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Addiction is a commonly misunderstood, and often poorly managed, health problem. All too often, preceptors model hopelessness, helplessness, or a callous disregard in their response to people struggling with either a substance-use disorder or a behavioural addiction. This primer is intended to help rectify that by providing medical students and other learners with an introduction to the biological, psychological, and social factors that often play into the development of an addiction. The importance of this information to one’s medical education and practice is also addressed, with additional information on clinical management, treatment, recovery, and prevention. Just as no segment of society is immune to addiction, so also no area of medicine is untouched by patients or families struggling with this disease. It is a privilege to help people who struggle mightily with the many challenges of addiction and to witness phenomenal transformation as they enter recovery. They have much to teach us about life, relationships, and attachment.

This introduction provides a brief overview of addiction and the knowledge and resources contained within the AFMC’s *Primer on the Biopsychosocial Approach to Addiction (AFMC Primer)*. The primer is organized into sections on biological, psychological, and social factors in the development and progression of addiction, followed by clinical approaches to screening, diagnosis, and management of the disease. Each section contains chapters where embedded links lead to supplementary content and virtual patients. Most of the virtual patient cases represent aspects of the care continuum. Although this primer has been written specifically for medical educators and undergraduate medical students, it has critical relevance to physicians wherever they are in their lifelong learning.

The *AFMC Primer* is designed to be read in its entirety, with later chapters often assuming knowledge provided in earlier ones. However, it can also be read non-linearly or used as a chapter based resource. To facilitate this, chapter content is cross-referenced where appropriate and some key concepts are reinforced in more than one chapter. It is not intended to exhaust the available information on addiction, but rather to introduce key principles and establish a foundation on which learners can expand their understanding and management repertoire. Advanced learners are encouraged to take advantage of other excellent learning opportunities through clinical fellowships or publications by the Canadian Society of Addiction Medicine (www.csam-smca.org), the American Society of Addiction Medicine (www.asam.org), the Canadian Centre on Substance Abuse (www.ccsa.ca), or the Centre for Addiction and Mental Health (www.camh.net).

Undergraduate medical students preparing for their Medical Council of Canada (MCC) examinations will appreciate the table in Appendix 1 that lists MCC objectives related to each
These objectives and roles apply equally to both the Royal College of Physicians and Surgeons and the College of Family Physicians of Canada. More importantly, the intent of those objectives and roles is to produce a highly competent physician to serve the Canadian public.

**Definition of Addiction**

The Canadian and American societies of addiction medicine subscribe to the following definition of addiction:

*Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social, and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviours.*

*Addiction is characterized by inability to consistently abstain, impairment in behavioural control, craving, diminished recognition of significant problems with one’s behaviours and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.*

*Addiction is characterized by:*

A. **Inability to consistently Abstain**

B. **Impairment in Behavioural control**

C. **Craving**

D. **Diminished recognition of significant problems**

E. **A dysfunctional Emotional response**

(www.asam.org / www.csam-smca.org)

Readers may be surprised by the reference to “spiritual manifestations” of addiction. Although not specifically explored in this primer, typically what one sees with addiction is the loss of a normal attachment to life, to its meaning and value. People who suffer with an addiction have a salience attribution to the substance or behaviour that eclipses anything else of value and meaning to them. The core work of recovery requires one to overcome the absence of insight into that loss and behaviour, coupled with the rebuilding of a more normal life with value, meaning, and purpose.
The **diagnostic criteria** for substance-use disorder are pragmatically grounded in the pathological behavioural patterns that one sees, related to the class of drug. The DSM-5 identifies 10 separate classes of drugs: alcohol; caffeine; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics, and anxiolytics; stimulants; tobacco, and other\(^1\). In addition to these substance-use disorders, there are substance-induced disorders. These include characteristic intoxication, withdrawal, and substance-induced mental disorders. Gambling and other behavioural addictions, such as sex addiction, exercise addiction, shopping addiction, or gaming addiction have also been described.

The diagnostic criteria are organized to fit within specific patterns: impaired control, social impairment, risky use, and pharmacological criteria.

**Substance-use disorder** is described as a problematic pattern of use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

**Impaired control:**

1. The substance is taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control use.
3. A great deal of time is spent in activities necessary to obtain the substance, use it, or recover from its effects.
4. Craving, or a strong desire or urge to use.

**Social impairment:**

5. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the use.
7. Important social, occupational, or recreational activities are given up or reduced because of the use.

**Risky use:**

8. Recurrent use in situation in which it is physically hazardous.
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
Pharmacological criteria:

10. Tolerance, as defined by either of the following:

   a. A need for markedly increased amounts to achieve intoxication or desired effect.

   b. A markedly diminished effect with continued use of the same amount.

11. Withdrawal, as manifested by either of the following:

   a. The characteristic withdrawal syndrome.

   b. More of it (or a related substance) is taken to relieve or avoid withdrawal symptoms.

Severity is measured by the number of symptoms and their total burden and consequences: mild 2–3 symptoms; moderate 4–5 symptoms; severe 6 or more symptoms.

Essential to this diagnostic construct is the understanding of a continuum, with no sharply demarcated line, such as existed in DSM-IV’s substance abuse and substance dependency or addiction. No one criterion is more important than another. Rather, the total burden of symptoms or consequences determines the severity of the disorder. When people encounter problems with their substance use, many pull back, reflect, and make changes. An increasing number of problems reflect increasing loss of control, increasing severity, and ultimately a complete loss of the ability to rationally manage one’s use and life. The behaviour is no longer rational and very much in need of treatment.

Burden of Care and Costs

Not all instances of problematic substance use meet the criteria for addiction or for a moderate to severe substance-use disorder. A significant amount of the costs related to substance use actually arise from the larger number of people who misuse or abuse substances, rather than being fully dependent. These could include everything from minor injuries to significant traumatic morbidity, or even death due to a single episode of impaired judgement and high-risk activity.

The Costs of Substance Abuse in Canada, 2002 estimated the overall social costs of substance abuse in 2002 at $39.8 billion. This was inclusive of the burden on services, such as health care and law enforcement, as well as the loss of productivity from premature death and disability. Based on specific substances, tobacco accounted for 42%, alcohol 36.6%, and illegal drugs 20.7%.

The Core Story of Addiction

How addiction is understood, and how those who struggle with addiction are perceived, influence the quality and quantity of services made available. These factors also determine the level of stigma attached to addiction. Research on addiction has firmly established the dysfunction in the mesolimbic areas of the brain, impacting not only reward and motivational pathways but
also executive function and response to stress (Chapter 1.1). Clearly these susceptibilities are beyond one’s control, yet many people still perceive addiction as a choice. To counter this bias, the FrameWorks Institute developed a narrative to explain the biopsychosocial factors that influence the genesis and expression of addiction. This approach emphasizes the presence of biological “fault lines” in the brain, which arise from underlying susceptibilities, including genetic, experiential and, more importantly, epigenetic (i.e., gene–environment interactions) factors. While pressure is required to activate fault lines and make them problematic, pressure can be alleviated with appropriate supports. Fault lines can therefore expand or contract as the individual progresses through life. In other words, addiction is the result of a complex interaction between biological and environmental factors rather than a result of poor choices.

**Biological and Psychological Factors**

Pressure or stress on brain fault lines increases the likelihood of problems. These pressures include high levels of stress in infancy, adverse childhood experiences (Chapter 2.4), lack of attachment, trauma, concurrent mental health disorders, and ultimately exposure to mood altering substances or behaviours in a pattern of abuse. This list of toxic stress factors is not exhaustive. They are common pressures, but many others will be described in the chapters in Part 1 of the AFMC Primer. Chapter 2.5 Adolescent and Young Adult Triggers for Substance Misuse emphasizes how these same changes can arise at any time in one’s life. Once again there is interplay between vulnerabilities and resilience.

**Social Factors**

Social factors play a role in both the genesis and mitigation of susceptibilities (Chapter 3). Public policy, social planning, healthy communities, family support, early childhood interventions, and appropriate care within our healthcare system can modify these factors. Addictions manifest in every culture and community, but are more evident amongst those who are marginalized, with typically fewer resources to address these challenges. Properly informed healthcare providers can play an important role, however, wherever they may serve. There should be “no wrong door” in the healthcare system. It is imperative that physicians be involved (Chapter 4.1). To be effective they need the skills to overcome stigma and discrimination in the clinical setting; screen for substance abuse and addiction; take appropriate histories of their patients; and conduct focused physical examinations (Chapter 5). A well-equipped physician will be able to address these clinical encounters in a self-assured, direct, but empathic manner. The treatment of addictions need not be marred by conflict or acrimony. The behaviours may be challenging, but an organized, reflective approach with good communication and boundaries can make a profound difference.
**Clinical Encounters**

Once identified, the treatment of addiction requires a continuum of care, not dissimilar to other chronic disease models (*Chapter 7*). This care involves individuals and families (*Chapter 4.4*), as well as a range of therapeutic interventions. These may include pharmacology (*Chapter 6.2*), psychotherapy, counselling, and environmental support. Integrated concurrent care for both mental health and addictions is imperative (*Chapter 6.3*). Care may be residential or community based. Success isn't achieved by detoxification alone, or in a 28-day program, but rather in a sustained and stage appropriate manner (*Chapter 4.4*). Recovery may be life-long (*Chapter 3*). Although the addiction may appear process- or substance-specific, the neurobiological changes render one vulnerable to a range of addictions. **These may be simultaneous or sequential, and may be present over the course of one’s lifetime.** The video gamer may become a gambler or Internet porn addict, concurrent with alcohol or cocaine dependency. The path and process may vary but the central nervous system changes are fundamentally similar. Care systems must therefore evolve to provide ongoing support. People do not progress in a linear fashion but rather through cycles of remission and relapse. Like brain rehabilitation from an acquired brain injury, a staged multidisciplinary approach works best.

**Prevention**

Prevention strategies are informed by our understanding of both the pathophysiology of addiction and the process of recovery. It is important to provide proactive care and support to communities, families, and individuals who are undergoing significant stress or trauma. Improving a population’s health determinants has an impact not only on physical health but also on mental health and addiction. Parenting support is important, especially for those families identified as high risk. Early childhood intervention and education provides a solid foundation for children undergoing stress. Access to education and recreational opportunities, including arts and culture, nurtures the developing child and provides alternatives to substance use or process addictions. Healthy relationships with adults as mentors or role models can instill hope and confidence in the future. Many adolescents lack the opportunity to develop or challenge their many gifts. Integration into community or environmental projects nurtures them as both individuals and citizens. Finally, access to good mental health care and support is crucial for managing issues that may arise throughout the life span. Many of these prevention strategies will improve health and well being generally, as well as provide a protective life style.

**Virtual Patients**

Most chapters have a link to one or more virtual patients that serve to illustrate concepts covered in the text. However, many of the virtual patients represent multiple concepts and various parts
of the care continuum. We encourage you to explore them all. Their association with a particular chapter is located in the table below:

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Part 2 - Clinical Aspects of Addiction: Diagnosis and Management

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| History, Screening, Detection, Investigations & Diagnosis | Miriam and Family; AFMC Case 1, Marilyn Age 74; AFMC Case 2, Judy, age 45; AFMC Case 3, Sue, age 35; AFMC Case 4, Paul, age 9; AFMC Case 5, Jake, age 15; AFMC Case 6, Phil, age 32; AFMC Case 7, Bill, age 48; AFMC Case 8, Joe, age 60; Agitated Adam; Alice in Slumberland; Ann with Green Labels; Beth; Boxer Bruce; Joan is Worried; Vomiting Vince |
CHAPTER 6

6.1 Community Based Treatment

6.2 Medication-Assisted Treatment
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6.3 Clinical Management of Concurrent Disorders
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CHAPTER 7

Chronic Disease Management: A Case Study
   Suicidal Behavior 105

SUMMARY

Improved prevention and treatment services could have a profound impact on the costs of addiction, as well as on the pain and suffering inflicted on individuals and families. Physicians need to be better educated; more engaged as clinical experts, collaborators, managers, advocates, and scholars; and consummate professionals. A generational shift is required to improve the service we provide to the people and families suffering from addiction. This shift will require a change in attitudes as well as knowledge and skills. Physicians can make a difference, however. You can make a difference, if the skill sets are acquired and applied.

REFERENCES


Introduction
At the end of this section the reader will have a comprehensive understanding of the biopsychosocial factors contributing to addiction. Biological factors include key components in brain development including genetics, epigenetics, neuroplasticity, and the neurobiology of addiction. Particular emphasis is placed on reward systems and pathways.

The exploration of the psychological effects of stress on brain development includes adverse childhood experiences, attachment difficulties, and the intergenerational transmission of vulnerability to addiction. In addition, other associated factors that impact adult psychological and behavioral function are explored. Special emphasis is placed on concurrent disorders.

The onset of addictive behaviors may occur at any time in one’s life. Although the presentation, pattern, and timing may differ, similar pathophysiology is in play.

Social factors that are explored include issues of inequality and equity; determinants of health; the presence or absence of social supports; as well as gender and cultural effects.
1.1 Neurobiology of Addiction

Learning Objectives

After completing this section, the learner will be able to:

1. Describe a three-stage conceptual model of addiction that can be applied to both drugs of abuse and behaviours.
2. Identify the key brain structures and functions involved in the binge/intoxication stage.
3. Identify the key brain structures and functions involved in the withdrawal/negative affect stage.
4. Identify the key brain structures and functions involved in the preoccupation/anticipation (craving) stage.

Introduction

Addiction can be defined as a chronically relapsing disorder characterized by the following:

1. compulsion to seek and take drugs of abuse/perform an action
2. loss of control in limiting intake/behaviour
3. emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug/behaviour is prevented (defined here as withdrawal)

Individuals struggling with addiction progress from impulsive to compulsive behaviours in a three-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving). These stages are thought to feed into each other, become more intense, and ultimately lead to the pathological state known as addiction. (Figure 1.1-1)
The Addictive Process

Two primary sources of reinforcement – positive and negative reinforcement – have been hypothesized to play a role in the addictive process.

Positive reinforcement is defined as the process by which exposure to a stimulus increases the probability of a response. Negative reinforcement is defined as the process by which removal of an aversive stimulus (or aversive state, in the case of addiction) increases the probability of a response.

1.1 Neurobiology of Addiction
Of note, reward is operationally defined similarly to positive reinforcement as any stimulus that increases the probability of a response but also has a positive hedonic effect.

The neural substrates for the two sources of reinforcement that play a key role in the allostatic neuroadaptations of the addiction cycle derive from two key motivational systems required for survival: the brain reward system and the brain stress system. In order to fully comprehend the process of addiction, is it necessary to understand its neurobiological basis and how these neurological systems change with the development of addiction.

Multiple interacting neural circuits play a role in each of the three stages of the addiction cycle, as follows:

1. The binge/intoxication stage involves reward and incentive saliency circuits.
2. The withdrawal/negative affect stage involves the reward and incentive saliency circuits as well as stress and aversion circuits.
3. The preoccupation/anticipation (craving) stage involves memory and learning-conditioning circuits and inhibitory control and executive function systems (Figure 1.1-2).

Drugs of abuse, despite diverse initial actions, produce some common effects on the ventral tegmental area (VTA) and nucleus accumbens (NAc). Stimulants directly increase dopaminergic transmission in the NAc. Opiates do the same indirectly: they inhibit GABAergic interneurons in the VTA, which disinhibits VTA dopamine neurons. Opiates also directly act on opioid receptors on NAc neurons, and opioid receptors, such as D2 dopamine (DA) receptors, signal via the Gi protein (Gi). Hence, the two mechanisms converge within some NAc neurons. The actions of the other drugs remain more conjectural. Nicotine appears to activate VTA dopamine neurons directly via stimulation of nicotinic cholinergic receptors on those neurons and indirectly via stimulation of its receptors on glutamatergic nerve terminals.
that innervate dopamine cells. Alcohol, by promoting GABA-A receptor function, may inhibit GABAergic terminals in the VTA and disinhibit VTA dopamine neurons. It may similarly inhibit glutamatergic terminals that innervate NAc neurons. Many additional mechanisms are proposed for alcohol. Cannabinoid mechanisms are complex and involve the activation of cannabinoid CB1 receptors (which, similar to D2 and opioid receptors, are Gi protein-linked) on glutamatergic and GABAergic nerve terminals in the NAc and on NAc neurons themselves. Phencyclidine (PCP) may act by inhibiting postsynaptic N-methyl-D-aspartate (NMDA) glutamate receptors in the NAc. Finally, evidence shows that nicotine and alcohol may activate endogenous opioid pathways and that these and other drugs of abuse (such as opiates) may activate endogenous cannabinoid pathways.

The neurobiology of addiction has benefited from a wealth of evidence from both animal models and the knowledge accumulated from human imaging studies. Such evidence shows that compulsive drug seeking involves the improper functioning of the neuronal circuits that regulate the top-down control of reward, stress, and consummatory behaviours.

Animal models of the positive reinforcing or rewarding effects of drugs are extensive and well validated and include intravenous drug self-administration, conditioned place preference, and brain stimulation reward. Drugs of abuse are readily self-administered by animals that are not dependent; therefore, positive reinforcement and intravenous drug self-administration have been used to predict abuse liability.

Animal models of the negative reinforcement associated with drug dependence include measures of conditioned place aversion (rather than conditioned place preference), precipitated withdrawal or spontaneous withdrawal from chronic administration of a drug, increases in reward thresholds using brain stimulation reward, and dependence-induced increases in drug-taking and drug-seeking behaviour. Such increased self-administration in dependent animals has been observed with cocaine, methamphetamine, nicotine, heroin, and alcohol.

**Neurocircuitry of the Binge/Intoxication Stage of the Addiction Cycle**

The activation of the circuitry related to the origins and terminals of the brain reward system, also known as the mesocorticolimbic dopamine system, has been a principle focus of research on the neurobiology of the positive reinforcing effects of drugs of abuse.

**Brain Reward System**

The brain reward system involves widespread neurocircuitry throughout the brain, but the most sensitive sites include the trajectory of the medial forebrain bundle (MFB) that connects the ventral tegmental area (VTA) with the basal forebrain\(^1,2,3\) (Figure 1.1-3).
Neural circuitry associated with the three stages of the addiction cycle in the context of four key neurobiological elements of dysregulation in addiction and neuroadaptation. In the binge/intoxication stage, the reinforcing effects of drugs may engage associative mechanisms and reward neurotransmitters in the nucleus accumbens shell and core and then engage stimulus-response habits that depend on the dorsal striatum. Two major neurotransmitters that mediate the rewarding effects of drugs of abuse are dopamine and opioid peptides. Thus, this stage involves not only the neural mechanism of drug reward but also incentive salience. In the withdrawal/negative affect stage, the negative emotional state of withdrawal may engage activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition area in the medial portion (or shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala hypothesized to play a role in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. Major projections of the extended amygdala are to the hypothalamus and brainstem. Thus, this stage involves neural mechanisms that engage reward deficits and the recruitment of brain stress systems. The preoccupation/anticipation (craving) stage involves the processing of conditioned reinforcement in the basolateral amygdala and contextual information in the hippocampus.

Executive control depends on the prefrontal cortex and includes the representation of contingencies, the representation of outcomes, and their value and subjective states (cravings and, presumably, feelings associated with drugs). The subjective effects termed “drug craving” in humans involve activation of the orbital and anterior cingulate cortex and temporal lobe, including the amygdala. A major neurotransmitter involved in the craving stage is glutamate localized in pathways from frontal regions and the basolateral amygdala that projects to the ventral striatum. Thus, this stage involves the neural mecha-
nisms engaged in drug-, cue-, and stress-induced craving and neural mechanisms involved in executive function deficits. Neuroadaptation occurs at the neurocircuitry level, and neurocircuits that ultimately drive behaviour are loaded by cellular and molecular neuroplasticity.

All major drugs of abuse activate this system, reflected by increased extracellular levels of dopamine in terminal areas, such as the nucleus accumbens (NAc), or activation of the firing of neurons in the VTA.

Although much emphasis was initially placed on the role of ascending monoamine systems, particularly the dopamine system in the medial forebrain bundle in mediating brain stimulation reward, other non-dopaminergic systems in the MFB clearly play a key role. And, as the understanding of the neural circuits for the reinforcing effects of drugs with dependence potential has evolved, the role of other neurotransmitters and neuromodulators in reward has also evolved. We now know that multiple neurotransmitter systems – including opioid, gamma-aminobutyric acid (GABA), glutamate, and endocannabinoid systems – play a role in mediating the acute reinforcing effects of drugs of abuse in these basal forebrain areas (Figure 1.1-2).

**Incentive Salience**

Drugs of abuse have a profound effect on encoding previously neutral stimuli to which they have been paired, termed a facilitation of incentive salience. Early work in the behavioural pharmacology of stimulants showed that these drugs could facilitate conditioned reinforcement.

Many studies suggest that activation of the mesolimbic dopamine system attaches incentive salience to stimuli in the environment to drive the performance of goal-directed behaviour or activation in general. Research on the acute reinforcing effects of drugs of abuse supports this hypothesis.

**Neurocircuitry of the Withdrawal/Negative Affect Stage of the Addiction Cycle**

The neural substrates and neuropharmacological mechanisms for the negative motivational effects of drug withdrawal may involve disruption of the same neural systems implicated in the positive reinforcing effects of drugs. Current research suggests changes in the function of neurotransmitters associated with the acute reinforcing effects of drugs (i.e., dopamine, opioid peptides, serotonin, and GABA) during the development of dependence, recruitment of the brain arousal and stress systems (i.e., glutamate, corticotropin releasing hormone, and norepinephrine), and dysregulation of the neuropeptide Y brain anti-stress system.
Neuroadaptations in the Reward System

Neuroadaptations are defined as the process by which the primary cellular response element to the drug (circuit A) itself adapts to neutralize the drug’s effects. The persistence of the opposing effects after the drug disappears produces adaptation.

Examples of such changes at the neurochemical level include decreases in dopaminergic transmission in the NAc during drug withdrawal measured by in vivo microdialysis, decreases in the firing of dopaminergic VTA neurons, and changes in signal transduction mechanisms associated with dopamine neurotransmission in the NAc during drug withdrawal.

The decreases in reward neurotransmitter function have been hypothesized to contribute significantly to the negative motivational state associated with acute drug abstinence and also to the long-term biochemical changes that contribute to the clinical syndrome of protracted abstinence and vulnerability to relapse.

Recruitment of Stress Systems

Other neurochemical systems involved in arousal and stress modulation may also adapt in an attempt to restore normal brain function despite the chronic overstimulation of the reward system caused by persistent drug taking.

Chronic excessive administration of drugs of abuse dysregulates both the hypothalamic–pituitary–adrenal (HPA) axis and brain stress systems mediated by corticotropin-releasing factor (CRF). Common responses include an activated pituitary adrenal stress response, elevated levels of adrenocorticotropic hormone and corticosteroids, and an activated brain stress response with activated amygdala CRF during acute withdrawal from all major drugs of abuse. Additionally, the brain’s emotional systems have endogenous buffers that have effects that are opposite to the effects of brain stress neurotransmitters. For example, neuropeptide Y is a neuropeptide with dramatic anxiolytic-like properties that is localized to multiple brain regions but heavily innervates the amygdala. It is hypothesized to have effects opposite to CRF in the negative motivational state of withdrawal from drugs of abuse. As such, increases in neuropeptide Y function may act to balance the increases in CRF and significant evidence now suggests that activation of neuropeptide Y in the central nucleus of the amygdala, similar to antagonism of CRF in the same region, can block motivational withdrawal from chronic ethanol administration and block the increase in ethanol intake associated with ethanol exposure.

The neuroanatomical entity termed the extended amygdala may also represent a common anatomical substrate for acute drug reward and for the negative effects stress produces on reward function that help drive compulsive drug intake. The extended amygdala receives numerous afferents from limbic structures, such as the basolateral amygdala and hippocampus, and sends efferents to the medial part of the ventral pallidum and a large projection to the lateral hypothalamus, thus
further defining the specific brain areas that interface classical limbic (emotional) structures with the extrapyramidal motor system.

**Neurocircuitry of the Preoccupation/Anticipation (Craving) Stage of the Addiction Cycle**

Animal models of craving involve the use of drug-primed, cue-induced, and stress-induced reinstatement of drug-seeking behaviour in animals that have acquired drug self-administration and then have been subjected to extinction of responding for the drug.

Most evidence from animal studies suggests that drug-induced reinstatement is localized to a medial prefrontal cortex–nucleus accumbens–ventral pallidum circuit mediated by the neurotransmitter glutamate. For example, glutamate neuroplasticity has been implicated in cocaine-induced reinstatement, in which increased glutamate release, combined with reduced basal glutamate function in the prefrontal cortex (PFC) to NAc-core pathway, has been hypothesized to explain increased glutamate release in response to repeated cocaine administration. This suggests that increased glutamatergic function contributes to increased drug seeking in addiction.

In contrast, neuropharmacological and neurobiological studies that used animal models of cue-induced reinstatement have indicated that the basolateral amygdala is a critical substrate with a possible feed-forward mechanism through the PFC system involved in drug-induced reinstatement. Stress-induced reinstatement of drug-related responding in animal models appears to depend on activation of both CRF and norepinephrine in elements of the extended amygdala (central nucleus of the amygdala and bed nucleus of the stria terminalis). Shifts in striatal–pallidal–thalamic–cortical function have also been hypothesized, where drug seeking moves from corticostriatal loops operating from the ventral striatum to corticostriatal loops operating from the dorsal striatum.

**Conclusion**

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 addiction. The acute reinforcing effects of drugs of abuse that comprise the binge/intoxication stage of the addiction cycle most likely involve actions localized to a nucleus accumbens–amygdala reward system, dopamine inputs from the VTA, and local opioid peptide and GABAergic circuits. In contrast, the symptoms of acute withdrawal that are important for addiction, such as dysphoria and increased anxiety associated with the withdrawal/negative affect stage, most likely involve decreases in the function of the extended amygdala reward system and recruitment of brain stress neurocircuitry. The preoccupation/anticipation (craving) stage involves key afferent projections to the NAc and extended amygdala, specifically the prefrontal cortex (for drug-induced reinstatement) and the basolateral amygdala (for cue-induced reinstatement). Compulsive drug-
seeking behaviour is hypothesized to engage a transition from ventral striatal–ventral pallidal–thalamic–cortical loops to dorsal striatal–pallidal–thalamic–cortical loops.
Study Questions

Multiple Choice Questions

1. Which of the following is an example of negative reinforcement?
   a. A person takes a drug at a party, experiences euphoria, and then takes the drug again.
   b. A person takes a drug at a party, friends tell him how cool he is for doing so, and then he takes the drug again.
   c. A person takes a drug at a party, feels her social anxiety ease, and then takes the drug again.
   d. A person takes a drug at a party, has frightening hallucinations, and never takes the drug again.

2. Which neurotransmitter systems are involved in the acute reinforcing effects of drugs of abuse?
   a. Dopamine
   b. GABA
   c. Opioid
   d. All of the above.
3. What is the major event that characterizes the withdrawal/negative affect stage of addiction?
   a. incentive salience increases
   b. incentive salience decreases
   c. behaviours shift from merely being habitual to being compulsive
   d. the stress system is engaged

4. What is one of the main brain regions involved in the preoccupation/anticipation (craving) stage of the addiction cycle?
   a. prefrontal cortex
   b. ventral tegmental area
   c. hypothalamus
   d. medulla
Reflective Question

Why are stressful life events often associated with relapses in addiction?

Further Reading


Koob GF. A role for brain stress systems in addiction. Neuron, 2008a, 59: 11-34. [parallel dysfunction, etc.]


Virtual Patient Cases

The following virtual patient cases relate to the content in this section. To access, click on the titles.

Case of Ethel

Case of Miriam (Age 42)
REFERENCES


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Psychostimulants cause rats to show compulsive-like lever-pressing behaviour in response to a cue that was paired with a non-drug reward. Later, in a series of studies that performed recordings of dopaminergic VTA neurons in primates during the repeated presentation of rewards and presentation of stimuli associated with reward, these cells fired upon the first exposure to a novel reward, but repeated exposure to dopamine caused the neurons to stop firing upon reward consumption and to fire instead when they were exposed to stimuli that were predictive of the reward, providing a basis for the supra-physiological phasic release of dopamine by drugs of abuse to lend incentive salience to cues paired with the drug. This drug-induced phasic dopamine signalling can eventually trigger neuroadaptations in other basal ganglia circuits that are related to habit formation.

The recruitment of dorsal striatal “habit” circuits is significant for progression through the different stages of the addiction cycle because such conditioned responses help explain the intense desire for the drug (craving) and compulsive use when subjects with addiction are exposed to drug cues. Thus, conditioned responses of the process of incentive salience may drive dopamine signalling to maintain the motivation to take the drug, even when its pharmacological effects are attenuated.
1.2 Neurochemistry of Substance Addictions

Mark S. Gold, Mahdi Razafsha, and Benjamin Srivastava

Learning Objectives

After completing this section, the learner will be able to:

1. Describe the significance of substance use disorders in individual and global health care.
2. Identify the neurobiology of addiction.
3. Discuss the common reward pathways of different substance use disorders.
4. Describe pharmacologic and neurobiological mechanisms involved in the treatment of substance use disorders.
5. Explain the logic behind new medications under investigation for the treatment of substance use disorders.

Introduction

Substance use disorders are a group of chronic and relapsing disorders characterized by the compulsion to seek drugs of abuse, a strong desire to take these drugs despite negative consequences, a loss of control in limiting drug intake, and withdrawal syndrome when access to the drugs of abuse is prevented1.

Treatment of substance use disorders is a challenging process for both providers and patients. In fact, the high rate of relapse with substance use disorders has caused many to think that it is not a medical disease and, thus, is not significantly improved by medical interventions. Another source of frustration in the treatment of substance use disorder comes from the fact that many view drug dependence as an acute curable condition. This is, however, in direct contravention with the bulk of research that shows that addiction is indeed a chronic disease similar to diabetes, hypertension, and asthma2. The expected outcomes from the treatment of substance use disorders are ultimately affected by the views of the practitioners and patients: is the glass half full or half empty3.

Despite the fact that different drugs of abuse vary chemically, they can produce common effects in the brain. Furthermore, research findings over the past decades confirm that addiction is a neurobiological disease that involves the neurocircuitry of the reward system.

Dopamine is a key neurotransmitter in the reinforcing effects (addiction) of drugs of abuse. Drugs of abuse are shown to activate dopaminergic neurons whose cell bodies reside in ventral tegmental area (VTA) of brain. The projections of the dopaminergic cell travel to the nucleus
accumbens (NAc), prefrontal cortex (PFC), and the amygdala. In addition to the reward system, several other circuitries with distinct neurotransmissions are involved in addiction.

The neurocircuitry of reward, craving, drug-seeking behaviour, and the negative emotions of withdrawal (listed below) have been studied in both animal and human studies.

- **Reward**: The mesolimbic system, which projects from the brain's ventral tegmental area (VTA) to the nucleus accumbens (NAc) is involved in the positive reinforcing effects of drugs. Dopamine is a major neurotransmitter in the neurocircuitry of reward system. Opioid peptides are other neurotransmitters involved in this process.

- **Craving**: Glutaminergic projections from prefrontal cortex to amygdala and NAc are involved in the drug-induced reinstatement of drug seeking. The basolateral amygdala is thought to be involved in the cue-induced reinstatement of drug seeking.

- **Drug-seeking behaviours**: Compulsive drug-seeking behaviours are thought to engage ventral striatal–ventral pallidal–thalamic–cortical loops.

- **Withdrawal**: Withdrawal involves disruption of the reward system and recruitment of the brain stress system.

Currently there are effective, well-tolerated medications available for the treatment of alcohol, opioid, and nicotine dependence, but not for cocaine, stimulants, and marijuana. In this chapter, we summarize the neuropharmacology of these disorders and their related pharmacotherapeutic interventions, with special attention to the neurobiological mechanism.

**Pharmacology of Alcohol Use Disorder**

Alcohol use disorder is a prevalent, but undertreated, disease. Alcohol dependence is also highly co-morbid with other substance and psychiatric disorders.

The dopamine, opioid, gamma-aminobutyric acid (GABA), and glutamate systems are organic systems in the brain that have significant functions in reinforcing alcohol addiction.

**The Dopamine System**

Dopamine, an organic chemical in the brain, plays a central role in reinforcing the effects of alcohol as alcohol increases the firing of dopamine neurons in the mesolimbic system. Lesions of the mesolimbic dopamine system, however, do not completely abolish alcohol-seeking behaviour, indicating that dopamine is not the only neurotransmitter involved in this process.
The Opioid System

Numerous studies have postulated that the rewarding effects of alcohol are mediated in part by the release of endogenous opioids in the brain, as alcohol consumption is associated with increases in levels of the endogenous opioid β-endorphin. It is also postulated that opioid receptors (both \( \mu \) and \( \delta \)) mediate ethanol-induced stimulation of dopamine release that contributes to the reinforcing effects of alcohol. The effect of alcohol on opioid systems has been confirmed in animal studies, for example studies of \( \mu \)-opioid receptor knockout mice show that complete inactivation of the \( \mu \)-opioid receptor blocks alcohol self-administration. This hypothesis is also supported by studies showing that opioid antagonists (such as naltrexone, a \( \mu \)-opioid receptor antagonist that blocks the euphoric effects of opioids) suppress alcohol consumption and help with abstinence by decreasing alcohol cue-induced activation of the ventral striatum.

The Gamma-Aminobutyric Acid (GABA) System

GABA is the major inhibitory neurotransmitter in the brain and there are two receptor subtypes of GABA: GABA-A and GABA-B. Alcohol increases GABA activity in the brain through two general mechanisms. First, it releases GABA in presynaptic neurons; second, it can act on the postsynaptic neuron, facilitating the activity of the GABA-A receptor. Baclofen, a GABA-B receptor agonist, has been assessed for its efficacy in reducing alcohol intake in alcohol-dependent patients, so far with mixed results.

The Glutamate System

Glutamate, the major excitatory neurotransmitter in the brain, exerts its effects via the N-methyl-D-aspartate (NMDA) receptor. The glutamate system has been implicated in reinforcing the actions of alcohol. In the absence of alcohol, neuronal excitatory and inhibitory activity is maintained in equilibrium. Alcohol facilitates the effect of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, and inhibits the N-methyl-D-aspartate (NMDA) glutamate receptor, an important excitatory neurotransmitter, thereby inhibiting glutamate activity in the NAc and amygdala.

In an attempt to maintain a normal state, with chronic alcohol use the brain reduces inhibitory GABA transmission and up-regulates excitatory glutamate neurotransmission in order to adapt.

When access to alcohol is denied in alcohol-dependent patients, the heightened functionality of glutamate receptors results in withdrawal symptoms and hyperexcitability. Glutamate receptors are also mediators of the synaptic plasticity involved in learning and memory. It is thought that glutamate system changes may underlie the compulsions to resume drug-seeking behaviour in alcohol and other drug addictions. Listed below, pharmacotherapies used in modulating glutamate transmission are acamprosate, naltrexone, disulfiram, and gabapentin:

1.2 Neurochemistry of Substance Addictions
Acamprosate: Modulates glutamate transmission by acting on NMDA receptors and, thus, is an effective medication for the treatment of alcohol dependence. Acamprosate is thought to stabilize glutamate and the GABA system and, by restoration of equilibrium between the excitatory and inhibitory systems, prevent some of the cravings²³.

Naltrexone: Originally used in opioid dependence because of its opioid antagonistic activity, it was later approved for the treatment of alcohol dependence¹⁷. Human studies have shown that naltrexone supports abstinence by decreasing alcohol cue-induced activation of the ventral striatum¹⁹. Several other studies have shown the effect of naltrexone in abstinence and prevention of relapse to heavy drinking¹⁸,²⁰. The efficacy of naltrexone was confirmed through the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) trial, a randomized, controlled study involving 1,383 recently abstinent alcoholics. The trial showed that naltrexone was more efficacious than a placebo in increasing the percentage of days of abstinence (80.6% vs. 75.1%) and in reducing the risk of heavy-drinking days (66.2% vs. 73.1%)⁶.

Disulfiram: An irreversible inhibitor of aldehyde dehydrogenase (a hepatic enzyme involved in the metabolism of alcohol). Inhibition of aldehyde dehydrogenase increases the level of acetaldehyde, a metabolite that normally metabolizes but accumulates when a patient is on disulfiram. High levels of acetaldehyde cause aversive symptoms via the disulfiram–ethanol reaction, such as nausea, vomiting, sweating, throbbing headache, facial flushing, chest pain, hypotension, vertigo, and confusion. The reaction occurs almost immediately after alcohol ingestion and can last up to 30 minutes, making disulfiram an effective treatment for alcohol use disorder²⁴-²⁶.

Gabapentin: A medication used for the treatment of epilepsy and neuropathic pain. It blocks voltage-gated calcium channels at presynaptic sites and indirectly modulates GABA neurotransmission. Gabapentin (particularly the 1800 mg dosage) is shown to be effective in treating alcohol dependence and craving²⁷,²⁸. One of the advantages of gabapentin is a favourable safety profile, making it applicable for use in primary care settings.

**The Pharmacology of Opioid Use Disorder**

Opioid use disorder is a chronic relapsing disease that often requires long-term treatment after detoxification. It is estimated that approximately 16 million illicit opioid users exist in the world, and, among them, only 650,000 are receiving maintenance treatment for opioid dependence²⁹.

Opiates impede GABAergic neurons, which normally inhibit the dopaminergic neurons in the VTA, leading to a surge of dopamine in the NAc and other parts of mesolimbic system. Increased activity of dopaminergic neurons is necessary for the reinforcing effects of opioids and contributes to the positive reinforcement seen with opioids such as morphine and heroin³⁰. Two drugs widely used to counter the effects of opioid use disorder are methadone and buprenorphine.
Methadone

As methadone is a synthetic long-acting \( \mu \)-opiate receptor agonist, that is, a chemical that largely prevents reward if the patient ingests opiates, it is an effective maintenance therapy for the treatment of opiate dependence\(^{31,32} \). Methadone’s mechanism of action is similar to opiates that fully attach to the receptor, such as heroin. The differences between methadone and heroin, however, are that methadone is less potent, has a longer half-life, and does not produce a quick burst of euphoria. Methadone occupies the \( \mu \)-opiate receptor with a high affinity and blocks the effect of heroin. Cross-tolerance acquired by methadone, however, would be overridden by a significantly higher dose of opioids. The use of methadone has been controversial for those who consider a drug-free state as the only valid treatment goal\(^{33} \).

It has been demonstrated that patients on a properly adjusted dose of methadone will experience fewer cravings, have better employment records, engage in fewer criminal activities, and have a lower risk of needle sharing and HIV infection\(^{34} \). Studies have also shown that moderate to high doses of methadone (above 60 mg/day) are more effective than lower doses (30–60 mg/day)\(^{35,36} \). However, since methadone can be fatal in non-tolerant patients, meticulous dosing is critical, particularly when treatment is first begun. Of note, methadone can cause respiratory depression and overdose is fatal.

Opiate use during pregnancy is associated with high rates of prematurity and neonatal death\(^{37} \). Since abrupt discontinuation of opioids in pregnant women with opioid-dependency can result in preterm labour or fetal death, methadone is the treatment of choice for opioid dependence in pregnant patients\(^{38,39} \).

Additionally, methadone can prolong the rate-corrected QT (QTc) interval of the electrocardiogram (ECG) and should not be combined with other medications that cause QTc interval prolongation.


Buprenorphine

Buprenorphine is a partial agonist of \( \mu \)-opiate receptors and an antagonist at \( \kappa \)-receptors, and thus exerts weaker opioid effects than methadone. Due to this limitation, buprenorphine has a “ceiling effect” on respiratory depression even at 100% \( \mu \)-opioid receptor saturation\(^{40} \) making buprenorphine safer in the event of overdose. Suboxone is a 4:1 combination of buprenorphine and naloxone, and when taken sublingually, the naloxone has no significant clinical effect. However, when Suboxone is parenterally administered (injected), the opioid antagonism of naloxone
causes withdrawal effects, making this combination of buprenorphine and naloxone an effective maintenance therapy for opioid dependence.

Buprenorphine is safe for use in office-based settings to reduce craving in opioid-addicted patients. It improves different pain phenotypes, including cancer pain and neuropathy, and is considered safe in elderly patients and patients with renal failure. Buprenorphine has similar effects compared to methadone in terms of abstinence, although some studies have shown lower efficacies. It is also associated with less QTc prolongation compared with methadone and appears to be a safe medication for use during pregnancy. Despite all of this, however, methadone remains the treatment of choice for many due to the years of experience they have with its use.


**Pharmacology of Nicotine Dependence**

Nicotine functions by binding to the nicotinic cholinergic receptors in the brain, bringing about a change in the conformation of the receptor and opening voltage-gated calcium channels. This results in the release of dopamine and other neurotransmitters, including serotonin, norepinephrine, GABA, glutamate, acetylcholine, and endorphins. The release of dopamine from dopaminergic neurons in the VTA and NAc appears to be critical for nicotine-induced reward and addiction.

The pharmacotherapy of nicotine dependence includes the following:

**Nicotine Replacement Therapies (NRTs)**

Nicotine-based medications mimic the effects of nicotine and alleviate withdrawal symptoms when a person stops smoking. NRTs also desensitize nicotinic receptors and make cigarettes less satisfying and should be initiated on the quit date. Gums, inhalers, sprays, and lozenges are short-acting agents that can be used to attenuate breakthrough craving, however nicotine patches produce more consistent nicotine levels. The combination of the patch with a short-acting agent is more effective than the patch alone. Since NRTs have some stimulating effects, patients with unstable cardiac disease should be carefully evaluated before initiation, with the risk of treatment weighed carefully against the risk of smoking. However, evidence shows that NRTs do not increase cardiovascular risk in patients with stable coronary disease nor are the risks of NRT more than those of cigarette smoking. Overall, NRTs increase the rate of long-time smoking cessation by 50% to 70%.
**Bupropion**

Bupropion, also known as Zyban and Wellbutrin, is an antidepressant medication that is also approved for use in smoking cessation. Bupropion functions by increasing the brain levels of dopamine and norepinephrine, thus mimicking the effect of smoking, and also acts as a nicotinic receptor antagonist that could contribute to reduced reinforcement in the event of relapse. The side effects of bupropion include nausea, insomnia, and dry mouth, and the rate of seizure associated with bupropion is approximately 1:1000056.

**Varenicline**

Varenicline, also known as Chantix or Champix, is a nicotinic receptor and partial agonist that blocks the reinforcing effects of smoking and decreases craving through the release of dopamine in the mesolimbic system. Varenicline increases the chance of smoking cessation by two to three times, and data has shown that varenicline is more efficacious than bupropion. While varenicline's most common adverse effect is nausea, other serious side effects have been noted including significant neuropsychiatric decomposition, changes in behaviour, hostility, agitation, depressed mood, suicidal thoughts and behaviour, and attempted suicide. Safety concerns have been raised about its potential to increase risk of adverse cardiovascular effects on patients, however, the risk is considered small and should be weighed against the risks of continuing to smoke.

