abstract

Addiction often results from using controlled (monitored by the Drug Enforcement Agency) or illicit substances to produce pleasure or to dissociate from the consequences of life's events. Current evidence suggests that the addictive disease process stems from biogenetic predisposition, individual psychological profile, sociocultural influences, and drug exposure.

Drug addiction places a significant burden on society due to its detrimental impact on health and its disturbance of social interactions in professional and personal contexts.. The prevalence of addictive disorders in the pain population remains unknown, and substance abuse and addiction in older adults is underestimated and poorly understood. By virtue of their disease states, older adults consume drugs of abuse at higher rates and, therefore, may be at increased risk of addiction. Few publications clarify the magnitude of the problem or suggest methods of prevention or treatment.

Key words: *addiction, substance abuse, opioids, benzodiazepines, chronic pain*

Aging and the Neurobiology of Addiction

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Introduction

There are currently 35 million adults 65 years and older in the United States and by the year 2030, older adults will comprise 20% of the population. The global population is aging at an unprecedented rate. For instance, the proportion of the population aged 65 and older in the industrialized nations is projected to double to nearly 30% by midcentury from about 15% today.[2] Less appreciated is that over half of the world's adults aged 65 years and older live in developing nations (59%), and by 2030 this proportion is expected to reach 71% (686 million people). As the aging population grows, there is a heightened need to uncover their specific economic, social, and medical requirements and to clarify the unique biologic and genetic dynamics of the aging process. Indeed, the effects of this stunning worldwide boom in the older population will impact not only individual nations but the global interdependent economy.

The aging population suffers from greater medical and psychological comorbidities as well as an increase in pain severity. Consequently, health care professionals tend to prescribe the older adult more medications in general compared to their younger counterparts, and recommend controlled substances (e.g., benzodiazepines and opioids) to a greater extent in order to treat sleep disturbances and pain, respectively.

There is a lack of published material that examines substance abuse and addiction in this specific population; however, some evidence suggests that it may be a significant and emerging problem. Recently, Nemes *et al.* found that 25% of adults aged 55 years and over were diagnosed with substance abuse or dependence at the time of the study according to two standardized screening tools.[3] Their results coincide with previous estimates from the literature that document that a substantial number of older adults abuse or are dependent on drugs, including alcohol.[4]

Several factors in the aging population may predispose them to using controlled substances and then secondarily developing addictive behaviour. For instance, the aging population often develops more severe pain due to osteoarthritis, degenerative spine disease, and postherpetic neuralgia; risk higher rates of oncologic morbidity and mortality; and are at higher risk of medical and psychological comorbid disease states.[3] Many of these disease states can induce painful symptoms for which opioids are often prescribed. Recent studies suggest that synaptic plasticity, a potential mechanism for traditional learning, occurs in

neural reward circuits and may contribute to learning addictive behaviours. Work by Jones and Bonci reveals that addictive drugs (e.g., opioids, cocaine, amphetamine, nicotine, and alcohol) may trigger neuroplastic changes in the ventral tegmental area (VTA) of the brain (which receives inputs from at least three regions of the brain associated with reward-related learning) that lead to reward-related learning and addiction.[5] In fact, cells in the ventral tegmental area may represent early neural adaptations in response to addictive drugs. Jones and Bonci hypothesized that addictive drugs may potentiate glutamate synapses in the VTA and in turn induce changes in dopamine cell signalling to the nucleus accumbens. There is evidence that both glutamate and dopamine are integral to the mechanisms involved in the learning processes of both reward and addiction.[6–8] Research has demonstrated synaptic plasticity from dopamine or addictive drugs in many of these brain regions including the VTA, nucleus accumbens, amygdala, and the prefrontal cortex. In sum, this complicated array of neural reward/addiction circuitry may contribute to the pathophysiology and ultimate expression of addictive behaviours (Figure 1).

Certain studies have reported a lower prevalence of substance abuse problems among older adults; yet, health care providers probably underestimate rates of abuse because the symptoms can easily resemble those of diabetes, depression, and dementia, which more commonly affect seniors.[3] Moreover, the aging population often feels ashamed of disclosing any substance abuse problems and therefore seeks treatment less frequently. Growing evidence illustrates that addictive processes may be a real and perhaps escalating phenomenon in the aging population.

