1992; Volpicelli *et* *al*., 1992). Two subsequent large meta-analyses upheld the findings of oral naltrexone’s efficacy in reducing relapse (Bouza *et* *al*., 2004; Srisurapanont and Jarusuraisin 2005). The effect size from these study reviews, however, appeared small, with a number needed to treat of 7 (i.e., seven individuals requiring treatment with naltrexone in order to prevent one individual’s relapse) (Johnson 2008). Certain clinical characteristics have been associated with greater effectiveness of oral naltrexone in preventing relapse, including strong cravings for alcohol, and having a high familial loading for alcohol dependence (Monterosso *et* *al*., 2001). Naltrexone is typically dosed at 50–100 mg daily. Because of relatively good tolerability and ease of dosing, naltrexone may be particularly useful in primary care settings where alcohol dependence is commonly encountered.

A major threat to the efficacy of oral naltrexone is the issue of compliance (Volpicelli *et* *al*., 1997). Consequently, three extended-release formulations of naltrexone for deep intramuscular injection have been developed. One of these, Vivitrol (Alkermes, Inc., Cambridge, MA, USA), gained FDA approval after a large, double blind, RCT demonstrated reduced heavy drinking days in men – but not women – with alcohol dependence receiving a high-dose (380 mg) intramuscularly (Garbutt *et* *al*., 2005). The lack of efficacy in women has been ascribed to less familial loading for alcohol dependence, higher placebo response, greater affective symptoms, more clinical heterogeneity or, perhaps, naltrexone’s effects on hormones mediating the menstrual cycle (Johnson 2008; Rossmanith *et* *al*., 1989).

In addition to oral and depot naltrexone, there is some evidence that another *mu*-opioid antagonist, nalmafene, might be efficacious in treating alcohol dependence (Mason *et* *al*., 1999) though initial findings failed replication in a relatively small multisite study (Anton *et* *al*., 2004). Nalmafene has a relative lack of doserelated hepatotoxicity, a decided advantage over naltrexone in this population at risk for hepatic injury; however, the evidence is too scarce to promote its clinical utility (Petrakis 2006).

There has been considerable recent interest in the moderating effects of genetic variation in the m-opioid receptor (OPRM) upon response to opioid antagonist pharmacotherapy. It has been proposed that individuals with the Asp variant of *mu*-opioid receptor (OPRM1) gene exhibit a greater response to opioid antagonist therapy (Oslin *et* *al*., 2003). Replication studies, however, have yielded mixed results (Anton *et* *al*., 2008; Arias *et* *al*., 2008; Gelernter *et* *al*., 2007).

**4.4 OTHER APPROACHES TO TREAT ADDICTION**

Medication and behavioral therapy, especially when combined, are important elements of an overall therapeutic process that often begins with detoxification, followed by treatment and relapse prevention. Easing withdrawal symptoms can be important in the initiation of treatment; preventing relapse is necessary for maintaining its effects. And sometimes, as with other chronic conditions, episodes of relapse may require a return to prior treatment components. A continuum of care that includes a customized treatment regimen addressing all aspects of an individual’s life, including medical and mental health services and follow up options (e.g., community- or family based recovery support systems) can be crucial to a person’s success in achieving and maintaining a drug free lifestyle.

# Medications

Medications can be used to help with different aspects of the treatment process.

**Withdrawal:** Medications offer help in suppressing withdrawal symptoms during detoxification. However, medically assisted detoxification is not in itself “treatment” it is only the first step in the treatment process. Patients who go through medically assisted withdrawal but do not receive any further treatment show drug abuse patterns similar to those who were never treated.

**Treatment:** Medications can be used to help reestablish normal brain function and to prevent relapse and diminish cravings. Currently, we have medications for opioids (heroin, morphine), tobacco (nicotine), and alcohol addiction and are developing others for treating stimulant (cocaine, methamphetamine) and cannabis (marijuana) addiction. Most people with severe addiction problems, however, are polydrug users (users of more than one drug) and will require treatment for all of the substances that they abuse.