Health Canada and the U.S. Food and Drug Administration (FDA) have required the manufacturers of the smoking cessation aids varenicline and bupropion to add new boxed warnings and develop patient medication guides highlighting the risk of serious neuropsychiatric symptoms in patients using these products. These symptoms include changes in behaviour, hostility, agitation, depressed mood, suicidal thoughts and behaviour, and attempted suicide. The same changes to the prescribing information and medication guide for patients will also be required for bupropion products (Zyban, Wellbutrin, and generics) that are indicated for the treatment of depression and seasonal affective disorder.

For further reading on varenicline (marketed as Champix in Canada) and bupropion (marketed as Zyban in Canada), visit the following Health Canada links for important safety information:

- Health Canada. Public communication: Health Canada endorsed important safety information on Champix (varenicline tartrate). [Internet]. Ottawa:
The Pharmacology of Cocaine, Amphetamine, and Other Stimulants

Stimulants act directly on dopaminergic neurons in the reward system and elsewhere. Cocaine acts primarily by blocking the presynaptic transporter for dopamine\(^61\) and also blocks the presynaptic transporters for serotonin and norepinephrine, thereby increasing the availability of dopamine, serotonin, and norepinephrine in the synapse.

Amphetamine and its derivatives not only potentiate monoaminergic transmission by blocking reuptake, they also enhance these neurotransmitters through their direct action on the vesicles that presynaptically store the neurotransmitters\(^62\).

Despite ongoing research, however, no pharmacotherapies have been found to be clinically effective in patients with cocaine and stimulant addiction. Although, hypothetically, antagonists of dopamine receptors can block the reinforcing effects of cocaine, amphetamine, and other stimulants, clinical studies have not found such benefits\(^63,64\). Baclofen\(^65\), Modafinil\(^66\), and N-acetylcysteine (NAC)\(^67\) are among medications currently under clinical investigation for the treatment of cocaine dependence. Although some of these medications are promising, the overall results are not conclusive. Methylphenidate, bupropion, naltrexone, and mirtazapine are medications that might be of use in subgroups of patients with stimulant addiction; however there is no consistent data supporting their routine use in clinical settings\(^68\).

In the absence of effective pharmacotherapeutic interventions, the treatments of choice remain symptoms-based treatment of acute intoxication, behavioural therapy, and addressing coexisting disorders, such as depression.

Pharmacology of Cannabis Use Disorder

The prevalence of cannabis use among Canadians 15 years of age and older was 9.1% in 2011\(^69\). (For more information, refer to Health Canada’s “Canadian Alcohol and Drug Use Monitoring Survey (CADUMS)” located at: [https://www.canada.ca/en/health-canada/services/health-concerns/drug-prevention-treatment/drug-alcohol-use-statistics/canadian-alcohol-drug-use-monitoring-survey-summary-results-2011.html](https://www.canada.ca/en/health-canada/services/health-concerns/drug-prevention-treatment/drug-alcohol-use-statistics/canadian-alcohol-drug-use-monitoring-survey-summary-results-2011.html) It is estimated that 4% of cannabis users became cannabis dependent within 24 months of beginning their cannabis use\(^70\), while another study showed that approximately 8% of cannabis users develop dependence within 10 years of their first use and that the risk of cannabis dependence is higher in those who begin cannabis use before late-adolescence, in those with a yearly family income of less than $20,000 USD, and in those who had experimented with more than three other types of drugs before their first use of marijuana\(^71\). The proportion of hospital admissions for primary cannabis abuse has increased from 12% in 1997 to 16% in 2007 in the U.S.\(^66\), with cannabis as the most common drug of abuse responsible for treatment admissions\(^72\).
Cannabis has detrimental effects on cognition and executive function, and acute use of cannabis can cause impairment in information processing, inhibition, and working memory. Additionally, chronic heavy use of cannabis can impair decision-making abilities as well as verbal fluency.

The cannabis plant contains over 60 cannabinoids, with delta-9-tetrahydrocannabinol (THC) as the major psychoactive cannabinoid that has been isolated and studied. Cannabinoids exert their effect by targeting specific cannabinoid receptors of which there are two: cannabinoid receptor type 1 (CB1) in the brain, and cannabinoid receptor type 2 (CB2) in immune cells. CB1 receptors are more condensed in the cerebral cortex, hippocampus, cerebellum, thalamus, and basal ganglia. THC has been shown to activate dopamine transmission in the NAc. This finding is consistent with the reinforcing mechanism of other drugs of abuse. One proposed mechanism indicates that the activation of CB1 cannabinoid receptors inhibits inhibitory GABAergic neurotransmission in the VTA that, in turn, increases the firing of dopaminergic neurons. Furthermore, there is an interaction between cannabinoid and opioid neurotransmission. In fact, it has been shown that THC releases endogenous opioids and thus enhances the potency of opioids.

Until recently, very little research has focused on the treatment of cannabis use disorder because of a misconception that no true dependency develops with prolonged use of cannabis. In fact, the rate of relapse from cannabis is similar to other forms of substance dependence such as alcohol, opiate, and tobacco smoking. About 70% of patients with cannabis dependence who achieved continuous abstinence during two weeks of outpatient treatment relapsed within six months. Further evidence of dependency on cannabis is the existence of a specific withdrawal syndrome. Abstinence following daily cannabis use can produce withdrawal symptoms characterized by irritability, anxiety, muscle pain, chills, and decreased appetite.

The first medications tested for cannabis dependence were sustained-release bupropion and divalproex. Both medications significantly worsened mood ratings (irritability, anxiety), and sleep. Oral THC (dronabinol), a cannabinoid agonist, is another medication that was tested for cannabis dependence. Data shows that oral THC administered during abstinence significantly decreased cannabis craving and improved withdrawal symptoms. Given the interaction between the cannabinoid and opioid systems, naltrexone has been proposed for the treatment of cannabis dependence. Gabapentin is another medication under investigation for the treatment of cannabis dependence, and preliminary data has supported its beneficial effects with a favourable side effect profile.

Despite promising approaches, however, no medication has been approved for cannabis dependence to date.
**Discussion Points**

1. Despite the fact that drugs of abuse are chemically different, their actions in the brain produce seemingly common effects. Dopamine is a key neurotransmitter in the reinforcing effects of drugs of abuse. Drugs of abuse are shown to activate dopaminergic neurons whose cell bodies reside in the ventral tegmental area (VTA) of the brain.

2. Alcohol increases the firing of dopamine neurons in the nucleus accumbens (NAc). It is postulated that opioid receptors mediate ethanol-induced stimulation of dopamine release.

   Several medications have been approved for the treatment of alcohol dependence, including disulfiram, acamprosate, and naltrexone.

3. Naltrexone is a $\mu$-opioid receptor antagonist that is used for the treatment of alcohol and opioid dependence. Patients who are starting naltrexone for treatment of alcohol use disorder have to be free of opioids for 7 to 10 days as naltrexone can cause severe opioid withdrawal symptoms in opioid-dependent patients.

4. Methadone is a synthetic long-acting $\mu$-opiate receptor agonist that occupies the receptor with a high affinity and blocks the effect of heroin. The reasoning behind the use of an opioid for opioid addiction is harm reduction as patients on a properly adjusted dose of methadone have better employment record, fewer criminal activities, and a lower risk of needle-sharing and HIV infection.

5. Buprenorphine is a partial agonist of $\mu$-opiate receptor and exerts weaker opioid effects, compared to methadone. Because of limitation to its opioid effect, there is a “ceiling effect” on respiratory depression that makes buprenorphine safer in the event of overdose.

6. Nicotine is the leading cause of preventable death. Smoking cessation counseling should be included in all primary care and psychiatric visits.

7. Three pharmacotherapies are approved for the treatment of nicotine dependence: nicotine replacement therapies (NRTs), sustained-release bupropion, and varenicline.

8. Varenicline is a nicotinic receptor partial agonist that blocks the reinforcing effects of smoking and decreases craving through release of dopamine in the mesolimbic system. Varenicline increases the chance of smoking cessation two- to threefold. However, varenicline can cause significant neuropsychiatric decomposition, depression, and suicidal ideation; it should be used with caution, particularly in patients with current psychiatric illness.

9. Currently there are no effective medications available for the treatment of cocaine, stimulants, and cannabis use disorder.

10. Scientific literature shows that cannabis has a potential for abuse and dependence. Delta-9-tetrahydrocannabinol (THC) activates the release of dopamine in the nucleus accumbens (NAc). This finding is consistent with the reinforcing mechanism of other drugs of abuse.
1. What common neurocircuitries are involved in the patho-physiology of substance use disorders?

2. What are the major neurotransmitters involved in the neurobiology of alcohol dependence?

3. What is the major role of the opioid system in the reinforcing effects of alcohol? How can opioid receptor antagonists help to maintain abstinence?

4. What are the most widely used psychotherapeutic interventions in the treatment of alcohol and opioid dependence?

5. What is the reasoning behind using an opioid agonist (with potential for addiction) in the treatment of opioid dependence?

6. What are the neurobiological mechanisms involved in nicotine dependence?

7. What are the most widely used medications for the treatment of nicotine dependence?

8. What is the main difference between the mechanisms of action for cocaine and amphetamine products?

9. Does cannabis dependence really exist?

10. Which receptors or neurotransmission systems are under investigation for the treatment of cocaine, stimulant, and cannabis dependence?
**Multiple-Choice Questions**

1. Which neurotransmitter plays the key role in the reinforcing effects of all drugs of abuse?
   a. GABA
   b. glutamate
   c. dopamine
   d. serotonin

2. Which neurotransmitter(s) are involved in the neurobiology of alcohol dependence?
   a. GABA
   b. glutamate
   c. dopamine
   d. opioid
   e. all of the above
3. A 47-year-old Caucasian man with a history of alcohol dependence presents for a follow-up visit. He has been abstinent from alcohol for the past four months. He reports that he has recently started drinking one or two drinks approximately every other day. The patient is fearful that his relapse may worsen. Which of the following medications is the most appropriate first line treatment for this patient?

a. naltrexone
b. fluoxetine
c. acamprosate
d. disulfiram

answer

4. A 37-year-old man with schizophrenia and alcohol dependence reports a problem with alcohol consumption. The patient is not currently compliant with his antipsychotic medication which has caused several hospitalizations over the past years. What would be the best medication to help with his alcohol dependence?

a. disulfiram
b. clozapine
c. acamprosate
d. naltrexone

answer
5. A 33-year-old patient with both alcohol and opioid dependence presents for the treatment of a substance use disorder. On several occasions the patient has presented as intoxicated from heavy alcohol consumption. What medication is the treatment of choice?

a. naltrexone  
b. methadone  
c. acamprosate  
d. disulfiram

6. A 25-year-old pregnant woman presents for evaluation and treatment for hydrocodone dependence. She is concerned about taking opioids and wants to stop using hydrocodone. She has gone through several opioid withdrawals in the past when she was trying to stop hydrocodone unassisted. At this time the best treatment recommendation would be to initiate:

a. methadone maintenance treatment  
b. symptoms management with the aid of clonidine  
c. buprenorphine maintenance  
d. daily clinical visit for supportive therapy
VIRTUAL PATIENT CASES

The following virtual patient cases relate to the content in this section. To access, click on the titles.

Boxer Bruce
Vomiting Vince
AFMC Case 2 (Judy Age 45)
References


1.2 Neurochemistry of Substance Addictions


82. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, Buffkins K, et al. A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and...
Nonpharmacologic Interventions

While the focus of this chapter is on the neuropharmacology of substance use disorders and the medications approved to treat them, it is worth mentioning that nonpharmacologic supportive services and psychosocial therapies, along with pharmacotherapy, are pivotal to enhancing program retention and positive outcomes in the treatment of substance use disorders. Alcoholics Anonymous (AA), Narcotics Anonymous (NA), and other twelve-step programs are among the nonpharmacologic interventions that have shown promising results. In a multicentre study that examined physicians with substance abuse disorder who were admitted to Physicians' Health Programs (PHPs), investigators found that nearly 80% of participants had no positive tests for either alcohol or drugs over the five-year period of intensive monitoring. The programs were abstinence-based, similar to the twelve-step programs of AA that require physicians to abstain from any use of alcohol or other substances as monitored by frequent random tests, and provided appropriate pharmacotherapy during the treatment phase. The finding that 70% of the physicians were continuing to practice medicine at post-treatment follow-up signifies that addiction is a chronic disorder that can be treated successfully over extended periods using a combination of evidence-based approaches.

Nicotine Dependence and Psychiatric Illness

Nicotine is the leading cause of preventable death, and every year five million people die from the adverse effects of smoking. Interestingly, there is a high rate of smoking among individuals with psychiatric illnesses. It is estimated that individuals with a comorbid psychiatric disorder consume 34% of all cigarettes smoked in the United States, while they make up only 7% of the overall population. While physicians usually identify the smoking status of patients with psychiatric diagnoses, the data shows that they provide counselling for these patients in less than a quarter of their visits. As only 2.5% to 7% of smokers are able to quit successfully each year without assistance, those who receive medical intervention are approximately twice as likely to quit smoking.
The Impact of Alcohol

It is estimated that 3.8% of all global deaths are attributable to alcohol. In a study of college students, a high prevalence of alcohol use was discovered as approximately 40% of students surveyed reported that they had binged in the previous two weeks. Additionally, alcohol consumption was found to be the third leading cause of death in the USA, and in a national survey in Canada approximately 25% of males and 10% of females reported engaging in hazardous drinking (as defined by Alcohol Use Disorders Identification Test, or AUDIT, scores of eight or higher). Further, alcohol use disorders are associated with car accidents, domestic violence, fetal alcohol syndrome, criminal activity, economic costs, and lost productivity. It is reported that approximately 24% of Canadian federal inmates were impaired by alcohol when they committed serious offences during their incarceration.

Alcohol has consistently been associated with the risk of cancer of the mouth, pharynx, larynx, esophagus, and liver. Alcohol use also significantly increases the risk of cancers of the stomach, colon, rectum, breast, and ovaries. The relationship between alcohol and cancer is dose-dependent; that is, the risk of cancer increases with increasing volume of drinking. However, even among patients who meet the criteria for alcohol use disorders, the problem frequently goes undetected and untreated and data shows that only 24% of those with alcohol dependence actually seek treatment. Despite this, several medications have been approved for the treatment of alcohol dependence, including disulfiram, acamprosate, naltrexone, and gabapentin.
1.3 Neurochemistry of Process Addictions

Learning Objectives

After completing this section, the learner will be able to:

1. Explain the behavioural similarities between process addictions and addictions to drugs of abuse.
2. Describe the currently accepted definitions of process addictions with regard to their place in the DSM-IV-TR and DSM-5.
3. Describe evidence of the underlying neurobiology and neuropathophysiology of process addictions based on current research.

Introduction

Process addictions comprise a series of compulsive behaviours that aim to achieve pleasure and have a potential for dependency. Several process addictions have been identified in the current literature, including addictions to gambling, various types of Internet use, sex, and compulsive spending. Interestingly, a growing number of research studies suggest that a wide range of substance use disorders and process addictions may have similar behavioural and neurobiological functions. In this chapter we will discuss the biology and basic pharmacology of process addictions.

Pharmacology of Gambling Disorder

Behaviourally, gambling disorder shares many features in common with the pathological use of substances of abuse, including tolerance, withdrawal, and continued engagement despite unfavourable effects. In the 2000 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) pathological gambling was classified as an impulse control disorder not otherwise specified (NOS), a category that includes trichotillomania (compulsive pulling out and sometimes eating one’s hair) and pyromania. In the 2013 DSM-5, pathological gambling was reclassified as a gambling disorder and grouped in the same category as substance use disorders.

The Dopamine System

As with substance use disorders, the mesolimbic and mesocortical systems appear to also play a role in gambling disorder. Research using functional magnetic resonance imaging (fMRI) has shown decreased activation in the ventral striatum of pathological gamblers, an important subcortical region central to the pathogenesis of substance use disorders. Also of importance,
fMRI imaging has shown decreased activation of the medial prefrontal cortex in pathological gamblers, an area of the brain that serves as the brain’s “chief executive officer” and thus modulates impulse control.

Similarities between gambling disorder and other substance use disorders can also be found on a neuropharmacological level. The neurotransmitter dopamine is central to the underlying neuropathology of any substance use disorder and, based on psychopharmacologic data, dopamine appears to play a role in gambling disorder. It was discovered that dopamine agonists used in the treatment of Parkinson’s disease produced pathological gambling as an adverse effect, suggesting the involvement of dopamine in gambling disorder. Interestingly, although dopamine agonists (the anti-Parkinson drugs) are known to produce a state of pathological gambling, evidence does not indicate that the atypical antipsychotic olanzapine, which blocks dopamine, has any efficacy in the treatment of gambling disorder.

The Opioid System

The release of endogenous opioids is also of possible importance in the pathophysiology of gambling disorder. This is somewhat similar to the effect of alcohol consumption, as alcohol enhances the release of endogenous opioids. Thus, opioid antagonists are thought to decrease the endogenous-opioid mediated hedonism associated with gambling. Evidence suggests that naltrexone is effective in the treatment of gambling disorder, which mirrors the mechanism of naltrexone in the treatment of alcoholism.

Pharmacology of Food Addiction

Obesity has profound medical consequences – the reduction in life expectancy caused by obesity is estimated to be 5 to 20 years. As the global prevalence of obesity (BMI ≥30) nearly doubled between 1980 and 2008, The Obesity Society (TOS), a nonprofit scientific and educational organization dedicated to expanding research, prevention, and treatment of obesity and reduction in stigma and discrimination affecting persons with obesity, supported categorizing obesity as a disease with the hope of soliciting more resources into research, prevention, and to encourage more health professionals to treat obesity. Additionally, although growing evidence points to a relationship between obesity and mental illness, it remains an area of debate.

While the term food addiction implies a relationship between food and addiction, the fact that food is necessary for survival puts into question the notion that food could be considered an addiction. However, it has become apparent that many people no longer eat with the goal of survival; rather, they primarily seek the pleasurable effects of eating. Though food addiction is not explicitly defined in either the DSM-IV-TR or the DSM-5, the Yale Food Addiction...
Scale (YFAS) has been preliminarily validated as a diagnostic tool for food addiction, based on substance dependence criteria in the DSM-IV\textsuperscript{21}.

The Dopamine System

Behavioural and neurobiological observations suggest that certain foods can produce changes in the brains of certain individuals that manifest themselves in behaviours quite similar to those observed with substance use disorders\textsuperscript{22-24}. This would suggest that the neurotransmitter dopamine and the neurocircuitry of the reward system play a central role in food addiction\textsuperscript{25,26}. Additionally, studies using fMRI have shown that similar areas of the brain are involved in both the compulsive use of food and in substance dependence. Neural activation of regions that play a role in substance dependence, including the anterior cingulate cortex, medial orbitofrontal cortex, and amygdala, are also involved in food addiction\textsuperscript{27}.

Endocrinologically, the adipose-derived hormones leptin, orexin-A, and orexin-B are believed to modulate eating behaviours. Interestingly, leptin acts directly on the ventral tegmental area (VTA)\textsuperscript{28}, an area of the brain that is strongly implicated in addiction, while the orexins are thought to increase dopamine release in the mesolimbic pathways, thus reinforcing addictive behaviours\textsuperscript{4,29}. Also of note, ghrelin, a gastrointestinal hormone that stimulates appetite, has been shown to increase synapse formation and dopamine turnover in the ventral striatum\textsuperscript{4}.

The Opioid System

The complex neuropharmacology involved in food addiction lends itself to many potential therapeutic interventions. The fact that the endogenous opioid system plays a role in food addiction suggests that opioid antagonist therapy might be a viable option for the treatment of food addiction, mirroring the mechanism of action in the treatment of alcoholism. Some studies have shown that medications that block the effects of opioids, such as naltrexone, naloxone, and nalmefene, can reduce caloric intake and may, thus, be viable treatment options for food addiction\textsuperscript{30-33}.

The Serotonin System

Serotonin is also implicated in maladaptive eating patterns, specifically in relation to the phenomenon of craving\textsuperscript{34}. Generally, drugs that modulate serotonin, such as selective serotonin reuptake inhibitors (SSRIs), have been shown to be effective in controlling cravings\textsuperscript{35}.

The Endocannabinoid System

Another important system implicated in eating and possibly food addiction is the endocannabinoid system. Cannabis and its main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), are known to stimulate the appetite. Therefore, antagonists of the endocannabinoid receptors, which are involved in the mesolimbic and mesocortical dopamine systems, could potentially restrict
appetite. Indeed, use of rimonabant, a selective type 1 cannabinoid receptor (CB1) antagonist, resulted in reduced food consumption and weight loss in patients. However, Phase IV clinical trial results showed side effects of anxiety, depression, and suicidal ideation, which led to its removal from the market\textsuperscript{36,37}.

**Current Pharmacologic Treatments**

Traditionally, the focus of anti-obesity medications has been to control appetite and eating behaviours (e.g., orlistat, phentermine). However, despite efforts, current pharmacologic treatments have failed to treat obesity effectively. One example is orlistat, the only obesity pharmacologic therapy that has been approved for long-term use of up to one year\textsuperscript{38,39}. It operates by inhibiting the absorption of fat in the gastrointestinal system by inhibiting oral lipase, resulting in an average weight loss of 2.9 kg a year\textsuperscript{39}. Adverse effects found with use of orlistat are largely of a gastrointestinal nature, including steatorrhea, fecal incontinence, and oily spotting\textsuperscript{39}. While fat-soluble vitamin levels are also lowered this is generally not considered clinically relevant\textsuperscript{39}. Phentermine is another medication approved by the FDA to treat obesity, but can only be used over a period of three months. A sympathomimetic amine that suppresses the appetite\textsuperscript{40}, data has shown that phentermine can induce a 5-10\% weight loss\textsuperscript{41}. However, phentermine is contraindicated in patients with uncontrolled hypertension, heart disease, history or potential for cerebral vascular disease, and psychiatric conditions that may be exacerbated by sympathetic stimulation.

Interestingly, new research has taken the view that obesity is in fact a consequence of food addiction. If this is true, then treating obesity using drugs already known to successfully treat addiction opens promising new avenues for the pharmacologic treatment of obesity. The current focus of these efforts is on pharmacotherapeutic interventions that reduce the reinforcing effects of highly palatable nutrients as a means of reducing body weight\textsuperscript{42,43}. Studies in animals have shown promise when using this approach\textsuperscript{44}, for example, baclofen, a GABA-B agonist, when combined with naltrexone, successfully reduced fat consumption in rats\textsuperscript{45}. It is important to note, however, that any pharmacologic therapy should be administered along with behavioural therapy for optimal treatment.

**Pharmacology of Internet Gaming Disorder**

While Internet gaming disorder is a condition that has been identified in Section III of the DSM-5, it has not yet been classified as a formal disorder and warrants more clinical research before being considered as such. However, it must be recognized that online games played compulsively on the Internet can result in clinically significant functional impairment.
The Dopamine System

Data suggests that the persistent and recurrent use of the Internet activates certain pathways in the brain similar to those affected by addictive substances. Studies using fMRIs have shown that individuals with Internet addiction, in particular those who engage in gaming, manifest enhanced sensitivity to winning (indicated by increased activation in the superior frontal gyrus) and decreased sensitivity to losing (indicated by decreased activation of posterior cingulate gyrus). This may explain why patients with Internet addiction continue to engage in online gaming even after they notice negative consequences. Interestingly, positron emission tomography (PET) and fMRI studies have shown that similar increased superior frontal activation also occurs with cues for drugs of abuse such as tobacco, methylphenidate, and cocaine.

The Opioid System

Given the phenomenological similarities between Internet addiction, substance use, and gambling disorders, one could hypothesize that a MOR-receptor antagonist like naltrexone might be effective in treating Internet addiction. While no clinical trials currently exist, a case report of a patient with compulsive cyber-sexual behaviour showed a three-year remission with the aid of naltrexone. The authors suggested that the blockage of dopamine release in the NAc through opioid receptor antagonism might have contributed to the therapeutic effects.

While current clinical guidelines focus on the comorbidities as the main target for pharmacotherapeutic intervention, comorbid anxiety and depression in these patients can be addressed using SSRIs or bupropion.

Pharmacology of Sexual Addiction

The classification of compulsive sexual behaviours is controversial and has been excluded from both the DSM-IV-TR and the DSM-5 (though hypersexual disorder was proposed for the DSM-5). Describing compulsive sexual behaviour is not easy as the symptoms are heterogeneous, and no population-based studies investigating the prevalence of compulsive sexual behaviour currently exist. Nevertheless, characteristic features gleaned from individuals seeking treatment include preoccupation with fantasies, hypersexual behaviour, and sexual urges that cause distress. Characteristic behaviours include excessive masturbation, having multiple sexual partners, and excessive use of Internet pornography. Though these behaviours themselves may be considered non-pathological, the defining characteristic of compulsive sexual behaviours is that they are excessive.

The Dopamine System

Neurobiologically, the mesolimbic pathway is thought to be involved in sexual addiction, which puts sexual addiction in line with other types of process addictions. Imaging studies show that
the striatum, orbitofrontal cortex, and medial prefrontal cortex are activated during sexual arousal and orgasm\textsuperscript{57}. However, no studies exist that compare the activation of these neuroanatomical areas in individuals who engage in compulsive sexual behaviour versus individuals engaging in “normal” sexual behaviour\textsuperscript{52}.

The Opioid System

While no randomized clinical trials exist that investigate pharmacologic therapies, a single case report demonstrated the success of using naltrexone in treating compulsive sexual behaviour. From this finding one could infer that, in a manner similar to the treatment of alcohol and other process addictions, naltrexone blocks the endogenous opioid-mediated release of dopamine in the ventral striatum of individuals engaging in compulsive sexual behaviour, thus reducing their sexual “cravings”\textsuperscript{48}.

**Pharmacology of Shopping Addiction**

Shopping addiction, also known as compulsive buying disorder, is not explicitly mentioned in either the DSM-IV-TR or the DSM-5\textsuperscript{2,3,59}. However, McElroy et al., have proposed diagnostic criteria which include a preoccupation with shopping, purchasing of unaffordable items, shopping over longer periods of time than intended, distress caused by impulsive shopping, and interference with social and occupational obligations. Important to note, in order to be considered a separate entity, these periods of compulsive buying must not occur exclusively during periods of mania or hypomania\textsuperscript{60}.

The Dopamine System

A study using fMRIs showed increased activity in the NAc and decreased activity in the insular cortex in compulsive shoppers versus controls\textsuperscript{61}.

The Serotonin System

It has been shown that SSRIs can be effective in treating compulsive buying\textsuperscript{62}.

The Opioid System

Case reports showing naltrexone as effective in the treatment of compulsive shopping suggest that, as with alcohol and other process addictions, it could be considered a successful intervention\textsuperscript{63}.

Additionally, both cognitive behavioural therapy and guided self-help have been shown to be effective in the treatment of shopping addiction\textsuperscript{64}.
Conclusion

In conclusion, we have seen that process addictions are comprised of a series of compulsive behaviours whose aim is to achieve pleasure and that have the potential to create dependency. Process addictions identified in the current literature include gambling disorder, food addiction, Internet gaming disorder, sexual addiction, and compulsive buying disorder. Mesolimbic and mesocortical neurocircuitries are involved in both substance use disorders and process addictions. Studies have shown that the neurotransmitter dopamine plays a key role in the reinforcing effects of gambling, eating, Internet gaming, sex, and shopping, similar to the way drugs of abuse are shown to activate dopaminergic neurons in the reward system in the brain. The interaction between the dopaminergic and opioid systems in the brain is one of the mechanisms involved in craving, which explains the effectiveness of opioid antagonists in reducing the reinforcing properties of opioids, alcohol, and certain process addictions.
Reflective Questions

1. What common features do process addictions and substance use disorders share?

2. What are the common areas of the brain that are involved in the various types of process addictions?

3. Why is gambling disorder the only process addiction that is classified with substance use disorders in the DSM-5?

4. Based on the addictive properties of certain foods and the public health consequences of obesity, should certain foods be regulated similarly to drugs of abuse?

5. While Internet gaming is the most commonly characterized Internet addiction, could other compulsive Internet uses also be viewed as addictions based on their behavioural features, such as, for example, the use of social media, instant messaging, and message boards?

6. Would you predict to see changes in the mesolimbic and mesocortical systems similar to those seen with substance use disorders when comparing patients seeking treatment for a sexual addiction versus controls?

7. Given that not all manic patients compulsively shop, do you think that there are neurobiological similarities between manic patients who do shop excessively and patients with compulsive buying disorder?
Study Questions

Based on neuroimaging studies, what are the common neurocircuitries involved in both process addictions and substance use disorders? Why would the same pharmacologic agents used in the treatment of certain substance use disorders have therapeutic benefits for process addictions?

Mesolimbic and mesocortical neurocircuitries are involved in both substance use disorders and process addictions. The neurotransmitter dopamine plays a key role in the reinforcing effects of drugs of abuse as drugs of abuse are shown to activate dopaminergic neurons in the VTA in the brain. The interaction between the dopaminergic and opioid systems in the brain is one of the mechanisms involved in craving, which explains the effectiveness of opioid antagonists in reducing the reinforcing properties of opioids, alcohol, and certain process addictions.

Multiple-Choice Questions
1. What neurotransmitter is inextricably linked to the pathogenesis of gambling disorder?
   a. norepinephrine
   b. dopamine
   c. serotonin
   d. glutamate
   e. GABA
2. What is the mechanism of action of naltrexone related to its therapeutic role in the treatment of food addiction?

a. It inhibits oral lipase thus inhibiting fat absorption.

b. It modulates serotonin through its action on the 5HT2A receptor, thus decreasing cravings for food.

c. It’s an antagonist at the CB1 cannabinoid receptor, thus reducing food consumption.

d. It's a MOR-opioid receptor antagonist, blocking the pleasurable effects of food through inhibition of activation of the endogenous opioid pathways.

3. With regards to Internet gaming disorder, which area of the brain shows similar patterns of activation as with the use of tobacco, methylphenidate, and cocaine?

a. superior frontal gyrus

b. dorsal striatum

c. mesial temporal lobe

d. occipital cortex
4. Behaviourally, what separates a person with possible sexual addiction from a control?
   a. use of Internet pornography
   b. having multiple sexual partners
   c. masturbation
   d. any of the above when taken to excess

5. What psychiatric disorder shares behaviour in common with compulsive buying disorder, and which must be ruled out in order to properly diagnose a shopping addiction?
   a. bipolar disorder
   b. major depressive disorder
   c. generalized anxiety disorder
   d. post-traumatic stress disorder
PODCASTS

Could Food Addiction Explain Rising Obesity Rates?

Addiction

Podcast 8: Different Kinds of Addiction

FURTHER READING


VIRTUAL PATIENT CASES

The following virtual patient cases relate to the content in this section. To access, click on the titles.

Case of Dudley
AFMC Case 4 (Paul Age 9)
REFERENCES


42. Avena NM, Gold MS. Animal models lead the way to further understanding food addiction as well as providing evidence that drugs used successfully in addictions can be successful in treating overeating. Biological Psychiatry. 2013;74(7):e11.

43. Avena NM, Bocarsly ME, Murray S, Gold MS. The effects of baclofen and naltrexone, alone and in combination, on overeating of palatable food in rats. Experimental and Clinical


1.4 The Genetics of Addiction

Heather Leduc-Pessah, Nicole Burma, Erik Fraunberger

Learning Objectives

After completing this section, the learner will be able to:

1. Explain how twin studies have contributed to our understanding of the genetic components of addiction.

2. Describe how large genome screening assays are used to identify gene variants implicated in addiction, as opposed to strictly studying candidate genes.

3. Explain how underlying genetic variations can produce different effects on protein function and modulate related pathways in unique ways that may or may not impact addiction. Appreciate that this relationship is key to understanding the potential impact on addiction.

4. Discuss how a predicted predisposition for addiction is based on genetic variations correlated with addiction and alters an individual’s likelihood to develop addiction after exposure to a substance or behaviour.

5. Describe how epigenetics alters the expression of a protein beyond the genetic coding and be aware that evidence shows extensive epigenetic modifications in addiction.

6. Discuss the value of gaining an in depth understanding of how genetics underlie addiction in order to inform for and improve patient care.

Introduction

Observations of traits running in families have been recorded for many centuries; however, an in depth understanding of human genetics did not develop until the early 1900s when Mendel’s work on patterns of genetic inheritance was rediscovered by de Vries, Correns, and von Tschermak. Since that time, rapid advances have been made in the field of genetics that have allowed for the study of the heritability of human traits and disorders. More recently, a major focus of medical research has been on identifying genes that modulate the likelihood of developing certain pathologies, such as addiction.

Historically, addiction was considered a highly stigmatized condition; patients experienced inadequate access to proper physical and mental health care, whether due to their reluctance to seek help, or the lack of those willing to provide it. As of late, ongoing research and advances
in understanding the genetics of addiction have greatly reduced the stigmatization surrounding addiction and have improved the accessibility of treatment for patients.

Any individual has the potential to develop an addiction. The brain’s reward circuitry provides an evolutionary advantage because it promotes the repetition of favourable or pleasurable behaviours through positive reinforcement. The initial decision to engage in a particular behaviour (whether it be smoking, gambling, or online shopping) is most often a cognitive decision influenced by psychological factors, socioeconomic status, social pressures, and many other reasons. Possessing a predisposition for addiction influences the probability for developing an addiction to a particular behaviour after the initial exposure. Early genealogy and twin studies led to an appreciation that the likelihood of developing addiction could be predicted based on family history; however, more recent research has focused on pinpointing what genes modulate this predisposition. Here, we provide a brief historical overview of the study of the heritability of addiction and then describe a select few of the genes and processes that have been identified to modulate the predisposition for addiction.

Historical Perspective to the Study of Addiction Genetics

“For children whose fathers have chanced to beget them in drunkenness are wont to be fond of wine, and to be given to excessive drinking.” — Plutarch, De Liberis Educandis

It is no secret that as long as humans have encountered psychoactive substances, or engaged in behaviour that mimics the effects of these substances (such as gambling), addiction has posed a public health problem. Plutarch and his contemporaries, while lacking a sophisticated understanding of genetics, relied on intergenerational behavioural observations to support their idea of what constitutes a propensity to engage in addictive activities or a so-called “addictive personality.” However, until the late 20th century the literature surrounding inheritance of addiction was sparse as a result of the widespread notion that addiction was a moral failing that stemmed from a lack of willpower. Considering that willpower, or lack thereof, was not considered to have a biological basis, there was little reason to believe that moral failings could be passed down from one generation to the next.

Twin Studies

In the late 1800s, Francis Galton was one of the first to set out to study nature versus nurture using sibling and twin studies; however, his lack of understanding of genetic heritability prevented him from making conclusive findings\(^2,3\). At this time, it was already understood that some twins came from one egg and others from two separate eggs, but without the knowledge that this resulted in an exact duplication of the genome in identical twins, the implications of commonalities between twins could not be grasped, and twins were not sub-classified according to their genomes.
With a new-found understanding of genetics in the 1900s, Hermann Siemens took the study of heritability one step further by distinguishing between mono- and dizygotic twins. He is credited as one of the inventors of the twin study with his research from 1924, where he correctly concluded that identical and fraternal twins share 100% or 50% of their genetic make-up, respectively. Siemens used these properties to apply statistically rigorous methods to the analysis of his data of heritability in twins and this understanding drastically changed observational studies of heritability. The power of twin studies for understanding genetic contributions to a variety of traits and diseases is still highly valued to this day. While Siemens did not directly examine the heritability of addiction, his new concept of observational twin studies and correlational analysis provided a new toolset that was elegantly employed in the late 1980s and early 1990s by a group of Dutch researchers at the University of Vrije, led by Dorrett Boomsma, to examine the proportion of genetic and environmental influences on offspring phenotype in humans.

Delving into the question of the heritability of “sensation-seeking” traits in twin pairs, Boomsma and colleagues conducted a multivariate analysis of the genetic contribution to possessing sensation-seeking proclivities. Sensation-seeking, while not a direct measure of propensity to addiction, includes traits such as experience-seeking (experience through unconventional means), thrill- and adventure-seeking (engaging in dangerous and fast-paced activities), disinhibition (lack of regard for social or sexual convention), and susceptibility to boredom (seeking novelty). Given that one or more of these traits have been linked to the development of addictive behaviours, these personality dimensions can serve as useful proxies for identifying at-risk individuals. Boomsma et al. found that “between 48 and 63% of the total variance in sensation-seeking scales was explained by genetic influences,” a statistic that has been replicated repeatedly in numerous addiction studies and cited by leading addiction researchers today. In other words, individuals of both sexes who possessed sensation-seeking personality traits had their genes contribute, on average, 55% of the influence behind their behaviour. This startling revelation opened the door to a novel exploration into the biological basis of addiction at a genetic level alongside the more traditional and macroscopic perspectives using pharmacology and behaviour.

It did not take long to have an explosion of literature that sought to quantify the genetic contribution to addiction. Using survey registries from all over the world, including Australia, Vietnam, and the United States, researchers compiled statistics related to the use of addictive agents from both mono- and dizygotic twins. Substantiating the previous findings of Boomsma and colleagues, the mean heritability of addictive substances or behaviours, such as gambling, was found to be anywhere from 0.4 to 0.7. These numbers indicate that an individual’s genome can account for as little as 40% and as much as 70% of the underlying predisposition to addiction.
Table 1.4-1 Mean Heritability with Associated Ranges of Addiction to Various Substances and Behaviours

<table>
<thead>
<tr>
<th>Drug/Behaviour</th>
<th>Mean Heritability (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinogens</td>
<td>0.4 (0.3 - 0.8)</td>
</tr>
<tr>
<td>Stimulants</td>
<td>0.4 (0.2 - 0.7)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>0.4 (0.2 - 0.8)</td>
</tr>
<tr>
<td>Sedatives</td>
<td>0.5 (0 - 0.9)</td>
</tr>
<tr>
<td>Gambling</td>
<td>0.55 (N/A)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.55 (0.45 - 0.7)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.55 (0.5 - 0.6)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>0.55 (0.5 - 0.75)</td>
</tr>
<tr>
<td>Opiates</td>
<td>0.7 (0.5 - 0.7)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.7 (0.45 - 0.75)</td>
</tr>
</tbody>
</table>

Adapted from: D. Goldman, G. Oroszi, F. Ducci.

see Nerd’s Corner: Refresher on Genetics

How to Study the Genetics of Addiction

Valuable insights and advances into understanding the genetics of addiction have been gained through both the analysis of human patient cohorts and the development of laboratory models of addiction. While many will argue that addiction is a human disease, animals that are exposed to substances known to be addictive in humans will display equivalent behavioural signs of addiction. Animal models permit the in-depth investigation of specific elements of addiction, and their use has allowed researchers to identify changes in the cellular and molecular machinery that underlie addiction.

Candidate genes have been identified through animal studies and have signified a functional role for particular proteins and systems in addiction. For example, the dopaminergic, serotonergic, endogenous opioid, and GABAergic systems have all been implicated in the progression from recreational to problematic use of various substances and behaviours. Genes from these systems (which are described in more detail in Part I Chapter 1.1 Neurobiology of Addiction) have received the most attention in the study of the genetics of addiction due to our understanding of their critical contribution to the development of addiction. The role of a particular gene can be selectively studied by interfering with its expression at the translational level (using small inhibitory RNA sequences that bind and prevent the translation of mRNA into protein) and observing behaviour in animal models of addiction. In addition, both global knock-out animals (where a gene is functionally deleted in all regions throughout life) and conditional knock-out animals (where a gene can be deleted from a specific cell type and induced at a specific time) can be generated, and both provide insightful information about the role of that gene when tested in animal models of addiction. These approaches rely on choosing candidate genes predicted to modulate the development of addiction, such as those implicated in the reward circuitry. However,
the identification of novel genetic targets that may be involved in pathways outside the current scope of our understanding of addiction requires the use of large-scale genetic screens.

Genome-wide association studies now provide a rapid way to screen thousands of genes in large cohorts of patients. In a genome-wide association study (GWAS), a large group of individuals are phenotypically characterised and sampled to determine if any genetic variants are associated with a trait. For example, one of the first genome-wide association studies conducted for addiction was done in 2012 and screened for just under 525,000 single nucleotide polymorphisms (SNPs) in a group of patients with alcohol use disorder compared to a control group. SNPs are a change in one single nucleotide in our DNA sequence. When a single nucleotide in the genetic code is altered, it can result in a complete change in the function of the protein through disruption of protein folding, trafficking, errors in transcription, or it may result in no noticeable change (silent mutation or occurring in an intron). Treutlein et al. identified up to 121 potential polymorphisms (or genetic variants existing in the patients) associated with alcohol use disorder and confirmed that two genes were directly linked with an increased risk of addiction using follow-up experiments.

In addition to SNPs, genetic screens can identify insertions or deletions into the genetic code, or instances where entire sections of the chromosome are inverted, resulting in altered expression of multiple genes in that chromosome. With this array of possibilities, the role of the SNPs, allelic variants, and mutations identified in large cohort studies are often confirmed through computational modeling, animal studies, or targeted analysis of patient cohorts to fully understand their implications.

Evolutionary biology and the study of genetic mutations have focused heavily on assessing changes in DNA and how these changes alter protein function. Throughout history, mutational events have produced multiple alleles (different versions of the same gene), common genetic variants, and SNPs that are only now being uncovered. In addition, we now know that decreased or increased expression of a protein can also impair or enhance its function accordingly, and that this can be regulated at both the transcriptional and translational levels. Epigenetic modifications to DNA alter the accessibility of the genetic code to the transcriptional complex, and post-transcriptional modifications to mRNA can alter the stability and accessibility of the transcript to ribosomes. These types of alterations in protein production have also been found to be linked to a susceptibility for developing addiction and can also be heritable.

**Notable Genes Identified to Play a Role in the Predisposition for Addiction**

The development of addictive behaviour is complex. It is influenced by multiple physiological and psychological processes; all the processes involve many different components. There are innumerable genetic loci through which the probability to develop addiction can be altered. In
The genetics of addiction can be grouped into several categories. Some specific genes, linked to substances known to be addictive, may alter the way an individual responds to a drug (i.e., physiological processing of a substance, metabolism, receptor availability). Several genes that fall into this category have been identified and correlated with addiction. Cytochrome P450 enzymes are a class of proteins that contribute to the first metabolic conversion of many drugs (oxidative metabolism). A genetic defect in the gene coding for one enzyme in particular, known as CYP2A6, is linked with decreased function of this protein which results in deficient nicotine metabolism, decreased amount of smoking, and a decreased risk of nicotine dependence. Similarly, a variety of alcohol dehydrogenase (ADH) genes exist: these protein products are responsible for the metabolism of alcohol. Variations in the ADH4 gene were found to be significantly associated with alcohol use disorder, and SNPs in other alcohol dehydrogenases (ADH1A and ADH1B) were found to modify the risk of developing alcohol use disorder. Functional modifications to the ADH genes alter the kinetics of the metabolism of ethanol to acetaldehyde, where modifications that lower the rate of metabolism typically increase the risk of alcohol use disorder and modifications that increase the rate are protective.