In a study by Wetterling *et al.*, 17.7% of males and 4.2% of females 64 years old and older admitted to the hospital had an ICD-10 diagnosis of dependency to alcohol. Furthermore, 5.8% of this population demonstrated substance abuse, most often to benzodiazepines.[9] In the largest sample of older patients to be screened for problem drinking in France, Ganry *et al.* showed that a substantial portion of participants (11.5% among 370 patients) fulfilled CAGE criteria for an alcohol problem and even suggested that limitations of self-reported data may have underestimated the degree of alcohol consumption among this cohort.[2] A review of the Broward County medical examiner's data showed that eight percent of deaths associated with illicit and prescription drugs were in the age group of 55 years and older. The vast majority of these deaths were actually due to prescription drugs.[10] Younger adults are more likely to use illicit substances, but older adults are much more likely to consume and become addicted to prescription drugs.[11] This is understandable considering older patients currently represent about 13% of the population yet account for 30% of overall prescription drug use.[3] The Center for Substance Abuse Treatment estimates that prescription drug and alcohol abuse affect up to 17% of older adults and this population is projected to rise given the large number of baby boomers (born post–World War II) who will reach senior status over the next 20 years. Other reporting vehicles such as The DAWN (Drug Abuse Warning Network) stratify the rates of benzodiazepine and opioid abuse among age groups by comparing the number of emergency department (ED) visits related to these drugs. Although the age group 55 years and older had the lowest rate of drug abuse based on ED admission, this cohort demonstrated an alarming increase in rate of abuse from 1995 to 2002 of 31% for benzodiazepines and 66% for opioids.[12–13] If this rate continues to rise and the expected growth in the aging population unfolds, the international community may face a substantial challenge in overcoming addiction in the older population. Higher consumption, as seen in aging populations, may result in an increase in substance abuse and addiction.