* **Opioids:** Methadone, buprenorphine and, for some individuals, naltrexone are effective medications for the treatment of opiate addiction. Acting on the same targets in the brain as heroin and morphine, methadone and buprenorphine suppress withdrawal symptoms and relieve cravings. Naltrexone works by blocking the effects of heroin or other opioids at their receptor sites and should only be used in patients who have already been detoxified. Because of compliance issues, naltrexone is not as widely used as the other medications. All medications help patients disengage from drug seeking and related criminal behavior and become more receptive to behavioral treatments.
* **Tobacco:** A variety of formulations of nicotine replacement therapies now exist including the patch, spray, gum, and lozenges that are available over the counter. In addition, two prescription medications have been FDA-approved for tobacco addiction: bupropion and varenicline. They have different mechanisms of action in the brain, but both help prevent relapse in people trying to quit. Each of the above medications is recommended for use in combination with behavioral treatments, including group and individual therapies, as well as telephone quitlines.
* **Alcohol:** Three medications have been FDA-approved for treating alcohol dependence: naltrexone, acamprosate, and disulfiram. A fourth, topiramate, is showing encouraging results in clinical trials. Naltrexone blocks opioid receptors that are involved in the rewarding effects of drinking and in the craving for alcohol. It reduces relapse to heavy drinking and is highly effective in some but not all patients this is likely related to genetic differences. Acamprosate is thought to reduce symptoms of protracted withdrawal, such as insomnia, anxiety, restlessness, and dysphoria (an unpleasant or uncomfortable emotional state, such as depression, anxiety, or irritability). It may be more effective in patients with severe dependence. Disulfiram interferes with the degradation of alcohol, resulting in the accumulation of acetaldehyde, which, in turn, produces a very unpleasant reaction that includes flushing, nausea, and palpitations if the patient drinks alcohol. Compliance can be a problem, but among patients who are highly motivated, disulfiram can be very effective.

# Behavioral Treatments

Behavioral treatments help patients engage in the treatment process, mod- ify their attitudes and behaviors related to drug abuse, and increase healthy life skills. These treatments can also enhance the effectiveness of medications and help people stay in treatment longer. Treatment for drug abuse and addiction can be delivered in many different settings using a variety of behavioral approaches.

**Outpatient behavioral treatment** encompasses a wide variety of programs for patients who visit a clinic at regular intervals. Most of the programs involve individual or group drug counseling. Some programs also offer other forms of behavioral treatment such as:

* Cognitive*-*behavioraltherapy*,* which seeks to help patients recognize, avoid, and cope with the situations in which they are most likely to abuse drugs.
* Multidimensionalfamilytherapy*,* which was developed for adolescents with drug abuse problems as well as their families addresses a range of influences on their drug abuse patterns and is designed to improve overall family functioning.
* Motivationalinterviewing*,* which capitalizes on the readiness of individuals to change their behavior and enter treatment.
* Motivationalincentives (contingency management), which uses positive reinforcement to encourage abstinence from drugs.

**Residential treatment** programs can also be very effective, especially for those with more severe problems. For example, therapeuticcommunities (TCs) are highly structured programs in which patients remain at a residence, typically for 6 to 12 months. TCs differ from other treatment approaches principally in their use of the community treatment staff and those in recovery as a key agent of change to influence patient attitudes, perceptions, and behaviors associated with drug use. Patients in TCs may include those with relatively long histories of drug addiction, involvement in serious criminal activities, and seriously impaired social functioning. TCs are now also being designed to accommodate the needs of women who are pregnant or have children. The focus of the TC is on the re socialization of the patient to a drug-free, crime-free lifestyle.

# Treatment within the Criminal Justice System

Treatment in a criminal justice setting can succeed in preventing an offender’s return to criminal behavior, particularly when treatment continues as the person transitions back into the community. Studies show that treatment does not need to be voluntary to be effective.

**CHAPTER FIVE**

**5.1 Conclusion**

Recent basic research has first, explored cellular mechanisms that regulate mu receptor activity in neurons, second, identified several genes associated with mu receptor signaling in vivo and third, revealed the crucial role of neuronal activation in the extended amygdala following mu receptor activation. Mu receptor signaling is activated by several drugs of abuse (opioid and non-opioid) and therefore represents a potential target for the therapeutics of addiction. In the clinic, strategies have been developed to either block (naloxone, naltrexone) or partially activate (methadone, buprenorphine) the mu receptor. These therapeutic agents are mainly used in the context of opioid addiction and have had some success in the treatment of alcoholism (Nestler 2002). Although this work is still speculative, it is possible that the clarification of downstream mu receptor effectors in the various recruited brain areas and the discovery of novel proteins that regulate mu-mediated responses will broaden the panel of possible molecular targets useful in the treatment of addictive disorders.

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