Opioids are a potent class of analgesics with a high risk for substance abuse, and there has been significant interest in gene variants linked to their activity. Several SNPs have been identified in opioid receptors; however, many of these occur in intronic or promoter regions (which do not code actively transcribed mRNA), and the roles of these silent SNPs are not fully understood. Of the opioid receptor subtypes, the μ receptor (μR) is the primary site of action for the most commonly used opioids (i.e., heroin, fentanyl). A SNP in the μR resulting in a single amino acid change was found in a group of former heroin addicts. The alteration to the protein structure had minimal functional affect other than altering the binding of the endogenous opioid beta-endorphin. Interestingly, this variant of the μR has also been linked to the likelihood of patients to respond to naltrexone therapy for alcoholism, suggesting opioid receptors have a more complex role in addiction than just mediating the binding of opioids. This may be explained by the emerging role for the endogenous opioid system in addiction, although much is still being discovered. [For review, see Contet et al. and Trigo et al.]

The identification of genes that are broadly associated with addiction supports data showing an increased risk of comorbid addictions, and are in line with the fundamental understanding of the overlapping neurobiological processes taking place during addiction. Variations in monoamine oxidase A (MAOA), which metabolizes monoamine neurotransmitters such as dopamine and serotonin, are implicated in numerous psychological disorders including substance abuse. With deficits in MAOA, the presence of these monoamine neurotransmitters persists, thus increasing their availability to act on downstream receptors and producing prolonged reinforcing effects following activation. Variants in the dopaminergic and serotonergic pathways themselves are also found to be highly associated with addiction. Activation of these pathways mediates the rewarding and reinforcing effects of addictive substances and behaviours. Therefore, alterations in the functional components can have profound implications on the development of addiction.
A SNP in the dopamine D2 receptor (DRD2) has been correlated with increased risk of cocaine abuse and opioid dependence, and variations in the serotonin receptor are also associated with risk of addiction. Serotonin signalling is highly involved in regulating mood but also regulates impulse control. Variants in the serotonin transporter have been found to produce both deficiencies in re-uptake prolonging serotonin signalling, and vice versa; therefore they have varying effects on risk of addiction but have been most heavily linked with alcohol use disorder. Variants in many serotonin receptors subtypes have been identified and implicated in substance use disorders and are described in detail by Herman and Balogh. Alterations in these pathways modulate the physiological response to addictive behaviours and the compulsion to repeat the behaviours, therefore contributing to the likelihood of developing an addiction.

Another prominent target identified in both human and animal addiction studies is the γ-aminobutyric acid (GABA) receptor. GABA is the primary inhibitory signal in the central nervous system, is widely expressed, and plays an important role in many pathways. Changes in GABA signalling have widespread implications in the central nervous system that are still not well understood; however, gene variants have been repeatedly implicated in substance addiction, suggesting a crucial role for GABA signalling.

While variability in genes can predict predisposition or risk of developing addiction, genetic variability also contributes to the initial response to the behaviour, as well as to the likelihood of relapse after overcoming an addiction. Although some of the same or similar genes have been implicated in various components of addiction, unique genes continue to be identified and may provide critical information on understanding the development of addiction and distinguishing the molecular changes of each component. Furthermore, regulation of genes extends beyond the variability in their genetic code to the regulation of the expression of the gene.

**Epigenetics of Addiction**

Our contemporary understanding of the expression and regulation of the human genome can be broadly subdivided into the study of genetics, the specific sequences of DNA that make up our genes and dictate their associated functions, and epigenetics. Epigenetics is the study of the regulation of gene expression. Just because a gene is present in a particular organism or in a particular cell type does not necessarily mean it will be expressed. For example, different cell types, such as red blood cells and bone cells, stably express specific complements of genes and silence others in order to fulfill their specific functions in the body. Epigenetics examines how the physical packaging of DNA in the cell nucleus affects the transcriptional potential of certain genes and how chemical modifications to the DNA that do not change the underlying DNA sequence affect how easily transcription factors can bind to promoter regions of a gene to begin the transcription process. Epigenetic changes can be induced through exposure to various compounds, such as drugs of abuse, or to various experiences and environmental conditions.
Most epigenetic modifications work through one of three mechanisms:

- They alter levels of transcription factors (i.e., proteins that bind directly to DNA to initiate transcription of a gene).
- They modify the physical accessibility of genes within the chromatin.
- They cause expression of non-coding RNA (microRNA) that can alter gene expression.

The occurrence of epigenetic modifications in addiction has been shown through numerous studies that demonstrate altered levels of mRNA and protein expression in brain regions involved in reward. These changes provide a working hypothesis for how the environment can modify susceptibility to develop addictive behaviours.

Following exposure to nearly all addictive compounds, there are changes in the expression of transcription factors within the brain's reward circuitry, such as in the nucleus accumbens and dorsal striatum [for review see Nestler29]. Some transcription factors influence the gene expression of proteins important for excitatory synaptic function, such as ΔFOSB, which promotes long-term synaptic changes and plasticity during states of addiction (a cellular mechanism thought to critically underlie long-lasting behaviours and memories). Other transcription factors act antagonistically, where some will exhibit enhanced activity following natural reward and exposure to addictive compounds, and others will exhibit directly opposing responses. For example, the activity of one transcription factor (MEF-2) is suppressed with the striatum30 and the expression of another transcription factor (NF-kB) is enhanced within the nucleus accumbens31 following exposure to addictive compounds. This illustrates the complexity of the mechanisms that underlie epigenetic modifications following drug exposure and how a single drug of abuse can produce very different cellular responses in distinct areas of the brain's reward circuitry.

While levels of transcription factors alter the expression of genes by directly binding DNA, other epigenetic modifications alter the physical accessibility of genes for transcription and, as a consequence, the frequency that the genes are expressed as functional proteins. Drugs of abuse have been reported to modify histone acetylation32, which affects the packaging of DNA in chromatin. For example, exposure to acute and chronic cocaine increases total acetylation within the nucleus accumbens33 and globally increases the transcription of many genes. In addition, DNA can become methylated, a phenomenon which, opposite to acetylation, decreases the transcriptional potential of genes. DNA methylation is highly responsive to environmental conditions and exposure to drugs of abuse, such as in the instance of cocaine self-administration where DNA methylation is increased within the nucleus accumbens34.

Beyond altering the transcription of certain genes, exposure to drugs of abuse can induce the expression of non-coding RNAs (called microRNAs) that silence gene expression35. Many abusive drugs have been shown to activate non-coding microRNAs, producing changes in the expression of proteins linked to addiction, such as the dopamine transporter36. For example, chronic morphine
exposure causes an upregulation of microRNAs that cause a downregulation of opioid receptors\textsuperscript{37}, a phenomenon hypothesized to contribute to the development of opioid tolerance.

Epigenetic modifications provide a framework for understanding how exposure to addictive compounds can create rapid and long-lasting physiological changes that influence the susceptibility to develop addiction. However, many environmental and situational triggers also increase the vulnerability to develop addiction. In particular, chronic stress as a result of psychosocial adversity, such as recent negative life events, post-traumatic stress disorder (PSTD), mood or anxiety disorders, and negative early life experiences, such as sexual or physical abuse, are all associated with increased risk for addiction\textsuperscript{38-41}. In animal models, stress has been shown to increase self-administration of nicotine and alcohol\textsuperscript{42}, a finding that provides a direct link between stress and substance use. The biological association between stress and addiction converges on the mesolimbic dopamine system, as chronic stress causes tonic release of glucocorticoids, which decrease dopamine synthesis within the nucleus accumbens\textsuperscript{43}. This decrease in dopamine activity following stress is hypothesized to underlie the susceptibility to engage in addictive activity following stressful life events, as abusive compounds provide a compensatory increase in dopamine release within the mesolimbic system.

Stress, and in particular early life stress, may also influence vulnerability to addiction through an epigenetic mechanism. In rats, poor maternal care during development is associated with altered chromatin structure and behavioural abnormalities in adolescence and adulthood\textsuperscript{44} and changes in acetylation of the glucocorticoid gene promoter\textsuperscript{45}. Both human and animal studies have shown that maltreatment during development modulates the stress response in the body by decreasing glucocorticoid receptor mRNA\textsuperscript{46}. These epigenetic modifications persist into adulthood, demonstrating that stressful early life events can have profound and long-lasting effects on the functioning of the brain’s stress and reward circuitry and increase vulnerability to stress-related disorders, such as addiction, over the course of an individual’s lifetime.

While more research is required to identify all of the ways in which gene expression is affected in addiction, epigenetic modifications can provide an important missing piece of the genetics of addiction puzzle, as they may account for the “missing heritability” observed in DNA-sequence based analyses of addicts\textsuperscript{47}. Epigenetic modifications, such as DNA methylation, are heritable but not detected using classical genotype analyses, which provides a biological explanation for both the heritable and rapidly changing adaptations to the environment observed in addiction.

**Conclusion**

While epigenetic modifications are becoming increasingly implicated in addictive behaviours, the vulnerability and risk to develop and maintain addiction is related to a complex array of environmental, genetic, and social cognitive factors. It is difficult to discern the contribution of one factor over another, as many individuals deemed to be at a high genetic risk to develop substance use disorders (i.e., born to addicted parents) are also immersed in high-risk environments. Furthermore, it is becoming increasingly clear that, like genetics, environmental factors cannot
solely explain the susceptibility for addiction, as many children born to addicted parents do not develop similar addictions, and other children born to non-addicted parents acquire substance-use disorders. Therefore, there is likely a complex interplay between genes, environment, and other factors, such as cognitive and social learning factors, in dictating the susceptibility to develop addiction.

To date, a wide variety of genes and their regulatory systems have been implicated, and are continuing to be implicated, in the vulnerability to develop addiction. With these findings, we have made great progress towards improving our understanding of the genetics of addiction. Still, the future of genetics research is rapidly advancing with the emergence of next-generation GWAS studies, and advanced pharmacogenetics. These methods take advantage of our increasingly sophisticated understanding of the genome and epigenome. The clinical implications are wide-reaching: improved preventative medicine by understanding who is most at risk, leveraging pharmacogenetic data for personalized medicine, and decreasing the stigmatization surrounding addiction. These advances in the field coincide with the integration of social science, psychology, and behaviour into the physician’s daily practice. Taken together, our capacity to comprehend vast amounts of genetic information will not only expand the fundamental understanding of the genetics of addiction, it will also enable a more holistic approach to health care for patients suffering from addiction.
Virtual Patient Cases

The following virtual patient cases relate to the content in this section. To access, click on the titles.

Case of Miriam (Age 15)


1.4 The Genetics of Addiction


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It is well known that the human body uses a common set of biological mechanisms to express and regulate its genetic material. These mechanisms work to produce functional proteins from the extensive genetic information stored in our DNA. Our contemporary understanding of human genetics follows the central dogma of molecular biology. This principle states that DNA is converted to RNA that is then converted to protein. While the precise mechanisms in this process are outside the scope of this chapter, the following paragraphs serve as a brief overview of each step to endow a basic understanding of genetics.

DNA is stored in a structure called a double helix, with two complementary strands of nucleotide base pairs. In order to convert specific subsets of the genetic code into workable templates for protein synthesis, DNA must be converted to RNA through a process called transcription. Taking place in the nucleus, transcription involves opening the double stranded DNA at a site of interest and producing a single-stranded RNA copy or transcript. Once the DNA is opened, enzymes that are responsible for copying the DNA into a RNA transcript, known as RNA polymerases, assemble in a complex at the promoter region of a gene, initiating the process of transcription. RNA polymerase moves along the gene to produce a single-stranded RNA molecule, complementary to the DNA, until a stop sequence is reached and transcription is terminated.

At this point, the RNA transcript must undergo post-transcriptional processing in order to increase its stability and to withstand degrading enzymes as it is exported from the nucleus and endoplasmic reticulum into the cytoplasm. Post-transcriptional processing also includes the removal of non-coding regions, known as introns, through splicing. The chemical modifications of the ends of the transcript, adding a methylguanosine group to the 5’ end and polyadenylation of the 3’ end, serve to protect the transcript from enzymatic breakdown and facilitate nuclear export. The splicing of introns and patching of the coding regions, or exons, creates the final template, or messenger RNA (mRNA), used for translation of a protein.

Following post-transcriptional processing and export from the nucleus, the mRNA can be recognized and assembled with a protein called the ribosome to produce a polypeptide chain that will become a functional protein. As the transcript moves through the ribosome, a systematic process occurs where triplet codons in the RNA are matched and bound by transfer ribonucleic acids (tRNAs) in the cytoplasm that are accompanied by specific amino acids. Amino acids are the building blocks of proteins; their unique properties, as well as the specific patterns in which they are assembled (dictated by the RNA sequence), allow for the production of a wide array of proteins. As each amino acid arrives at the ribosome, they are chemically linked together to form a polypeptide chain until a stop codon is reached. This chain then
undergoes several stages of folding through chemical interactions between the amino acids to form the final structure of the protein. While there are many integrated mechanisms to reduce errors throughout these processes, the mutations or deficits that occur at any stage can be detrimental to the final protein product.

NERD’S CORNER

Genetic Mutation

Our genes carry the code for synthesizing all of the individual proteins that, when produced, interact in complex pathways. When a single nucleotide in this code is altered (usually by a random mutation) it can result in a complete change in the function of the protein. Alternately, many single nucleotide polymorphisms (SNPs) result in no noticeable change. An important biological mechanism to reduce the effects of SNPs is a built-in redundancy system, where codons containing similar nucleotides encode for the same amino acid. These types of changes can be referred to as silent SNPs, or SNPs that have no effects. Further to this, some regions of the gene are not critical to the structure of the protein and may be later spliced from the final transcript. SNPs in these regions, referred to as introns, have minimal effects on protein function. When a nucleotide substitution results in a code for a different amino acid, the changes to the protein function can vary. If the amino acid was critical for proper protein folding, or for a binding site, for example, the protein’s function can be critically altered. An alteration in the genetic code can also produce a premature stop codon in the DNA sequence preventing the proper transcription of the gene and preventing the full-length protein from being synthesized. Changes in the genetic sequence that produce major changes in the protein sequence, which result in either a change or loss of function of that protein, are the mutations that cause a noticeable effect or alteration to the model being studied. With all these possibilities, even though SNPs are often identified in genome wide screens, it is important to first assess localization of the SNP and the effect it has on protein coding to determine the potential for impairing the function of the protein.
DNA Packaging

If you uncoiled the entire DNA in the nucleus of one cell and laid each strand end to end, it would measure almost two metres. In order to fit this entire DNA into the nucleus, cells store genetic material by wrapping DNA around proteins known as histones. These positively-charged storage proteins attract the negatively-charged backbone of DNA, allowing it to act as a spool with DNA as the thread. Histones then aggregate and are further packed into nucleosomes, which under a microscope resemble beads on a string. These nucleosomes condense into what is known as chromatin and, finally, into chromosomes.

Chemical modifications that alter the charge of either the histone or the DNA itself can affect the transcriptional potential of various genes by changing how the DNA wraps around the histone. Adding combinations of methyl, acetyl, phosphate, and nitric oxide groups can affect the packing of DNA in various ways, leaving some genes inaccessible to the cell’s transcriptional machinery. This type of change to DNA, which does not involve changes to the DNA sequence itself, is called an epigenetic change.
2.1 Toxic Stress and Brain Development

Robbin Gibb and Nicole Letourneau

Learning Objectives

After completing this section, the learner will be able to:

1. Describe the basic features of brain development.
2. Explain how developmental experiences influence gene expression.
3. Discuss how stress affects brain development.
4. Describe the factors that affect brain development.

Introduction

The human brain is an incredible organ that possesses vast potential for adaptation and change in response to experience. Referred to as brain plasticity, this powerful characteristic enables humans and other animals to learn, solve new problems, and recover from brain injury. Research into brain plasticity has revealed two important insights:

- Plasticity is influenced by a surprisingly large number of life experiences.
- Although the brain retains plasticity over its entire life span, the rapidly developing brain of the early stages of life possesses both a much greater capacity for change and an increased vulnerability to organizing and disorganizing influences such as stress.

As such, prenatal and early postnatal experiences are integral factors in the formation of fetal brain anatomy. An interactive process between genetic programming, environment, and cell function, the influence of plasticity on brain construction can be discussed in the context of the interaction between our inherited genes (nature) and our environmental experiences (nurture). Brain structure and function may be partly under epigenetic control, potentially via the hypothalamic pituitary adrenal (HPA) axis and cortisol. Although brain changes and adaptation are part of a lifelong process, research has shown that the earliest maturation phases are perhaps the most important.

The brain develops through the lifelong interplay of generative (cell birth and synapse formation) and degenerative (cell death and synaptic pruning) processes, which are modulated to varying degrees by an individual's experience. The process of brain development is intricately programmed by information carried on DNA. Although the process is fundamentally the same for each individual, environmental exposures can alter the manner in which DNA programs develop. With certain environmental exposures, a gene may be read, translated, and, ultimately, produce
a protein, in which case the environment has “endorsed” or signed off on the production of the protein. Conversely, other environmental exposures can block gene transcription, translation, and the production of a protein, in which case no environmental signature was received to allow protein production to proceed. In this way, we see that the environment can exert a powerful influence over the genome. This environmental modulation of genetic expression is called epigenetic programming, and its effects can be seen in the preconception period, the prenatal period, and throughout the entire life span of an individual. Additionally, mounting evidence has demonstrated that even the experiences of our ancestors can result in epigenetic changes in our own gene expression, ultimately changing the expression of our proteins. Because proteins are the building blocks of the brain, it follows that the expression of different proteins will result in the formation of different brains through modification of cell number, cell connectivity, brain size, and ultimately, behaviour. Epigenetic programming, therefore, provides an adaptive means for an organism to prepare its brain for the unique environmental challenges that it will face without changing its genetic blueprint.

**Human Brain Development**

Human brain development is a prolonged process that proceeds in seven distinct phases:

1. **Cell birth or neurogenesis**: The first phase begins shortly after conception and continues until about halfway through pregnancy. Most neurons found in the adult brain have formed by the end of this phase. Although it is important to note that the hippocampus, an area of the brain involved in memory formation, spatial processing, and the regulation of stress hormone production, continues to produce neurons throughout the lifespan of the brain.

2. **Cell migration**: In the second phase, cells born in the centre of the brain migrate outward to the cortical areas where they are destined to perform their programmed activities. Cells that will populate the deepest cortical layers migrate first, and then cells that will inhabit the more superficial areas push past these first cells in order to reach their final destination.

3. **Cell differentiation**: In the third phase, immature cells transform into their final cell type.

4. **Cell maturation**: In the fourth phase, cells begin to extend their dendrites and axons in preparation for cell-to-cell communication.

5. **Synaptogenesis**: In the fifth phase, through establishing synapses, which are the sites of signal transmission between cells, mature cells begin the process of finding target cells that will form circuits through which information is relayed.

6. **Cell death (apoptosis) and synaptic pruning**: During the sixth phase, cells that are superfluous undergo programmed cell death, and synapses that are underused are pruned away.
7. **Myelination**: In the final phase, myelin sheaths envelop axons to speed up cell-to-cell communication. Although myelination begins in the prenatal period, it is not complete until well into the third decade of life. Brain areas that myelinate early include sensory and motor areas, whereas association cortices, which are involved in higher-order processing, myelinate later. The last area of the brain to complete the myelination process is the prefrontal cortex. This area can be likened to an air traffic control system for the brain and is responsible for executive functions that include organization, planning, working memory, creativity, flexibility, inhibition, self-regulation, and emotional control. Because the prefrontal cortex has such a protracted timeline for development, it is the most sensitive to the experiences of an individual.

**Experience and Brain Development**

While the basic plan for the construction of the human brain is encoded within the genome, much of the brain’s connectivity remains unspecified and is dependent on the input of an individual’s experiences in order to complete the wiring. Processes described as experience independent can proceed without the need for input from external experiences; such developmental processes rely on internally generated activity to proceed rather than on externally generated environmental input. Experience can modify the construction of the brain through a process called experience-dependent plasticity. In this form of plasticity, structures in the developing brain may be modified or changed by environmental exposures; all seven phases of brain development can be altered to a certain extent by experience. One of the key mechanisms by which experience affects brain development is via epigenetics, and one of the key experiences that organize or disorganize the brain is stress, especially of the chronic or traumatic type called toxic stress.

**Epigenetic Mechanisms**

The Oxford dictionary defines epigenetics as “the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself” (en.oxforddictionaries.com/definition/epigenetics). The two most common forms of epigenetic regulation are methylation and histone modification. Methylation involves the conversion of cytosine, one of the four nucleotides that comprise DNA (adenosine, cytosine, guanine, and thymine), in regions involved in gene regulation into a variant called 5-methylcytosine, which functions to essentially silence the gene. This typically happens at a 5’–C–phosphate–G– 3’ (CpG) site, a segment of DNA in which a cytosine occurs next to a guanine in the DNA sequence. Histone modification, however, involves a different process. Histones organize the DNA into structural units and act as spools around which DNA is wound. One example of histone modification is the acetylation of histones, where the DNA strand is relaxed so that genes are more available for transcription. In contrast, de-acetylated histones limit or entirely silence gene expression on the DNA target site. Whether or not a gene is silenced contributes to changes in gene expression.
and therefore may result in a specific change in phenotype. Although methylation and histone de-acetylation are two rather different mechanisms for epigenetic regulation, they both influence phenotype by limiting or silencing gene expression\textsuperscript{16,17}.

Gene expression is highly changeable during prenatal development and early life\textsuperscript{18-25}. Experience-dependent epigenetic change allows the developing brain to remain plastic and to change responsively to experiential inputs, thus adapting to the unique environmental challenges an individual may face.

It is well understood that stress can influence epigenetic change. One example occurred during the 1998 Quebec Ice Storm: the high levels of prenatal maternal stress experienced by some mothers who endured the storm predicted the DNA methylation patterns in their children, as compared to the children of mothers who reported lower prenatal stress from the experience. In particular, high maternal prenatal stress was associated with lower methylation of the SCG5 gene, which codes for secretory granule neuroendocrine protein 1, expressed in neuroendocrine tissues. Another example is childhood exposure to poverty or to parental stress, which is associated with altered HPA axis responsiveness and with changes in methylation pattern in the child\textsuperscript{20,26,27}. Further, post-mortem examinations of suicide victims show that epigenetic regulation of the hippocampal glucocorticoid receptor (GR) is affected by childhood abuse, with decreased levels of GR messenger RNA (mRNA) and transcripts bearing a GR variant and by increased cytosine methylation of the GR promoter in abused suicide victims\textsuperscript{28}.

**Stress and the Hypothalamic Pituitary Adrenal Axis**

The stress response is defined as an evolutionary means for providing an adaptive mechanism causing behavioural and physiological changes to improve an individual’s chances of survival in the face of homeostatic challenges. The HPA axis forms part of the neuroendocrine system and is responsible for controlling the stress response. The hypothalamus releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) that act on the pituitary to stimulate the release of adrenocorticotropic hormone (ACTH) that ultimately stimulates the release of glucocorticoids from the adrenal gland. The hormones secreted from the HPA axis are under negative feedback control in the hypothalamus but also in the pituitary gland, hippocampus, and prefrontal cortex\textsuperscript{29}. Under normal stress conditions, the stress response is activated, the challenge is resolved, and glucocorticoid levels return to a baseline level. Under conditions of toxic stress, the HPA axis becomes dysregulated and glucocorticoid levels remain elevated for extended periods of time. \textsuperscript{30}
Perinatal Stress and Brain Development: Rodent Models

Stress has been extensively studied in animal models, and these studies have provided us with a better understanding of how stress affects behaviour and health. For example, prolonged separation from the mother in the early postnatal period causes rodents to show exaggerated responses to stress later in adulthood. In addition, exposure to stress in pregnant rats can cause greater emotionality and anxiety in their offspring. This heightened reactivity to stress is associated with increases in size of the lateral nucleus of the amygdala, which regulates anxiety, and with fewer GRs in the hippocampus and frontal cortex. Further to this, it is important to note that other factors, such as the amount of stress, the sex of the offspring, and the timing of the stressor, play a key role in determining the extent of the behavioural and anatomical consequences of the stress exposure.
Early Stress and Human Brain Development

Associations between stress and alterations in brain structure have been noted in the amygdala, hippocampus, the prefrontal cortex, and in the white matter that links these regions. The amygdala and hippocampus are deep, gray matter structures within the limbic system that tend to be associated with emotional function. The prefrontal cortex is associated with attention and response inhibition. The white matter connections between these regions facilitate efficient communication among them\(^1,32\). Additionally, the mesolimbic dopamine system that projects to the prefrontal cortex and forms the basis of the reward system allows an organism to attend to stimuli in the environment that are behaviourally relevant.

It appears that repeated stressful experiences during development can alter the balance of excitation and inhibition in the circuitry involved in both emotional control and reward, suggesting a structural change in the associated areas of the brain. Emotional control and self-regulation issues have been shown to arise from impaired prefrontal cortex function as a result of excess exposure to stress hormones. Also, prenatal exposure to maternal stress has been associated with a reduction in infants' gray matter in various brain regions, including the prefrontal cortex, premotor cortex, medial temporal lobe, and lateral temporal cortex\(^33\); increased white matter integrity in right frontal areas\(^34\); and cortical thinning in prefrontal areas of the right hemisphere\(^35\). Institutionalized children exposed to neglectful care have reduced brain volume in the amygdala, hippocampus, and corpus callosum\(^36\). In addition, impairments in the reward system may lead to inappropriate behavioural choices in situations of uncertainty or risk\(^37\).

Serve-and-Return as a Protective Factor

Serve-and-return is defined as a style of interaction in which parents respond appropriately (return) to their children's bids for attention (serves). Maternal caregiving characterized by healthy serve-and-return relationships may modulate the effects of toxic early stress on children\(^37\); indeed, stress is only considered toxic in the absence of supportive relationships\(^39\). However, much of our knowledge of the influence of maternal caregiving on DNA methylation and neuroanatomic development has been confined to non-human animal models. These studies have shown that rodent pups stressed by receiving low levels of maternal caregiving have increased DNA methylation in the hippocampus\(^40,41\) and have anterior hypothalamic nucleus differences\(^42\). For the most part, studies involving human children examined severe maternal deprivation or abuse, especially those in institutional settings\(^43\), which resulted in atypical brain structure and activity. It is important to note that smaller less extreme variations in early maternal caregiving can also underlie children's behaviour. For example, children experiencing low levels of maternal caregiving have higher HPA axis reactivity to stress\(^44\); and low levels of maternal sensitivity and responsiveness in mother–infant interactions have also been shown to predict frontal electroencephalogram (EEG) asymmetry, linked to more fearfulness of novelty and reduced attention in infants\(^45,46\). In contrast, studies among depressed mothers revealed that those who managed to maintain healthy serve-and-return
relationships with their infants predicted reduced levels of cortisol in the infants⁴⁷ – early evidence of the protective function of healthy relationships on children’s development.

**Conclusion**

An individual’s early experiences can have immense effects on their brain construction and behavioural outcomes. In particular, early exposure to toxic stress can impair brain connectivity and cause behavioural issues such as impaired executive function and altered sensitivity to rewarding situations. However, healthy serve-and-return relationships in childhood can protect an individual from the effects of toxic stress.
MULTIPLE-CHOICE QUESTIONS

1. Most human traits and diseases are derived from:
   a. genes
   b. experiences
   c. the interaction between genes and experiences
   d. the additive effects of genes and experiences

   answer

2. At approximately what age does the brain finish maturing?
   a. 16
   b. 20
   c. 25
   d. 30

   answer
3. Which developmental experiences have been associated with epigenetic modifications of gene expression?
   a. learning to read
   b. prenatal maternal stress
   c. winter storms
   d. prenatal paternal stress

4. Exposure to stress during development produces what effect?
   a. decreases in gray matter volume across multiple brain regions
   b. increases in gray matter volume in multiple brain regions
   c. impaired prefrontal cortex function
   d. a and c
Reflective Questions

1. Why is it important to routinely screen women for both prenatal and postpartum depression?

2. Studies have shown that children born to mothers who were pregnant during the Dutch famine of 1944-1945 show higher instances of obesity and metabolic disorders than the general population in adulthood. Based on the information you learned in this section, what biological processes do you think are at work here?
Podcasts

Core Concepts of Early Child Development

Podcast 2: Brain Architecture and Development
Podcast 3: Early Experiences and Gene Expression
Podcast 5: Positive, Tolerable and Toxic Stress
Podcast 6: Brain Plasticity and Behavioural Change

Addiction

Podcast 10: Early Trauma in Addiction

Short Video

Brain Builders Video

How Brains Are Built: Core Story of Brain Development

Further Reading


Virtual Patient Cases

The following virtual patient cases relate to the content in this section. To access, click on the titles.

Case of Ashley
Case of Miriam (Age 15)
AFMC Case 6 (Phil Age 32)
AFMC Case 7 (Bill Age 48)


2.1 Toxic Stress and Brain Development


35. Sandman CA, Buss C, Head K, Davis EP. Fetal exposure to maternal depressive symptoms is associated with cortical thickness in late childhood. Biological Psychiatry. 2015;77:324-34.


2.2 Concurrent Disorders

Learning Objectives

After completing this section, the learner will be able to:

1. Describe three biological mechanisms that can confer risk of developing concurrent disorders.
2. Explain how negative early life experiences contribute to trajectories of poor mental health outcomes in adolescence and adulthood.
3. Describe the common cognitive, social, and emotional factors that contribute to substance misuse and psychopathology.
4. Explain how substance misuse can increase the likelihood of developing a concurrent mood disorder.
5. Explain how mood disorders can increase the likelihood of developing a concurrent substance misuse disorder.

Introduction

Risk factors for addiction and other psychiatric illnesses are not limited to those that are heritable. Cognition, behaviour, and emotional regulation emerge from a complex interaction of genetic factors and environmental experiences. Traumatic early life experiences such as maltreatment, abuse, and neglect affect neuroendocrine, psychophysiological, and cognitive activities. These in turn increase vulnerability to psychopathology, including mood disorders, substance abuse, and personality pathology. This section provides an overview of the neurobiological factors that may confer risk for both addiction and mood and anxiety disorders, accounting in part for the high rates of co-morbidity between these conditions.

Neurobiological Risk Factors For Mental Health and Addiction

see Callout: Gene–Environment Interactions

HPA Axis Dysfunction

Early negative experiences are associated with disturbances of the hypothalamic–pituitary–adrenal (HPA) axis in people with major depressive disorder. In one study, women with early negative experiences and major depressive disorder had HPA axis profiles distinct from those of depressed women without early negative experiences. Elevated cerebrospinal fluid CRH
concentrations have also been found in people who have had multiple early negative experiences\textsuperscript{6}. Additionally, early negative experiences in animal models, in the form of repeated maternal separation, are associated with increased CRH mRNA expression in the hypothalamus, the locus coeruleus, and the amygdala\textsuperscript{7}.

Corticotropin-releasing hormone (CRH) also regulates drug-seeking behaviour. For example, the CRH system appears to be involved in stress-induced reinstatement of drug seeking for alcohol\textsuperscript{8}, cocaine\textsuperscript{9}, heroin\textsuperscript{10}, and nicotine\textsuperscript{11}. Studies have shown that CRH receptor antagonists reduce drug-taking behaviour in animal models of addiction\textsuperscript{12}, suggesting that modulating stress through modulation of CRH might be a way to decrease drug-seeking behaviour.

Early maternal deprivation is also linked to low levels of serotonin 1B receptor expression\textsuperscript{13}, decreased expression of gamma-aminobutyric acid (GABA) A receptors\textsuperscript{14}, and impaired dopamine transporter expression\textsuperscript{15}. These are further mechanisms through which early experiences and genetics interact to confer risk for mood, anxiety, and substance use disorders. Dopamine D2 receptors may also be important in regulating stress and drug-addiction-induced synaptic remodelling\textsuperscript{16}. Animals bred to have depression-like phenotypes have blunted mesolimbic dopamine signalling and abnormal patterns of psychostimulant self-administration\textsuperscript{17}. Hence, in addition to disruption of the stress system, disruption of dopamine systems may also be an important, but less thoroughly examined, link between mood and substance use disorders.

Increased Innate Immune Gene Expression

Negative affect, anxiety, and depression are all associated with increased innate immune gene expression. Given that chronic glucocorticoid elevation promotes nuclear factor-κB (NF-κB) proinflammatory transcription in the frontal cortex, this may be a molecular mechanism common to drug abuse and stress, which promotes common changes in neurobiology and parallels the long-lasting sequelae of addiction.

Cognitive and Emotional Development

Changes in neurobiological systems as a consequence of early adverse experience may also alter both cognitive function and emotional regulation in a way that increases vulnerability to addiction. Prefrontal cortex functions modulate activity in limbic structures to determine goal-directed behaviours, sensitivity to consequences, perception of social cues, and inhibition. As such, the development of the prefrontal–limbic circuitry, which underlies cognitive function and emotional regulation, may be particularly sensitive to early negative adversity\textsuperscript{18,19,20}.

Mood disorders, anxiety disorders, and addiction do not emerge at random in adults; neither is the high co-occurrence of these disorders due to chance. Rather, early adverse experiences in concert with heritable factors alter the brain and the behaviour (cognition, emotional regulation, and social interaction styles) of children from a young age. These alterations often create a vicious
cycle, one in which vulnerable neural networks and maladaptive behavioural styles result in poor academic performance or unstable relationships that then further contribute to a risk of addiction and other forms of psychopathology. In this way, we see that genetic vulnerability interacts with early life experiences to confer risk for mood and anxiety, as well as substance use disorders.

Early negative experiences are also associated with psychological difficulties in both the short- and long-term. Studies have shown that reactions to negative experiences involve the disruption of normal psychological development, painful emotions, and cognitive distortions\(^\text{21}\). For children with early negative experiences, we find chronic self-perceptions of helplessness and hopelessness, impaired trust, self-blame, and low self-esteem, as well as feelings of guilt and other dysfunctional and inaccurate attributions\(^\text{22,23}\). Resulting alterations in social functioning\(^\text{24}\) can include feeling less socially competent, more socially withdrawn, and more aggressive\(^\text{25}\), all of which are likely to add to the risk of addiction and other pathology.

Additionally, dysregulation of the stress system is common in mood, anxiety, and substance use disorders, and likely provides a common pathway through which genetic factors and early experience contribute to risk. Disturbances in other systems, such as the dopamine system and inflammatory pathways, may also be common to both conditions.

In adolescence or adulthood, proximate factors such as stress, trauma, and loss confer risk of mood and substance use disorders. And, once one of the illnesses is present, factors inherent to that illness will further increase the risk of the emergence of other disorders. For example, patients with low mood or symptoms of anxiety may attempt to self-medicate with illicit substances or with the excessive use of alcohol, both of which may have a depressogenic effect on the nervous system.

Heavy consumption of alcohol or substances during adolescence has been associated with an increased likelihood of experiencing a mood or anxiety disorder\(^\text{29}\). Co-morbid substance abuse disorders in people with mood disorders are associated with male gender, impulsive–aggressive traits, number of suicide attempts, and co-morbid conduct and Cluster B personality disorders\(^\text{30}\).

The presence of clinically significant personality features in adolescents and young adults has been described as a prodromal phase of illness in individuals with early-onset mood disorders\(^\text{26,27}\). Other illnesses, such as substance abuse, attention deficit hyperactivity disorder (ADHD), and anxiety disorders, occur concurrently in this group\(^\text{28}\).

From genetic vulnerability, through early life experience, adolescent development, and final expression of illness, we have seen that multiple factors link substance use disorders with mood and anxiety disorders. Hence, the presentation of a patient with concurrent mood and substance use disorders—which often looks complex and fragmented—is understandable within a coherent neurobiological framework.
Development of cognitive and emotional systems extends well beyond early childhood. Social reasoning ability, for example, undergoes an extended period of development from early childhood to adolescence\textsuperscript{31,32,33}. Adolescence is, however, a period characterized by marked changes in social relationships with peers and family\textsuperscript{34,35}, and alterations in social cognitive processes during this period of development can contribute to the onset of various disorders, such as mood or anxiety disorders and substance abuse disorders. Additionally, the development of mental illness or addiction during adolescence can alter or delay the development of social reasoning abilities.

**One Illness Conferring Risk of Another**

Sustained or regular use of drugs or alcohol can cause changes to neurobiology that can result in reduced attention, poor decision-making, increased impulsivity, anxiety, and dysphoria. These outcomes further contribute to a loss of behavioural control over the drug use. As frontal lobe executive function involves the ability to choose between helpful and harmful behaviours, to suppress unacceptable social responses, and to determine the relationship between events (cause and consequences), it would follow that any changes to the functionality of this area of the brain may have adverse consequences for the expression of these behaviours. It is not surprising then that reduced frontal–cortical executive behavioural control, increased impulsivity, and an inability to modulate the emotional response of the limbic system are apparent in both mood disorders and addiction. These features are likely why the presence of one disorder increases the likelihood of the other.
Reflective Questions

1. Describe two common biological pathways to developing either a mood disorder or a substance misuse disorder that are common to both.

2. Negative early life experiences can alter both neural circuits and behaviours. Describe how these two types of alterations can work together over time to increase the risk of developing either a substance misuse or mood disorder, or both.

3. If a person who is depressed chronically uses alcohol to self-medicate, what is the most likely long-term prognosis?
   a. relief from the depressive symptoms
   b. worsening of the depression
   c. development of a concurrent alcohol use disorder
   d. both b and c

4. Should patients with either a mood or substance misuse disorder be screened for a concurrent disorder? Why or why not?
Podcasts

Introduction

Podcast 1: The Neuro-Developmental Pathway Origins of Addiction

Core Concepts of Early Child Development

Podcast 3: Early Experiences and Gene Expression
Podcast 4: Building Cognitive, Emotional and Social Capacities
Podcast 5: Positive, Tolerable and Toxic Stress

Addiction

Podcast 10: Early Trauma in Addiction

Virtual Patient Cases

The following virtual patient cases relate to the content in this section. To access, click on the titles.

Alice in Slumberland
REFERENCES


12. Koob GF. The role of CRF and CRF-related peptides in the dark side of addiction. Brain Res. 2010 Feb 16;1314:3-14


2.2 Concurrent Disorders


2.2 Concurrent Disorders


Gene–Environment Interactions

Childhood stress may interact in complex ways with genetic variations to increase vulnerability to illness. Polymorphisms in gene coding for the serotonin transporter, the corticotropin-releasing hormone (CRH) receptor, the FK506-binding protein 5 (FKBP5), the serotonin-transporter-linked promoter region (5-HTTLPR), and brain-derived neurotrophic factor (BDNF) have all been implicated in stress-related disorders.3
Learning Objectives

After completing this section, the learner will be able to:

1. **Describe the basic methodology of the ACE Study.**
2. **List 10 different types of common adverse childhood experiences (ACEs).**
3. **List five different health outcomes that are associated with the presence of ACEs.**
4. **Explain the strong association between ACEs and later substance misuse.**

**Introduction**

Specific traumatic experiences, such as childhood physical or sexual abuse, childhood neglect, and combat exposure, can cause major long-term difficulties for survivors. However, only recently have we begun to understand the full physiological and psychological implications of trauma. In particular, studies of the effects of exposure to adverse childhood experiences (ACEs), or various traumatic events, have provided insight into the impact that such experiences can have on physiological and psychological functioning.

Studies have also shown the effect of trauma on an individual’s risk of developing a variety of chronic health conditions associated with high morbidity and mortality, including many of the leading causes of death in Canada. Some of the health problems linked to trauma exposure include addiction, mental illness, cancer, cardiovascular disease, cerebrovascular disease, respiratory illnesses, accident-proneness, chronic pain disorders, gastrointestinal problems, and an overall reduced health-related quality of life. Although many researchers have investigated this topic, for the purposes of this chapter we will focus on the methodology and findings of the Adverse Childhood Experiences (ACE) Study, one of the largest collaborative studies in this area.

**Background on the ACE Study**

The Adverse Childhood Experiences (ACE) Study is an ongoing collaborative effort between the U.S. Centers for Disease Control and Prevention (CDC) and the Kaiser Permanente Health Appraisal Center in San Diego, California. Participants in the study were first sent the ACE survey by mail between the years 1995 to 1997 after completing a standardized biopsychosocial medical exam at their primary care clinic. A total of 18,175 participants (68% of those contacted) were enrolled in the study after mailing back the completed survey. The survey included questions...
about the respondents’ history of physical and mental health problems and about health-related behaviours, such as the use of alcohol, tobacco, and other drugs, as well as sexual activity. Importantly, the researchers also asked a number of questions about childhood experiences, including sexual, physical, or emotional abuse; physical or emotional neglect; witnessing of domestic violence; parental divorce or separation; and household members who suffered from a mental illness, alcohol, or substance abuse, or who were incarcerated. The researchers then used this information to calculate a score for the respondent based on the number of these situations they had experienced.

ACE Score Calculation

An example of an ACE score calculation for a respondent whose father was an alcoholic, and who was physically and verbally abusive toward the respondent and her mother until her parents divorced, would be calculated as follows:

<table>
<thead>
<tr>
<th>Event</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her father abused alcohol.</td>
<td>1</td>
</tr>
<tr>
<td>Her father physically and verbally abused her.</td>
<td>2</td>
</tr>
<tr>
<td>She witnessed domestic violence.</td>
<td>1</td>
</tr>
<tr>
<td>Her parents were divorced.</td>
<td>1</td>
</tr>
</tbody>
</table>

Total ACE Score 5

ACE Study Design

Using a retrospective research design, the researchers examined the relationships between respondents’ ACE scores and various other physical and mental health problems and symptoms, as well as behaviours that increase the risk of developing health problems, all assessed through self-reporting. Using health records, the researchers also used a prospective, or longitudinal, design to track respondents’ health outcomes over time (hospital admissions, prescription records, emergency department visits, and outpatient visits).

ACE Study Findings: Connections with Adult Health and Psychological Function

From the results of the ACE study, investigators found that adverse childhood experiences are highly interconnected. As demonstrated below in Table 2.3-2, 78%–98% of respondents who indicated experiencing any one ACE category had also experienced at least one additional type of ACE. Of the various types of experiences, emotional abuse and domestic violence showed
the highest degree of overlap with other ACE categories, with 93%–98% of respondents who indicated these types of experiences also indicating one or more additional types of ACE\textsuperscript{18}.

Table 2.3-2: Prevalence of Each ACE Category and Report of Additional ACEs\textsuperscript{19}

<table>
<thead>
<tr>
<th>ACE Category</th>
<th>N</th>
<th>%</th>
<th>0</th>
<th>≥1</th>
<th>≥2</th>
<th>≥3</th>
<th>≥4</th>
<th>≥5</th>
<th>≥6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>878</td>
<td>10.2</td>
<td>2</td>
<td>98</td>
<td>77</td>
<td>62</td>
<td>42</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>2,275</td>
<td>26.4</td>
<td>17</td>
<td>83</td>
<td>64</td>
<td>46</td>
<td>32</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Sexual</td>
<td>1,812</td>
<td>21.0</td>
<td>22</td>
<td>78</td>
<td>58</td>
<td>42</td>
<td>29</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Neglect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>1,274</td>
<td>14.8</td>
<td>7</td>
<td>93</td>
<td>79</td>
<td>63</td>
<td>47</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>Physical</td>
<td>855</td>
<td>9.9</td>
<td>11</td>
<td>89</td>
<td>75</td>
<td>61</td>
<td>50</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>Household Dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental separation or divorce</td>
<td>1,125</td>
<td>13.0</td>
<td>18</td>
<td>82</td>
<td>61</td>
<td>43</td>
<td>30</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Household substance abuse</td>
<td>2,435</td>
<td>28.2</td>
<td>19</td>
<td>81</td>
<td>60</td>
<td>41</td>
<td>29</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Household mental illness</td>
<td>1,749</td>
<td>20.3</td>
<td>16</td>
<td>84</td>
<td>65</td>
<td>48</td>
<td>34</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Domestic violence</td>
<td>2,081</td>
<td>21.1</td>
<td>5</td>
<td>95</td>
<td>82</td>
<td>64</td>
<td>48</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Household crime</td>
<td>516</td>
<td>6.0</td>
<td>10</td>
<td>90</td>
<td>74</td>
<td>56</td>
<td>43</td>
<td>30</td>
<td>23</td>
</tr>
</tbody>
</table>


The individuals’ number of ACEs (as reflected by their ACE score) increased both their odds of engaging in a variety of health risk behaviours and their odds of developing psychological and physical health conditions. Nearly all of the measured outcomes showed a significant dose–response relationship – that is, the odds of having negative health outcomes increased with higher ACE scores\textsuperscript{19,20}. Some of the major outcomes significantly related to ACEs are listed below in Table 2.3-3.