Neurobiology of Addiction

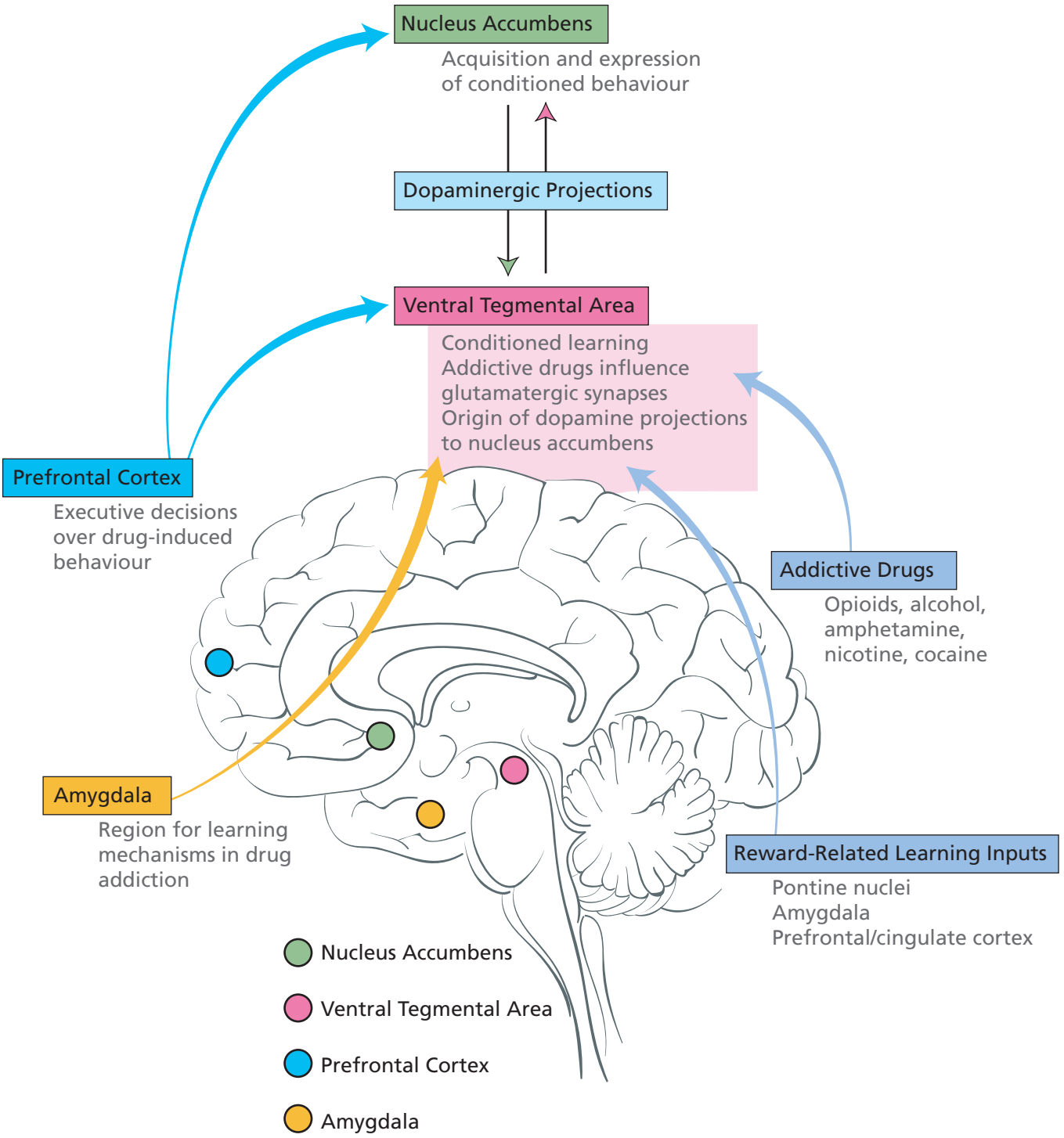
Neuroimaging

The use of human brain imaging to uncover neural pathways involved in addiction has added to the understanding of substance misuse on the brain and highlighted regions of the brain affected by drugs of abuse. For example, positron emission tomography (PET) and single photon emission tomography (SPECT) can measure blood flow and metabolic activity in "activated" regions within the brain. Neuroimaging studies consistently demonstrate activation in areas such as the amygdala, anterior cingulate, dorsolateral prefrontal cortex, and orbitofrontal cortex in individuals exposed to different substances of abuse. These areas reflect increased brain activity from cue exposure (for instance, the cue of alcohol exposure to an alcoholic) and craving, and also function in the complex integration of attention, emotional processing, goal-directed behaviour, associative learning, decision making, and analysis of information.[14] In particular, nicotine cues have been shown to enhance activity in the mesolimbic reward system (VTA) and increased activity in the anterior cingulate was noted while opioid addicts listened to audiotapes of their craving. In fact, researchers have discovered that activity in brain regions involved in memory, attention, and sensory processing coexists with activity in brain regions associated with cue exposure and craving, such as the anterior cingulate or orbitofrontal cortex.[15] Interestingly, there is speculation that these processes (memory, attention, and sensory processing) are controlled by the addictive state due to their overlap in activity (Figure 2).

Neuroadaptation

Current concepts of addiction recognize craving as a prime force for ongoing drug abuse as well as for relapse following a period of abstinence. Relapse is an important factor in the understanding of drug addiction; therefore, recent research has focused on this topic. For example, craving and stress exemplify two major factors that promote relapse. Furthermore, neuroadaptive changes that induce withdrawal symptoms and comorbid conditions such as psychiatric

Figure 1:
Critical Elements of Addiction/Reward Pathways



illness, low socioeconomic status, and perceived drug availability all potentiate relapse. Even single use of a drug can cause prolonged craving. Animal research has revealed an interconnected set of cortical and limbic regions important in associative learning that underlies craving and relapse. Neuroadaptation following drug use is critical to understanding the etiology of craving. For instance, these neuroadaptations mediate enduring associations between drugs and associative stimuli. The relationship between the drug and stimulus can trigger an intense craving. Moreover, both stress and the avoidance of withdrawal symptoms probably exacerbate cravings, though this is poorly elucidated.[16] The aging population may be at higher risk of developing neuroadaptive processes leading to addiction due to the greater likelihood of receiving drugs of abuse (e.g., opioids and benzodiazepines) to treat pain-associated disease states and associated comorbidities. In effect, the risk of addiction in older adults may stem from larger quantities of polyanalgesic substances prescribed to them for the treatment of pain and suffering related to chronic disease states (Figure 3).