Table 2.3-3: Major Findings of the ACE Study: Relationships of Adverse Childhood Experiences to Behavioural Risk Factors, Psychological Difficulties, and Health Conditions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Odds Ratio for ACE ≥4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addictive/Compulsive Behaviours</td>
<td></td>
</tr>
<tr>
<td>Alcoholism (self-reported)\textsuperscript{19}</td>
<td>7.2</td>
</tr>
<tr>
<td>Illicit drug use\textsuperscript{19}</td>
<td>4.5</td>
</tr>
<tr>
<td>Injected drug use\textsuperscript{19}</td>
<td>11.1</td>
</tr>
<tr>
<td>Sexual Risk Behaviours</td>
<td></td>
</tr>
<tr>
<td>≥30 intercourse partners\textsuperscript{19}</td>
<td>3.6</td>
</tr>
<tr>
<td>Smoking (nicotine), current\textsuperscript{19}</td>
<td>1.8</td>
</tr>
<tr>
<td>Mental Health Difficulties</td>
<td></td>
</tr>
<tr>
<td>Anxiety\textsuperscript{19}</td>
<td>2.4</td>
</tr>
<tr>
<td>Condition</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Autobiographical memory disturbance (cannot recall large parts of childhood)</td>
<td>4.4</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>3.6</td>
</tr>
<tr>
<td>Difficulty controlling anger</td>
<td>4.0</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2.7</td>
</tr>
<tr>
<td>Intimate partner violence perpetration</td>
<td>5.5</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>2.1</td>
</tr>
<tr>
<td>Suicide attempts during childhood/adolescence</td>
<td>11.9–50.7*</td>
</tr>
<tr>
<td>Suicide attempts during adulthood</td>
<td>3.8–29.8*</td>
</tr>
<tr>
<td>Increased Use of Psychotropic Medication</td>
<td></td>
</tr>
<tr>
<td>Antidepressant medication</td>
<td>2.4–2.9*</td>
</tr>
<tr>
<td>Anxiolytic (anti-anxiety) medication</td>
<td>1.6–2.1*</td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>4.8–10.3*</td>
</tr>
<tr>
<td>Lithium-based (bipolar/mood stabilizer)</td>
<td>8.4–17.3*</td>
</tr>
<tr>
<td>Health Risk Factors</td>
<td></td>
</tr>
<tr>
<td>Family history of premature death</td>
<td>1.8</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>1.3</td>
</tr>
<tr>
<td>Severe obesity (BMI ≥35)</td>
<td>1.9</td>
</tr>
<tr>
<td>Medical Conditions (Non-Psychiatric)</td>
<td></td>
</tr>
<tr>
<td>Cancer (all types)</td>
<td>1.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.6</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2.2</td>
</tr>
<tr>
<td>Hepatitis or jaundice</td>
<td>2.4</td>
</tr>
<tr>
<td>Lung disease</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.9–2.3*</td>
</tr>
<tr>
<td>Chronic bronchitis/emphysema</td>
<td>3.9</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2.5–3.2*</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.8–2.6*</td>
</tr>
<tr>
<td>Multiple somatic symptoms</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Note: Odds ratio of having specified condition for those with ACE score ≥4, compared to ACE score = 0 (after adjusting for age, sex, race, and educational attainment).

*The article reported more than five categories of ACE scores, so a range is reported.

Although all of the listed conditions were found to be associated with higher ACE scores, individuals who had experienced four or more ACEs were particularly likely to engage in impulsive or addictive behaviours. They were found to be 7.2 times as likely to describe themselves as an alcoholic, 4.5 times as likely to have used illicit drugs, and more than 11 times as likely to have injected drugs as compared to those without this history (results were adjusted for age, sex, socioeconomic status, and educational status). Even more pronounced, however, was the association between ACEs and suicide attempts (21). Compared to those with no history of
ACEs, individuals with two or more ACEs were more than six times as likely to have attempted suicide before the age of 18. Those with an ACE score ≥7 were more than fifty times as likely to have a history of attempting suicide during childhood or adolescence, and thirty times as likely to attempt suicide during adulthood – a lower likelihood than during childhood or adolescence, but still a high number (Figure 2.3-1).

Figure 2.3-1: Adjusted Odds Ratios of Having Attempted Suicide as a Child/Adolescent or as an Adult, Based on ACE Score

Note: All odds ratios are adjusted for age, sex, race, and educational attainment.


Although prospective designs may be able to use a relative risk ratio, the statistic reported may be expressed as an adjusted odds ratio based on the statistical tests used. The adjusted odds ratio is a measure of effect size used in binary logistic regression, a statistical analysis used to test the relationship of a set of variables to a binary (yes/no) outcome. An adjusted odds ratio indicates that other variables have already been controlled in the statistical model. In this case, age, sex, race, and educational attainment were part of the model, and therefore are factored out of the

2.3 Adverse Childhood Experiences: The ACE Study
reported odds ratio.

For more information on the difference between the odds ratio and the relative risk or risk ratio, this YouTube video provides a nice illustration of the mathematical difference between the two. For a more detailed explanation of odds ratio and relative risk, see Grimes and Schulz, 2008\textsuperscript{28}.

**Conclusion**

The landmark ACE Study revealed the strong association between childhood toxic stress and a wide spectrum of adult health problems, including addiction, depression, cancer, and heart disease. It also demonstrated that ACEs are remarkably common yet typically unrecognized by health practitioners. Early adopters have been using the ACE Questionnaire in practice: first to help identify which individuals have been affected by early toxic stress and to what degree, and second by using this information to guide treatment planning and break the intergenerational cycle of ACEs. Acting to identify, prevent and mitigate the effects of ACEs can help us get in front of the predictable health problems of tomorrow.
REFLECTIVE QUESTIONS

1. Why do ACEs tend to cluster in individuals?
2. Why is substance misuse so prevalent in people with ACE histories?
3. What other types of ACEs might be prevalent in your community/region?
PODCASTS

Introduction

Podcast 1: The Neuro-Developmental Pathway Origins of Addiction

Core Concepts of Early Child Development

Podcast 3: Early Experiences and Gene Expression
Podcast 4: Building Cognitive, Emotional and Social Capacities
Podcast 5: Positive, Tolerable and Toxic Stress

Addiction

Podcast 10: Early Trauma in Addiction

FURTHER READING


A full list of ACE study publications is located at the ACE Study website, through the U.S. Centers for Disease Control. www.cdc.gov/violenceprevention/acestudy/

VIRTUAL PATIENT CASES

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

Harriet Head Case
Polly Farmercie
Case of Miriam (Age 15)
Case of Miriam (Age 42)
AFMC Case 5 (Jake Age 15)


Calculate Your Own ACE Score

Prior to your 18th birthday:

1. Did a parent or other adult in the household often or very often...
   Swear at you, insult you, put you down, or humiliate you?
   or
   Act in a way that made you afraid that you might be physically hurt?
   Yes   No                   If yes enter 1    ________

2. Did a parent or other adult in the household often or very often...
   Push, grab, slap, or throw something at you?
   or
   Ever hit you so hard that you had marks or were injured?
   Yes   No                   If yes enter 1    ________

3. Did an adult or person at least 5 years older than you ever...
   Touch or fondle you or have you touch their body in a sexual way?
   or
   Attempt or actually have oral, anal, or vaginal intercourse with you?
   Yes   No                   If yes enter 1    ________

4. Did you often or very often feel that …
   No one in your family loved you or thought you were important or special?
   or
   Your family didn’t look out for each other, feel close to each other, or support each other?
   Yes   No                   If yes enter 1    ________

5. Did you often or very often feel that …
   You didn’t have enough to eat, had to wear dirty clothes, and had no one to protect you?
   or
   Your parents were too drunk or high to take care of you or take you to the doctor if you needed
6. Was a biological parent ever lost to you through divorced, abandonment, or other reason?
   Yes  No  If yes enter 1  

7. Was your mother or stepmother:
   Often or very often pushed, grabbed, slapped, or had something thrown at her?
   or
   Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard?
   or
   Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?
   Yes  No  If yes enter 1  

8. Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?
   Yes  No  If yes enter 1  

9. Was a household member depressed or mentally ill or did a household member attempt suicide?
   Yes  No  If yes enter 1  

10. Did a household member go to prison?
    Yes  No  If yes enter 1  

   Now add up your “Yes” answers:  
   This is your ACE Score.
2.4 Intergenerational Transmission of Addictive Behaviours

Ruth Lanius, Doris Payer, Mischa Tursich

Learning Objectives

After completing this section, the learner will be able to:

1. Describe the effect of family dysfunction on coping skills.
2. Describe the effect of family dysfunction on emotional regulation.
3. Describe the effect of family dysfunction on interpersonal skills.
4. Explain how addiction can be transmitted to the next generation through a combination of early adversity, family dysfunction, and skills deficits.

Introduction

As discussed throughout this primer, a variety of factors interact within a biopsychosocial framework to influence vulnerability to addictive disorders. In this section, we will provide a basic framework for understanding the complex interactions among psychological and social factors leading to psychological dysfunction and addictive behaviours in adulthood. This is not meant to be an exhaustive list of involved factors, nor is it meant to imply that each factor would be necessary to create difficulties later in life. Rather, this model is offered as a framework for understanding the complex nature of the factors involved in the transmission of vulnerability to addiction from one generation to the next; specifically, this section will focus on the means of transmission of psychological and behavioural risk factors for the development of dysfunction.

The Dysfunctional Family Environment and Adverse Childhood Experiences

Early life stress can come in a variety of forms that may be interrelated in complex ways. Adverse childhood experiences (ACEs) tend to cluster; individuals who experience one often also experience additional ACEs (see Chapter 2.3 Adverse Childhood Experiences: The ACE Study). This leads to the theoretical framework of the long-term effects of familial dysfunction and childhood abuse, which is illustrated in Figure 2.3-1. Individuals exposed to childhood abuse and neglect not only display attachment deficits (as discussed in Chapter 2.3) and specific PTSD symptoms related to incidents of abuse, but also often lack the basic skills for managing daily life stresses and challenges¹. These deficits may span a wide range of domains, including problems coping with and regulating emotions, and deficits in interpersonal, social, and instrumental skills (such as time management, organization, and financial management). In popular literature,
deficient family environments have been most closely associated with adult children of alcoholics, but it is clear that such familial dysfunction extends more broadly. Multiple aspects of family functioning have been found to influence relative resilience or risk for negative mental health outcomes following childhood abuse and maltreatment\textsuperscript{2,3}.

**The Role of Attachment in Child Development**

The term *attachment* is generally used to refer to the relational bond between a child and his or her primary caretaker(s). According to psychiatrist and psychoanalyst John Bowlby, the intact attachment behavioural system consists of behaviours that promote the child’s proximity to his or her attachment figure, and of fear responses to threatening stimuli that produce further contact-seeking behaviours\textsuperscript{1,2}. Although the attachment system primarily orients the infant towards a single attachment figure within the first six to nine months of life, children can and do form multiple meaningful attachment relationships under various circumstances.

From behaviours exhibited during The Strange Situation Paradigm, infants can be classified into one of four attachment types:

- insecure avoidant (Group A)
- secure attachment (Group B)
- insecure ambivalent/resistant (Group C)
- insecure disorganized/disoriented (Group D)

These classifications are based on the infant’s observed behaviours, whether the infant maintained a close proximity to and contact with the parent, avoided the parent, or resisted the parent. In general, secure attachment (Group B) infants seek and attempt to maintain closeness with their parents, particularly when reunited after the separation episodes. Infants in the insecure avoidant (Group A) group display a lack of proximity-seeking or contact-maintaining behaviours toward their parents, and, while often showing avoidant behaviours such as turning away, they do not display active resistance behaviours. The insecure ambivalent/resistant (Group C) infants, on the other hand, display actively resistant or angry behaviours toward their parents and, often, toward the stranger. However, these infants also attempt to seek closeness to the parent, resulting in an overall appearance of ambivalence. Lastly, the insecure disorganized/disoriented classification (Group D), later described by Main and Solomon\textsuperscript{11}, demonstrates an attachment strategy characterized by contradictory and disintegrated infant behaviours during The Strange Situation Paradigm.
Attachment and Parental Sensitivity

In general, attachment classifications are associated with levels of maternal sensitivity. Whereas mothers who display appropriate responses to infant behaviours are associated with secure attachment, intrusive or insufficient maternal responses are associated with avoidant or ambivalent/resistant attachment patterns in infants. For example, Smith and Pederson, when describing maternal responses to infant cries during a divided-attention task, reported that the mothers of secure attachment infants (Group B) took time away from their questionnaire to soothe their infants. In contrast, the mothers of insecure ambivalent/resistant infants (Group C) tended to react passively and “seemed quite helpless to do anything” to soothe their infants. The behaviour displayed by mothers of insecure avoidant infants (Group A) was found to be somewhat more active than the mothers of insecure ambivalent/resistant (Group C) infants, but less responsive than mothers of secure attachment infants (Group B).

The insecure disorganized/disoriented (Group D) classification, on the other hand, is related to more obviously dysfunctional maternal behaviours, including “frightened or frightening” behaviours, contradictory or conflicting responses to the infant, and other unbalanced mother–infant relational patterns. Lyons-Ruth and colleagues described several examples of such patterns, including dominant–submissive parenting, in which “the parent coercively opposes and counters the initiatives of the child”; unresponsive parenting, in which the parent appears withdrawn and helpless to respond effectively to the child; and parenting responses to the child’s needs based primarily in attempts to meet the parent’s own needs (for example, a depressed parent having difficulty modulating her own emotional state).

Insecure attachment, and particularly the insecure disorganized/disoriented (Group D) classification, has also been associated with increased physiological sensitivity (such as heightened cortisol response to stressful situations), with both internalizing (depression, anxiety) and externalizing (acting-out) behaviours later in childhood, and with disintegrated mental processes in adulthood. Disorganized attachment appears to be one mechanism for the observed intergenerational transmission of trauma-related difficulties, and may lead to a perpetuation of the disrupted attachment cycle, with or without traumatic life experiences.

Inadequate Transmission of Living Skills

One of the essential functions of parents and caregivers is to provide children with the skills necessary to manage everyday life, to solve problems, to learn from their experiences, and to develop skill sets to manage increasing levels of environmental and social complexity. Perhaps the most fundamental of these skills is the capacity to recognize and self-regulate emotional states.
Self-Regulation of Emotion and Coping Strategies

This capacity is transmitted through a variety of mechanisms, including external regulation of the child’s autonomic arousal through attachment figures, attuned identification of the child’s emotional states, and modelling of effective coping strategies. Over time, children begin to internalize these capacities for physiological and psychological affect regulation, or emotional regulation, and the role of the attachment figure becomes less prominent. In many ineffective families, however, parents may be unaware or too absorbed in their own emotional states to accurately identify and regulate their child’s affective states. This, in turn, may result in poor emotional awareness (alexithymia), emotional numbing, and/or rapidly shifting intense emotional states (Figure 2.4-1). In addition, many adults within such families, rather than modelling effective coping strategies, instead use maladaptive coping mechanisms, including addictive and compulsive behaviours. Consequently, rather than learning competent self-regulation, children in such families may instead feel that they are helpless to control their emotions and may seek to regulate them through self-destructive, addictive, or compulsive behaviours.

Basic Instrumental Skills and Interpersonal Skills

In addition to helping children develop affect (emotion) regulation strategies, parents also provide children with a variety of basic skills needed to function as an adult, including basic instrumental skills (how to manage money, complete homework assignments and projects, and so on) and interpersonal skills. Parents with significant emotion regulation difficulties, psychological disorders, and/or addictions may have difficulty even meeting their own basic needs, thus providing inconsistent modelling of daily living skills for their children.

Interpersonal Skills

Additionally, parents who have substantial social skills deficits may be unable to provide their children with the interpersonal skills necessary for forming and maintaining healthy interpersonal relationships. In addition, in some abusive or neglectful homes, association with individuals outside of the family may be explicitly or implicitly discouraged, or children may be strategically isolated from outside influences. As such, these children may have reduced opportunities for remedial skills training from external sources, such as teachers, coaches, and friends. As a result of these various skills deficits and emotional dysregulation, these children become increasingly vulnerable to abuse by both intra-familial and extra-familial perpetrators. If they do experience traumatic events, they are also at a higher risk for significant psychological and physiological difficulties due to their existing physiological vulnerabilities, emotion regulation and skills deficits, and social isolation. This results in an even higher likelihood of having substantial psychological impairments in adulthood, as illustrated in Figure 2.4-1.
2.4 Intergenerational Transmission of Addictive Behaviours

**Effects on Adult Psychological and Behavioural Functioning**

The most important concept to keep in mind is that addictive and compulsive behaviours are often an attempted solution to problems that have been decades in the making. Adverse childhood experiences coupled with a lack of parental support to learn coping, self-regulation, and other life skills can set individuals on life course trajectories that elevate risk for developing an addiction or other mental health problem. Whether it is alcohol, illicit drugs, gambling, or eating, these behaviours often represent maladaptive attempts to self-soothe and manage emotions because
they can provide quick relief from subjectively uncomfortable experiences despite the fact that they create additional problems in the long term.

In this primer, Chapter 1.1 Neurobiology of Addiction, and Chapter 1.2 Neurochemistry of Process Addictions, cover these strategies in further detail.
Reflective Question

Individuals who grow up in dysfunctional families often miss out on opportunities to learn adaptive coping skills, emotional regulation, and interpersonal skills from their own parents, either because the parents are focused on their own issues or because the parents lack skills themselves. What does this suggest about the goals of treatment for individuals with addiction?
PODCASTS

Core Concepts of Early Child Development

Podcast 4: Building Cognitive, Emotional and Social Capacities
Podcast 5: Positive, Tolerable and Toxic Stress

VIRTUAL PATIENT CASES

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

A Short Introduction to Addiction as a Family Disease: Miriam and Family
REFERENCES


2.4 Intergenerational Transmission of Addictive Behaviours


In the 1960s, developmental psychologist Mary Ainsworth, a contemporary of Bowlby’s, began to systematize the study of mother–infant attachment through close observation of the behaviour exhibited by mothers and their infants, aged 1 to 24 months. Much of this research has focused specifically on mother–infant attachment, although several recent studies have addressed father–infant attachment patterns as well. [For more information, see the 2010 paper by Lamb and Lewis21]. Through these observations, Ainsworth and her colleagues developed The Strange Situation Paradigm9–11, a systematic laboratory procedure designed to elicit exploration and contact-seeking behaviours in one-year-old infants.

The Strange Situation Paradigm consists of the following eight “episodes,” designed to elicit exploratory and proximity-seeking behaviours in one-year-old infants9:

1. The parent and infant are brought to a room that holds a variety of toys. The procedure is videotaped and observed from an adjacent room through a one-way glass.
2. The parent and infant are then left alone in the room. The infant explores the room while the parent looks through a magazine.
3. A stranger enters the room and begins to play with the infant.
4. The parent leaves the room while the stranger remains in the room with the infant (first separation).
5. The parent enters the room and the stranger leaves (first reunion).
6. The parent exits, and the infant is left alone in the room (second separation).
7. The stranger enters the room again and is alone with the infant.
8. The parent enters the room and the stranger leaves (second reunion).
2.5 Adolescent and Young Adult Triggers for Substance Misuse

Learning Objectives

After completing this section, the learner will be able to:

1. Describe five different psychosocial factors that can increase the risk for substance misuse in youth.
2. Explain ways to promote healthy self-esteem and youth connectedness to family, school, and community.
3. Understand the role of peer pressure and identity in adolescent development and risk for substance misuse.

Introduction

As illustrated throughout this primer, substance use is a complex issue. Through solid research, however, some themes are becoming clearer, such as the role of genetics, the role of early life experiences, and the relevance of maltreatment and trauma.

Despite all of this information, there are also people with no clear risk factors who experiment with substances or develop substance use disorders. Their genetic histories may be unremarkable, their early life full of nurturance and affection, and their development healthy. Yet, there are factors known to contribute to substance use in otherwise healthy individuals.

In this section, we will consider several of these factors: normal experimentation, self-esteem, (dis)connectedness, peer pressure, and identity issues.

see Case Study: Jake and Chen

Normal Experimentation: An Ontario Model

Research has consistently demonstrated that adolescence is a time of joy, delight, and success. This is a far cry from the myth of adolescence as a time of angst, disconnect, angry rebellion, and dangerous experimentation. The Ontario Student Drug Use and Health Survey (OSDUHS) is the longest ongoing school survey of adolescents in Canada. It has been collecting data since 1977 and guides our understanding of population-level behaviour amongst students in grades 7 through 12.
The OSDUHS data suggests that drug use was at a peak in the late 1970s, declined during the late 1980s and early 1990s, peaked again in the late 1990s and early 2000s, and has been falling steadily ever since. This decrease has been seen across all drug classes with the exception of cannabis and inhalants (which have shown an increased use) and heroin (which has shown a negligible and stable pattern of use).

Thirty-three percent of students report using no substances at all during the past year, with percentages decreasing as they progress through high school (57% of grade 7 students; 16% of 12th graders). Thirteen percent of students report symptoms of substance use problems on average, with 22% of grade 12 students reporting such symptoms. One percent of students report being in a treatment program in the past year.

Rates of early initiation of substances are also falling across all drug classes with the exception of cannabis. Perceived risk and disapproval associated with regular drug use is also rising, in particular for cocaine, ecstasy, smoking, and binge drinking. Additionally, access to drug use is also reported as becoming more difficult.

Thus, a few reasonable conclusions can be made:

• It is within our current framework of North American adolescent development to observe experimentation with substances.
• Rates of early initiation of experimentation have been falling consistently for many years.
• Adolescents are increasingly concerned with the risks associated with substance use.
• Access to substances is becoming increasingly difficult.

**Self-esteem**

Low self-esteem has been identified as one of the most relevant risk factors associated with youth developing substance use disorders later in life. Self-esteem is a term used to describe how individuals feel about their own worth, how they assess and judge themselves as an individual and as a member of society, and how they identify aspects of their self that promote resiliency. Low self-esteem is associated with a number of complicating factors: negative and distorted self-cognitions; limited confidence; reduced ability to manage stress; and limited interpersonal, occupational, and social success.

Promoting self-esteem isn’t complicated but it can be made difficult in families and communities dealing with distress and strain. Parents and caregivers can have tremendous positive impact on their children by treating them with respect, listening to them, nurturing and acknowledging their successes, and appropriately managing their failures.

Without a strong sense of self-worth, an individual may have little motivation or intent to protect him- or herself. When tempted to make choices associated with risk, people with low
self-esteem may feel that they have little of worth to lose. Thus, many community programs offer supports and services designed specifically to help people enhance their sense of self-worth. Community recreational services, such as sports or arts, help people harness their undiscovered talents. Education and training programs can sharpen the mind and enhance abilities. Therapy offers insights and skills to challenge negative and self-defeating thoughts and feelings. And, of course, the simple act of being involved in group activities and programs enhances social competence and skills.

(DIS)Connectedness

Connectedness is a term that speaks to the degree to which people feel bonded, attached, or related to others. For example, children are connected to their parents when they feel understood, nurtured, and cared for by them. Youth feel connected to their schools when they believe they are personally cared for by their peers and teachers. This naturally extends to community connectedness; feeling connected to a social network is developmentally appropriate—and necessary.

Fostering connectedness isn't complicated. Ensuring that youth have a voice and a role in the decisions that affect them is one way to create a sense of connectedness. Being actively engaged in activities that promote the identity of the family, school, or community also brings value.

Yet, connection is easy to fray and fracture. Dismissed children can grow into youth who dismiss others. Schools that fail to meet the needs of individual children and youth may promote disenfranchised and underprepared graduates. Communities that choose not to include the innovation and perspectives of their children may find themselves having to deal with the natural consequences of alienated and disaffected youth. Endless hours of being plugged into electronic devices, often with themes of violence, erode social skills and social engagement. And for some teenagers and adults, over-involvement with social media can promote a sense of superficiality, perfectionism, and shallowness that comes at a cost of real human friendship.

For some disconnected people, drug use and drug culture can bring with it a sense of identity, social connectedness, and even community. For children, youth, and adults who feel barely tolerated at home, ineffective at school or work, and unsupported by their neighbourhood, the temptation to connect to any other social substrate can be seductive.

Peer Pressure

Social motivation is one of the most powerful forces influencing human behaviour. Peer conformity is a normal part of adolescent development and brings with it a number of challenges and benefits. On the challenging side, youth vulnerable to the influence of negative peer pressure show higher rates of involvement in risky activities, including substance use. On the beneficial side, not all peer pressure is negative. Youth leadership, empowerment, and advocacy can be harnessed to encourage prosocial and healthy behaviours.
For many, however, choosing healthy behaviours isn’t easy. The “just say no” campaigns associated with the war on drugs in the 1980s often fell on deaf ears⁶. Saying “no” is difficult and requires concrete and actual skills; and negative peer pressure is best managed when youth and adults have skills to do so. Critical appraisal skills, problem-solving skills, willingness to seek assistance from others, and assertiveness skills can help youth and adults resist strong peer pressure to use substances.

**Identity Issues**

The development of identity is a classically described task of adolescence. Dr. Erik Erikson, a famous psychologist, described this phase of normal development as “identity achievement versus identity diffusion.” This phase, typically occurring in adolescence, perceives youth as contemplating their connection to society in ways aligned to their gender, their sexuality, their values, their academic and occupational pathways, and their relationships with others⁷.

Contemporary researchers suggest that two dimensions—commitment and exploration—further illustrate identity development⁸ and complement Erikson’s theory. That is, youth and adults who are high in both dimensions achieve a sense of strong identity, whereas those who are low in both experience a sense of diffused identity.

For some, identity issues can be a threat to resiliency. For example, youth who are struggling with their sexual identity, such as youth with unclear heterosexual, homosexual, bisexual, or transgendered identities, are 190% more likely than heterosexual youth to experiment with substances⁹.

For others, having a diffused identity can contribute to trying on the identities of others either as part of normal exploration or as part of unhealthy interpersonal relationships. As an example, relationships that focus on the needs of others at the expense of the self can lead to an inability to tolerate being independent or alone, can erode one’s sense of worth or competence, and can lead to an increased vulnerability to substance use problems.

[see Case Studies: Jake and Chen prognosis]
Reflective Questions

1. What are some of the challenges faced in preventing substance use disorders in the absence of known biological or psychological risk factors?

2. What can families, schools, and communities do to promote resiliency factors amongst children and youth?

3. How might treatment services for vulnerable populations, such as youth struggling with identity issues, be best designed to promote access and success?

Virtual Patient Cases

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

Case of Miriam (Age 15)
Agitated Adam
Boxer Bruce
Joan is Worried
AFMC Case 5 (Jake Age 15)


Additional Material

» CASE STUDY

Jake and Chen

Jake
Jake is a 16-year-old high school student. He has done well both academically and socially, is well liked, respected, and involved in his family, sports, and church. He has no history, nor does his immediate family, of any genetic or environmental risk factors for mental health problems or substance use disorders.

Jake has tried marijuana a few times socially but didn’t find that it offered much in the way of pleasure or enjoyment. A few months ago, a friend introduced him to a joint mixed with cocaine at which point Jake stopped using pot and started to use cocaine regularly. Over a matter of weeks, his use quickly escalated and he is now using upwards of 15–20 times a week.

To the shock of his parents, friends, and pastor, he has just been arrested for possession and intent to traffic. Collectively, they wonder how such a “good kid” ended up making such “bad” choices.

Chen
Chen is a 22-year-old second-year university student. She has consistently enjoyed success in her life to date, has her heart set on a medical career, and often thinks about rural family medicine.

This particular year, however, has been quite challenging for her. Her boyfriend of three years told her that he had fallen in love with another woman and then moved out of their apartment. Left with a lease that she cannot afford, she took on additional hours at work to make ends meet. As a result, her grades have suffered and she has found herself frustrated, irritable, and heartbroken.

Her best friend offered her a lot of support, typically over drinks at a campus pub. Soon, Chen found herself enjoying five or six standard drinks a day, with more on the weekends. She finds that she likes how the alcohol makes her feel.

Six months later, she was fired from work for being late, rude to customers, and irritable with co-workers. She is also failing most of her courses, largely due to incomplete work.
Jake and Chen prognosis

Jake

Jake is, in many ways, living the unanticipated consequences of normal experimentation. There are very few biological risk factors in his case and not many psychological variables either. Simply put, he experimented with a powerful substance and quickly developed a substance use disorder.

His prognosis, however, is excellent. He has multiple factors associated with resiliency, such as a strong connection to family and community, high intelligence, good physical health, a high degree of motivation, and access to treatment services. He is able to move through acute assessment and treatment phases without complication.

Chen

Chen is at a pivotal stage of her identity development. Like Jake, she does not have any known biological risk factors. However, she does have some psychological factors related to her identity, self-worth, and connection to others.

Chen reaches out for and accepts counselling. Over the course of a year of therapy she begins to appreciate some of the identity and connectedness issues that have contributed to her difficulties, particularly with her intimate relationships and career motivations. She returns to work with the support of her family, begins to date again but is more mindful of her own wants and needs, and eventually returns to university.
3. Social Factors in Addiction

Identifying and Addressing Determinants of Health

Medical and non-medical risk factors contribute to, and even determine, an individual’s health status. While one cannot predict outcomes due to the complex interplay of mitigating factors, the opportunities for intervention, the impact of the social and physical environment, and the role of innate resiliency, one can predict the likelihood of more significant challenges. The medical, or biological, factors, including genes, gender, and innate resiliency or immunity, are impacted by the environment, particularly in early childhood when an individual is less able to exert influence over the stressors being imposed upon them (see Chapter 2.4 Intergenerational Transmission of Addictive Behaviours). The non-medical factors, or social factors, that impact an individual’s health are also highly complex, interwoven, and difficult to measure. Organizations, agencies, and governments working to address these factors have created a framework of key non-medical factors that together function to determine an individual’s health status. These factors or conditions, called the determinants of health, are considered the primary influences on health inequity according to the World Health Organization (WHO). The WHO defines these social determinants as “the conditions in which people are born, grow, live, work, and age, including the health system”¹. This chapter will explore a number of issues related to the social determinants of health.

While the specific determinants vary depending on the organization, agency, or government, some factors are commonly included. The Association of Faculties of Medicine of Canada (AFMC) includes the following²:

- education and literacy
- social support networks
- socio-economic status
- physical environment
- individual and public health services
- gender
- culture

Both on their own and in combination, each determinant can significantly shape and affect an individual’s addiction risks and cycles. Physicians play an important role in both the social and biological determinants of health. While the vast majority of their training is directed towards the biological, physicians are also perceived as community leaders due to their unique knowledge and
influential role. Their contributions are important not only in the health care system but also at the community and societal levels as advocates for improvements to social and physical environments and promoting access to care, particularly for the marginalized. In fact, the social accountability of physicians is an increasingly important discourse in medical education. As indicated by the illustration below, more is sometimes needed by those who have less in order for them to enjoy the same benefits from society.

![Figure 3-1](image)

**Addiction and Early Childhood**

Addictive behaviours may first emerge in childhood, or in some cases may not be triggered until later in life. A life course perspective of addiction development indicates that the conditions and behaviours that increase the likelihood of addiction can be traced back through early childhood development and sometimes even further back to parental behaviour before conception and during pregnancy. Prenatal, postnatal, and early childhood physical, mental, and social development all effect an individual’s brain architecture as well as stress, resilience, and coping mechanisms across the lifespan. (See also Chapter 2.3 Adverse Childhood Experiences: The ACE Study.)

**Social and Economic Factors and Addiction**

Social and socio-economic status indicators (SES) are understood as the social and economic status of an individual, family, or group with respect to others in the population. Identifying or measuring SES often involves an examination of an individual’s education, income, and occupation.
while social status is determined by a much broader range of attributes, from education, income, and occupation to personality, lifestyle, and culture.

Social status and socio-economic status act as strong determinants of addiction. Earning an income that is inadequate to meeting basic needs such as food, housing, education, transportation, and healthcare forces an individual to live in a context of crisis where they are unable to make decisions freely to support their physical and mental health. Barriers may also exist to an individual’s development of their ability to change the circumstances in which they live through education, vocational training, and work. When social status results in a lack of social connection, bonding, and respect from others, the result for the individual is a context of isolation.

With social and socio-economic status acting as barriers to social and economic integration, an individual can develop feelings of stress, shame, hopelessness, desperation, and anger, which can lead to acute and cyclical addiction. These barriers can also reduce the likelihood of accessing treatment or other support resources.

Conversely, elevated socio-economic status can also play a role in the development of an addiction. The stress of work, the perceived need to consume and display material wealth, the need for disposable income to purchase substances or to gamble, and the sense of entitlement that comes from working both hard and successfully may drive an individual towards increased substance use. These individuals may be high-functioning in the work world, as evidenced by their success, and may have the social capital to hide escalating levels of use. They may consume less in a sitting but on a more regular basis, for a higher level of consumption overall\(^5\)\(^-\)\(^7\). Eventually however, with tolerance, daily levels also escalate. Nevertheless, the home is where things first begin to unravel and many so-called “high-functioning users” are already experiencing negative consequences. It is simply a matter of time before the work domain is impacted if the substance use continues or escalates. Additionally, youth who have not experienced the adversity of poverty or neglect may develop a substance use disorder simply through prolonged and peer-reinforced consumption in a progressive pattern of escalating use. These complex and sometimes contradictory patterns will be explored in this chapter through the lens of different substances.

We will next look at the social and economic factors and specific addictions.

Social and Economic Factors in Addiction: Alcohol

The relationship between socio-economic status and alcohol consumption is complex. Low SES has been associated with binge drinking, alcohol abuse, and alcohol dependence\(^5\)\(^-\)\(^7\). By contrast, high SES has been associated with being a current drinker and higher overall consumption, but with lower levels of alcohol consumed per drinking occasion\(^5\)\(^,\)\(^8\)\(^,\)\(^9\). Socio-economic status plays a role in the development of an addiction, but simplistic assumptions based purely on socio-economic status often miss the complexity of risk and the range of issues that need to be addressed in recovery.
Social and Economic Factors in Addiction: Tobacco

Social and economic factors have always played an important role in the use of tobacco. In most industrial societies, smoking is increasingly concentrated amongst the socio-economically disadvantaged\(^{10-17}\). And while smoking rates have been falling in the developed world, these reductions have been slower amongst disadvantaged smokers, and these inequalities in smoking rates have increased in recent years\(^{18}\).

Several researchers have pointed out that addressing the socio-economic status gap in smoking with cohort-focused anti-smoking campaigns is essential in order to reduce the prevalence of smoking at a population level\(^{11,18}\). It is also important to address the divergence in smoking prevalence as it leads to health inequalities\(^{19}\).

Social and Economic Factors in Addiction: Gambling

Research has shown that several groups have been affected disproportionately by problem gambling, including the following:

- **People living in poverty**: Researchers have found that people living in poverty are more likely to spend a higher proportion of their household income on gambling than those living in higher-income households\(^{20}\).
- **New Canadians**: Recent immigrants are more likely to experience unemployment and underemployment, which can lead to poverty and increased financial risk-taking. Newcomers may also experience high levels of social isolation, which can contribute to problem gambling\(^{20}\).
- **Seniors**: Seniors are more likely than other population groups to live on fixed incomes and accumulated savings. In this case, problem gamblers can cause long-term financial harm by gambling more than they can afford. Older people also have less time to recover from the adverse consequences of problem gambling and are less likely than other adults to seek treatment\(^{21,22}\).
- **Young people**: This population group also tends to rely on fixed incomes and may miscalculate gambling odds.

These contextual factors create challenges in identifying “low-risk” gambling levels. The Canadian Centre on Substance Abuse is currently engaged with researchers to develop guidelines, such as the national Low-Risk Alcohol Drinking Guidelines, to inform the public on reasonable limits. Clearly they will correlate, at some level, with disposable income.

Social and Economic Factors in Addiction: Poverty, Education, Literacy

Education and literacy are also impacted by an individual’s socio-economic position and context. Children growing up in households limited by social and economic constraints may have restricted
access to education and fewer learning supports outside of the classroom (such as adequate nutrition or help with homework) relative to children in wealthier or more socially integrated families. These early limits to education can later limit access to higher education and career opportunities. This can create long-term financial and social stressors that can lead to addiction as a coping mechanism and to a reduction in treatment-seeking behaviour.

Limited education can also create struggles with literacy, comprehension, and communication for an individual, and act as a barrier to full access to the healthcare system and direct patient care. As a result, early signs of addiction, active addiction, and addiction cycles may go unacknowledged and untreated and may worsen over time.

Social and Economic Factors in Addiction: Social Inclusion, Support

Social inclusion is both a feature of daily life and necessary for good health. It involves interacting positively with others, participating in social activities, and being recognized and welcomed as part of a group. Social inclusion also involves having access to the support and care provided by others when facing challenges and stressors in life.

Social exclusion can lead to feelings of isolation, hopelessness, anger, and shame. Exclusion can be a factor not only at the individual level but also at the community or population group level, especially when there are negative perceptions about income disparities, social inequalities, and cultural or ethnic differences.

Without the benefits of social support from others in order to cope with the challenges and stressors of life, and with exclusion itself posing a challenge, addiction can come to be perceived as a support. When care from others is lacking, the benefit of their knowledge and competency in navigating the healthcare system in order to find support and to access treatment is also missing. It is not surprising to find higher rates of substance misuse amongst the most marginalized and stressed segments of the population, regardless of their social, racial, or religious background.

The Role of Social Support Networks

Networks play an important role in several of the pathways to addiction, including initiating and maintaining substance use, accessing treatment, remaining in treatment; and participating in post-treatment recovery and staying sober. One of the most consistent predictors of substance use is whether friends or peers engage in substance use. Peer influences on substance use may refer to both perceptions of actual use by peers as well as more general perceptions of social norms that are supportive of substance use.

It is particularly challenging in adolescence to escape the influence of problematic peers and cyclical heavy substance use. A change in an individual's social milieu is typically required in order to move out of that phase. Similarly, adults must also change the social dynamic around their
substance use in order to navigate triggers and avoid relapse. The difficulty becomes compounded when an individual becomes immersed in a substance use subculture, or perhaps trapped in an extended family of users. In such cases, alternative social supports and specific strategies to negotiate both relationships and use must be developed if the individual is to succeed.

**Employment, Working Conditions, Occupational Health, and Addiction**

Many aspects of work can affect an individual’s physical and mental health, including job security, physical conditions, stress levels, hours, and expression of self-identity. Jobs with high stress levels can lead to depression and anxiety, and lack of control in meeting job demands is often related to strain at work. When work injuries occur, they often go unreported, which can add to the stress of an injured employee.

An employee with unreported injuries and feelings of high stress, little control, or vulnerability, may cope with these feelings through substance use. Conversely, an employee already living with addiction may be more likely to struggle with these feelings.

Finally, the workplace culture may reinforce unhealthy substance use. Typical patterns include alcohol at business meetings or lunch, substance use in the workplace, or heavy episodic use after a day or week of work. These patterns, coupled with greater business concern over mental health and addiction issues and their related costs, create an opportunity for workplace programs and interventions.

**Environment and Addiction**

Research has shown that one’s environment plays an important role in addiction. Theories of stress and coping suggest that exposure to stressors such as neighbourhood disadvantage can deplete an individual’s coping resources, which can lead to substance use in response to stress or strain. Other features of disadvantaged neighbourhoods that may place residents at risk of substance use include the targeted marketing of alcohol and the prevalence of drug-related crime.

In the case of tobacco use, perceived neighbourhood problems and low neighbourhood safety ratings have been associated with increased smoking prevalence. Mistrust among neighbours has been associated with both smoking prevalence and the number of cigarettes smoked per day. Other researchers have pointed out that there is both a greater density of tobacco retail outlets and more tobacco advertising in lower socio-economic status neighbourhoods. Additionally, tobacco retail outlet density has been associated with the number of cigarettes consumed per day among smokers in at least one prior study.
3. Social Factors in Addiction

**Gender and Addiction**

Researchers have pointed out that, “gender relations of power constitute the root causes of gender inequality and are among the most influential of the social determinants of health. They determine whether people’s health needs are acknowledged, whether they have a voice or a modicum of control over their lives and health, whether they can realize their rights”45.

Addiction is gendered in that it is affected by the different societal roles and expectations attributed to women and men. The roles interact with sex and other determinants of health to influence both addiction patterns and the harm associated with use, as well as the medical and social responses in the forms of policies and programs46. Across all age groups, Canadian women are more likely to live in lower-income households than men. This is due in part to a combination of wage inequity, the large number of female single parents with inadequate income and social support, and elderly women left widowed and alone. Further, there is also evidence that women are likely to encounter more barriers than men with respect to accessing and entering treatment47. For example, treatment beds are more likely to be dedicated as male rather than female due to the larger number of males seeking treatment. There is also the challenge of childcare and the lack of both trauma-informed and gender-specific treatment. Additionally, women are at greater risk for interpersonal victimization, including childhood abuse, sexual abuse, and intimate partner violence. Substance use problems frequently occur among women who are survivors of violence, trauma, and abuse, often in complex, indirect, and mutually reinforcing ways48.

Until the past few decades, addiction was considered to be primarily an issue for men, with addiction and treatment research conducted primarily with male participants. However, more recent studies of gendered addiction show that addiction in women involves gender-specific features and treatment for women involves gender-specific challenges47. In Highs and Lows: Canadian Perspectives on Women and Substance Use46, it is well documented that there are different profiles of use and appropriate treatments among women depending on age, ability, social status, economic status, and geographic or cultural location. Because these trends can have an impact on policies and programs, and even today much of the data is not examined using a gender-based analysis, much could be learned by analyzing data to look for evidence of sex differences and gender influences on addictions.

**Gender and Gambling in Canada**

In the past, legal constraints and social norms deterred women from gambling, as gambling activities typically took place in the illegal and/or male-dominated areas of dog- and horse-racing, card playing, and sports betting49. However, the legalization and the proliferation of gambling activities have made gambling both widely accessible and socially acceptable to women. While estimates suggest that at least one-third of gamblers are now female, an increasing proportion of women have been reporting their own gambling addictions50-52. Despite the evidence that
women’s gambling has become widespread and problematic, female problem gamblers remain poorly understood and under-represented in research, literature, and treatment.

**Culture and Addiction**

There are cultural differences in the ways that addiction is viewed and in who receives treatment. Patients from different cultures seeking addiction treatment may present different symptoms based on how they make sense of their experience. Patients from cultures where addiction is highly stigmatized, or not considered to be a real illness, may delay seeking treatment or may mistrust the treatment, resulting in worse outcomes.

Immigrants are also more likely to have higher levels of psychological distress arising from adaptation to new cultural norms, experiences of trauma, loss, poverty, and racism. There is a “healthy immigrant effect” in which new immigrants typically have better health than non-immigrants residing in their new country, but over time they begin to match the non-immigrants in health status. According to one study, after living in the United States for ten years immigrants’ substance abuse patterns were similar to those of non-immigrant Americans. One hypothesis that accounts for this effect is that the stress of immigration may be mitigated at first by relief from the distress of homeland tension and displacement and by optimism for a better future. Non-refugee immigrants are also screened for language, education and job skills. In many instances, they represent the best their homeland has to offer and may not be immigrating under duress.

It is widely understood that the impact of colonization, racism, and adverse government policies has had a detrimental effect on the culture and identity of indigenous people in Canada. As part of recovery treatment, cultural programming implemented in treatment centres has had a positive impact on treatment success. It has increasingly become a core component in Aboriginal community-based and residential programs. These activities provide culturally aligned psychosocial and spiritual engagement. They also improve the participant’s sense of identity and belonging, both of which can be healing to the socially isolated.

**Individual and Public Health Services and Addiction**

In Social Determinants of Health: The Canadian Facts, the most basic aim of the public health system is “to protect the health of citizens and spread health costs across the whole society.” The World Health Organization (WHO) gives health services a central and important role, stating that promoting health and reducing health inequities are the appropriate direction for the health sector in addressing determinants of health.

Historically, addiction services were provided by faith-based or community-based organizations. More recently, there has been an increased migration of patients into the health care system within various models of integrated mental health and addiction services. This shift is in transition, with many programs not embracing evidence-based or informed care, including pharmacotherapy. The
system also has a heavy reliance on episodic acute care (detox, rehab) rather than on a chronic disease management approach with long-term support into recovery.

**Addressing the Determinants of Health**

The WHO (2008) reported on three recommendations for reducing the increasing disparities of health status:

- Improve daily living conditions.
- Tackle the inequitable distribution of power, money, and resources.
- Measure and understand the problem and assess the impact of action.

Specific to healthcare, the 2011 Rio Political Declaration on Social Determinants of Health listed “further reorienting the health sector towards promoting health and reducing health inequities” as an action area.

These are more than high-level ideals. Healthcare providers can take action in a clinical setting, one patient at a time and across their organizations. For each determinant listed, taking steps to reduce inequitable access to services is a good place to start.

**Family Systems and Addiction**

Family Systems and Substance Abuse

Family plays an important role in both the pathways to addiction and to recovery. (Genetic risks are discussed elsewhere in this primer; see 1.4 Genetics and Addiction.) With regards to substance use, it is useful to view family systems as social systems, transmitting both risks and resiliency to an individual. The relationship between parental substance abuse and subsequent alcohol problems in their children has been documented. A 25-year longitudinal study found that parental illicit drug use significantly predicted substance abuse in their children. A prospective birth cohort study from New Zealand of almost 1,000 individuals showed family history to be a strong predictor of alcohol and drug dependence.

Further, illicit substance use in older siblings seems to predict substance abuse problems. It is interesting to note that when parental and sibling influences on drug use have been compared, each factor appears to predict unique risk.

Several studies have also shown that childhood maltreatment is an important predictor of alcohol and drug addiction. More broadly, numerous studies have shown that childhood maltreatment and exposure to stressful life events can predict adverse health outcomes, including alcoholism and drug dependence.
Furthermore, several studies have shown that the relationship between childhood maltreatment and alcohol and/or drug dependence is much stronger for women than for men\textsuperscript{75,76}. For example, a longitudinal cohort study of almost 900 children with court-documented cases of childhood sexual and physical abuse and neglect, who were followed through to middle-age (40 years), showed that childhood maltreatment predicted the development of alcohol disorder in women but not in men\textsuperscript{77}. For women, a composite risk factor (including prostitution, homelessness, delinquency, crime, and poor school performance) together with post-traumatic stress disorder mediated the pathway from childhood maltreatment to middle-age drug use\textsuperscript{78,79}. For men, neither childhood maltreatment nor the mediating factors were predictors of adult drug use\textsuperscript{79}. However, severity of childhood emotional abuse has been correlated with increased risk for substance abuse for both men and women\textsuperscript{74}. In addition to this study, the Virginia Adult Twin Study of 3,527 men reported that men who had experienced childhood maltreatment before the age of 15 were 1.7 times more likely to meet criteria for alcohol abuse dependence than men not exposed to maltreatment. This association was attributable to environmental adversity that was shared between twins\textsuperscript{80}.

**Family Systems and Process Addictions**

Family plays an important role not only in substance abuse but also in process addictions. The relationship between parental gambling and subsequent gambling attitudes and behaviour in their children has been well documented in the literature\textsuperscript{81-89}.

Drug and alcohol use have been linked with young adult gambling\textsuperscript{90-94} and with trauma\textsuperscript{95}. Numerous studies have also shown gender to be important, with young men reporting higher levels of pathological gambling\textsuperscript{96,97}, more positive attitudes and irrational beliefs about gambling\textsuperscript{98,99}, and more frequent gambling activity\textsuperscript{82,83,100} than young women. Although gambling problems are more prevalent in men than in women, clinicians should be cognizant of gender-related differences. For example, women generally begin to gamble and to develop problems with gambling later in life, and they more frequently develop problems with non-strategic, machine-based forms of gambling such as casino slots.

Problem gambling affects families, colleagues, employers, and communities. It is associated with family breakdown, divorce rates, intimate partner violence, and a variety of familial psychological problems including stress and loss of trust\textsuperscript{101-103}.


**Conclusion**

This chapter has explored a number of issues related to the social determinants of health. The interplay of risk and resiliency is complex, and socio-economic factors are not alone in influencing the development and expression of a substance use disorder or process addiction. They do play
a role, however. It is important to consider public policies that will create a healthier society, as well as advocate for better access to evidence-informed care. Interventions that target the most vulnerable or those at increased risk, such as families and children involved with child protection services, are a good place to start. When it comes to treatment, care should assist individuals to better navigate the family and social environment that may have contributed to their addiction, in order to support their transition into remission and long-term recovery.
Podcast

Addiction

Podcast 10: Early Trauma in Addiction

Virtual Patient Cases

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

Case of Miriam (Age 42)
Case of Dudley
Case of Ethel
Ann with green labels
3. Social Factors in Addiction


2. The Association of Faculties of Medicine of Canada Public Health Educators’ Network. AFMC primer on population health: a virtual textbook on public health concepts for clinicians. [Internet]. Ottawa: AFMC; [cited 2016 Sept 27]. Available from AFMC Primer on Population Health Chapter 2 Determinants of Health and Health Inequities on AFMC.ca


3. Social Factors in Addiction


3. Social Factors in Addiction


3. Social Factors in Addiction


3. Social Factors in Addiction


In this section the reader will understand the importance and relevancy of physician involvement in addiction medicine. Readers will also grasp the importance of reflective practice in their delivery of health care while addressing stigma and discrimination in the clinical setting. Key aspects of history and physical examination, including screening for the early detection of addictive disorders, will be covered. Basic principles of clinical management include acute and chronic care, pharmacologic interventions, care for both individuals and families, and the management of concurrent disorders. Treatment contexts cover both community based and specialized care. The stages of recovery are explored in a patient-centred manner. Finally, key elements of the biological, psychological, and social factors are used to inform prevention strategies.
4.1 Future Management Strategies of Substance Use Disorders

**Learning Objectives**

After completing this section, the learner will be able to:

1. Describe the consequences of medically harmful substance use.

2. Explain how the chronic care management model can be applied to substance misuse disorders.

3. Describe the components of screening, brief intervention, and referral and how this can be applied in primary care settings.

**The Case for Substance Use Disorders: Legal or Medical Problems?**

Addictions have historically been considered bad habits, hedonism, or a moral failing on the part of the individual—not an acquired health condition. Unlike other medical illnesses, the problematic use of alcohol and other drugs has been reliably linked with delinquency, child neglect, divorce, homelessness, and violence\(^1\)\(^2\). Given the remarkable rates of social harms associated with addiction, it is understandable that individuals suffering with addictions are considered public safety concerns best dealt with through legal enforcement and punishment, rather than as individuals with health concerns best dealt with through medical interventions such as prevention, treatment, and continuing management.

However, following three decades of research into the epidemiology of addiction, and parallel clinical research into the most effective prevention and treatment strategies, the emerging view is that addictions are in fact acquired chronic illnesses. There is now substantial evidence of genetic vulnerability to nicotine, alcohol, opioid, and other substance addictions\(^3\) and well-replicated findings of significant and persistent changes in brain reward, memory, and motivational circuitry following heavy use of most substances\(^4\). Addictions, like many other chronic illnesses, are fundamentally acquired through critical health risk behaviours and are progressively undermined by genetic and (usually) environmental vulnerabilities. While addictions cannot yet be cured, like most other chronic illnesses they can be managed effectively with long-term use of medications and family and social interventions\(^5\)\(^7\).
The Medical Consequences of Ignoring Substance Use Disorders

It is important to remember that addictions are merely the most severe of the substance use disorders. In the United States, over 23 million adults meet diagnostic criteria for an addiction to alcohol or other drugs, but approximately 40 million additional adults manifest less severe, or medically harmful substance use. While it is estimated that 90% of this population does not recognize the extent of their problem and never seek treatment for their substance use, they do seek primary care for numerous other medical conditions that are related to or exacerbated by their substance use.

Additionally, there are many examples of moderate substance use negatively affecting the adherence and effectiveness of treatments for other illnesses. Even mild to moderately severe substance use disorders have been associated with poor adherence to medications; failure to achieve control of hypertension and diabetes; increased risk for a host of cancers and medical illnesses; and decreased effectiveness of treatments for chronic pain.

To illustrate, a young, otherwise healthy, adult woman who drinks two glasses of wine each evening would clearly not meet the diagnostic criteria for addiction. However, if that young woman were pregnant, even that moderate level of alcohol use would be considered medically harmful to the fetus. If this same young woman were also under treatment for breast cancer, even this moderate level of alcohol use would be considered medically harmful because alcohol at any dose can accelerate the growth of breast (and several other) tumours.

Unfortunately, physicians are generally not trained to consider these less severe forms of substance use as an issue because individuals such as the “young, otherwise healthy, adult” do not conform to the popular stereotypes of “alcoholics” or “drug addicts.” As a result, they are rarely identified or addressed despite their prevalence and negative effects on the individuals’ health outcomes. Failing to address substance use disorders is serious and constitutes a large missed opportunity for improving the quality of care in general medical settings.

And yet, when recognized, substance use disorders have been shown to be effectively managed in general health settings. Efforts to improve the linkage between primary care and specialty care have resulted in reduced substance use, substantially enhanced medical outcomes, and greater cost-effectiveness.

Substance Use Disorders and the Chronic Care Model

While there are still significant barriers to broad integration of prevention, treatment, and management of substance use disorders in mainstream healthcare, recognizing that substance use disorders should be considered chronic illnesses offers a helpful framework for medical management.
The general approach to chronic illness management is itself evolving toward the chronic care model (CCM) first described by Wagner\textsuperscript{20} and Bodenheimer and colleagues\textsuperscript{21}. The CCM is a proactive management strategy that involves multidisciplinary teams of health care providers and replaces the traditional model of primary care delivered by a single clinician. The major preventive goals of the CCM are to improve disease screening, better anticipate illness progression or relapse, and provide patients and their families with the motivation, skills, and supports necessary for self-management of disease control and prevention of relapse and complications, all in a cost-effective manner\textsuperscript{20,21}.

Evidence suggests that the CCM is more effective than traditional clinical care in the treatment of many chronic medical illnesses\textsuperscript{22,23}, including depression\textsuperscript{24}; is more appreciated by patients and physicians\textsuperscript{23}; and does not appear to cost more than traditional care\textsuperscript{24}. Conceptual\textsuperscript{25,26} and mounting methodological indications\textsuperscript{27-29} indicate that a properly staffed and supported CCM offers a good framework for managing substance use disorders using the same care team and the same methods used to manage other chronic illnesses such as diabetes.

**Screening and Brief Interventions**

One highly effective strategy for identifying and managing many substance use disorders within medical settings involves screening, brief intervention, and referral to treatment, or SBIRT\textsuperscript{30}. SBIRT involves a short (4–8 item) set of screening questions regarding cigarette, alcohol, and other drug use. Positive screens (presumptive indication of harmful use patterns) are followed by a brief (5–10 minute) motivational conversation designed to get the patient to recognize the harmful nature of his or her use and to convince the patient that he or she has the power to reduce that use. Patients with more severe substance use are referred to brief treatment and specialty care if necessary\textsuperscript{30}. Alcohol screening and brief counselling are now considered essential services and carry a strong recommendation from the U.S. Preventive Services Task Force (USPSTF). In fact, of all preventive services recommended by the task force, brief alcohol interventions (discussed below) yield the fastest and greatest reductions in healthcare costs\textsuperscript{31}.

Bien and colleagues\textsuperscript{32} reviewed thirty-two controlled trials of brief intervention for alcohol abuse, which included over 6,000 patients, and found that interventions as short as one brief, well-executed conversation were adequate to alter alcohol abuse patterns. Additionally, a large-scale field trial of SBIRT in six American health systems (screening approximately 460,000 patients) reported that SBIRT for illicit drug use produced marked reductions in usage\textsuperscript{33}. Finally, the WHO conducted a four-nation controlled trial that demonstrated that brief intervention resulted in three-month reductions in the use of cannabis, cocaine, and heroin versus an assessment-only control\textsuperscript{34}.
While there are still only a few formal evaluations of the cost-effectiveness of treating substance use disorders in general health settings, there are some promising findings. For example, a study of SBIRT for unhealthy substance use in Washington State from eight general health clinics compared screening alone to screening followed by one or two brief (10-minute) motivational conversations designed to promote the patient’s self-recognition of the substance use problem and willingness to reduce that substance use. Screenings produced the expected positive rate of about 23% of adults who screened positive for self-reported medically harmful substance use. Healthcare utilization of all patients was examined one year later, revealing a US$3,500 cost reduction per patient among the full intervention group, with the majority of savings derived from reductions in emergency department and inpatient utilization rates.

**What to Do with Severely Affected Patients**

Though SBIRT can be an efficient and potent intervention for mild to moderately severe substance use, it should be noted that patients with severe addiction are unlikely to respond to a brief intervention. Most of these individuals will require the attention of the entire clinical management team, perhaps a prescription for an anti-craving medication such as naltrexone, or a referral to a specialty substance abuse treatment program.

**Conclusion**

For decades, general medicine has ignored substance use disorders—even the most severe and obvious cases. This wilful ignorance has not only produced needless suffering for addicted patients and their families, but has also dramatically reduced the quality, while increasing the costs, of treating the many other illnesses and health conditions so clearly associated with substance use disorders such as chronic pain, gastrointestinal disorders, chronic obstructive pulmonary disease (COPD), asthma, chronic sleep disorders, and many forms of cancer.

It is important to emphasize that severe addictions represent only the most obvious group of individuals with substance use disorders. Low severity or early onset cases of medically harmful substance use are ubiquitous, commonly affecting over 20% of patients seen in primary care settings and over 50% of patients in higher acuity settings such as hospitals, emergency departments, or trauma centres. Low severity substance use problems are often under-diagnosed and under-treated and, as a consequence, interfere with treatment of other illnesses, reduce adherence to medication and care plans, and contribute to hospital readmissions at great expense to the healthcare system.

However, as with pre-diabetes, medically harmful substance use can be easily, quickly, and accurately screened. It is now possible, and expected, that cigarette, alcohol, and other substance use screening will be made a part of the initial work-up of every new adolescent and adult patient, and that this procedure will be repeated annually, or sooner, if warranted.
As is the case with diabetes management, research on the management of substance use disorders has shown little behavioural change in patients following simple disease education or scolding-and-confrontation methods. Instead, clinical techniques such as motivational interviewing—an empathic, respectful, and collaborative approach to promoting behaviour change—can significantly reduce substance use and can also improve the clinical outcomes of many common chronic illnesses and medical conditions, reduce healthcare costs, and reduce risk factors for hospital readmissions\textsuperscript{31-36}. Due to this success, this technique is being increasingly applied to other areas of unhealthy behaviours, such as those relevant to diabetes, where a primary care team member such as a nurse or health behaviourist can easily and efficiently deliver it.

This area of medicine is rapidly developing, but there is not yet a rich body of research to guide clinical decision-making. Until that research is more developed, there are three recommendations for primary care teams to adopt:

1. Implement screening and brief intervention.

Clinical information systems such as the electronic health record (EHR) should be adapted to facilitate screening and brief counselling interventions for medically harmful substance use. These practices are evidence-based, practical, efficient, provided by most provincial health plans through a broad range of coordinated community services in conjunction with psychiatric units in general hospitals and associated regional mental health care centres\textsuperscript{37}, and can improve care for a wide range of other illnesses negatively affected by undetected medically harmful substance use.

2. Acquire behavioural health expertise within the primary healthcare team.

Hire or train a member of the care team—typically a nurse, social worker, or health educator—to assume responsibility for (a) screenings and brief interventions for emerging substance use disorders, (b) facilitating linkage to community resources, and (c) teaching and encouraging patient self-management skills. These practices are also evidence-based, efficient, and reduce costs such as rapid rehospitalization.

3. Identify and collaborate with local addiction specialists.

Brief interventions are not adequate for severely addicted patients. It will be important to identify addiction medicine experts to consult on diagnosis, prescribing, and adjusting addiction medications, and to suggest referrals to specialty care when needed. Expert advice in addiction medicine is also available through standard protocols, as well as through telephone or Web contacts. (see Chapter 4.4 Building a Bridge: The Therapeutic Alliance)
Reflective Questions

1. Why does the chronic care model (CCM) offer a better framework for managing substance use disorders than specialty substance use treatment programs?

2. What elements of practice would you use to increase the likelihood that patients would truthfully report their substance use?

3. Are you routinely screened for substance use in your own medical appointments? If not, why do you think that is?


Podcasts

Addiction

Podcast 9: Prevention, Intervention and Treatment of Addiction
Podcast 11: Chronic Disease Management Model of Addiction Treatment: A Healthcare System Response
Podcast 12: Quality Improvement Strategies and Evaluation for Addiction Treatment Programs

Further Reading


Virtual Patient Cases

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

Polly Farmercie
AFMC Case 1 (Marilyn Age 74)
AFMC Case 3 (Sue Age 35)
AFMC Case 4 (Paul Age 9)


4.1 Future Management Strategies of Substance Use Disorders


A Chronic Care Model

The Kaiser Permanente Early Start program is an example of a CCM that incorporates team-treatment principles in addressing substance use in prenatal clinics. Because the usual process of screening and passively referring patients to specialty substance abuse treatments rarely led to pregnant patients actually entering treatment, this program was initiated in 1990 to integrate treatment for substance use into regular prenatal care. All patients are screened for tobacco, alcohol, and other drug use at the intake visit via questionnaire and urine toxicology. At the first prenatal visit, substance-using patients meet with the on-site behavioural health specialist, who is a licensed and experienced clinical social worker. Those who meet the criteria for unhealthy substance use continue to meet with the behavioural health specialist during each of their regularly scheduled prenatal visits for substance use counselling, support, and linkage to specialty drug or alcohol treatments when needed. The program has demonstrated significant improvement in birth outcomes and maternal health and also saves the Kaiser system almost US$6 million per year in avoided or reduced neonatal intensive care unit stays.

Project Engage

The Project Engage program in the Christiana Care Health System is a practical example of a health system’s effort to promote and coordinate access to community resources as part of chronic care management for substance use disorders. The program, located in Delaware, employs peer counsellors to meet with chronically and severely addicted patients who are among the most costly to treat as a result of multiple hospitalizations related to substance use. The counsellors are trained and equipped to engage these patients during hospitalization; facilitate entry into community addiction treatment; and provide ongoing help securing drug-free housing and Alcoholics Anonymous (AA) engagement. Preliminary evaluation results have shown decreases in annual health care expenditures of US$6,000 per patient, primarily from reduced hospital and emergency department visits.
4.2 Stigma and Reflective Practice: Overcoming Stigma and Discrimination in Clinical Settings

Sonya Lee and David Topps

Learning Objectives

After completing this section, the learner will be able to:

1. Discuss stigma, prejudice, and discrimination.
2. Discuss how stigma negatively impacts health.
3. Describe strategies to reduce stigma (reflective practice).

What is a Stigma?

One of the challenges facing people dealing with substance abuse and addictions is the stigma associated with these conditions. Stigma is defined as “a mark or disgrace associated with a circumstance, quality, or person.” It results directly in negative attitudes or prejudice toward the individual, which can manifest as negative behaviour or discrimination\(^1\),\(^2\).

There are many ways in which people experience stigma related to their substance abuse or addiction. Family, friends, and colleagues may stigmatize them, perhaps owing to frustration over their behaviour; however, an approach free of negative attitude is expected of physicians. Stanbrook states, “Health professionals too often think and behave negatively towards addicts and addiction. In this, we share the attitude of our society, in which substance abuse is one of the last remaining socially acceptable targets for public discrimination”\(^3\). In such instances, people may be blamed for their illness or viewed as having chosen to become addicted, or they may be viewed as difficult or non-compliant patients, or deemed unworthy of treatment. Healthcare providers may also feel cynicism; they may think that nothing can be done to care for these individuals effectively. Carl Rogers recommends the adoption of an attitude of “unconditional positive regard”\(^4\) towards others as people in turmoil, in order to remain empathic despite the behaviour demonstrated.

Does Stigmatization Matter?

The added burden of the stigmatization of disease can significantly affect the health outcomes for people coping with illness. Stigmatization has a profoundly negative effect on people, resulting in exclusion and isolation, decreased likelihood to seek care, low self-esteem, loss of hope, and hindered recovery\(^1\),\(^2\). Stigma on the part of healthcare providers can also impede the quality of
care received. Negative attitudes from the healthcare provider may result in reluctance to treat individuals with addiction, a lack of motivation to acquire the skills and knowledge required to provide care, and therefore a deficiency in providing quality care. Further, stigma can undermine factors critical to the patient’s recovery, such as the development of supportive relationships and extra-therapeutic factors such as hope and expectancy.

Healthcare providers should consider their professional attitudes and behaviour when working with all patients, not only those with substance abuse or addiction problems. This process of reflection “can build greater understanding of the experience, thus helping learners incorporate new information into their existing knowledge.”

**THE ROLE OF REFLECTIVE PRACTICE IN REDUCING STIGMATIZATION**

Reflective practice starts with reflective learning, which is the process of retrospectively thinking about what we have experienced in order to learn. Reflective practice is an activity to be studied and continued because it supports ongoing professional learning and is increasingly linked to professional competence. Reflection can have many triggers. By enabling a shift to deeper learning, it is powerful, enlightening, and transformative.

Boud and colleagues describe one model for reflective practice:

- returning to experience
- attending to feelings
- re-evaluation of experience
- outcome and resolution

Therefore, the reflective practitioner is “one who uses reflection as a tool for revisiting experience both to learn from it and for the framing of murky, complex problems of professional practice”.

**OTHER STRATEGIES TO REDUCE STIGMATIZATION**

**Know Yourself**

It is important to be realistic about our attitudes and beliefs and how they affect our behaviours. Having an increased awareness and understanding of any biases, no matter how they came about, allows them to be addressed through reflecting, learning, and changing. Using reflection and reflective practice when faced with biases may help to keep them from interfering with work as a healthcare professional.
The genogram exercise (see Chapter 4.3 Assessment and Management of ACEs in Primary Care A Canadian Perspective) is a way of exploring family history and dynamics and is a helpful tool.

Know the Facts

Recent data suggests that the prevalence of substance abuse in Canada is 11%, and that 10% of Canadians 15 years of age and over report symptoms consistent with alcohol or illicit drug dependence\textsuperscript{12,13}. For healthcare professionals involved in the care of people with substance abuse and addictions, it is important to recognize that individuals are not at fault for their illness and that they do not choose their illness. Addictions develop due to a complicated interplay between genetics, neurobiology, the environment, and experience\textsuperscript{1,2}.

Challenge Assumptions

It is important to challenge assumptions, to reframe the way we think—understanding that substance abuse and addictions are a type of chronic disease, and that chronic diseases are generally ongoing and long in duration, have a variable and changing clinical course, are multi-factorial, and have no cure\textsuperscript{14}. Would attitudes and behaviour be similar when caring for a patient with diabetes, vascular disease, or chronic lung disease?

What You Say and How You Say It Matters

“One must turn the tongue in the mouth seven times before speaking.” — Roland Barthes

Healthcare workers must think about the words they use to describe patients and the manner in which they say them. Words can perpetuate labels that result in prejudice and discrimination\textsuperscript{1,2}. How would the following phrases used to describe a patient differ?

- a 43-year-old alcoholic woman
- a 43-year-old woman with a history of alcohol use

See, Listen, and Understand

Everyone wants to be seen, heard, and understood. This means acknowledging the person and not only his or her substance use or addiction. Healthcare providers must ask about patients’ experiences in order to enhance their understanding of their patients’ illnesses, thereby demonstrating genuine empathy\textsuperscript{1,2}.
Be Positive

Everyone has positive qualities, and all patients are more than just their disease or illness. Healthcare providers should focus on what individuals can do and what they can change, remembering to empower and engage their patients¹.

Advocate and Educate

Healthcare providers can be a support to patients, families, and organizations that assist and care for individuals with substance abuse and addictions. They can contribute to educational, professional, and public discussions to dispel myths that perpetuate prejudice and discrimination¹².

see Callout: Stigma 101
**Multiple-Choice Questions**

1. Which of the following statements about stigma is true?
   a. Stigma is a mark or disgrace associated with a circumstance, quality, or person.
   b. Stigma results in negative attitudes or prejudice toward the individual that can manifest as negative behaviour or discrimination.
   c. Stigma negatively impacts health outcomes.
   d. All of the above statements are true.

2. Reflective practice is:
   a. reflection and learning while in front of a mirror
   b. not associated with professional competence
   c. the process of retrospectively thinking about what we have experienced in order to learn and to transform behaviour
   d. none of the above
PODCASTS

Addiction

Podcast 8: Different Kinds of Addiction
Podcast 9: Prevention, Intervention and Treatment of Addiction
Podcast 10: Early Trauma in Addiction

VIRTUAL PATIENT CASES

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

Beth
Case of Miriam (Age 42)
Harriet has a fit
REFERENCES


3. Stanbrook MB. Addiction is a disease: we must change our attitudes towards addicts. CMAJ [Internet]. 2012 [cited 4 October 2016];184(12): 5.


Where Does the Word Stigma Originate?

The Latin word stigma (noun) is derived from the Greek verb stiezen, meaning “to tattoo.” In ancient Greece and Rome, stigma referred to a mark made by a hot iron or needle that was branded onto criminals or slaves. In the Middle Ages, it described a wound on the hands and/or feet, usually in a religious context and related to crucifixion. In the late 17th century, stigma took on a more figurative meaning: a mark of shame or discredit, which it still carries today.

Reflective Exercise

Think about a time when you personally experienced prejudice or discrimination, or when you might have demonstrated this attitude or behaviour.

- How did it make you feel? How do you think others felt?
- Did anything surprise you about your experience?
- What did you learn?
- Did you change your attitude or behaviour based on your experience?

Stigma 101

Complete the online learning module, Mental Health and Addiction 101 Series: Stigma, from the Centre for Addiction and Mental Health (CAMH). The course views definitions and factors that contribute to stigma, provides reflective exercises and resources, and challenges myths.

For further reading, see the Canadian Medical Association Journal (CMAJ) editorial by Stanbrook, “Addiction Is a Disease: We Must Change Our Attitudes Towards Addicts.”
Learning Objectives

After completing this section, the learner will be able to:

1. Discuss the effects of adverse childhood experiences (ACEs) on adult health.
2. Discuss the effects that ACEs may have on primary care patients in Canada.
3. Discuss the major aspects of an ACE-informed model of primary care.

Introduction

This chapter addresses the issues of adverse childhood experiences (ACEs) from the perspective of working in primary care with adults. Several questions are posed about optimal strategies to assess and manage adults who experienced ACEs and have ongoing disease or disability. These questions include the optimal time and place to identify and treat people who have been exposed to ACEs, the best way to measure ACEs, what a treatment for ACEs should look like, and how to evaluate the effects of treatment for ACEs in adulthood. Data are presented from recent research on adults in primary care, and a model for care is proposed which draws upon these data, past research in the field, and practical considerations.

The Long-Term Effects of Adverse Childhood Experiences (ACEs)

Adverse childhood experiences (ACEs) have a well-established and critical set of effects on adult health and functioning. The original findings of Vincent Felitti and Robert Anda, in San Diego in the late 1990s, showed that health-risk behaviours, chronic diseases, mental illnesses, and addictions in adulthood were strongly related to a child’s exposure to abuse, neglect, and other forms of familial dysfunction. Indeed, while the specific results varied somewhat from one disorder to another, there was generally a stepped function in this early work, such that exposure to an incremental ACE (e.g., two versus one, or three versus two) led to a significant increase in relative risk, until about four or five ACEs were experienced. Further, it is now clear that medical expenses are incrementally related to increased exposure to ACEs, as is even the risk of early death. These initial findings have been replicated elsewhere, and symposia about the “ACE phenomenon” have become increasingly common at mental health conferences.
Although the relationship between ACEs and adult disorders is now well established, a major question remains: what can be done about ACEs? ACEs are distal factors associated with adult dysfunction and disability; they are unmodifiable, as they are historical facts. ACEs can also be contrasted with proximal and potentially modifiable risk factors such as coping strategies, behavioural and emotional regulation strategies, behavioural engagement, and other targets of adult treatments. Given the stifling personal, social, and economic burdens of conditions such as depression, addictions, and chronic diseases, it is important to find ways to identify those who, due to their early life experiences, are most vulnerable to developing these problems and then to offer them treatment in order to reduce their likelihood of developing these serious and costly problems as adults. Further, successful treatment of adults with a history of ACEs has the potential to reduce their intergenerational transmission. In this chapter, we present recent data about ACEs in Canada and consider strategies to address ACEs in primary care settings.

The Hidden Cost of Untreated ACEs in Canada

Healthcare costs in Canada comprise a considerable proportion of the national budget. In 2015, total health expenditure in Canada was expected to reach $219.1 billion, or $6,105 per person, which represents 10.9% of Canada's gross domestic product. Of this total amount, a considerable proportion is associated with conditions with a behavioural, or preventable, component, such as chronic disease, depression and other mental health conditions, and addiction. Chronic disease alone accounts for 67% of all healthcare costs in Canada, which doesn't even take into account the $122 billion in lost productivity associated with these conditions. The rate of growth in health expenditures associated with chronic conditions alone has, in fact, outpaced the Canadian economy. Depression is projected to be the second leading cause of global disease burden by 2020; treatments represent a major healthcare cost. The direct and indirect costs of depression to the Canadian economy had been estimated to total $14 billion annually; a recent estimate suggests a cost of $51 billion. Addictions also take a major toll on the economy. The Canadian Centre on Substance Abuse estimated the cumulative costs associated with substance abuse at $40 billion annually, an estimate that only took into account the use of tobacco (43% of the overall cost), alcohol (35% of the overall cost), and illegal drugs (21% of the overall cost). Such an estimate would rise substantially if it were also to include the costs associated with prescription drug abuse and behavioural addictions (such as gambling and sex addiction). When the enormous costs associated with chronic disease, depression and other mental disorders, and addiction are considered globally, the need for prevention and treatment of these conditions as a public health priority becomes clear.

As noted above, ACEs are strongly associated with the risk for developing chronic disease, mental health problems, and addiction. Thankfully, not every person with a chronic disease, mental health, or addiction problem has experienced ACEs in their childhood. However, the association between ACEs and these conditions is strong enough to support the conclusion that forceful direct efforts to address the problems associated with ACEs would be a way to lower
the healthcare costs of the conditions that are likely to result from ACE exposure in childhood. Further, these strategies could reasonably help to stem the intergenerational transmission of ACEs, as approximately 25% to 35% of parents who were abused or neglected as children will themselves mistreat their own children, in addition to lowering the likelihood that these individuals will also experience marital discord and substance abuse\textsuperscript{10}.

Strategies to deal with ACEs could take several forms. Ideally, efforts geared towards the reduction or eradication of ACEs would be at the forefront. Such efforts are considered primary prevention, in that they aim to prevent a condition before it occurs. Examples of this type of prevention effort include strong social sanctions against child abuse, child neglect, and the inability to provide adequate care for children or dependents, as is typical in many jurisdictions. Parenting classes that provide information about the healthy treatment and discipline of children, commonly found at maternity clinics, is another specific model that could reasonably reduce rates of ACEs. At a broader social level, it is also important to maximize the ability for society to provide sufficient supports to young families who may struggle with poverty, isolation, unsafe neighborhoods, or injustice. For example, organizations such as the Canadian Paediatric Society have adopted models for early child health promotion (see the CPS Early Years Task Force at www.cps.ca/en/documents/authors-auteurs/early-years-task-force). However, while such efforts are desirable, they are also costly and a long period of time is required to discern outcomes.

Another prevention approach would be to identify people who have experienced significant levels of childhood adversity and to offer them treatments in order to ameliorate the expected or potential impact of that maltreatment on their adult health. This secondary prevention strategy is desirable in that it allows treatments to be offered to those individuals who are at risk by virtue of their childhood experiences. A related strategy would be to provide prevention and early intervention to individuals who experienced adversity in childhood and who are beginning to present with problems that could be reasonably associated with these experiences. These approaches are still in their infancy and researchers still grapple with fundamental questions such as the following:

1) What is the optimal time and place to identify and treat people who have been exposed to ACEs?

For example, while school-based programs make sense from a pragmatic perspective, schools are already very busy with pedagogical, social, and other development goals; therefore, addressing ACEs in this context may be challenging. On the other hand, waiting until a person suffers the longer-term impacts of childhood trauma may be too late in the developmental sequence to make significant improvements. We have an evolving understanding of the long-term pathways from traumatic exposure to mental and physical health outcomes\textsuperscript{11}, which makes the ultimate answer to this question impossible to know. That said, it seems intuitive that public policies and funding that assist adults with parenting difficulties or that provide services for families in which ACEs
are occurring would be natural points of possible intervention. As discussed below, the provision of services to all adults who suffer the long-term effects of ACEs is impractical and prohibitively expensive. As such, preventive, or early assessment, and intervention programs are preferable to those that wait to treat those with long-term problems in adulthood.

2) What is the best way to measure ACEs?

Should assessment rely on self-report, which has the potential for over-reporting and inaccurate memory, or on formal reports of child abuse or neglect, which highly under-estimate the amount of adversity that children might experience?

3) What would a treatment for ACEs look like?

It would need to be developmentally appropriate, depending on the age at which it is delivered, and would either need to be truly preventive, if done early, or focused on early assessment and treatment, if delivered somewhat later in the cycle of adversity and its consequences.

4) How can the effects of treatment for ACEs be optimally measured?

Should the focus be on improvements in perceived functioning, reduced symptomatology, reductions in chronic diseases and mental and substance abuse disorders, healthcare costs, or some combination of the above?

Each of these questions will be addressed later, in the context of adult primary care. However, we acknowledge that a final approach would be to simply treat individuals who demonstrate the ongoing consequences of ACEs and to help patients find ways to live with their ACE-related problems as meaningfully and productively as possible. These types of programs are already widely available; they include chronic disease or pain management programs and support groups for people living with addictions. Referral of patients with a history of ACEs to specialized services is often appropriate, depending on the nature and history of their presenting problems. However, relatively few of these programs explicitly connect the experience of ACEs to the later adult health problems. It remains an open question whether chronic disease and health programs that are “ACE-informed” would yield better results than programs that simply focus on the adult presentations of disease and illness.

**ACEs in Primary Care**

It comes as no surprise that the most common place for Canadian people to receive care for chronic disease, mental health problems, and addiction is in the primary care system. The Canadian model of healthcare suggests that the family physician should be at the centre of the “wheel” of healthcare, and while he or she should make appropriate referrals to other specialists as required, the patient’s overall program of care should be monitored and coordinated by that primary care physician. Thus, while people who live with chronic disease or other long-term health conditions
People who struggle with chronic disorders and illnesses that include a behavioural component (e.g., mental disorders, chronic pain) are most likely to be first seen in primary care. As such, it is reasonable to assume that individuals with high ACE histories are also likely to seek treatment mainly in primary care. However, while little research has been published that reports the incidence of ACEs in Canadian primary care populations, a recent study in Calgary, Alberta\textsuperscript{12}, represents an initial effort to assess these issues. In this study, 4,009 patients in family medicine clinics were asked to report their ACE scores using the original ACEs questionnaire\textsuperscript{1}. The patients were also asked to self-report a variety of lifestyle factors, health-risk behaviours, and current physical and mental health diagnoses, in addition to completing a current measure of depression. Also, in an effort to assess possible moderator variables, the patients were asked to fill out measures of resilience, emotional regulation, and interpersonal problems.
The obtained sample of patients was relatively well educated and affluent. For example, 20% of the sample had a college diploma, and 30% had at least one university degree. Consistent with this relatively high level of education, 67% reported at least part-time work, and the average family income was over $80,000 per annum for 49% of the sample. Notwithstanding these demographic characteristics, the study, which was essentially a replication and extension of the original ACE study by Fellitti and Anda in San Diego, showed that ACEs are very common among patients in primary care settings (see Figure 1), as 66.7% of the sample reported experiencing one or more ACEs. The two most common types of ACEs reported were household mental illness (45%) and household substance abuse (32%), but sexual abuse (21%) and emotional abuse (20%) were also reported fairly commonly. Patients with higher ACE scores were more likely to report problems with depression, anxiety, addiction, back problems, chronic fatigue syndrome, fibromyalgia, stomach ulcers, irritable bowel syndrome, COPD, chronic bronchitis, and asthma than patients with lower ACE scores. Additionally, statistical analyses revealed that personal resilience and levels of emotional dysregulation mediated the relationship between ACEs and depression as an outcome. In other words, patients with higher ACE scores were more likely to present with symptoms of depression later in life, but this was especially the case for patients who did not report much personal resilience, or did not have good emotional regulation skills.

The fact that current resilience and emotion regulation mediates the relationship between ACEs and depression (as one outcome; other analyses are continuing) may prove to have great clinical significance. If two-thirds of the Canadian population have been exposed to at least one ACE, and if even one ACE increases the risk of later health problems, a massive treatment effort would have to be expended to treat all adults who are at risk. Even if a more conservative ACE cut-off score of three were used, the data suggest that a population-based approach would still require that fully one-third of the adult population receive appropriate treatment. However, while reserving treatment for those who report only the highest ACE scores might be realistic in terms of numbers, it would result in many vulnerable people with an ACE score of two or three still developing chronic diseases, addictions, or mental disorders. A more rational approach, therefore, would be to identify people who are most at-risk based on a combination of their ACE score and the presence of an additional moderator/risk variable (e.g., low resilience, emotional dysregulation). Moreover, just as early assessment and intervention programs should focus on modifiable risk factors, treatments for ACEs should include components that are designed to affect these same risk factors.

Ongoing work by the ACEs–Alberta team has been focused on the development and validation of an ACE-informed treatment program for adults with ongoing chronic disease and illness. They have conducted a large literature review that has revealed that short-term treatments, and especially those derived from cognitive-behavioural therapy principles, have evidence to support their efficacy in reducing symptomatology in adults with ACEs. Based on this review, the team has developed a preliminary therapist and treatment manual that addresses resilience, emotional dysregulation, personal habits, and social connection as themes in a group-based program. This
program is currently being evaluated in an open trial. The ACEs–Alberta team intends to conduct focus groups with both therapist and patient participants to examine the outcomes over a pre-post, three-month follow-up period. Then, based on the results, they will refine the manuals and conduct a randomized clinical trial in which they will compare the ACE-informed program with comparisons, to determine if they can successfully modify the identified risk factors and thereby reduce the current symptoms of adults who suffered ACEs and, as a second effect, reduce healthcare utilization and costs.

**Designing an ACEs-Informed Model in Primary Care**

Returning now to the four questions posed earlier in this section, each will be addressed based on a combination of other research, the study of ACEs in Canada, and practical considerations:

1) **What is the optimal time and place to identify and treat adults who have been exposed to ACEs?**

The optimal time is when these adults first present in primary care with symptoms that already are, or that could transform, into a chronic disease or disorder. When faced with a patient who is returning for what appears to be developing into a chronic problem (e.g., sleep issues, startle and anxiety, interpersonal problems), all family physicians would be encouraged to ask themselves and their patients if this problem might be related to earlier experiences with adversity or trauma. For example, it may be possible to time the onset of the problem to childhood adversity or traumatic events. Further, the earlier that modifiable risk factors can be identified and changed the more likely it is possible to minimize or eliminate the longer-term consequences of ACEs in adulthood. Thus, family physicians are encouraged to consider if there are lifestyle, cognitive, emotional coping, or interpersonal behaviours that could be successfully changed, to help reduce the current symptomatology.

2) **What is the best way to measure ACEs?**

Currently, the best advice is simply to ask the patient. These questions will often provoke anxiety on the part of the physician, in part because of the mandatory reporting laws in some jurisdictions that require certain reports if the questions uncover a history of significant abuse, and especially if other children might be at risk from the individual(s) responsible for the actions. From the point of view of the relationship with the adult patient, however, the experience is that patients who have suffered childhood adversity are cognizant of this fact and are unlikely to be disturbed by such questions. Indeed, they are often relieved for the opportunity to talk about their experiences and to make sense of their current problems in light of their past.

It is not recommended to conduct an interview process to assess ACEs, as interviewers and interviewees tend to focus on one or two major issues (e.g., child sexual abuse), which may be traumatic and certainly can affect future development but are relatively uncommon. A result of focusing on more dramatic events, however, may result in the full range of ACEs not being fully
evaluated. Given this concern, the use of a more comprehensive, but relatively brief assessment of the ten most common types of ACEs through a self-report format is recommended (see Table 4.3-1 for a list of items), and the computation of an overall ACE score that ranges from zero to ten. Research suggests that there is an increase in the likelihood of a range of negative outcomes as the number of ACEs increases, up to about four or five ACEs, when the relative risk starts to level off. Further, at this stage of research, the data does not suggest that specific forms of ACEs are more or less associated with specific disorders in adults; rather, it seems that the accumulation of ACEs of any type confer risk. Therefore, although self-report of childhood memories has the potential for over-reporting and inaccurate memory, the global evaluation of an ACE-intensive history appears to be the critical issue.