Psychiatric Factors

Trafton *et al.* found that patients in pain displayed more severe medical and psychiatric problems and utilized more health care resources than those without pain.[17] Moreover, pain patients reported more struggles with depression, anxiety, suicidal ideation, and hallucinations than nonpain patients. Pain was associated with an increased propensity to misuse substances with analgesic effects, suggesting that ongoing pain contributes to drug-seeking behaviour. Alternatively, ongoing pain may simply reflect improperly treated pain (pseudoaddiction) and effective dosing of analgesics would extinguish perceived drug seeking behavior. Trafton's group found that even mild pain was associated with higher use of substances with weaker analgesic properties, such as cannabis and sedatives.

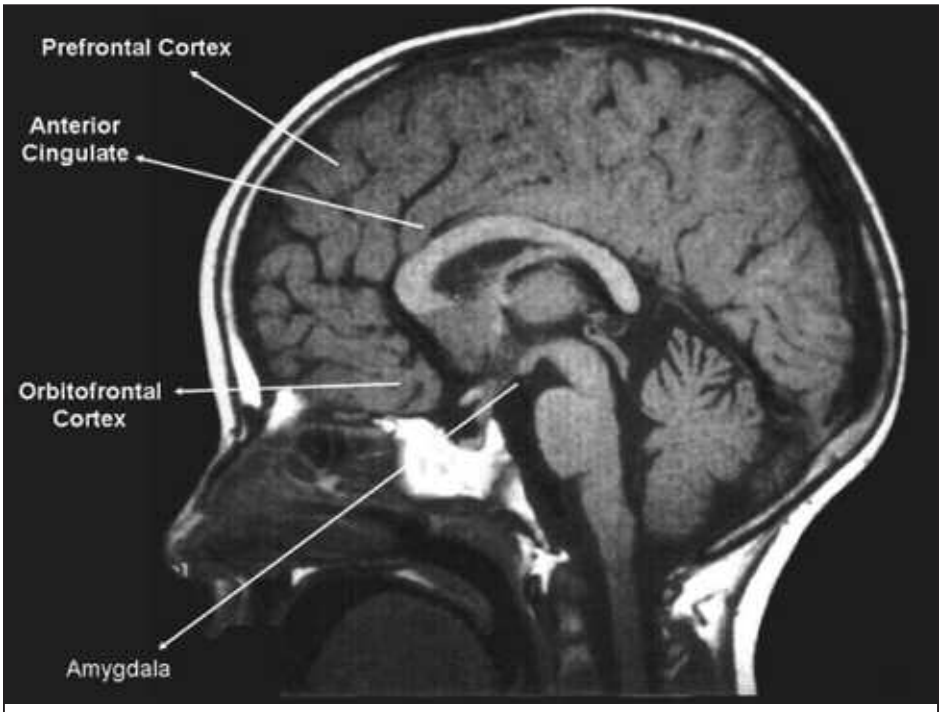


Figure 2: MRI Demonstrating Neuroanatomic Regions Associated with Addiction.

In all, the study revealed that drug-seeking behaviour progressed with more severe pain.