Several self-report scales exist to measure ACEs in adults. Before any instrument is integrated into clinical practice, it is important to ascertain that the scale provides measurements that are both reliable and valid (see Nerd’s Corner: Evaluating Assessment Measures). Considerable effort has been put into determining the psychometric characteristics of the various ACE scales. In some of our own research15, three commonly-used measures were applied to the same patients. The study was able to demonstrate that all three scales had similar and high-internal reliability and that they all correlated highly among each other. However, scales vary in the manner in which they ask about ACEs. One common difference is whether they ask if the event ever occurred, in a binary fashion, or its frequency, if the event occurred. While the latter format takes slightly longer to rate, it does provide more complete information about the intensity, or “dose” of childhood adversity, and thus the scores can be used both in terms of an overall tally of adverse events and their accumulation. Second, some of the scales that have been developed are for international research and ask about events specific to war, dislocation, and other issues that are less likely to occur in a stable population. A final consideration is the extent to which a scale has been employed in past research and, therefore, if it has a reference point against which to compare current research. It was for these reasons that the original ACE tool was used in the ongoing research1, although with a reduction in some of the peripheral items on the scale that were not used in the computation of the ACE score.

3) What would a treatment for ACEs look like in adulthood?

Based on the extant literature14, it is recommended that the focus placed on adults who suffer from chronic dysfunction and/or disease should be on current and modifiable risk factors, rather than on an in-depth exploration of childhood trauma and its effects. This is recommended for several reasons. First, childhood adversity is a distal and static risk factor. While its effects are long lasting, attempts to minimize or change the memories themselves are likely problematic and could even be perceived as minimization of a difficult past. While some time might be spent exploring the links between childhood adversity and current problems, in an effort to understand these relationships, or in an effort to reduce the likelihood of the adult patient repeating such a history with his/ her own potential children, treatment as such is not recommended. Second, data suggest that current coping and emotional strategies mediate the relationship between ACEs and
current disorders, and as these current issues are potentially modifiable and are more proximal risk factors, it seems that efforts in this direction are the most logical. Third, there is evidence that treatment focused on current and modifiable risk factors can reduce distress, and negative symptomatology\(^{14}\), and therefore treatment at this level has a higher likelihood of benefit.

ACE-informed treatment for adults with chronic disease and disorder is at present somewhat imprecise [for examples see\(^{16}\) Cloitre, Cohen & Koenen, 2006, and\(^{17}\) Cloitre, et al., 2010]. The suggested treatment should be oriented towards common problems and skills-based in order to encourage the development and application of useful skills in the patient’s life. It is believed that the treatment can be delivered in a group format [cf. Litwack, Beck, and Sloan\(^{18}\)], based on the premise that the therapist or group leader can retain focus on common and current issues and coping, and will not allow the group to be diverted to personal histories. This model has divided these skills into behavioural skills (e.g., eating, sleeping, dietary, and other healthy behavioural strategies), cognitive (identifying and challenging negative thought patterns), emotion regulation strategies, and social/interpersonal coping (risking relationships with others; becoming appropriately inter-dependent). Predicated on the assumption that the program has overall benefit, the program has been broken into modules, which can be taken out selectively, to assess the added value of specific components of the program. One set of issues about treatment relates to its delivery. Although no clear data exists on which to make this recommendation, researchers believe that any such programs should ideally be delivered in the primary care setting itself with healthcare providers who are known to the patients. Ideally, the family physician will recognize the need for the program and will have trained staff embedded within the primary care setting who can use a collaborative care model of healthcare\(^{19}\) to provide care that is physically in, or very close to, point of care and that can explicitly also entail feedback from the program back to the physician\(^{20}\). The program could entail a self-management approach, with a combination of an education and skills-based approach, which could be minimally disruptive of usual care and yet offer a stepping-stone to more intensive services, if warranted.

4) How can the effects of treatment for ACEs be optimally measured?

This question is best approached from two distinct perspectives: clinical and systemic. From the perspective of clinical care, improvements in perceived functioning and reduced symptomatology should be the focus. The assessment of these outcomes can be similar to any other clinical programs and could involve standardized assessments, or more simple self-report of adaptive functioning. Assessment of the proposed mediators of the clinical outcomes is also encouraged, including emotion regulation, behavioural coping, and social engagement, in an effort to link changes in proximal and modifiable risk factors with improvements in adaptive functioning. From a more systemic perspective, the assessment of larger health outcomes is also suggested. Such outcomes could include reductions in chronic diseases and mental and substance abuse disorders, reduced use of urgent and emergency care services, and reduced healthcare costs. Such latter outcomes are unlikely to manifest themselves at the level of the individual patient; some effort at an organizational assessment is needed. For example, the use of ancillary health services should decrease if care is
provided, and both the amount of this use and its associated costs could be estimated. Wide-scale adoption of such programs would require the widespread integration of mental health services into primary care settings. Standardized training programs and adherence monitoring would be needed to ensure relatively consistent application of an evidence-based model of care. In countries such as Canada, and with appropriate development and validation, it may also be possible to use on-line approaches to reach people who are unwilling to attend group sessions or who simply live too far away to make participation in therapy groups practical.

<table>
<thead>
<tr>
<th>Table 4.3-1. Content areas of the ten most common types of ACEs</th>
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<tbody>
<tr>
<td>1. Household mental illness</td>
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<tr>
<td>2. Household substance abuse</td>
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<tr>
<td>3. Household criminal behaviour</td>
</tr>
<tr>
<td>4. Sexual abuse</td>
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<tr>
<td>5. Emotional abuse</td>
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<tr>
<td>6. Physical abuse</td>
</tr>
<tr>
<td>7. Physical neglect</td>
</tr>
<tr>
<td>8. Emotional neglect</td>
</tr>
<tr>
<td>9. Parental divorce</td>
</tr>
<tr>
<td>10. Caregiver violence</td>
</tr>
</tbody>
</table>

**Conclusion**

This chapter has focused on the implications of ACEs for adult health and disease. It has discussed how ACEs can be measured with adult patients and how to conceptualize the effects of ACEs for long-term development. It has argued that, while ACEs are a significant distal risk factor for many forms of dysfunction and disease, physicians and clinicians in primary care need to focus their assessment and intervention on more proximal and modifiable risk factors. These risk factors include emotional regulation, cognitive processes, behavioural self-care, and interpersonal relationships. This chapter has also described a nascent program for ACE-informed care in primary care that can be delivered in a modularized group format. Emerging data will inform the developers about the efficacy of the program, and will direct further development of the program, including a possible distance delivery methodology.
SELF-TEST QUESTIONS

1. Most Canadian people with chronic diseases, mental health problems, and addictions receive care in the _________________ system.

2. According to the authors, the assessment of ACEs in adults should rely on:
   a. Retrospective self-report scales
   b. Detailed interviewing
   c. Police and school reports of documented ACEs
   d. None of the above

3. Based on Canadian data, about ____% of adults report one or more ACEs.
   a. 10%
   b. 33%
   c. 50%
   d. 70%
4. The authors recommend that ACE-informed care in adults should use:
   a. An in-depth focus on the experience of trauma and its meaning
   b. A skills-based approach to modifiable risk factors
   c. An individualized approach to patient management
   d. All of the above, as appropriate to the case

5. Which of the following is NOT commonly recognized as an ACE?
   a. Sexual abuse
   b. Household criminal behaviour
   c. Household poverty
   d. Parental divorce
VIRTUAL PATIENT CASES

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

Polly Farmercie
AFMC Case 5 (Jake Age 15)
References


Evaluating Assessment Measures

The psychometric characteristics of assessment tools allow researchers and clinicians to assess the interpretability and generalizability of the constructs being measured. Reliability refers to the extent to which a specific instrument measures a construct consistently, both across the instrument's items (e.g., internal consistency, split-half reliability) and across time (e.g., test-retest reliability). Cronbach's Alpha ($\alpha$) is one of the most common measures of reliability. Generally, scientific instruments that have a $\alpha$ of at least .7 are considered to be reliable. For a construct such as ACEs, it could be hypothesized that measurement should be almost perfectly reliable, as the events being asked about are historical and, in theory at least, either did or did not occur. Validity is an index of the extent to which a specific instrument measures what it purports to measure. Validity is traditionally measured in several ways. Content validity refers to the extent to which the specific test items actually represent the construct the test is trying to measure. Construct validity refers to the overall extent to which the test actually measures the construct that it purports to measure. Two common aspects of construct validity include convergent validity (the degree to which scales that measure the same construct are correlated; generally, the higher the better) and discriminant validity (the degree to which scales measuring different constructs are correlated; generally, the lower the better). Criterion validity considers the relationship between the test and a criterion variable (or variables) taken as representative of the construct being measured. For example, a measure of ACEs might be used to predict a patient's healthcare status. The patient's use of healthcare services might be used as a criterion to define the success of the ACE measure as a prediction tool.
4.4 Building a Bridge: The Therapeutic Alliance

Ralph Earle, Brenda Garrett, and Amy Hesler

Learning Objectives

After completing this section, the learner will be able to:

1. Discuss the key components and strategies required for physicians to be effective in providing quality care for their patients.

2. Discuss the strategies that help a physician remain involved and connected to both the patient and the providers of care before, during, and post treatment.

3. Discuss the importance of treatment resources and options of care for the patient.

Introduction

In order for physicians to care for their patients they must know both themselves and their patients. They must also know how to build relationships with the patients’ families as well as with the team of healthcare professionals and providers with whom they and their patients interact. While there is no substitute for the extensive education, training, and technical skills required to become a physician, it is vitally important to remember that interpersonal awareness and knowledge are the building blocks for making the best decisions regarding patient care. Familiarity with treatment resources and options of care for the patient is critical in determining the best fit and services required for the patients’ needs.

The following graphic sums up the essence of this chapter: building a bridge between the physician, the patient, the patient’s caregivers and family, and out to referrals.

Figure 4.4-1
Ph y s i c i A n, Kn o w Th y s e l f

Physicians as healers and human beings are vulnerable to maladies and wounded spirits as much as their patients. Doctors need to give themselves permission to name and mine their strengths while accepting lessons in light of their limitations. Thales, an ancient Greek philosopher, spoke of the challenges of self-knowledge. When asked what was the most difficult thing he replied, “To know thyself.”

One way for physicians to begin this process is by knowing their own medical history and how the relationships in their family may influence self-knowledge. The exercise in the Callout “Create Your Own Genogram and Explore Your Family Background is an example of how genograms are used to explore family backgrounds.

T h e T h e r A P e u t i c A l l i A n c e

In order to be effective, the physician needs to intentionally consider the patient as a whole: the individual, their family, and the social system in which they live.

The Patient

The initial gathering of data begins with inquiries about the patient’s physical and biological symptoms. A thorough physical and biological history can help detect additional indicators or risk factors for addiction, even if a patient does not initially identify a problem. This process is covered in more depth in Chapter 5.

The Family

Another key aspect is to explore the family system in which the patient was raised and the family rules, patterns, beliefs, boundaries, and communication styles. Asking patients to complete their own genogram can be a useful exercise here. This helps the physician identify any other natural supports that already exist for the patient because, while the family system may itself be a stressor for the addicted patient, extended family members can often help to provide structure, boundaries, and positive reinforcement for change. Conversely, a patient who is highly motivated to change, and yet is financially or functionally dependent on a dysfunctional family system, can sometimes be undermined in his or her attempts to make the necessary changes that support recovery. Understanding these dynamics and knowing their patients and families helps a physician to make an informed decision regarding referrals and treatment options for them.

see Callout: Create Your Own Genogram and Explore Your Family Background
The Social System

Once the physician has explored the family system it is equally important to explore other influencing systems such as school, church, work, culture, and community. The physician should assess the educational, occupational, legal, community, and spiritual-cultural systems that influence and affect the patient’s recovery environment and support system. Additionally, asking questions that further explore a patient’s religious belief system can promote trust and aide the physician with valuable information regarding the customs, rituals, preferences, and practices. The final step is to explore and help formulate the patient’s goals in preparation for the appropriate referral and outsourcing of the treatment process.

Once the physician has explored the individual, family, and social systems, the clinician will have a broader scope and understanding of the patient’s needs. From this vantage point, the knowledge of outsourcing referents will help educate the patient and offer a discussion of the specific options, range of cost, and modalities of care to make a better decision about the treatment process.

A physician must be cognizant of the fact that their patients are people with vibrant histories consisting of painful and negative experiences, as well as positive life experiences, relationships, and connections. More often than not, patients have experienced loss, sadness, disappointment, fears and anxieties, as well as episodes of insecurities and suffering. If a physician can empathize and attend to the whole person (including his or her history) with genuine care and interest, patients will feel more secure and will deepen their trust in the process. This often makes a huge difference in allowing physicians to obtain the critical and key points of information that they require in order to create the most appropriate care and treatment plans for their patients, thus improving their quality of care.

In getting critical and key points of information much emphasis is placed on asking the right questions. Certainly, a physician is less likely to obtain pertinent information if the right questions are never asked; however, listening to the patient’s responses, attentively and without interruption, is key. A physician should start by making eye contact as they greet their patient. This may sound simple, but if patients feel that their physician is distracted or buried in paperwork then they are less likely to feel valued and cared about. Following the evaluation the physician should take the time to reflect upon what he or she heard the patient report, not only to ensure accuracy but also to validate the patient’s experience.

Health care is a complex profession. To reflect upon circumstances and outcomes, and to balance them with perspective, promotes meaning to the workplace milieu. A cornerstone of treatment in medicine is the therapeutic alliance—the therapeutic relationship between a healthcare professional and a patient. This contract can become complicated, however, if there is patient transference onto the doctor. Conversely, while many believe that the ability to have empathy for a patient is an important dimension of the treatment process, this may come at a high price for
the physician who has his or her own wants, vulnerabilities, and desires, which offer fertile ground for counter-transference from the doctor onto the patient.

As a physician, the facilitation of the effectiveness of team partnering and leadership requires the subordination of individual needs and the promotion of the needs of the whole in order to create successful outcomes and healing. This is a key component in the “making of a physician” and of knowing thyself.

**Know Your Options**

Various levels and types of services are available to treat addiction. While not all patients require each type of service, it is important for a physician to be aware of the options available in order to help their patients choose the types of services that are right for them. Many programs offer variations within each service type and are able to adjust to special populations and patient needs, but this must often be arranged in advance. Good treatment programs should provide an aftercare and relapse prevention plan, along with a discharge summary before the patient is released. Other key characteristics of quality services include the utilization of evidence-based treatments, licensed and credentialed staff, tailoring care to the individual needs of the patient, accreditation by local or national credentialing bodies, and prioritizing coordination of care with other providers. It’s important to keep these key components in mind while reviewing the basic categories of services below.

**Detoxification Services**

Patients who are actively using substances will need to go through a detoxification phase before they can physically and mentally engage in the treatment process. This is a critical point in the assessment and placement of the patient. Detoxification may need to be medically supervised or managed, given the severity of possible withdrawal symptoms. Medically managed detoxification is appropriate for patients who need medical intervention to manage the symptoms of detoxification and to ensure the safety of the patient during this phase. Other patients may need to be medically supervised, where a medical team oversees the detoxification process and can intervene if necessary to maintain stability. Detoxification services may be provided both through inpatient or outpatient programs.

**Inpatient and Residential Services**

Within the category of inpatient or residential programs there are a variety of different levels. The general characteristic of this service, however, is that the patient lives and sleeps at the facility. Such programs create a safe, stable, and structured environment for patients to focus on their treatment and to establish sobriety. At the higher level of intensity, inpatient programs are medically managed, meaning that medical staff monitors the patient. Medical monitoring may include the support of a full hospital and is helpful in situations where a patient has coexisting
medical, emotional, or behavioural issues. A clinical team that oversees the patient’s recovery process manages these residential treatments. Such programs help a client to establish sobriety and to focus on learning the skills required to maintain their recovery and to manage any other coexisting conditions. Long-term residential programs, such as halfway houses, are also included in this category. These facilities provide housing and a structured environment for patients while they participate in other recovery services.

**Outpatient Services**

Outpatient services are provided to patients who are able to maintain their safety and self-care outside of a residential setting. While outpatient services vary in intensity and type, they include individual, group, couples, and family therapy, as well as outpatient medication management.

Standard outpatient services typically total less than nine hours per week; intensive outpatient programs include an average of nine hours of therapy per week and can vary in length (generally 6 to 12 weeks). Partial hospitalization, however, generally provides 20 or more hours per week of addiction treatment in addition to daily medical supervision and psychiatric care.

Less intensive services, such as standard individual therapy, are tailored to the individual needs of the patient, though most are scheduled weekly. Overall, the intensity of outpatient services should be based on the intensity of the individual's need, the severity of the addiction, and the motivation level of the patient.

**Medication Management**

Medication management includes medical support programs, such as opioid treatment, in which patients utilize ongoing medication services to support their recovery. This also includes psychiatric services to address other comorbid issues, for example, depression and anxiety.

**Self-help**

Self-help services may take many different forms. In this category, the patient engages in addiction recovery work without direct contact with a treatment professional. This category includes 12-step programs, faith-based recovery programs, at-home recovery workbooks and bibliotherapy, and on-line recovery programs. A patient may find self-help reading, groups, or activities helpful in maintaining a recovery program as ongoing care after completing treatment. Self-help activities may be an appropriate recommendation for a patient who is generally high-functioning, highly motivated, and in a stable environment for change.

**Specialized Services**

There is a growing field of specialized treatment programs that do not fit the typical categories listed above. Many treatment providers across the world have special programs tailored to specific
needs. For example, extensive assessment from a multidisciplinary treatment approach, or intensive outpatient programs that utilize individual and group therapy for a few days or weeks deepen the recovery work and trauma healing in order to address the underlying causes of addiction.

**BUILD A BRIDGE**

Physicians can act as a bridge to other services and supports. Whether directly treating the addiction or referring patients to other service providers, physicians can help their patients become connected to professional and natural supports. Remaining connected throughout the treatment process also helps to bridge the patient back to the physician.

**Personal Connections**

A physician’s personal connections with other treatment providers can greatly affect the physician and the patient. The decision to go into treatment can be wrought with fear and uncertainty.

 Patients feel more secure knowing that their physicians personally know the providers to whom they are being referred and that their physicians stand behind their work. This helps to instill trust in the patient for the service provider—knowing they are in good hands can help them feel safer and less anxious.

 Building connections with treatment providers, however, takes effort on the physicians’ part. They are certainly not expected to know every treatment provider in their area; often their patients may have to travel to receive treatment. However, different strategies can be employed to build their network of connections. They can reach out directly, attend conferences, take referrals from other colleagues, or through other personal recommendations. Another option is to develop connections with the providers while a patient is in treatment. In either case, it is important for a physician to get to know the treatment providers, their treatment approach, and the population with which they work. While it is important to ensure the provider offers quality care, it is equally important to assess whether the provider utilizes the fundamental skills of being non-judgmental, genuine in their care, empathetic with their patients, and able to assess the family and community systems within which the patient lives. If a physician feels confident in these skills and tools, then they can feel more confident in a treatment provider’s foundation to implement their treatment approach.

**Coordinate—Bridges to Services**

Once a physician has made a connection with treatment providers, explored their treatment philosophy and approach, and feels confident in the quality of care for their patients, he or she must then work to sustain the relationship. With an established connection, physicians can speak confidently and knowledgeably about the provider to their patients. When the patient is ready
to make the step into treatment, the physician can make a personal phone call to the provider, bridging the patient to the provider.

If the physician is able to brief the service provider about their patient in advance of the appointment it can help the patient to feel more secure about the treatment program, as the treatment facility is both prepared to receive them and will already have foundational of knowledge about them. Similarly, this allows the treatment provider to be more prepared and to be able to tailor the program to the patient’s specific needs. Sharing what they have gleaned about their patients’ family system, their strengths, fears, insecurities, severity of use, and other relevant data, physicians can facilitate a smooth transition for the patients and the providers.

At other times, patients may select a treatment provider with whom their physician is not familiar. This creates an opportunity for physicians to know a new provider and learn about their patient, based on the reasons the patient selected the provider. Taking the time to get to know a new provider and sharing knowledge about the patient shows care and concern on the part of the physicians for their patients and supports a smooth transition into services.

**Stay Involved—Bridges Back**

Once a physician has supported a patient into treatment, the next steps begin. Maintaining contact with the treatment program or provider allows the physicians to stay abreast of the status of their patients. Also, they will likely learn more about their patients in the process, which can help them in providing their own medical services. Additionally, when a patient hears that their physician called to check in on their progress, it sends a message of care to that patient during what can often be a difficult and emotional process. Knowing that their physician is interested in their progress is meaningful. Further, the physician may be involved to some extent in the discharge planning and set-up of the patient’s return to their care—thus facilitating a bridge back to “everyday life.” This can be a much-needed welcome as the transition between services can be marked by mixed emotions for some patients. A physician who takes small steps to coordinate with the treatment team can carry significant meaning for a patient.
REFLECTIVE QUESTIONS

1. Create a list of at least 10 of your personal character strengths and 10 character shortcomings. In what ways could your strengths become a weakness in your role as a physician? How could knowing your weaknesses help you in your professional role?

2. Following the completion of your own genogram, what insights have you gleaned from your family dynamics that could positively or negatively affect you as a physician?

3. What would you want to know about treatment programs that would allow you to trust your patients to their care?

4. How does coordination of care between providers benefit the client, the referring physician, and the treating physician?
Podcasts

Addiction

Podcast 9: Prevention, Intervention and Treatment of Addiction
Podcast 10: Early Trauma in Addiction
Podcast 11: Chronic Disease Management Model of Addiction Treatment: A Healthcare System Response
Podcast 12: Quality Improvement Strategies and Evaluation for Addiction Treatment Programs

Virtual Patient Cases

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

Polly Farmercie
Harriet has a fit
Create Your Own Genogram and Explore Your Family Background

Exploring your own family history and dynamic is an important aspect of getting to “know thyself” as a physician. Creating a genogram, a pictorial display of a person's family relationships and medical history, can be a very helpful tool. In this exercise, you can go back as many generations as you’d like, but be sure to include at least your parents and grandparents.

What you’ll need:
- one large piece of paper
- markers (at least four different colours)
- basic genogram components located at www.genograms.org

Once you’ve created the basic structure of your genogram, add the known medical history of your family. If you’d like, you can create your own key to represent medical issues in your family. Notice any patterns that repeat. You may also see the risk factors for younger generations.

Next, identify mental health conditions such as anxiety, depression, attention-deficit hyperactivity disorder (ADHD), alcohol addiction, substance abuse, or other process addictions.

Finally, draw relationship patterns between family members. You do not need to draw the relationship lines between everyone on the page, but do include the relationships between the primary people in your life. For example, parents and spouses should be included; if you had a particularly strong relationship with a grandmother, note it; if you get along well with most of your siblings but are cut off from one that would be a relevant note.

As you look at your genogram, what do you notice? What does the structure tell you about your family? What is the family message about marriage, divorce, affairs, or unplanned pregnancies? What does it say about life expectancy or fertility?

What does the medical history suggest to you? Are there addictions in your family? What medical issues could interfere with an addiction if they were present in the same individual? Are there patterns of behaviours that may get passed down intergenerationally? What does
As you explore the relationship patterns, can you see if your family is highly connected? Or, is it cut off? Do some people get cut out, or, are there close bonds despite significant conflict? Are there good boundaries between parents and children? Or, are the emotional needs of parents filled by their children? What kind of support would this family provide if a member developed an addiction?

Establishing Rapport

As a physician, it is vital to cultivate a solid foundation of interpersonal skills that provide a non-judgmental approach and genuine care and empathy towards your patients. A calm, non-judgmental, attentive stance fosters an environment in which patients feel respected and valued. Genuine care for patients as a whole, and not just as symptoms checklists, is critical to building rapport with them.
Learning Objectives

After completing this section, the learner will be able to:

1. Describe how substance abuse and addiction relate to the chronic disease model.
2. Describe how to integrate substance abuse and addiction screening into history-taking.
3. Describe the three types of screening.
4. Identify resources to learn about screening for various substances.
5. Describe the approach to physical examination in a patient with substance abuse or addiction.
6. Describe a focused physical examination pertinent to substance abuse and addiction.
7. Identify key physical findings that should alert healthcare providers to the possibility of substance abuse and addiction.
8. Identify resources to learn about screening for various substances.
9. Discuss the diagnostic paradigm primarily utilising the framework of DSM-5, making reference to other diagnostic approaches.

Substance Abuse and the Role of the Primary Healthcare Provider

Screening for substance abuse and addiction is an important aspect of practising clinical medicine in Canada. Recent data suggests that the prevalence of substance abuse in Canada is 11%, and that 10% of Canadians 15 years of age and over report symptoms consistent with alcohol or illicit drug dependence\(^1\,^2\). The 2010 National Physician Survey (NPS) indicated that 69% of Canadian family physicians and general practitioners reported seeing patients with addictions, and that 30% offer substance abuse care\(^1\). NPS data also demonstrated that addiction is prevalent across the country, including inner city, suburban, rural, and remote populations equally\(^1\).

Despite this national prevalence, physicians may feel unprepared to provide adequate clinical care to people suffering from substance abuse or addiction. This is due to numerous factors, including lack of training during medical school, lack of an acceptable therapeutic model, lack of role models and positive attitudes, lack of advocacy, and/or a personal or family history of substance abuse\(^3\). Research from the United States reports that undergraduate medical trainees
received only 12 hours of training related to alcohol- and drug-related conditions during a four-year program. Similarly, in Canada substance abuse and addiction are often not recognized as core curricular elements during family medicine clerkship rotations. Visit Street Drug Guide.

Primary care team members are in an excellent position to provide chronic disease care, including for patients with substance abuse and addiction problems. In providing continuous care, they can effectively screen, detect, diagnose, manage, and follow individuals with substance abuse and addiction problems.

Specialists also need to be aware of the role of addiction and of their local resources for providing integrated care. Root causes should always be addressed.

**History-taking**

It is important to adhere to the following general principles and practices of effective history-taking:

- Make active attempts to understand the patient’s experiences and perspective.
- Employ strategies to build relationship and rapport. *(see Chapter 4.4 Callout: Establishing Rapport)*
- Start with open-ended questions and move to more closed-ended questions throughout the clinical encounter.
- Demonstrate the use of non-judgemental language and behaviour.
- Ask questions regarding substance abuse and addiction, generally during the lifestyle section of the history.
- Use “signposting” as a strategy to guide the interview (see the following Callout), and advise patients that these questions can provide information important to their health and well-being.
- Identify situations in which the history may be limited or should be deferred, such as when the patient is acutely intoxicated or in withdrawal (which can result in an altered level of consciousness) or when the presenting complaint must be adequately addressed before exploring the root cause.
SCREENING AND DETECTION

When to Screen for Substance Abuse and Addiction

Clinical encounters present a number of valuable opportunities to screen for substance abuse and addiction. Screening provides the opportunity to identify substance abuse or addiction, as well as medical complications and other addiction-related risks. Risk factors may be identified, and interventions and treatment initiated (see Risk factors in Chapter 2.3 Adverse Childhood Experiences: The ACE Study and 2.4 Intergenerational Transmission of Addictive Behaviours). Three different scenarios in which screening may occur are as follows:

- Screening may be performed opportunistically.
- Screening may be performed as part of the periodic health examination (PHE).
- Screening may be prompted by a presenting symptom, a red flag in the patient’s history, or a clinical finding upon physical examination.

Opportunistic Screening

This type of screening may occur during a routine clinical encounter that generally does not include a presenting history or finding related to substance abuse or addiction. The healthcare provider may choose to dedicate a portion of the visit to screening strategies. For example, a 24-year-old female visits her physician to discuss contraception and testing for sexually transmitted infections. During the visit, her physician takes the opportunity to review her use of alcohol and tobacco, and therefore screens for substance abuse.

During the Periodic Health Examination

During the PHE, the physician performs a history, risk assessment, and focused physical examination relevant to the patient’s age, gender, and ongoing medical issues. Preventive health strategies and the delivery of preventive services are also discussed. Evidence supports the benefits of the PHE and has demonstrated reduced patient anxiety. The College of Family Physicians of Canada (CFPC) supports screening for alcohol, tobacco, and drug use during the routine PHE.

Prompted Screening

Prompted screening is in response to a particular trigger, either on history-taking or physical examination. This type of screening should be considered when red flags are noted in the patient’s history, including the following: frequent absences from school or work, history of frequent trauma, adverse childhood experiences or accidental injuries, depression or anxiety, labile hypertension, gastrointestinal symptoms, sexual dysfunction, sleep disorders, relationship difficulties, convictions for driving while impaired, suspicious presenting clinical symptom, suspicious presenting medical
disorder (see Table 5-1), a typical response to an existing condition, and clinical examination finding.

Table 5-1: Medical Disorders Associated with Specific Substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>Medical Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td><strong>Gastrointestinal</strong>: esophagitis, Mallory-Weiss tear, gastritis, peptic ulcer disease, fatty liver, alcohol-induced hepatitis, cirrhosis, acute or chronic pancreatitis</td>
</tr>
<tr>
<td></td>
<td><strong>Cardiovascular</strong>: hypertension, cardiomyopathy, coronary artery disease</td>
</tr>
<tr>
<td></td>
<td><strong>Neurological</strong>: Wernicke encephalopathy, alcohol-related dementia, cerebellar degeneration, peripheral neuropathy, stroke, seizures</td>
</tr>
<tr>
<td></td>
<td><strong>Hematological</strong>: thrombocytopenia, anemia</td>
</tr>
<tr>
<td></td>
<td><strong>Neoplastic</strong>: cancers of the esophagus, liver, and pancreas</td>
</tr>
<tr>
<td></td>
<td><strong>Other</strong>: sexual dysfunction, sleep disorders, vitamin B deficiency, peripheral myopathy</td>
</tr>
<tr>
<td>Nicotine</td>
<td><strong>Cardiovascular</strong>: coronary artery disease, vascular disease</td>
</tr>
<tr>
<td></td>
<td><strong>Respiratory</strong>: chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td><strong>Neoplastic</strong>: cancers of the mouth, esophagus, and lung</td>
</tr>
<tr>
<td>Cocaine</td>
<td><strong>Cardiovascular</strong>: ischemic heart disease, cardiac arrhythmias, cardiomyopathy, aortic dissection, myocardial infarction</td>
</tr>
<tr>
<td></td>
<td><strong>Respiratory</strong>: spontaneous pneumothorax, pneumomediastinum, bronchitis, pneumonitis and bronchospasm (when drug is smoked)</td>
</tr>
<tr>
<td></td>
<td><strong>Neurological</strong>: seizures, stroke</td>
</tr>
<tr>
<td></td>
<td><strong>Other</strong>: sinusitis, nasal irritation, septal bleeding and perforation (with intranasal use), HIV and hepatitis (with intravenous use), weight loss and malnutrition</td>
</tr>
<tr>
<td>Opioids (when used intravenously)</td>
<td><strong>Gastrointestinal</strong>: acute and chronic viral hepatitis</td>
</tr>
<tr>
<td></td>
<td><strong>Cardiovascular</strong>: endocarditis</td>
</tr>
<tr>
<td></td>
<td><strong>Respiratory</strong>: tuberculosis (which may be treatment-resistant)</td>
</tr>
<tr>
<td></td>
<td><strong>Neurological</strong>: meningitis</td>
</tr>
<tr>
<td></td>
<td><strong>Other</strong>: cellulitis, abscesses, osteomyelitis, HIV</td>
</tr>
</tbody>
</table>


How to Screen for Substance Abuse and Addiction

Patients do not routinely volunteer information regarding substance abuse or addiction, and healthcare providers often fail to inquire about substance use. This results in missed opportunities for detection. Therefore, it is imperative that healthcare providers know how to screen appropriately for these conditions. Healthcare providers may use general questions or formal validated tools to
screen for substance abuse and addiction. Each tool has different questions and varying abilities to detect substance use. Ideally, screening tools should be simple, quick, and easy to use.

A formal screening tool for alcohol use is the Alcohol Screening, Brief Intervention and Referral (ASBIR). This tool is a resource for healthcare professionals to help reduce alcohol-related risks in the population and is supported by the CFPC. The ASBIR is available from: www.sbir-diba.ca. Visit the ASBIR web site to review and work through the entire tool.

The CFPC recommends the ASBIR as the preferred screening tool for alcohol use. Healthcare providers inquire about alcohol use and quantify intake in relation to Canada’s Low-Risk Alcohol Drinking Guidelines. If responses indicate that intake levels are above the established guidelines, a risk level assessment is completed which stratifies individuals into three categories: elevated risk, alcohol abuse, or alcohol dependence.

The next steps involve advising and assisting individuals based on their risk level by implementing appropriate brief primary care interventions. Interventions may include support, education, motivational interviewing, stage of change assessment, referral, treatment with medications, and monitoring for withdrawal when appropriate. Ongoing follow-up and support are essential for all risk categories.

Finally, it is important to recognize that once substance abuse or addiction is detected on screening, a complete assessment of the clinical situation is warranted. Elements to further explore might include the following:

- other substance use and associated history, recovery, or relapse issues
- effects such as intoxication, withdrawal, tolerance, dependence, or behaviour changes
- general medical history of substance-related complications
- psychiatric history
- family history, related substance abuse
- educational and social history
- work history, including such details as driving, for example
- safety and consequences, legal issues including driving offences
- collateral history-taking from family and friends, if possible

see Chapter 4.4 Building a Bridge: The Therapeutic Alliance
Investigations

Healthcare providers may choose to order investigations to assist with the detection and confirmation of suspected substance abuse or addiction. A number of drug and toxin screens are available that test for substances in the blood or urine. Such testing may be reported as either qualitative (positive or negative) or quantitative (reported as a number value), and varies depending on city or region. The gamma glutamyltransferase (GGT) and mean corpuscular volume (MCV) may be useful when assessing for alcohol use as they demonstrate elevated values in patients with ongoing alcohol use. Although not diagnostic, the results may add to the overall clinical picture and assist in the screening process. However, it is important to note that both the GGT and MCV may be elevated due to other common conditions such as liver disease and B12 deficiency, respectively.

Physical Examination

Performing an appropriate physical examination is a critical step in the assessment of any patient. It supports clinical reasoning by providing objective information regarding the health status of the patient, and findings on examination may confirm or refute the diagnosis generated by the history or presenting complaint, or may trigger a new diagnosis or clinical question. A physical examination may be required as part of a routine PHE, office visit, emergency or hospital visit, or other clinical encounter. Or, it may be conducted specifically for screening purposes or directly in response to a presenting symptom or complaint.

When examining a patient, it is important to adhere to the general principles of effective physical examination. Additionally, when working with patients who suffer from substance abuse and addiction (such as acute intoxication or withdrawal), it is important to remember that unique situations may arise in which altered levels of consciousness or aggressive behaviour on the part of the patient may limit a healthcare provider’s ability to perform a thorough examination.

Physical Examination Advice

- The healthcare provider must ensure her or his own safety and the safety of the patient.
- The healthcare provider must always demonstrate respect for the patient during the examination.
- In a calm and patient manner, the healthcare provider’s must communicate to the patient what he or she is going to do and how it will be done. It is important to remember, however, that communication may be difficult in situations where a patient presents with acute intoxication or severe withdrawal, as their understanding may be limited.
• Consent for examination is required under most circumstances, except in the case of preventing conditions that threaten life or limb.

• Parts of an examination should be deferred if conducting them would compromise the safety of either the healthcare provider or the patient (for example, if the patient is aggressive or delusional). Finding the right balance can be tricky in some unusual situations, but a calm, confident, and non-confrontational approach often helps.

• The healthcare provider must be sensitive to the patient’s history of trauma. Healthcare services can sometimes retraumatize patients who have a history of abuse. Strategies such as having a chaperone for the patient can help.

• The healthcare provider must follow standard procedures such as preparation, positioning, draping, appropriate exposure, and chaperones.

• Perform a primary survey for obvious distress (ABCs, vital signs, level of consciousness).

• Use the common systems approach to physical examinations.

• Perform focused and appropriate examination manoeuvres that are guided by the patient’s history, presenting complaint, and clinical query.

• Identify potential specific findings based on the addiction in question and know the various syndromes present.

• Have an understanding of the physiologic effects of drug and substance classes across systems to enhance the healthcare provider’s synthesis of findings. As a general rule, withdrawal symptoms are the opposite of those seen in acute intoxication1,2.

### Systems Approach to the Physical Examination

Physical examinations may detect specific findings that suggest substance use disorder or addiction. Some signs of process addiction could be unexplained weight gain, frequent sexually transmitted infections (STIs), or needle track marks.

Initially, a healthcare provider may look for general manifestations of malnutrition or weight loss, dishevelled or unkempt appearance, skin lesions, needle tracks, etc. However, addictions are often missed as patients may be well dressed and appear healthy. As such, it is important that healthcare providers’ avoid being trapped by their own assumptions. Similarly, while behavioural clues such as delirium, confusion, visual hallucinations, and aggressive or inappropriate behaviour should alert a healthcare provider to the possibility of substance abuse or addiction, many patients are well-rehearsed at hiding behind convincing alternate histories. The healthcare provider must be aware that the presence of concurrent mental illness and self-medication may be compounding factors.
Particular neurological signs, such as dilated or pinpoint pupils, conjunctival or nasal inflammation, dry mouth, flushing, sweating, tremor, or liver flap, may alert a physician to the presence of substance use. Knowing the underlying physiology allows a healthcare provider to group constellations of symptoms more effectively. For example, the intense vasoconstriction induced by snorting cocaine causes ischemic necrosis and the perforation of the nasal septum.

Cardiovascular symptoms such as tachycardia and hypertension, hypotension, shutdown of the peripheral circulation, or even the lack of veins in an otherwise healthy young adult should alert a healthcare provider to the possible presence of substance abuse or addiction. In the respiratory system, however, the associations are less obvious, but crackles, pulmonary consolidation, and unexplained pneumonia are all possible alerting factors. Of note, tuberculosis, with its broad range of findings, is once again being detected in at-risk populations.

Gastrointestinal symptoms that are otherwise hard to explain may also suggest substance use. For example, narcotics and substances with anticholinergic properties tend to constipate, while withdrawal (or cholinergic stimulants such as hallucinogenic mushrooms) have the opposite effect. Additionally, if a healthcare provider’s findings detect esophagitis or gastritis, this could suggest substance use as many substances act as irritants to the gastrointestinal mucosae. Concomitant liver damage and hepatitis may arise from alcohol use or from infections associated with substance abuse or addiction. It is important to remember that in the early phases of cirrhosis, the liver may be enlarged, but a chronically scarred cirrhotic liver is shrunken and hard to feel.

The genito-urinary system should also be properly assessed. While it is uncommon for substance use to cause signs such as urinary retention, the population and/or individuals with sex addiction engage more often in high-risk sexual practices, either because of associated social/lifestyle factors or because they have resorted to alternate forms of income to support their substance use.

**Diagnosis of Substance-Related and Addictive Disorders**

Addiction is a process where individuals ingest a substance or engage in a behaviour that, although perhaps initially pleasurable, is associated with progressively compulsive use or behaviour that adversely impacts other domains of their life, such as work and relationships. This behaviour can be associated with tolerance and withdrawal; frequently, it is a response to emotional or psychological stress.

The purpose of this section is to present a diagnostic paradigm primarily utilizing the framework of DSM-5, and also to make reference to other diagnostic approaches.

DSM-IV had no reference to behavioural addictions, but DSM-5 now includes gambling disorder as an example of a behavioural addiction. DSM-5 has combined the categories of substance abuse and dependence, which were categories in DSM-IV, into the broader category of
Substance Use Disorder and measures symptoms on a mild to severe continuum, depending on the number of diagnostic criteria that are met. Substance-induced disorders include intoxication, withdrawal, and substance-induced mental disorders. Ten classes of substances are described in DSM-5, ranging from alcohol to caffeine; each is described in its intoxication, withdrawal, and persistent syndromes as applicable. This is shown in the following Table 5-1.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Psychotic disorders</th>
<th>Bipolar disorders</th>
<th>Depressive disorders</th>
<th>Anxiety disorders</th>
<th>Obsessive-compulsive and related disorders</th>
<th>Sleep disorder</th>
<th>Sexual dysfunctions</th>
<th>Delirium</th>
<th>Neurocognitive disorders</th>
<th>Substance use disorders</th>
<th>Substance intoxication</th>
<th>Substance withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W/P</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
<td></td>
<td></td>
<td>I/W</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>I</td>
<td></td>
<td></td>
<td>I</td>
<td>I/W</td>
<td>I</td>
<td></td>
<td>I</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td></td>
<td>I</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other hallucinogens</td>
<td>I*</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td></td>
<td>I</td>
<td></td>
<td>I</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalants</td>
<td>I</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td>I</td>
<td></td>
<td>I</td>
<td>I/P</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>W</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sedatives, hypnotics, or anxiolytics</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W/P</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stimulants**</td>
<td>I</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I</td>
<td>I</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td></td>
<td>W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other (or unknown)</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W</td>
<td>I/W/P</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Note. X = The category is recognized in DSM-5. I = The specifier “with onset during intoxication” may be noted for the category. W = The specifier “with onset during withdrawal” may be noted for the category. I/W = Either “with onset during intoxication” or “with onset during withdrawal” may be noted for the category. P = The disorder is persisting. *Also hallucinogen persisting perception disorder (flashbacks). **Includes amphetamine-type substances, cocaine, and other or unspecified stimulants.

Table 5-1 From: American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5®), 5th ed., 482. Copyright 2013 by the American Psychiatric Association. Used with permission.

Comorbidity (having more than one illness at the same time) is the rule rather than the exception in dealing with substance-related or behavioural addictions. Dual diagnosis is the presence of more than one psychiatric diagnosis in an individual. Frequently, multiple addictions co-exist in an individual, and there may be medical comorbidities as a direct or indirect result of these addictions.
Thus, an individual may have multiple diagnoses, although the immediate focus of attention may be on one or two diagnoses during a clinical encounter. When it comes to substance-use disorders, the use of one substance may be in remission while the use of another substance may be spiralling out of control. At any one time, there may be concurrent addictions, and individuals may also be suffering physical and social consequences of their current and previous addictions. For example, they may have an opioid addiction that is currently in remission, but they may be using alcohol and cannabis in a harmful manner, such that they are experiencing damage to their physical health, and they now have developed depressive symptoms in response to their disconnection from their social and familial networks. Using the biopsychosocial model of understanding, the clinician can use a broader approach over time, while still being able to focus on a particular diagnosis, at a particular time, thus reducing the complexity of treatment. This approach further underscores the importance of using a chronic disease model in treating these individuals with comorbidity. In Canada, at least 20% of people with a mental illness have a comorbid substance-use disorder. Likewise, 15% of people with addictions also have a mental illness.

In DSM-5 a pathological pattern of behaviour related to the addiction(s) must exist in order to be diagnosed as a disorder. Within Criterion A, which deals with “impaired control, social impairment, craving, risky use and pharmacological criteria,” there are eleven criteria, of which two must be present for a diagnosis.

Commonly used screening tools used to screen for alcohol and drug abuse include the following:


These are examples of screening tools but are not necessarily diagnostic tools. Diagnosis is based upon a thorough history, physical, and other investigations, where appropriate, as in all areas of medicine.

The APA Diagnostic and Statistical Manual of Mental Disorders, fifth edition, provides a table of medical disorders associated with specific substances, on page 482.
MULTIPLE-CHOICE QUESTIONS

1. Which of the following statements is most commonly true?
   a. Good history-taking will usually reveal substance abuse patterns.
   b. When challenged in a neutral manner, most abusers will admit to their abuse.
   c. Low socioeconomic class is the most reliable predictor of abuse.
   d. Laboratory screening is a reliable method of substance abuse detection.

2. Addiction in Canada is:
   a. more likely to be prevalent in urban areas
   b. prevalent in inner city, suburban, rural, and remote populations
   c. related to socioeconomic status
   d. none of the above
3. Types of screening for substance abuse and addiction include:
   a. opportunistic screening
   b. screening during the Periodic Health Examination
   c. prompted screening
   d. all of the above

4. Substance abuse and addiction should be viewed through the perspective of chronic disease.
   a. true
   b. false
**Podcasts**

Addiction

**Podcast 8: Different Kinds of Addiction**

**Podcast 9: Prevention, Intervention and Treatment of Addiction**

**Podcast 10: Early Trauma in Addiction**

**Further Reading**


3. CAMH and McMaster Addictions Curriculum Project: Screening Questionnaires. This collaboration between the Centre for Addiction and Mental Health (CAMH) and McMaster is an educational initiative to promote curriculum innovation and resources related to the spectrum of alcohol use disorders. Available from: machealth.ca/programs/camh_and_mcmaster_addictions_curriculum_project/p/teaching-resources


**Virtual Patient Cases**

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

- Case of Miriam (Age 15)
- Case of Ethel
- Case of Dudley
- Case of Miriam (Age 42)
- Case of Ashley
- AFMC Case 1 (Marilyn Age 74)
- AFMC Case 2 (Judy Age 45)
AFMC Case 3 (Sue Age 35)
AFMC Case 4 (Paul Age 9)
AFMC Case 5 (Jake Age 15)
AFMC Case 6 (Phil Age 32)
AFMC Case 7 (Bill Age 48)
AFMC Case 8 (Joe Age 60)
Agitated Adam
Alice in Slumberland
Ann with green labels
Beth
Boxer Bruce
Joan is Worried
Vomiting Vince
References


Chronic Disease Management of Addiction

Substance abuse and addiction should be viewed through the perspective of chronic disease. Chronic diseases are generally ongoing and lengthy, have a variable and changing clinical course, are multi-factorial, and have no cure. The impact of chronic disease on the patient is significant, resulting in both impaired physical activity and ability to perform daily activities, as well as a reduced quality of life. Chronic disease can, however, be effectively controlled and managed by the patient given appropriate support from healthcare professionals. Effective chronic disease management includes the following elements:

- developing a multi-disciplinary and team-focused collaborative approach
- including the patients’ families in the care team
- engaging, enabling, and empowering patients
- assisting patients in taking an active role in managing their disease
- assisting patients to develop skills for self-management

Signposting

Signposting is an interviewing technique that helps patients understand the relevance of where interviewers are going with their questions. This technique provides the opportunity to explain why certain elements of the patient’s history are important. An example of such a question is, “Now I’d like to ask you about your family.” Signposting is covered in communications courses and again in some form or other during medical school but rarely labeled as such. The technique helps to keep the interview transparent and the tone neutral.
Giannini’s Model and Algorithm

In the paper, “An Approach to Drug Abuse, Intoxication and Withdrawal,” Giannini presents a model and algorithm that can be very useful in the clinical environment. The article describes the effects of substances on the brain, as well as their symptoms and clinical presentations. Classes of drugs are linked to their physiology and to the clinical picture. Remember, however, that presentations are not exclusively sensitive or specific.

To Learn More

To learn more about alcohol abuse, review the Alcohol Curriculum Project from the Centre for Addiction and Mental Health (CAMH) and McMaster University, which has two e-learning modules reviewing at-risk drinking and alcohol dependence.

For information on the screening and assessment of tobacco and opioid use, CAMH has developed educational material as part of the Primary Care Addiction Toolkit.
Driving

When assessing for substance abuse it is imperative to determine whether the patient is fit to operate a motor vehicle. This entails physician assessment based on the patient’s functional capacity and includes the physical, mental, and emotional realms. If a patient is found unfit, their driving may not only harm themselves but may also bring harm to others. An excellent resource for those learning, as well as practising healthcare professionals, is the Canadian Medical Association’s Driver’s Guide: Determining Medical Fitness to Operate Motor Vehicles, 8th Edition.

Overlooked Signs of Addiction

- Cirrhotic livers are small, not big.
- Look for concomitant illnesses — they contribute hugely to overall harm.
- Smart, well-presented patients may nevertheless be substance or process addicts.
- Polysubstance abuse may complicate the physiological presentation.
6.1 Community Based Treatment

Learning Objectives

After completing this chapter, the learner will be able to:

1) Demonstrate the complexity of recovery from addiction.
2) Describe ways that our treatment system can become more recovery oriented.
3) Discuss, in an informed way, the learner’s role as an advocate for evidence-based care.
4) Access a wide range of resources to improve his or her skills and knowledge.
5) Discuss, in an informed way, how the knowledge translation and self-management used in addiction treatment can inform chronic disease management more generally.

Introduction

This chapter addresses personal, system, and clinical approaches to the treatment of addiction. It weaves together information from previous chapters on the neuroscience and risk factors of addiction so one can better appreciate what is happening in the brains of people transitioning into recovery. It also addresses system issues in order to advocate for a more rational approach to care for those suffering from the disease of addiction. Finally, it will discuss some of the clinical and treatment information addressed in this book. Nevertheless, it begins with the attitudes and experiences of the physician in order to help future clinicians to be better prepared when they encounter the complexity of patients struggling with addiction. Too much of the behaviour modelled in the healthcare system is either counter-productive or frankly abusive. In some instances, it reflects a level of ignorance imposed on patients with mental health problems from the last century (see Chapter 4.2 Stigma and Reflective Practice Overcoming Stigma and Discrimination in Clinical Settings). The community of the healthcare system and physicians can and must do better. The following is a reflective exercise to address an individual’s personal experiences and attitudes.

Reflective Questions

1. Have you, a friend, or anyone in your family ever had problems with alcohol, drugs, gambling, gaming, or any other addiction?
2. What was it like for them? What was it like for you and others around them?
3. How did it impact your life or that of those close to you?
4. What were their risk factors?
5. How did the addiction progress?
6. What helped them to get better?
7. Would that experience influence how you view, and potentially treat, people suffering from addiction?

You may wish to process these questions with someone you trust. Be frank. Self-awareness requires honesty.

As part of this reflective exercise, see also the genogram section in 4.4 Building a Bridge: The Therapeutic Alliance.

**RECOVERY**

The goal of treatment is to help patients establish a meaningful life in the absence of addiction. For a life to be authentic and durable it must be rooted in an individual’s sense of identity, worldview, and social milieu. Physicians, counsellors, and therapists are therefore change agents, helping patients make the necessary alterations in their lives in order to achieve recovery. While this is a very broad definition of recovery, there are others that both provide further insight into the journey that patients must take and inform the approach required to support the process.

The Betty Ford Institute defines recovery as “a voluntarily maintained lifestyle characterized by sobriety, personal health, and citizenship”. This is echoed in the United Kingdom Drug Strategy’s principles of “wellbeing, citizenship, and freedom from dependence”. Additionally, the American Substance Abuse and Mental Health Services Administration (SAMHSA) defines recovery as “a process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential”.

The Canadian Centre on Substance Abuse has identified six broad principles essential to recovery:

1. There are many pathways in Recovery. Recovery involves a process of personal growth along a continuum leading to abstinence. It includes a range of services and supports that span peer support, mutual aid, early identification and intervention, outreach and engagement, specialized treatment, relapse prevention and continuing care.

2. Recovery requires collaboration. Recovery focused systems require collaboration across sectors, including peer support and mutual aid, health, social, educational, criminal justice, employment, economic, spiritual and housing sectors.
3. Recovery is a personal journey toward wellbeing. Recovery is an ongoing and dynamic process that is unique to the individual’s strengths, culture, gender, personal qualities and experiences.

4. Recovery extends beyond the individual. Recovery involves family, peers, workplaces and the community.

5. Recovery is multidimensional. Recovery enhances physical, social, mental, emotional and spiritual health.

6. Recovery involves everyone. Everyone has a role to play in overcoming the stigma of addiction and in supporting and celebrating Recovery.⁴

Clearly, recovery from addiction is more layered and nuanced than a typical biomedical definition, such as the return of lost function or the mere cessation of a pathophysiological process such as pneumonia.

In order to achieve these goals, a treatment process must be similarly layered and nuanced. The American Society of Addiction Medicine (ASAM) observes that:

Many factors may influence the duration of treatment including, but not limited to, the age of the patient, the stage of illness, the existence of co-occurring addictions, the degree of associated physical and psychiatric disability, the extent of social, family, vocational and legal problems, and the patient’s readiness to change. Therefore, the length of the treatment and rehabilitation process will necessarily vary widely from case to case. In all cases, however, a continuum of care and a structural social support system (e.g., self-help groups, professional therapy, and medical supervision) are needed because of the severe nature of the illnesses and potential for relapse. Addiction is a chronic disease. Relapse prevention efforts are ongoing, especially during the first months to two years. Maintenance of disease remission is a life-long process and should be followed as with all other chronic relapsing illnesses such as diabetes and hypertension⁵.

This approach is decidedly more complex than the commonly understood linear approach of detox, rehab, and home.

In reality, patients cycle forward with periods of relapse and remission as they learn, grow, and make the necessary changes.

6.1 Community Based Treatment
The process is also layered with efforts at outreach and engagement in an effort to connect with the most marginalized patients. Various harm reduction strategies, such as needle exchange or safe injection sites, not only mitigate the potential harms of active use but also provide a place for patients to connect with healthcare providers, develop a rapport, receive information, and become engaged in care.

Once engaged in care, people with moderate to severe levels of a substance use disorder may require detoxification, or withdrawal management. This is most often done in detox facilities following established protocols based on the specific substance and the severity of the withdrawal symptoms. As it is difficult to manage well what one does not measure, there is a need for standardized and validated withdrawal scales for alcohol, such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA), or the Clinical Opiate Withdrawal Scale (COWS). Well-managed detox is safe and patient-centred; however, detox alone is not treatment. While detox holds people in care for the duration of their withdrawal, it also provides them with the opportunity to plan their transition to the treatment required after detox is complete.

The transition from detox to treatment is a high-risk time for relapse. Patients are frequently left without the psychosocial support required for this transition as treatment centres may not have the capacity to transition people directly. Without a supportive network and sober housing many people begin a cycle of use, detox, and relapse. This period is described as post-acute withdrawal and is marked by dysphoria and poor emotional containment. As will be discussed later, this is the time when the receptors in the brain, no longer awash with external substances or stimulation,
are beginning the process of returning to normal. It is a very vulnerable time, as illustrated in the following case:

**A Systems Approach**

There is a need to ensure that patients are properly assessed in order to match services with acuity and needs, to provide appropriate care, and to seamlessly transition when different levels or types of services are required. Treating addiction is no different than the treatment of any other chronic disease marked by relapses and remission, such as brittle diabetes. The National Treatment Strategy recommends a tiered approach to care in order to transition people from community-based outreach, through primary care, to various highly specialized services, and back.

Healthcare providers must commit to the principle of No Wrong Door and advocate for the appropriate services. Concurrent care for comorbid conditions, such as addiction and mental illness, or addiction and infectious diseases, requires thoughtful triage and braiding of the appropriate
level of care for each. Collaboration across services and sectors is essential, with coordinated information technology.

If this is the norm for most chronic diseases, why is it not so for addiction services? Historically, unless there were acute complications, addiction care was managed outside of the healthcare system. Community-based organizations provided the services they could, with the resources they had, using abstinent-based recovery models. Evidence-based care is relatively recent, driven by a surge in brain research and a greater integration of addiction services with mental health and other domains of the healthcare system. Progress is being made, building on the strengths and compassionate care of the past, with new knowledge, pharmaceutical tools, and better integration of the complex, comorbid care with existing services. More work, however, is needed to advance the science of addiction medicine, more that will draw on all the CanMEDS and CanMEDS-FM competencies of the next generation of physicians10.

**The Complexity of Recovery**

Caring for people whose minds and lives have been taken over by an addiction is complex (see Chapter 1.1 Neurobiology of Addiction). It is also often marked by trauma, either early childhood (See Chapter 2.1-2.5) or related to their substance use. Trauma informed care is an approach that recognizes the pervasiveness of trauma and attempts to create more compassionate care. Timing of more direct trauma work requires cessation of substance use, stable internal coping mechanisms, and good psychosocial support. Premature exploration without good emotional containment skills and support may result in relapse. On the other hand, someone struggling with recurrent relapses may wish to engage in addressing those core issues. Previous trauma or genetic loading are not required to develop an addiction although they do increase the risk, often shorten the trajectory, and may make the behaviour more deeply embedded. Adolescence and young adulthood are vulnerable times in their own right, when incomplete brain and personal development may be disrupted through repeated exposure to potent, mood-altering substances or repetitive addictive behaviours (see Chapter 2.5 Adolescent and Young Adult Triggers for Substance Misuse). Peer mentoring or binge use, in a pattern of sustained and progressive intoxication, can create the same brain changes without the epigenetic vulnerabilities. In Chapter 1.1 Neurobiology of Addiction, Koob described the primary mechanisms involved in both positive reinforcement from intoxication and in negative reinforcement from the relief of withdrawal symptoms. This cycle of salience attribution, craving, memory, intoxication, and withdrawal is illustrated in Figure 6.1-411.
Eventually, through prolonged exposure and increasing tolerance, the dopamine system is down-regulated to such a degree that people struggle to feel normal. These changes have been demonstrated on PET neuroimaging studies as shown in Figure 6.1-5.

**Figure 6.1-4: Drug Reinforcement (Salience Attribution)**

**Figure 6.1-5. Decreased Brain Function in Methamphetamine Abuser**
Loss of the innate ability to experience normal pleasure eventually finds people using merely to avoid withdrawal or dysphoria (Figure 6.1-6).

When a patient is prone to compulsive relapse, how does one treat this acquired brain injury in order to regain normal function and behaviour? Clearly, treatment must be sustained over time and tailored to the individual. Although residential rehabilitation in 28-day programs has become a standard of care, this approach is not based in either science or efficacy. Such programs were designed to achieve as much as possible in the time and funding allotted by American health insurance companies. Most programs, whether in-patient or out, use variations on a matrix approach to care. The best programs include a workbook-based structured curriculum with group education and discussion; personal counselling using CBT and/or motivational interviewing; family education; body fluid monitoring; concurrent mental healthcare; pharmaceutical support, as required; and introduction to self-help twelve-step groups. Pharmacotherapy is being increasingly added, as the science and systems evolve.

The best evidence for treatment efficacy comes from North American Physician Health Programs, which are highly scrutinized processes due to the potential for public harm from inadequately treated physicians re-engaging in patient care. In the United States, a five-year longitudinal cohort outcome study found 78.7% of patients were in remission. A similar Canadian study found 71% of patients had no episode of relapse and another 14% only had a single relapse event, with a total of 85% in sustained remission. The 15% who remained ill had complex, concurrent mental health problems. The treatment approach had common features. Entry into and continued engagement with treatment was buttressed by the potential for loss of licensure. Detox was followed by an extended residential rehab of six to eight weeks. Aftercare included weekly counsellor-facilitated...
peer group sessions, 12-step recovery groups, personal counselling, family therapy as indicated, body fluid monitoring, and a contracted, graduated return to work. Contract elements were informed by their extensive assessment and initial progress in treatment, with structured mentoring and monitoring in the workplace. These conditions were maintained for three to five years, with regular case-management reviews. This sustained, comprehensive approach has both intensity and longevity, with a nurturing of personal agency. While we know how to treat addiction, capacity, however, remains an ongoing challenge.

**Medical Intervention**

Typical of most medical conditions, early intervention produces a better prognosis. Screening is therefore important in identifying those in need in order to provide them with either advice or more active intervention. In the case of alcohol, the evidence-based national low risk drinking guidelines\(^{16}\) require broader social marketing to promote a culture of moderation in Canada (Figures 6.1-7 and 6.1-8).

![Figures 6.1-7: Canada’s Low Risk Drinking Guidelines](image-url)
Alcohol Screening, Brief Intervention and Referral (ASBIR)\textsuperscript{17} is buttressed by excellent evidence as well (multiple references) and is designed for seamless inclusion in the primary care environment. Screening is typically based on elevated risk drinking (five or more standard drinks at a time for men, four or more for women), with intervention guided by the patient’s consequences or severity of their alcohol use disorder. Screening is discussed further in \textbf{Chapter 5. History, Screening, Detection, Investigations & Diagnosis}. Additionally, the College of Family Physicians of Canada has an open source site located at \texttt{www.sbir-diba.ca} dedicated to ASBIR (Figures 6.1-9,6.1-10).
6.1 Community Based Treatment

Figures 6.1-9. Alcohol Screening, Brief Intervention and Referral

Figures 6.1-10. Alcohol Screening, Brief Intervention and Referral
An important part of medical care for addiction and substance use disorders, and indeed for most medical conditions, is an understanding of the Transtheoretical Model of Change\textsuperscript{18}. This theory identifies the various stages people go through when dealing with a significant issue. These are typified as follows:

1. pre-contemplation (marked by denial)
2. contemplation (ambivalence)
3. planning (a stage of increasing determination)
4. action (change is attempted)
5. maintenance (change becomes more permanent)
6. success (durable change is achieved)
7. relapse (attempted change is not so durable, requiring a review of their change process)

Further, Motivational Interviewing (MI)\textsuperscript{19} is the process by which people are assisted to advance from one stage to another. A significant challenge to action-oriented physicians who are taught more often to “prescribe” rather than to explore solutions, it necessitates “starting where the person is.” MI involves four processes:

1. engagement or the establishment of a rapport
2. working with the individual to uncover, and focus on, their barriers to change
This process requires rolling with resistance in order to avoid a power struggle between physician and patient. The Centre for Addiction and Mental Health (CAMH) provides an online course that emphasizes a relational approach based on the PACE philosophy (Partnership, Acceptance, Compassion, and Evocation) and employing an OARS skillset (Open-ended questions, Affirmations, Reflective Statements, and Summarization), based on Miller and Rollnick, Motivational Interviewing: Helping People Change. As the resulting change is very much rooted in the patient’s own context, values, and motivation, it is therefore more likely to be both successful and sustained. Patient relapse in this therapeutic construct is not viewed as an abject failure, but rather provides an opportunity to revisit their plan and process.

Earle, Garrett, and Hesler provide a depiction of Motivational Interviewing in action in Chapter 4.4 Building a Bridge: The Therapeutic Alliance. It depicts how people change, and how the roles played by physicians or counsellors supports or guides the process.

People often negotiate change in order to achieve maximum results with minimum adjustment. Case 2 illustrates how people may be at different stages of change in their approach to a central issue.

Physicians are uniquely placed to assist people with addiction. CAMH promotes a model of Counsel, Prescribe, and Consult in addiction medicine. It uses the strength of the physicians’ rapport and knowledge of their patients, encourages appropriate prescribing (see Table 6.2-1 for medications currently approved for the treatment of addictive disorders). Rx Files, Addiction section has excellent evidence-based summaries and links people with appropriate community resources. While many doctors may feel disempowered by their lack of formal training in counselling, Asay and Lambert have reported that there is much more to a therapeutic relationship than formal training.
Training is but a small component, outstripped by the relationship itself, equalled by the level of expectancy or hope that can be incited, and profoundly impacted by the extra-therapeutic environment. The physician’s knowledge of this environment, exploration of potential supports, and connection with community-based resources makes the doctor–patient relationship highly therapeutic and healing.

Although the process is not well understood by many physicians, the mainstay of longitudinal, community-based care in North America has been self-help or 12-step recovery programs. While efficacy is regularly questioned in the media, a balanced review by Kaskutas\textsuperscript{22} demonstrates twice the levels of sobriety compared to controls. Participation is critical, however, in any endeavor. The 12-step process requires more engagement than passively attending meetings. Bibliotherapy is a part of the process, with daily readings and meditations. There is also the need for a personal sponsor to facilitate a patient’s work through the 12 steps and to apply them to the patient’s own experience. The work requires engaging and reaching out to others in recovery. Ultimately, the arc of recovery in the 12-step process includes a reconciliation with one’s “higher power,” however that may be defined; reconciliation with oneself; reconciliation with others; and finally a process of redemption to extinguish the burden of pain and shame that frequently accompanies an extended period of addictive behaviour. It can be a potent recovery tool, but admittedly does not speak to everyone.
Research and the development of clinical practice guidelines are expanding the evidence base for a range of treatment services. These are typically placed within a continuum of care, with outreach and engagement of active users through harm reduction strategies, withdrawal management, various forms of personal and group treatment, pharmacotherapy, and sustained community support. A common denominator in success is the willingness to persevere and use a range of support options until remission is achieved.

see Callout: The 12 Steps of Alcoholics Anonymous
see Callout: Treatment Works!

Those who engage and work therapeutically, will be both honoured and privileged to witness profound changes in people whom others have written off as hopeless and unworthy of care. Much like medicine in general, however, it takes time and a long-term commitment to chronic disease management.

Let’s allow David the last word.

see Case Study: David struggling with severe alcohol use disorder
6.1 Community Based Treatment


12. Those programs were designed to achieve as much as possible in the time and funding allotted by American health insurance companies.


Because recovery is a lifelong process, there is no wrong way to approach the 12 steps as participants work to figure out what works best for their individual needs. In fact, most participants find that they may need to revisit some steps, or even tackle more than one of the steps at a time.

Here are the 12 steps as defined by Alcoholics Anonymous (AA):

1) We admitted that we were powerless over alcohol—that our lives had become unmanageable.
2) We came to believe that a Power greater than ourselves could restore us to sanity.
3) We made a decision to turn our will and our lives over to the care of God as we understood Him.
4) We made a searching and fearless moral inventory of ourselves.
5) We admitted to God, to ourselves, and to another human being the exact nature of our wrongs.
6) We were entirely ready to have God remove all these defects of character.
7) We humbly asked Him to remove our shortcomings.
8) We made a list of persons we had harmed and became willing to make amends to them all.
9) We made direct amends to such people wherever possible, except when to do so would injure them or others.
10) We continued to take personal inventory, and when we were wrong we promptly admitted it.
11) We sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
12) Having had a spiritual awakening as the result of these steps, we tried to carry this message to other alcoholics and to practice these principles in all of our affairs.
**Treatment Works!**

The successful treatment of addiction, with close attention paid to good concurrent care, can lead to transformational change. It can be both life altering and lifesaving; it can have both family and community impact; and treatment can be successful in reversing the acquired brain injury of addiction.

![Figure 13. Treatment Works: Recovery of Brain Function with Prolonged Abstinence.](image)

*Those who engage and work therapeutically, will be both honoured and privileged to witness profound changes in people whom others have written off as hopeless and unworthy of care. Much like medicine in general, however, it takes time and a long-term commitment to chronic disease management.*
**CASE STUDY**

**John**

John is a 35-year-old who struggles with chronic alcoholism. The police or EMS often pick him up off the street. He is frequently assessed in the emergency room and referred to the local detox centre. His social supports are reduced to his street family; he has no contact with his next of kin, is unemployed, and has become homeless. He has cycled through detox and the occasional 28-day rehab program on many occasions, much to the annoyance of the emergency department staff. When asked what services he would require to help him make a more substantial change he noted, “I am not stupid. I am an alcoholic. But I once had a home, a family, and a job. I know exactly what is in those programs because I have been there many times. What I need is a place to stay. When they send me out I go back to where I came from, with the people I know will look after me. So nothing really changes. Rehab is a respite from the street but it doesn’t give me a place to live. Maybe if I had my own place things would get better. You know, this life sucks. There are days when I just don’t care. Why live longer if this is all that life has to offer?”

In John’s case, a sober, supportive housing initiative such as Housing First, or a therapeutic community such as Oxford House, would provide the environmental support required for his recovery to take hold and to be successful. A central issue is the re-establishment of hope for John that his life really could be better. Without that hope, he is unlikely to invest the work or sustain the effort required to achieve substantial change.

**CASE STUDY**

**Jasmine**

Jasmine has worked hard to address her cocaine use. She has worked through her ambivalence around the desire to get high with the reality of the negative consequences; developed a supportive network of people and programs; identified her triggers (especially alcohol and certain social settings); and begun to achieve some of her personal goals. Her partner, Carl, is not as engaged in changing his behaviour. He continues to drink and use cocaine on weekends and expects Jasmine to party with him. This has created problems in their relationship as Jasmine makes progress in her life. She had hoped Carl would join her in her recovery efforts, but instead they are drifting apart. She has become increasingly ambivalent about their relationship.
Jasmine has reached an action stage of change with regards to her substance use, but is in an initial pre-contemplation stage with her relationship with Carl. Over time, and recurrent relapses, she has reached this ambivalent place of contemplation. She will need empathic support as she explores her relationship as a barrier to success, and considers her options.

David had been struggling for years with a severe alcohol use disorder. He was homeless, on the streets, and frequently presented to the emergency room with epistaxis or gastrointestinal (GI) bleeding from his chronic consumption of mouthwash and hair spray. He was invariably intoxicated, terribly dishevelled, and difficult to engage.

Eventually, through the interventions and support of several health care providers and counsellors, he was able to engage in care. He went through detox and rehab and obtained long-term shelter and care in supportive housing. He connected with a recovery network and was able, in time, to address his history of sexual abuse and the rampant dysfunction of his family of origin. One day he returned to the emergency department to accompany someone who was very ill and inebriated. They did not recognize him at first, but in observing his interactions the staff soon realized it was the same “frequent flier Dave.” They shared this recognition, complimented him on the transformational change, and inquired into what made the difference. He shared his story of recovery and his hopes for the future. They were profoundly moved to know that there was hope and treatment for addiction.
6.2 Medication - Assisted Treatment

Pharmacological Interventions

Compare and contrast these two case scenarios:

1. Joe was found dead in his hotel room with a hypodermic needle and other drug paraphernalia. There was no suicide note. His face was red and there was a pinkish froth around his lips and nose. He had checked into the hotel a few days earlier on a business trip. He had a long-standing history of injection drug use and had been to a private intensive recovery-based facility twice before. He was never offered medication-assisted treatment such as methadone or buprenorphine as his family was against him being treated with these medications and believed that he should be able to recover with counselling alone. He had been abstinent for about two months before his death after being released from the treatment facility.

   What are the reasons for Joe’s death? List all of the ways that his death could have been prevented.

2. Rob is Joe’s friend. They started using heroin together in their late teens. Rob had a near-fatal overdose but was revived by another drug user who injected him with the naloxone he had been given by the local public health unit. In the emergency department, Rob was started on buprenorphine and naloxone (2 mg sublingually) and referred to his family doctor who continued to adjust his dosage, up to 12 mg sublingually per day. He attended counselling once a week for the three-month period when he was in school, after which he got a job. He suffered a few relapses, but they didn’t last long. He never experienced overdoses, even though he used the amounts he had previously used. He experienced no pleasure from the heroin and reported that the medication was blocking its effects.

   What are the reasons why Rob didn’t meet the same fate as his friend Joe? What are some of the reasons why people refuse to accept methadone or buprenorphine as treatment?

The three major phases of addiction treatment are:

1. Detoxification: Involves achieving abstinence in a way that safely reduces immediate withdrawal symptoms.

2. Initial recovery: The goal is to develop sustained motivation to remain abstinent and to avoid relapse by learning to tolerate cravings and by developing new behaviour that replaces drug-induced reinforcement with alternative rewards.

3. Relapse prevention: Follows a period of sustained abstinence and involves the development of long-term strategies to replace past drug behaviour with new, healthy behaviour.
Of note, pharmacotherapy can be a useful adjunct to behavioural counselling and social support at each phase of addiction treatment. Medications can be used to effectively and safely manage withdrawal during the detoxification process and are often necessary in order to prevent sometimes lethal withdrawal symptoms such as seizures. Further, some medications are effective in preventing relapse to specific drugs of abuse.

**Detoxification and Management of Acute Withdrawal**

Alcohol withdrawal presents as a special cluster of symptoms that emerge when blood levels of alcohol drop in a person who has developed a certain level of tolerance. These symptoms can be neurological, such as tremors and sweating, insomnia, restlessness, and expressed desire or craving to drink. For most, these symptoms are mild, develop within a few hours of reduced consumption, and resolve within a week (although the cravings can persist for months). In some patients, however, withdrawal seizures can develop (typically generalized tonic-clonic type seizures) with the peak risk occurring about 72 hours after their last drink. In severe cases, this acute withdrawal might be complicated by delirium tremens (DTs), in which the patient suffers from illusions, hallucinations, and disorientation of time, place, or person. DTs often occur during the unrecognized and untreated early withdrawal that occurs in medically compromised patients and such patients often require admission and monitoring in intensive care units.

Treatment of acute withdrawal involves the use of symptom-triggered dosing based on a Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA), Revised CIWA-Ar score ≥ 10, with a long-acting benzodiazepine such as diazepam. The principle is to exploit the cross-tolerance between alcohol and benzodiazepines; the wide therapeutic window, which makes this choice safe; and the long half-life of diazepam. Dosing every hour leads to accumulation, and dosing is stopped once the CIWA score remains below eight for two consecutive hours and the patient is asymptomatic. The diazepam is then gradually eliminated from the body over the next few days with no emergence of withdrawal. In patients with a previous history of withdrawal seizures, a minimum of 60 mg in three divided doses should be administered in order to prevent seizures. In patients with severe liver compromise, or the frail elderly, lorazepam may be used instead of diazepam.

Alternatively, fixed-dose tapering, although not ideal, is an option in some settings. The goal is to reduce the total daily dose by approximately 10% per day while eliminating withdrawal symptoms.

Of note, all patients being treated for alcohol withdrawal should also be treated with thiamine for a five to ten day period in order to prevent Wernicke’s encephalopathy and/or Korsakoff’s psychosis. This may be administered orally or intramuscularly, depending on the patient’s state of health and the treatment setting resources.
After withdrawal is complete, it is imperative to reassess the patient for motivation and residual mood symptoms, and to treat accordingly. Treatment might include intensive behavioural treatment, pharmacotherapy, and/or mutual aid attendance. Withdrawal management is not sufficient to induce a permanent remission in patients with moderate to severe alcohol use disorder.

**Benzodiazepines**

Withdrawal from benzodiazepines is best managed by switching a patient to a long-acting benzodiazepine such as diazepam. The dose is then tapered over the following weeks to months, while behavioural treatments are provided to help the patient cope, and non-benzodiazepine treatment is administered for any underlying mood or anxiety disorder, as appropriate. The equivalence tables offer appropriate dosages for these medications when substituting these drugs. The diazepam should be given in divided doses and dispensed in daily to weekly amounts, depending on the level of supervision required to ensure safety. Each tapered step is about 10% of the dose. Sustained support and encouragement, with good boundaries around prescribing and access, is often required.

**Barbiturates**

Barbiturate dependence is rarely seen anymore as these drugs are now rarely used because of their narrow therapeutic window and risk of fatal overdose. However, despite advances in the management of migraine and tension headaches, some patients are still treated with a medication called Fiorinal, which contains butalbital (a barbiturate), aspirin, and caffeine. Some formulations also contain codeine, either 15 mg or 30 mg. For barbiturate-dependent patients, the biggest risk is a withdrawal seizure. While tapering might be tried on an outpatient basis, it is not often successful. Managing withdrawal requires loading with phenobarbital (120 mg per hour) to the point of mild intoxication in a supervised setting. Thereafter, the long elimination half-life of phenobarbital prevents the re-emergence of withdrawal symptoms without requiring additional dosing.

**Opioids**

Opioid withdrawal is very uncomfortable but not immediately life threatening. Although it lasts only five to seven days, the symptoms are usually intolerable due to autonomic instability and pain, with most patients finding it extremely difficult to endure. Because the highest risk for overdose death occurs immediately following acute withdrawal treatment, treatment should only be attempted once the patient understands the risks associated with relapse post-withdrawal. The danger of this phase is due to the patient’s loss of tolerance to opioids paired with the strong urge to use that persists in the post-withdrawal stage. However, in otherwise stable patients who have developed physical dependence to opioids, tapering by 10% per day or week, as tolerated,
may be attempted. If the patient has developed an addiction, however, then withdrawal should be attempted only after appropriate post-withdrawal treatment and counselling has been arranged. In an outpatient setting, symptomatic treatment with non-opioids such as clonidine (0.1–0.2 mg tid to qid) for seven days as long as blood pressure is above 90/60 mm Hg, loperamide (prn) for diarrhea, non-steroidal anti-inflammatory drugs (NSAIDs) for pain, and dimenhydrinate (prn) for nausea may be used. Benzodiazepines should be avoided, however, due to the risk of overdose that they present should the patient mix them with opiates in the case of a relapse. Induction onto low dose buprenorphine or methadone might also be tried, with a prompt tapering off as indicated. Given the high rate of relapse, it is important to monitor the patient closely and offer maintenance treatment with either methadone or buprenorphine, which are the only strategies shown to prevent overdose deaths and allow for sustained recovery.

Preventing Relapse: Pharmacotherapeutic Targets to Treat Addiction

As indicated by Potenza, Sofuoglu, Carroll, and Rounsaville, in their table of medications currently approved for the treatment of addictive disorders, medications fall into three main pharmacological categories: full agonists; antagonists and partial agonists; and medications that target downstream or secondary neurotransmitter systems associated with the adaptive changes that occur in the brains of addicted individuals².

<table>
<thead>
<tr>
<th>Type of Addiction</th>
<th>Medication</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>Nicotine replacement therapy</td>
<td>Transdermal (patch); buccal (gum, lozenge);</td>
<td>Full agonist at nAchRs</td>
<td>Two-fold increase in the odds of quitting smoking³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>upper airway (inhaler, mist), the new “cigarettes”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>Oral tablet</td>
<td>Competitive antagonist at nAchRs</td>
<td></td>
<td>Two-fold increase in the odds of quitting smoking⁴</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Oral tablet</td>
<td>Partial agonist at α4β2 and full agonist at α7 nAchRs</td>
<td></td>
<td>Two- to three-fold increase in the odds of quitting smoking⁵</td>
</tr>
</tbody>
</table>

Table 6.2-1: Medications Currently Approved for the Treatment of Addictive Disorders
<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulation</th>
<th>Mechanism of Action</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Disulfiram</td>
<td>Oral tablet</td>
<td>Alcohol and aldehyde dehydrogenase inhibitor; May reduce drinking in compliant patients; overall efficacy is questionable.</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td>Oral tablet</td>
<td>µ-opioid receptor antagonist; Significantly reduces relapse to drinking.</td>
</tr>
<tr>
<td></td>
<td>Acamprosate</td>
<td>Oral tablet</td>
<td>Glutamate modulator; Two-fold increase in abstinence rates at one year.</td>
</tr>
<tr>
<td>Opioid</td>
<td>Methadone</td>
<td>Oral solution or tablet</td>
<td>µ-opioid receptor agonist; Effective in retaining treatment and reducing opioid use.</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine</td>
<td>Sublingual tablet alone or with naloxone; sublingual film</td>
<td>µ-opioid receptor agonist; naloxone is a short-acting antagonist to deter injection of the tablet; Effective in treatment retention and reducing opioid use.</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td>Oral tablet, extended release depot injection</td>
<td>µ-opioid receptor antagonist; Better outcomes in “high retention” groups.</td>
</tr>
</tbody>
</table>

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**Medications to Treat Nicotine Addiction (Tobacco Dependence)**

Nicotine is the primary addictive component of cigarettes, and it acts as an agonist to directly stimulate nicotinic acetylcholine receptors (nAchRs) in the brain. This stimulation, in turn, stimulates the release of dopamine in various areas of the brain, including the prefrontal cortex as well as mesolimbic reward pathways involving the nucleus accumbens (via stimulation of nicotinic receptors in the ventral tegmental area [VTA]) and the basal ganglia (see Chapter 1.1 Neurobiology of Addiction). In addition, stimulation of nAchRs by nicotine causes the release of several other neurochemicals that are responsible for various aspects of nicotine’s effects that lead to its continued use and eventual addiction. See Figure 6.2-1, which follows, for a summary of these effects.
Stimulating nicotinic receptors (nAchRs) cause the release of many neurotransmitters, all of which contribute to the effects of nicotine\textsuperscript{13}.

### Nicotine Replacement Therapies

There are currently five nicotine replacement therapies (NRTs) approved by Health Canada: the transdermal patch, gum, lozenge, inhaler, and oral spray (mist). NRTs are examples of agonist substitution therapy in which the nicotine delivered via cigarettes is replaced by pure nicotine delivered by one or more of the above formulations, thereby reducing the reinforcing properties of nicotine delivered by cigarettes as well as the severity of cravings and withdrawal. Meta-analyses have shown that all forms of NRTs approximately double the chance of long-term abstinence when compared to a placebo\textsuperscript{13}.

### Bupropion

Bupropion was the first non-nicotinic drug approved by Health Canada for the treatment of tobacco dependence. Bupropion acts as a reuptake inhibitor of both dopamine and norepinephrine and is also a weak antagonist at nAchRs\textsuperscript{14}. However, it is not known exactly how bupropion, originally developed and marketed as an anti-depressant, affects the desire to smoke. Indeed, there is no difference in efficacy between smokers with and without depression so its anti-depressant actions likely have no impact on its anti-addictive actions. A meta-analysis of existing clinical trial data shows that bupropion approximately doubles the chance of long-term cessation compared to placebo\textsuperscript{15}.
Varenicline

Varenicline is the latest medication to be approved by Health Canada for the treatment of tobacco dependence. It acts as a partial agonist at the alpha-4 beta-2 nicotinic receptor (a4ß2) nAchRs subtype and as a full agonist at the alpha-7 nicotinic receptor (a7) subtype. The partial agonist effects mean that the receptor receives enough stimulation to alleviate nicotine withdrawal and craving, but without any of the addictive potential. Also, because it binds to the a4ß2 nAchRs with greater affinity than nicotine, it acts as a functional antagonist by preventing the nicotine from cigarettes from binding to the receptor and exerting its effect. A meta-analysis of clinical trial data using Varenicline has demonstrated a two- to three-fold increase in long-term cessation compared to placebo.

Medications to Treat Alcohol Addiction

Alcohol affects a variety of neurotransmitter systems, including agonist effects at GABA, serotonin, nicotinic, opioid, and cannabinoid receptors, as well as antagonist effects at glutamate receptors. These receptor effects result in the release of dopamine, serotonin, and endogenous opioids. As a result, there are many possible targets for medications designed to treat alcohol addiction. The medications currently approved are outlined below.

Disulfiram

Disulfiram was the first medication approved by Health Canada for the treatment of alcohol dependence. It acts by inhibiting aldehyde dehydrogenase, the enzyme responsible for the catabolism of acetaldehyde to acetate. When acetaldehyde, a metabolic product of alcohol, is not converted to acetate and then excreted, it builds up in the blood leading to adverse reactions such as sweating, flushing, nausea, vomiting, tachycardia, hyperventilation, and hypertension. These effects are very unpleasant, so much so that alcoholics taking disulfiram will avoid drinking in order to avoid them. However, since disulfiram is taken daily by mouth, the patient can simply choose not take it if he or she wants to drink alcohol. As a result, the medication compliance for this pharmacotherapy is very low. However, for those who are highly motivated to remain abstinent, the medication will be very effective for them as they will be highly compliant with dosage. Indeed, the patient characteristics associated with improved outcomes on disulfiram are the following: high motivation to remain sober, attendance at Alcoholics Anonymous (AA) meetings, social stability, lack of cognitive disturbances or deficits, and a long drinking history. The aversive nature of the medication, however, has led to decreased availability. As such, it may need to be compounded by a properly trained pharmacist.
Naltrexone

Naltrexone is an opiate antagonist and, as such, has the opposite effects of opiate drugs of abuse such as heroin and oxycontin, which are full agonists at the \( \mu \)-opioid receptor. The U.S. Food and Drug Administration (FDA), and later Health Canada, approved it for the treatment of alcohol dependence based on the positive results derived from two small clinical trials\(^{17,18}\). However, a meta-analysis of Naltrexone has demonstrated only a modest effect compared to placebo on measures of drinking, such as number of drinking occasions and number of drinks per occasion, but not on absolute abstinence\(^{19}\). Despite this, it has been shown that the depot injection formulation, not currently available in Canada, increases compliance and is therefore more effective than the tablet form. Further, additional research indicates that those with a positive family history of alcoholism, increased opioid activity in response to alcohol, or a specific genetic polymorphism at the \( \mu \)-opioid receptor (OPRM A118G)\(^{20}\) respond best to naltrexone. For additional information on the genetics of addiction, see Chapter 1.4 The Genetics of Addiction.

Nalmefene

Nalmefene is an opiate antagonist like naltrexone but with a longer half-life and fewer serious side effects. Clinical trials using nalmefene have produced similar effects on drinking as naltrexone\(^{21,22}\).

Acamprosate

Acamprosate was approved by Health Canada in 2008 to prevent relapse in alcohol-dependent patients. It is a safe and well-tolerated medication primarily because it is not metabolized by the liver, and is excreted unchanged through the urine. It is therefore safe to give to patients with liver disease but is contraindicated in those with severe renal disease. Acamprosate acts as an antagonist at both the n-methyl-d-aspartate receptor (NMDA) and the metabotropic glutamate receptor 5 (mGluR5). It is most effective when given after the acute withdrawal phase, as it is thought to prevent relapse by reducing the hyperglutamatergic state that seems to drive negative reinforcement craving and relapse\(^{23}\). Unlike naltrexone, acamprosate is effective in promoting complete abstinence, especially in more severe alcoholics with a high level of motivation to remain abstinent.

**Medications to Treat Opiate Addiction**

Opiates exert their positive-reinforcing euphorogenic effects by acting as agonists at \( \mu \)-opioid receptors, while in contrast the dysphoric effects of opiates are due to agonist activity at \( \kappa \)-opioid receptors (KOR)\(^{24}\). Stimulation of \( \mu \) receptors increases dopamine transmission in the mesolimbic reward pathway by either inhibiting GABA neurons in the VTA or directly modulating dopamine neurons in the nucleus accumbens. Medications to treat opiate addiction all act at the \( \mu \)-opioid receptors as full agonists, full antagonists, or mixed agonist/antagonists.
Methadone

The most common treatment for opioid addiction is to replace the opiate of abuse, such as heroin, with a long-acting prescription opiate. Methadone is the most widely used medication of this type. Since methadone has a half-life of 24 to 36 hours, it only needs to be taken once a day, unlike heroin whose half-life of one hour requires it to be administered several times a day in order to avoid withdrawal in addicted patients. Further, methadone maintenance has been shown to be most effective in treatment retention and relapse prevention. However, a drawback of methadone maintenance treatment is that patients can become physiologically dependent, thus requiring a very slow taper when discontinuing its use. Many remain in treatment for several years – some for the rest of their lives. It is often provided in highly structured and regulated programs however, which may play an important role in assisting patients to stabilize and improve their level of function.

Buprenorphine

Buprenorphine was approved by Health Canada in 2007 for the treatment of opiate addiction. It is available in two formulations: one containing buprenorphine alone, the other containing a combination of buprenorphine and naloxone (a μ-opioid antagonist). The formulation of the latter was developed to mitigate the potential for abuse by parenteral (injection) administration. Buprenorphine has a long duration of action and acts as both a high-affinity μ-opioid partial agonist and a κ-opioid antagonist. Because of its high affinity for the μ-opioid receptor, buprenorphine acts as a functional antagonist because it blocks the receptor and prevents other μ-agonists (such as heroin) from binding to the receptor. Because it is a partial agonist, its safety profile is improved over full agonists, with no risk of respiratory depression due to its ceiling effect, but its efficacy is decreased, especially in patients on high doses of full opioid agonists.