Genetic Influences

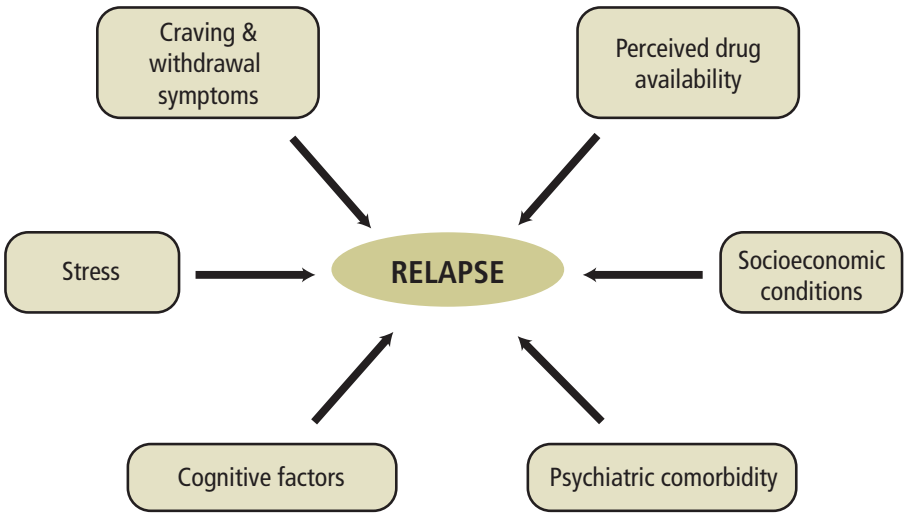
Regarding the genetic disposition to addictive disorders, preliminary findings suggest that regulators of gene expression may substantially influence the addiction process.[18] It is not yet possible to conclusively identify a gene or sets of genes that confer susceptibility to addiction, though powerful tools such as DNA chips are now available to examine DNA markers and genes. Many leaders in the field believe that drugs of abuse change gene expression (noted by mRNA levels) in the central nervous system by affecting transcription factors in cell nuclei. This genetic process may be critical in defining addictive behaviour. Greater insight into addiction genes obtained by new DNA technology may permit the identification of cohorts (for instance, older, young, educated, married, or divorced cohorts) susceptible to addictive substances and could aid in the development of novel approaches to addiction therapy.

Use of Opioids in Older Adults

Controversy exists over the long-term treatment of nonmalignant chronic pain with opioids as well as the outcome of long-term opioid use on depression and cognitive impairment in older adults.[19] Research by Turk *et al.* revealed that physicians disagree regarding the prescription of opioids for the treatment of nonmalignant chronic pain.[20] Factors such as geography and specialty seem to impact these attitudes. Fear of iatrogenic addiction or abuse is a primary impediment for the prescription of opioids for pain in the noncancer population. Clinicians expect improved function as a critical measure for opioid treatment whereas patients focus on symptomatic relief as their treatment goal. Both physicians and patients express concern about the potential for addiction associated with opioid use; however, rational and proper use of opioids helps control this risk.[20–21] Benzodiazepine dependency in older adults exists but very little data is available to guide the prevention and treatment of this disease in the aging population.[22]

Treating pain in the aging poses challenges to health care professionals.

Figure 3: Relapse Model in Addiction



Increasing numbers of older patients coupled with their higher incidence of pain and their greater susceptibility to the adverse effects of substances of abuse make rational use of opioids and benzodiazepines crucial to treatment.[23] Urine drug testing (UDT) is a valuable tool in testing the compliance of all patients, including older adults who are engaged in treatment with controlled substances.[11] UDT provides information that can assist the practitioner in diagnostic and therapeutic decision making related to chronic treatment with frequently prescribed substances such as opioids and benzodiazepines in the aging population. In fact, continuous use of opioids and benzodiazepines in older patients may be more problematic because tolerance to chemical agents diminishes with age. That is, the aging process affects drug pharmacokinetics by increasing the drug's volume of distribution and by reducing organ function, specifically the liver and kidney.[24] Therefore, it is important for the practitioner to evaluate and monitor each patient individually and make prudent choices when considering controlled substances as a treatment modality.

Conclusion

The interplay between aging and the neurobiology of addiction remains elusive and understudied; yet, the psychic and health care costs of this problem escalate as the world population ages. Knowledge of the pathophysiology and treatment of addiction in older adults through scientific and clinical research will provide insights that can favourably impact the lives of a substantial portion of the world's growing population and assist in creating health promotion programs and practices that lower the drain on economic and human resources. ◆

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