A recent review (Kahan et al, Cdn Family Physician, 2015) found methadone outcomes better in those with lower levels of psychosocial stability, as opposed to buprenorphine and naloxone. The latter worked well for people who were generally more stable.

Naltrexone

As described under Medications to Treat Alcohol Addiction, naltrexone is a μ-opioid receptor antagonist. While naltrexone has favourable benefits such as the lack of addiction potential, overdose, and stigma associated with methadone maintenance, a meta-analysis demonstrated no significant improvement over placebo in abstinence-related outcomes. However, American depot injection formulations that increase medication compliance have shown some improved outcomes when compared to placebo.
While there are several approved effective medications for the treatment of alcohol, tobacco, and opioid addiction, there remains a need for more effective pharmacotherapies to treat these common addictive disorders. There also remains a large unmet need for medications to treat stimulant (cocaine and methamphetamine) and cannabis addiction, as well as process addictions such as pathological gambling. Development of new treatments requires taking novel approaches, such as developing drugs that target neural systems that have been adapted by long-term drug use, as well as focusing on individual vulnerabilities to drug addiction such as psychiatric comorbidities, sex differences, and cognitive function.
**VIRTUAL PATIENT CASES**

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

- Case of Ethel
- Beth
References


Methadone

Does methadone maintenance treatment make sense? Or, is it simply the substitution of one addiction for another?

Prior to the use of methadone to treat heroin addicts, patients died from an overdose or from complications arising from injection, such as infective endocarditis, hepatitis, or suicide. Moreover, detoxification (or withdrawal) followed by behavioural treatments was ineffective. Dole and Nyswander identified and promoted methadone as a long-acting orally bioavailable synthetic opioid that suppressed withdrawal and cravings for 24 hours in heroin addicts, allowing them to function and to fulfill their responsibilities as employees, parents, and so on. However, methadone treatment was both restricted and stigmatized until the HIV epidemic of the 1980s and 90s. Since then, the expansion of methadone programs has been associated with reduced mortality from opioid overdose, and the evidence for its effectiveness is overwhelming.

Despite these findings, however, many practitioners and patients believe that these programs are simply substituting one addiction for another. While it is true that methadone does cause physical dependence and may cause the withdrawal period to be prolonged, according to the DSM criteria, a stabilized and functional patient on methadone is not addicted. There is no methadone use despite harm or loss of control, even in programs where there is no restriction or ceiling dose of methadone. Moreover, the pattern of use is adaptive, and therefore the definition does not apply. However, the stigma persists, and much remains to be done in order to remove it, allowing more patients with opioid addiction to be treated with effective life-saving medications.

« return
6.3 Clinical Management of Concurrent Disorders

**Objectives**

After completing this section, the learner will be able to:

1. Develop and describe an integrated approach to concurrent substance use and psychiatric disorders.
2. Discuss the role of screening.
3. Discuss the presentation of specific classes of psychiatric disorders, including psychotic, mood, anxiety, trauma and impulse control.
4. Describe the interface between the classes of psychiatric disorders and substance use.

**Introduction**

The term concurrent disorder refers to a diagnostic condition in which a patient is living with both mental illness and an addictive disorder\(^1\). In some clinical settings, however, the terms dual diagnosis or dual disorder are used, but these terms are also sometimes used to describe a different condition in which a patient is living with both psychiatric disease and mental retardation or other cognitive disorder. For the purposes of this primer, it is most practical to conceptualize this section as focusing on the needs of a patient living with not only addiction but also with psychiatric illnesses, such as major depression, generalized anxiety, or post-traumatic stress disorder.

Treatment of concurrent disorders can be challenging\(^2\) as many tertiary care services are streamed by diagnostic presentation (a mood disorders service or psychotic disorders team) and many do not accept patients with a co-morbid addiction disorder. In some healthcare systems, concurrent disorders teams or clinics do exist but they often struggle with patient volumes and clinical resources. This highly vulnerable and at-risk population is often poorly served by this fragmentation of the healthcare system\(^3\).

While concurrent disorders can involve any psychiatric diagnosis, the focus of this primer will be psychotic disorders, mood disorders, anxiety disorders (including trauma related diagnosis), and impulse control disorders.

**Principles and Approaches to Screening**

Screening for mental health disorders is a common part of general medical practice, particularly given how common these conditions are in Canada. Open-ended questions regarding a patient’s
mood, level of stress or anxiety, commonly used coping mechanisms, social supports, family functioning, occupational or educational engagement, cognitive abilities, thoughts of death or self-injury, domestic maltreatment, and basic biological functioning (sleep, appetite, energy, sensory systems) can provide useful information efficiently. Some providers use screening instruments in their practice for certain conditions such as depression or attention deficit hyperactivity disorder that are quick and easy to score, and on-line screening tools are increasingly used by a savvy public.

There will be more detailed information on screening for substance use disorders elsewhere in this primer. However, it is helpful to know that substance use disorders are common in Canada and important to remember that they affect Canadians from all walks of life. With that in mind, an index of suspicion may be elevated when working with certain populations such as those living with social or legal problems, living with partners and/or family members with substance use disorders, those with a past history of substance use difficulties, and those living with mental health issues. As with mental health disorders, there are many screening tools that practitioners can use, for example the MAST (Michigan Alcoholism Screening Test) and the DART (Drug Abuse Screening Test).

This chapter will speak to the importance of recognizing that mental health disorders can present at the same time as substance use disorders, adding to the complexity of care and to the burden of illness. Many health systems are designed to tackle substance use issues first and mental health issues second. On the one hand, this approach can be helpful as it ensures that substance-induced psychiatric conditions are understood as such and that appropriate treatment is put into place. However, this approach can be very threatening to patients who may be relying on their substances of use in order to help them cope with severe psychiatric symptoms. In such cases, abstinence or even a harm-reduction approach may be impossible. Thus, integrated approaches that address both psychiatric and substance-related symptoms are often required. Unfortunately, not all healthcare systems offer such integrated approaches. Additionally, integrated approaches require that healthcare professionals be more open to collaborating with other forms of providers (e.g., substance use counsellors) and other forms of treatment support (e.g., multi-stage group therapy and non-medicalized residential therapy).

**Psychotic Disorders**

Psychotic disorders describe a cluster of diagnoses characterized by the brain's creation or misinterpretation of stimuli (hallucinations, illusions), its inability to process thoughts and ideas accurately (delusions, nonsensical language), and the loss of previously acquired functioning (often called negative symptoms). They present as psychotic episodes, which are periods of time where symptoms of psychosis interfere with, and dominate, normal functioning. Left untreated these episodes can last for very long periods of time and lead to severe impairment. Not all patients living with symptoms of psychosis understand that they have lost contact with reality; their experiences can seem very real to them and can trigger strong emotions that range from happiness to terror.
Screening for symptoms of psychosis by healthcare providers should be done in a straightforward and non-judgemental way. For example, “I’d like to ask you some questions about your five senses,” or “I’m now going to ask you a few questions about how your eyes and ears are working.” Practitioners can also reflect their own behavioural observations. For example, “I notice that you seem preoccupied with the corner of the room – is there something there that is getting your attention?” or “I’ve noticed that you seem to be talking with someone, is that right?” or “Do you see or hear things that other people don’t see or hear?” Finally, practitioners may need to indicate what others have noticed and then provide patients with an opportunity to respond. For example, “Your girlfriend tells me that you’ve been very concerned for your safety. I understand that you feel that you’re being followed and that someone is trying to kill you. Can you tell me more about that?”

Bear in mind that psychotic symptoms are perhaps the most stigmatized symptoms in psychiatry, and patients may be very reluctant to acknowledge their experiences. A gentle approach is required and, often, multiple interviews are required to fully appreciate the depth and complexity of a patient’s psychotic symptoms.

The phases of psychotic illness are:

- prodromal
- acute
- recovery

The prodromal phase describes the gradual onset of symptoms, for example, social withdrawal, anxiety, skipping work or school, and suspicion. This phase usually occurs in adolescence or early adulthood. Some people may turn to substances to help them cope, for example alcohol may lessen a patient’s feelings of fear or anxiety. Sadly, this strategy may lead to addiction.

The second phase is referred to as the acute phase of illness as symptoms are more obvious and are easy for others to recognize. Most people will start to access medical services for the first time during the acute phase, despite having been ill for months or even years. Care is often offered on an outpatient basis and involves medication, education, support, rehabilitation, and therapy.

The third phase is recovery. During this time, symptoms begin to respond to treatment and functionality improves. However, the risk for depression and anxiety is high as patients begin to come to terms with their diagnosis and the natural consequences of living with a serious mental health problem. It is, therefore, essential for support, education, and rehabilitation services to be in place for the patient and their loved ones. For some patients, the risk of substance use and abuse is high during this time and needs to be monitored carefully.

While most patients living with psychotic disorders enjoy full or near-full recovery, some struggle with poor or partial recovery. The reasons for this are diverse and range from biological to psychological. Regardless, rates of addiction are particularly high for this group. In some cases, substance use, for example cannabis or hallucinogenics, may contribute to the onset of an episode
of psychosis. Conversely, substance use for this group can also offer relief, albeit a short-term and risky relief, from the pain and distress associated with psychiatric symptoms, including psychosis. It can increase a patient’s level of energy, relieve insomnia, improve appetite, decrease fear and anxiety associated with psychosis, and modulate anxiety or mood to a more tolerable state. Such relief can be self-reinforcing and may be referred to as self-treatment.

Treatment of psychosis is largely biological in nature, and includes newer antipsychotic or neuroleptic medications such as quetiapine, olanzapine, aripiprazole, and risperidone, as well as older medications such as chlorpromazine or haloperidol. Psychological treatments such as cognitive behavioural therapy and group therapy are also very helpful and help enhance insight and resiliency. Other treatments are also critical: occupational therapy helps enhance reintegration into work or training, and social treatments, such as housing support and community living advocacy, offer practical and needed strategies for the challenges of living life with a severe and complex mental health challenge. Most treatments are offered in outpatient settings with access to inpatient services as needed. Sadly, many patients and families struggle with the natural consequences of illness while waiting for access to services.

**Mood Disorders**

Mood disorders tend to be one of the most common clusters of chronic psychiatric illness in Canada. They include a number of disorders (major depression, bipolar disorder, dysthymia and cyclothymia) that often have other co-morbidities (anxiety disorders, psychosis). The impact on the quality of life of patients and their families is high; the risk of completed suicide is a complicating factor.

Some patients may struggle to manage their impulse control when suffering from a mood disorder, particularly in the case of mania or hypomania. With poor insight and impaired judgment, patients may turn to increased drug or alcohol use. For those struggling with profound sadness, substances such as alcohol or stimulants may diminish some of their angst and pain, albeit in a dysfunctional fashion. As with other conditions, it is essential to inquire carefully and non-judgmentally about what patients may use regularly, or what they may have tried, in order to alleviate their symptoms.

Risk assessments are a crucial component of mental healthcare, particularly in the case of mood disorders where the risk of completed suicide is high. Concurrent disorders carry with them a higher rate of completed suicide, and suicide attempts often involve substances either as a form of suicide or as a form of self-treatment for the anxiety associated with a suicide attempt. Thus, asking questions about suicidal thinking, suicide attempts or plans, and making the connection between substance use and suicidal ideation are essential components of care.

Treatments for mood disorders vary. In concurrent disorders, simultaneous treatment of both conditions may be necessary. Such treatment plans tend to be complex and involve multiple
systems of care. Patience, robust collaboration, and careful monitoring for a long period of time will likely be required.

Bipolar disorders often require vigorous biological interventions using mood stabilizers (lithium), neuroleptics (olanzapine, quetiapine), or anti-epileptic medications (lamotrigine, valproic acid). Other mood disorders, such as depression or dysthymia, respond well to psychotherapy (cognitive behavioural therapy, psychodynamic therapy) and/or medication (specific serotonergic or noradrenergic reuptake inhibitors, tricyclic antidepressants). While bipolar disorders require ongoing care throughout a patient’s life and tend to have a fluctuating course, other mood disorders can fully stabilize after one episode, however, recurrent or chronic episodes are not uncommon. Sadly, some patients struggle with treatment-resistant mood disorders, which places them at particularly high risk of severe disability and suicide. Involvement of tertiary-level mental health services may mitigate such negative outcomes.

**Anxiety Disorders**

Anxiety disorders are one of the most common psychiatric conditions in Canada. They represent a cluster of disorders (phobias, panic, generalized anxiety) that tend to have a high degree of symptom and diagnostic overlap.

Many anxiety disorders have their origins in childhood but often go undiagnosed until adulthood. This can result in well-ingrained patterns of anxious thinking, somatic responses, and dysfunctional coping strategies.

Many substances of abuse can directly interfere with the body’s stress response. Alcohol and benzodiazepines, for example, counteract physiological anxiety and can induce a state of relaxation or increased ability to tolerate distress. In light of the near-instant relief from their chronic suffering, it is easy to see how a patient may seek these effects repeatedly. For example, a medical student with an undiagnosed history of social phobia may find alcohol to be a useful substance for helping them function at parties and other social functions. Over time, however, this strategy can devolve healthy coping skills and contribute to the development of Alcohol Use Disorder.

There are also a few other links between anxiety disorders and addiction. It is thought that some substances, particularly stimulants such as cocaine, may actually lead to the development of anxiety disorders. In addition, there is evidence to suggest a genetic link between addiction and anxiety disorders where certain genes may place a patient at a higher risk for both.

Careful screening for anxiety disorders is essential in all patients presenting with addiction concerns. A practitioner may wish to start with broad and general questions such as, “Do you struggle with worries or feelings of anxiety?” Then carefully screen for common anxiety syndromes by inquiring about any bursts or attacks of anxiety, intense and specific fears, or ongoing and pervasive physical symptoms of anxiety. For example, alcohol is often used to decrease social anxiety, reduce inhibition, and increase socialization. In moderation, such use is associated with
few negative health related outcomes. However, for those living with social phobia, successful self-treatment with alcohol can reinforce its use and spiral out of control.

The good news is that anxiety disorders respond well to intervention. Treatment typically includes an integrated course of psychotherapy (cognitive behavioural therapy, exposure/response prevention) and pharmacotherapy (specific serotonergic or noradrenergic reuptake inhibitors, tricyclic antidepressants).

**Trauma and Stress Disorders**

Many Canadians have struggled with life-threatening or profoundly stressful experiences. Experiencing sexual assault, child maltreatment, natural disasters, or involvement in acts of war can increase one’s risk of using drugs or alcohol. Furthermore, early life exposure to trauma can sensitize the brain and the body in such a way that future responses to less severe stressors may be equally vigorous. This can result in a chronic pattern of intense stress reactions that can further alter normal brain and body functioning and lead to a spiralling pattern of decreased functioning and loss of health.

Practically, it is important that health practitioners explore possible trauma and chronic stress with their patients. For example, asking about current stressors or ongoing sources of stress may shed light on aspects of their life that they may not readily volunteer or recognize as being relevant. Asking questions about abuse or maltreatment is a particularly sensitive issue and should only be done in the context of good rapport and safety. One approach is to discuss this with the patient while exploring their family history. For example, ask, “What was it like growing up in your family?” or “How did your parents (or caregivers) show their displeasure or frustration?” or “What methods of discipline or punishment were used?” It can also be explored while discussing the patient’s current relationship history, for example, asking, “Is there any physical or emotional violence in your life at present?” If exploring sexual functioning, the practitioner can also query sexual maltreatment. For example, “Has anyone ever touched you in a way that made you feel uncomfortable or forced you to touch them when you did not want to?” Sometimes, a practitioner may simply be able to ask, “Have you ever been abused in any fashion – sexually, physically, or emotionally?” It is important to remember that many patients will simply answer, “No,” for reasons of stigma, shame, or anxiety. However, some will reflect on your openness to discuss these issues and disclose at a later visit.

Substances of abuse, such as alcohol, amphetamines, opiates, or hallucinogens, can offer patients initial respite from their suffering. Many will suggest that they feel better when painful memories are forgotten, nightmares are suppressed, and hypervigilance is dulled. However, this response can contribute towards a rapidly escalating pattern of use, leading to escalating negative consequences.

Should a practitioner uncover a possible diagnosis of a stress or trauma disorder, they should consider referring the patient to an appropriate and accessible clinical service. Mental health
professionals are familiar with these diagnoses and can make further assessments. Treatments typically focus on psychotherapy (cognitive behavioural therapy, eye-movement desensitization and reprocessing, psychodynamic therapy, or group therapy) and pharmacotherapy (specific serotonin reuptake inhibitors or specific noradrenergic reuptake inhibitors).

**Impulse Control Disorders**

A number of psychiatric diagnoses are associated with impulse control disorders. Perhaps the best known is attention-deficit hyperactivity disorder (ADHD), a neuropsychiatric condition that is commonly associated with a small percentage of children and youths. Characterized by difficulties with attention, taking turns when speaking (turn-taking), distractibility, and hyperactivity, ADHD can cause significant impairment to scholastic and occupational functioning and can also be associated with higher rates of accidents, underperformance, and social stressors.

Some patients with impulse control disorders find benefit in the use of nicotine, amphetamines, and high doses of caffeine. However, such benefits may be short term, require use of other substances to manage side effects (benzodiazepines, alcohol), and lead to further impairment.

Treatment of impulse control disorders may involve biological treatments (stimulant and non-stimulant medications such as methylphenidate or atomoxetine), psychological treatments (behavioural therapy), and educational interventions and supports.

One common myth often raised by patients and their families is that treatment with stimulant medications can lead to experimentation with, and addiction to, other stimulants or substances. Studies have repeatedly demonstrated, however, that early identification of impulse control disorders is, in fact, associated with a lower rate of addiction development.

**Wrapping It Up**

Mental health problems or substance use problems are challenging to address on their own. When they present or develop together, serious complications and threats to recovery arise. As such, early identification and treatment of co-morbid mental health conditions is essential to reduce the risk of negative outcomes from substance use or abuse. While there are many of models of intervention, integrated treatment approaches are often the most effective. However, this can create challenges for systems of care that are, at best, fragmented. But, such challenges can inspire opportunities for system integration and evolution.
**Reflective Questions**

1. What are concurrent disorders and in what ways can they complicate our collaboration with patients living with them?
2. What are the common psychiatric conditions that are associated with addiction?
3. How might you approach a patient presenting with potential co-morbid substance use issues?

**Podcast**

**Addiction**

[Podcast 9: Prevention, Intervention and Treatment of Addiction](#)

**Virtual Patient Cases**

The following virtual patient cases were prepared by Open Labyrinth for the TIDE Project. To access, click on the titles.

[Alice in Slumberland](#)

[Case of Miriam (Age 42)](#)
REFERENCES


**7. CHRONIC DISEASE MANAGEMENT: A CASE STUDY**

Derek Puddester

**INTRODUCTION**

Medical schools offer students many opportunities to learn and develop their clinical skills. What they cannot offer, however, is the richness of experience that develops from caring for patients over long periods of time. Such shared experiences with patients allow for a deeper appreciation of the social determinants of health, the longitudinal course of illnesses and treatments, and the human- and system-level dynamics that affect patient outcomes.

To illustrate some of the principles involved with chronic disease management, this chapter will follow a medical student with a history of addiction over the course of his career.

**FIRST PRINCIPLE: DEVELOP A GENUINE RELATIONSHIP WITH THE PATIENT**

The relationships that physicians form with their patients are one of the most important, and most dynamic, forms of treatment. It allows them to assess patients robustly and thoroughly, build alignment in care, and communicate information to patients and their families. By demonstrating and earning respect, trust, and alliance, physicians can develop a collaborative approach to health care.

Various elements come together to shape the dynamic of this relationship. To begin with, as all physicians bring elements of themselves to the patient relationship, they must learn how to modulate their values, beliefs, and skills in order to ensure that their patients are treated without undue bias or influence. Physicians also bring with them elements associated with the system of care in which they work—this can vary by geography, legislation, culture, or context. Finally, they respond to elements from the patients—their personality, culture, story, history, and presentation.

**SECOND PRINCIPLE: COMPLETE A ROBUST ASSESSMENT AND ESTABLISH A CLEAR DIAGNOSIS AND EVIDENCE-BASED TREATMENT PLAN**

In most Canadian provinces and territories provincial medical associations operate Physician Health Program (PHPs). While these programs differ widely in their scope and structure, most readily support medical students and physicians dealing with addiction issues. The process
typically begins with a thorough physical examination as well as a mental health and substance use assessment. History is often obtained from collateral sources and concurrent diagnoses identified and triaged.

see Case Study: Jean met with a psychiatrist

**Third Principle: Empower the Patient to Manage His or Her Own Health**

Life is full of stressors and challenges, and most are unpredictable or underestimated. Yet, most patients have the internal resilience to manage these stressors appropriately and to plan for them mindfully. In a chronic care model, it is essential to normalize the challenges of life in the context of recovery and to work collaboratively to enhance the resilience of patients.

Education about the underlying diagnosis is essential and can be provided through direct teaching, group work, bibliotherapy, or e-learning. In the case of substance use disorders, risk of relapse can be determined by history, formal measurement scales, or consideration of concurrent diagnosis. However, emotional issues (stress, guilt, stigma, and/or depression) and physical issues (craving, anxiety, and/or pain) are largely at the root of most episodes of relapse. Working with patients to identify the role that these issues play in their lives is essential and may help prevent or manage relapse successfully.

see Case Study: Jean is a consistently bright medical student

**Fourth Principle: Plan for Continuity of Care**

Our world is increasingly mobile; patients and healthcare providers frequently move and transition as time passes. Thankfully, clinical services are usually designed to readily manage the ebb and flow of personnel and protocols have been established to maintain continuity as patients move from age-based or geographically-based treatment programs.

see Case Study: Jean was matched

**Fifth Principle: Plan to Manage Relapse Without Judgement and With Expertise**

While relapse is not an inevitable part of recovery, it is a well-understood phenomenon that can be managed with dignity and success. For many patients in recovery, relapse is viewed with strong and complex emotions, including shame and its associated defence: denial. Clinicians and peer-supports are familiar with the complex issues related to relapse and can provide a supportive approach to intervention and treatment.
It is important to note, however, that those not involved clinically in the care of physicians who are patients may not take a similar approach\(^6\). Hospital leadership, university administration, and licensing authorities are designed to protect patients and health services from professionals who are ill or who have impaired health. This is an important part of self-regulation and is a natural part of our healthcare system. That said, most regulatory agencies, administrators, and leaders are typically open to working with PHPs and supporting a physician in recovery.

**Sixth Principle: Carefully Facilitate Return to Work and Training After Relapse**

As discussed earlier in this primer, treatment is a largely successful intervention for those living with substance use disorders. Most people moving into recovery are understandably eager to return to their former roles and responsibilities, and physicians are no different\(^7\). However, physicians and other healthcare professionals may return so quickly that various aspects of their treatment and recovery are not yet in place. This can place their recovery at risk and contribute to additional episodes of relapse. Thus, using a robust framework for ongoing treatment and monitoring of recovery can help to promote a more sustainable and successful return to occupational functioning\(^8\).

**Seventh Principle: Life Happens, and Often**

One of the joys of long-term patient care is the depth of mutual understanding that the patient and physician develop over time. Managed well, the relationship can become a critical component to both the treatment of the patient and the sustainability of the healthcare provider. Being open to the challenges and opportunities that inevitably arise in both their own lives and in the lives of their patients allows physicians to gain meaningful and sometimes profound insights as well as shifts in behaviour.

**Conclusion**

A number of principles are involved in the long-term care of illness. This chapter summarizes some of the most basic—but most human—aspects of chronic disease management. It is important to be aware that health system issues, including system design, model of access, funding design, program evaluation and continuous quality improvement, patient education, patient-centred care, and others, are also relevant.
**Reflective Questions**

1. What are some challenges facing a physician in the development of long-term relationships with their patients? How might you react to them?

2. How might patients and healthcare providers understand and manage their emotions in regards to the relapse of illness? How might negative reactions such as blame, cynicism, and hopelessness be assessed and managed?

3. How might you react to having to work with a PHP on a mandatory basis? How might that help you appreciate the monitoring that patients experience when living with a chronic illness?
REFERENCES


Additional Materials

» CASE STUDY

Introducing Jean

Jean is 24 years old and preparing to enter medicine. Due to his parents’ struggle with alcoholism, Jean's early years were peppered with violence and uncertainty until his mother left the family. Jean was a studious undergrad and worked hard as a volunteer in his community. However, he also played hard in his social life, enjoying binge drinking, recreational use of marijuana and, occasionally, cocaine and ecstasy. Regardless, he never experienced any severe consequences from use except for occasional fights and unprotected intercourse, which led to treatable sexually transmitted infections.

When he entered medical school he was elated and ready to celebrate. Frosh week provided ample opportunity to do so.

Jean repeatedly drank

Jean repeatedly drank to excess during frosh week. Other than causing a bad hangover, his actions had no major consequences. However, he made a number of new friends who also enjoy drinking while socializing, and they began to hang out on weekends. Over the course of the first semester, Jean got drunk three to four times per week, which began to affect his ability to study and participate robustly in case-based group learning. Group and faculty members became concerned and suggested that he meet with a counselor at Student Affairs. He declined their advice until he failed two academic blocks and was mandated to meet with a counselor. After an intake interview, he was referred to his provincial physician health program (PHP) for an assessment.

Clinical programs, such as PHPs, work hard to offer a safe and respectful environment to their patients. Student affairs programs work hard at this, as do physician health programs. Issues of confidentiality, excellence, and patient-centred care are respected and paramount to establishing a solid foundation to what will likely be a long-term relationship.
CASE STUDY

Jean met with a psychiatrist

Jean met with a psychiatrist and an addiction specialist. He was diagnosed with an alcohol use disorder, a cannabis use disorder, and a stimulant use disorder. In addition, he was diagnosed with social phobia, which is thought to have contributed to his vulnerability to substances over time. He began to work with a psychologist to treat his anxiety, joined a Caduceus group (a form of group therapy for medical students and physicians working to maintain their recovery), and joined an outpatient treatment program to treat his addiction. The Faculty of Medicine was fully supportive of his ongoing training, provided that he remain in recovery and that his health be formally monitored to ensure that he is safe and fit to be part of the health care team.

CASE STUDY

Jean is a consistently bright medical student

Jean is a consistently bright medical student who earns average grades and solid evaluations from peers and faculty members. In his final year of clerkship, he had a five-month block of intensive training (pediatrics, surgery, and internal medicine) during which his girlfriend decided to end their relationship. Sleep deprived, stressed, and lonely he began to experience strong cravings. Having learned from others in his Caduceus group, he attended a meeting and openly discussed his stress. The group intervention was helpful and sustaining. He also reached out to his therapist and arranged to see his family physician. This integrated support helped him to work through this difficult experience and maintain his sobriety and good health.
Jean was matched to his first choice in the Canadian Resident Matching Service (CaRMS)—a surgical program several provinces away. His educational license was granted on the provision that he periodically provide evidence of his good health to his college. The PHP in his new province is small but helps him find a new family physician and psychologist. However, he does not find a new Caduceus group and doesn't feel comfortable attending a community-based group program for reasons of confidentiality. In spite of this, he does well and maintains good health for a number of years.

Jean in his final year

In his final year of training, Jean faced a number of academic and personal challenges and began to skip treatment sessions. He started to feel that he was in full recovery and no longer needed any external supports. However, the unexpected death of one of his patients triggered a number of strong emotions and Jean found himself drinking again, although in small amounts. Over a few months, his use increased; his colleagues became concerned about his mood changes, erratic behaviour, and poor attendance. After suspecting the smell of alcohol on his breath, a patient registered a complaint to the College at which point the PHP was notified and an intervention arranged. As a result, just months shy of completing his training, Jean was admitted to a residential treatment program for alcohol withdrawal, suicidal ideation, and severe anxiety.
Jean responded very well to residential treatment and was discharged to outpatient services after six weeks. He alerted his program director that he was ready to finish his last few months of training and asked to be placed back on the schedule. In return his program director met with him and requested that a return to work plan be developed in collaboration with the PHP. Although Jean was irritated and frustrated with what he perceived to be bureaucratic interference, he agreed to the plan. As part of the collaboration, a more gradual return to work plan was developed and linked to successful treatment milestones. And, over the course of two months, Jean was able to return to full responsibilities and successfully completed his training.

Jean enjoyed ongoing recovery well into his early and mid-career. He fell in love, married, and had children. His clinical work was well regarded, and he was eventually named chief of his department at the community hospital. His family physician works closely with him on an ongoing basis to monitor his health, including modifications to treatment of his anxiety disorder as needed. Jean continues to attend Caduceus group meetings regularly and reaches out for psychological help during times of increased stress.
Definitions are from *AFMC Addiction Primer on Biopsychosocial Approach* to Addiction unless otherwise noted.

**Affect regulation / emotion regulation**: the capacity to self-regulate one's emotional state and develop coping strategies in order to adaptively meet the demands of one's environment. (See 2.4, Intergenerational Transmission of Addictive Behaviours.)

**Afferent / efferent**: carrying toward or away from, respectively; used to indicate the direction of cell–cell communication within a neural circuit or system. Afferent fibres carry a signal to a target cell or nucleus, and efferent fibres carry a signal from the target cell or nucleus.

**Agonist**: an exogenous chemical or drug that binds to and activates a cellular receptor. For example, morphine is an opioid agonist; this drug binds to all types of opioid receptors and activates them in a manner similar to an endogenous opioid.

**Alexithymia**: the inability to identify and express or describe one's feelings. People with alexithymia typically display a lack of imaginative thought, have difficulty distinguishing between emotions and bodily sensations, and engage in logical externally-oriented thought. Medline Plus [Internet].

**Allostasis**: stability through variation; a process whereby biological systems actively adjust to new environments or stimuli and then return to equilibrium. For example, the body's peripheral systems are activated to support “fight or flight” responses when a threat is perceived, but once the threat is gone, these systems return to normal functioning. Allostatic load refers to the cost to, or wear and tear on, biological systems from repeated, significant deviations from equilibrium.

**Antagonist**: an exogenous chemical or drug that blocks the activity of neurotransmitters and peptides by binding to and occupying cellular receptors so that other ligands cannot bind. Antagonists bind to cellular receptors but do not activate them. For example, naltrexone is an opioid antagonist: this drug binds to mu- and kappa-opioid receptors without activating them and can block the effects of both endogenous opioids and opioid drugs such as morphine and heroin.

**Attachment**: a strong emotional bond that an infant forms with a caregiver (such as a mother) especially when viewed as a basis for normal emotional and social development. Medline Plus [Internet]. (See 2.4, Intergenerational transmission.)

**Attachment behavioural system**: According to Bowlby, the attachment behavioral system is an inborn, pre-set program of the central nervous system that evolved via natural selection. It governs the choice, activation, and termination of behavioural sequences that produce a predictable and generally functional change in the individual's environment, in this case, proximity between the infant and a caregiver.
Brain plasticity: the capacity of the brain to change its structure, function, or organization in response to experience or injury. This ability persists throughout the lifetime, but specific types of plasticity are age-dependent.

Caduceus group: a form of group therapy for medical students, healthcare practitioners, and/or physicians striving to maintain their recovery from substance abuse. (See 7.0 Case Study.)

Chronic Care Model (CCM): a proactive management strategy that involves multidisciplinary teams of health care providers and replaces the traditional model of primary care delivered by a single clinician (See 4.1, Future Management Strategies of Substance Use Disorders.)

Concurrent disorder: a diagnostic condition in which a patient is living with both mental illness and an addictive disorder. (See: 2.2 Concurrent Disorders.)

Connectedness: a term that speaks to the degree people feel bonded, attached, or related to others. (See 2.3 The ACE Study.)

Depressogenic: something that causes or can cause depression.

Detoxification phase: achieving abstinence in a way that safely reduces immediate withdrawal symptoms. One of the three major phases of addiction treatment; the other phases are initial recovery and relapse prevention. (See 6.2 Medication Assisted Treatment.)

Dysphoria: a state of feeling unwell or unhappy. MedlinePlus [Internet].

Dysregulation: impairment of a physiological regulatory mechanism (as that governing metabolism, immune response, or organ function). Medline Plus [Internet].

Epigenetics: changes in gene expression that do not involve alterations to the DNA itself. Epigenetic change is a regular and natural occurrence but can also be influenced by several factors including age, the environment, and disease state. (See 1.4 Genetics and Addiction.)

Equality in health: “aims to ensure that everyone gets the same things in order to enjoy full, healthy lives. Like equity, equality aims to promote fairness and justice, but it can only work if everyone starts from the same place and needs the same things.” Clow B, Hanson Y, HaworthBrockman, Bernier J. SGBA e-learning resource: Rising to the challenge: sex- and gender-based analysis for health planning policy and research in Canada [Internet]. 2009 [cited 2017 Apr]. Available from: http://sgba-resource.ca/en

Equity in health: “Health equity is created when individuals have the opportunity to achieve their full health potential. Conversely, equity is undermined when preventable and avoidable systematic conditions constrain life choices… Systematic conditions are largely the social and economic factors known as the social determinants of health. The World Health Organization defines the social determinants of health as the circumstances in which people are born, develop, live and age.” CMA. Health equity and the social determinants of health. Available from: https://www.cma.ca/En/Pages/health-equity.aspx
Genogram: a diagram outlining the history of the behaviour patterns (as of divorce, abortion, or suicide) of a family's members over several generations in order to recognize and understand past influences on current behaviour patterns; also: a similar diagram detailing the medical history of the members of a family as a means of assessing a family member's risk of developing disease MedlinePlus [Internet]. (See 4.3 Assessment and Management of ACEs in Primary Care: A Canadian Perspective.)

Incentive salience: a type of motivation created in the brain whereby a rewarding stimulus gains additional, and at times irrationally strong, motivational power. Incentive salience is mediated by brain circuits in the reward system and produces the intense desires and cravings observed in people with addiction.

Index of suspicion: refers to what the physician’s initial impression is of the likelihood of a disease or condition. A high index of suspicion means the doctor considers the diagnosis a strong possibility; a low index of suspicion means the converse. “A phrase broadly used to indicate how seriously a particular disease is being entertained as a diagnosis.” McGraw-Hill Concise Dictionary of Modern Medicine (Online). (See 6.3. Clinical Management of Concurrent Disorders.)

Inequalities in health: differences in health status or in the distribution of health determinants between different population groups. World Health Organization [Internet.]

Initial recovery: one of the three major phases of addiction treatment. The goal is to develop sustained motivation to remain abstinent and to avoid relapse by learning to tolerate cravings and by developing new behaviour that replaces drug-induced reinforcement with alternative rewards. The other phases are detoxification phase and relapse prevention. (See 6.2 Medication Assisted Treatment.)

Korsakoff syndrome: a chronic memory disorder that is caused by brain damage related to a severe deficiency of thiamine (as that associated with alcoholism or malnutrition) and is characterized by impaired ability to form new memories and by memory loss for which the patient often attempts to compensate through confabulation. The DSM-5 defines Korsakoff syndrome as “alcoholinduced confabulatory neurocognitive disorder” (DSM-5, p. 630). (See 6.2 Medication-Assisted Treatment.)

Labile hypertension: term used to describe blood pressure measures that may fluctuate abruptly and repeatedly from normal to high. Increases in blood pressure may be a reaction to emotional stress. From: What is labile hypertension? Patients Like Me. www.patientslikeme.com/conditions/1013-labile-hypertension

Lipase: an enzyme (as one secreted by the pancreas) that catalyzes the breakdown of fats and lipoproteins usually into fatty acids and glycerol. MedlinePlus [Internet]. (See also 1.3 Neurochemistry of Process Addictions.)

Microdialysis: a technique that allows continuous monitoring of concentrations of various
compounds in extracellular fluids.

**Motivational interviewing (MI):** “a technique in which you become a helper in the change process and express acceptance of your client. It is a way to interact with substance-using clients, not merely as an adjunct to other therapeutic approaches, and a style of counselling that can help resolve the ambivalence that prevents clients from realizing personal goals….

The clinician practices motivational interviewing with five general principles in mind:

- Express empathy through reflective listening.
- Develop discrepancy between clients’ goals or values and their current behavior.
- Avoid argument and direct confrontation.
- Adjust to client resistance rather than opposing it directly.
- Support self-efficacy and optimism.”


**Myelination**: the process of coating nerve axons with myelin, a fatty sheath derived from the bodies of oligodendrocytes (central nervous system) or Schwann cells (peripheral nervous system). Myelin acts as an electrical insulator and increases the speed of electrochemical signalling between cells.

**Negative reinforcement**: the process by which removal of an aversive stimulus increases the probability of a response.

**Neurotransmitter transporters**: part of a neuron’s reuptake mechanism. In the brain, a neurotransmitter transporter is a trans-membrane protein complex located on the presynaptic neuron that enables neurotransmitters to be removed from the synapse and reused or recycled by the presynaptic neuron. (See 1.2 Neurochemistry of Substance Addictions.)

**No Wrong Door**: an approach that provides clients with a universal gateway to community services and government programs. “Staff of community organizations are able to connect individuals and/or families with the appropriate service(s) in a manner that is streamlined, effective and seamless from the individual’s and/or family’s perspective, even if that service(s) is not offered by their organization or within their sector.” Anderson W. What do “no wrong door’ and “warm hand-off” really mean? Hastings & Prince Edward Children and Youth Services Network [Internet]. 2014 Aug [cited 2017 Apr]. From: [http://www.hpechildrenandyouth.ca/2013/08/what-does-no-wrong-door-and-warm-hand-off-really-mean/#sthash.bpZyhGcz.dpuf](http://www.hpechildrenandyouth.ca/2013/08/what-does-no-wrong-door-and-warm-hand-off-really-mean/#sthash.bpZyhGcz.dpuf) (See also 6.1 Community-Based Treatment and Recovery.)

**Odds ratio (OR)**: is a measure of association between an exposure and an outcome. In statistics, it
is the ratio of the odds of an outcome occurring in an exposed group versus the odds of this same outcome occurring in an unexposed (control) group.

**Parenteral dosage**: drug administration by intravenous, intramuscular, or subcutaneous injection. (See 6.2 Medication Assisted Treatment.)

**Positive reinforcement**: the process by which presentation of a stimulus increases the probability of a response.

**Prodromal**: describes the gradual onset of symptoms, for example, social withdrawal, anxiety, skipping work or school, and suspicion. This phase usually occurs in adolescence or early adulthood. (See 6.3 Clinical Management of Concurrent Disorders.)

**Psychosis**: a serious mental illness (as schizophrenia) characterized by defective or lost contact with reality often with hallucinations or delusions. Medline Plus [Internet].


**Relapse prevention**: One of the three major phases of addiction treatment. It follows a period of sustained abstinence and involves the development of long-term strategies to replace past drug behaviour with new, healthy behaviour. The other phases are detoxification and initial recovery. (See 6.2 Medication Assisted Treatment.)

**Relative risk**: See “risk ratio.” (See also 2.3, Adverse Childhood Experiences: The ACE Study.)

**Reuptake**: the reabsorption of a secreted substance by the cell that originally produced and secreted it. The process of reuptake, for example, affects serotonin. MedicineNet [Internet]. (See also 1.2 Neurochemistry of Substance Addictions and 1.3 Neurochemistry of Process Addictions.)

**Reward**: operationally defined similarly to positive reinforcement as any stimulus that increases the probability of a response but also has a positive hedonic effect. (See 1.1 Neurobiology of Addiction.)

**Risk ratio**: a measure of association between an exposure and an outcome. In statistics, it is the ratio of the probability of an outcome occurring in an exposed group versus the probability of this same outcome occurring in an unexposed (control) group. Also referred to as the relative risk. (See 2.3, Adverse Childhood Experiences: The ACE Study, Nerd’s Corner Odds Ratio Versus Relative Risk.)

**Self-esteem**: how individuals feel about their own worth, how they assess and judge themselves as an individual and member of society, and how they identify aspects of their selves that promote resiliency. Low self-esteem has been identified as one of the most relevant risk factors associated
with youth developing substance use disorders later in life. (See 2.5 Adolescent and Young Adult Triggers for Substance Misuse.)

**Sequelae (plural):** a negative aftereffect. MedlinePlus [Internet]. “A pathological condition resulting from a disease, injury, therapy, or other trauma. Typically, a sequela is a chronic condition that is a complication that follows a more acute condition. It is different from, but is a consequence of, the first condition.” (Wikipedia.) “The use of alcohol or drugs may result in many different medical sequelae. Some effects are acute and may be transient, while others may only manifest after long-term use.” Weaver M. Research paper: medical sequelae of addiction [Internet]. 2010 [cited 2016 Apr]. Available from: [https://www.researchgate.net/publication/286329212_Medical_sequelae_of_addiction](https://www.researchgate.net/publication/286329212_Medical_sequelae_of_addiction) (See also 2.2 Concurrent Disorders.)

**Signposting:** “is a useful way for a doctor to give structure to a consultation. For example…, the doctor says, ‘We’ll talk about options later on. Would you tell me a bit more about your back pain?’ This indicates to the patient that he has heard her request, but allows him to shift the topic to get the information he currently needs. Signposting helps the patient understand the direction the consultation is going in and why, and allows doctors to share their thoughts and needs with the patient.” Doctors speak up: communication and language skills for international medical graduates: signposting. Available from: [http://doctorspeakup.com/content/signposting](http://doctorspeakup.com/content/signposting) (See also 5.1, History, Screening, Detection, Investigations, and Diagnosis.)

**Stigma:** an identifying mark or characteristic; specifically: a specific diagnostic sign of a disease. MedlinePlus [Internet]. (See 4.2, Stigma and Reflective Practice.)


**Wernicke’s encephalopathy:** an acute inflammatory hemorrhagic encephalopathy that is caused by thiamine deficiency (such as that associated with chronic alcoholism or malnutrition) and is characterized by loss of muscle coordination, visual disturbances (such as abnormal eye movement and diplopia), and confusion and memory loss. MedlinePlus [Internet]. (See 6.2, Medication Assisted Treatment.)

**Withdrawal:** The discontinuance of administration or use of a drug. The syndrome of often-painful physical and psychological symptoms that follows discontinuance of an addicting substance. MedlinePlus [Internet]. (See 6.2. Medication-Assisted Treatment.)
### APPENDIX 1

**MCC Objectives**

(https://apps.mcc.ca/objectives_online/objectives.pl?lang=english&loc=home)

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**Appendix 2**

**Street Drug Guide** *(http://vp.openlabyrinth.ca/renderLabyrinth/index/37)*

This resource contains seven mini virtual patient cases focused on misuse of various street drugs. It also contains a web notebook with Calgary-based information on the street drugs mentioned in the cases. You can save this notebook on your own computer and then edit or update it with information on the street drugs used in your local area.

**Medical Careers Game** *(http://vp.openlabyrinth.ca/renderLabyrinth/index/45)*

Medical Careers is an online game based on the classic board game Careers, developed by James Cooke Brown in 1955. Players start as young physicians and must navigate through multiple choices that produce different effects on their career trajectories. It features both single and multiplayer game play.