



## Early Life History of Drug Exposure Has Long Lasting Effect on Pain Sensitivity

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### ABSTRACT

Nowadays pain is the most commonly reported symptom in clinical practice. It is defined as “a complex emotional and sensorial experience that is associated with potential or actual damage” [1, 2]. Pain pathways represent a complex sensory system, with emotional, cognitive, and behavioral elements having evolved to detect and integrate a protective response to noxious stimuli [3, 4]. The protective nature of pain is true for acute pain, which is provoked by a specific disease or injury. However, chronic pain is not protective and is considered a disease state [5]. Pain sensitivity is one of the factors that determine the perceived severity, course, prognosis, and also treatment efficacy of clinical pain. It can be defined as increased or decreased pain responsiveness to noxious or non-noxious stimuli [6, 7]. Reduced sensitivity to pain is associated with the risk of delayed diagnosis or undermined treatment efficacy of conditions associated with acute pain. On the contrary, hypersensitivity is unpleasant and increases health care costs, risk of anxiety, and susceptibility to chronic pain conditions [8, 9]. Pain sensitivity widely varies among different individuals.

There are several reports that factors, including genetic and environmental factors, affect an individual pain perception and sensitivity [8]. One of the environmental factors affecting pain perception that has not yet received much attention is the history of drug abuse [10].

Drug abuse is considered a growing global public health care problem, characterized by compulsive behaviors for taking drugs and notable molecular changes in various parts of the brain [11]. In recent years, drug abuse has become increasingly prevalent and poses a particular threat to children and adolescents [12-14]. Early life, which includes both the prenatal and postnatal periods, is a sensitive time for neural development. The prenatal period refers to intrauterine life, during which a developing fetus can be impacted by environmental or genetic factors resulting from parental exposures. On the other hand, the postnatal period extends from birth through adulthood [15, 16]. Exposure to any harmful substance, especially drugs of abuse consumed by mothers during pregnancy or lactation periods, as well as during childhood or adolescence may

lead to enduring behavioral, molecular, or epigenetic changes in the brain [12, 17, 18]. There are reports that early life exposure to different drugs of abuse, such as opioids or nicotine, may change the different physiological functions, such as learning, memory, anxiety, and also pain perception later in life [19-25].

Opioids, such as morphine, are widely used for the relief of moderate to severe pain. However, they are also among the most frequently abused drugs. Studies have shown that early life exposure to opioids may alter synaptic plasticity and pain sensitivity [26, 27]. For instance, research on rats has demonstrated that prenatal opioid exposure induces hypersensitivity to pain [27]. It is also reported that the consumption of morphine during the neonatal period can increase the thermal and mechanical pain threshold in adulthood [24]. Previous studies have also highlighted the long-term effects of morphine on the perception of inflammatory pain. One study found that morphine consumption during the neonatal period increases pain-induced behavior in the formalin tonic pain model during adulthood in rats [28]. Similarly, morphine consumption during adolescence results in sensitization and an increase in pain-related behaviors later in life [22]. Moreover, inter- and transgenerational studies have shown that exposure to morphine during adolescence can affect pain perception in the offspring of both male and female rats [23, 29]. In addition, in-utero exposure to buprenorphine and methadone in rats has shown a decreased sensitivity to the analgesic effect of morphine and faster development of morphine tolerance [30]. These findings suggest that opioid consumption during early life may lead to long-lasting alteration in pain circuits, which could change one's sensitivity to pain [24]. Cigarette smoking, both first- and second-hand, is highly prevalent among

individuals, including pregnant mothers, children, and especially adolescents [31]. Cigarettes serve as a device for delivering nicotine. Epidemiological reports indicate a relationship between cigarette smoking and pain, suggesting that nicotine exposure is a risk factor for developing chronic pain [32]. Nicotine exposure during prenatal or adolescent periods may induce long-lasting alterations in the brain structure and thereby affect an individual's behaviors [33]. The alteration of pain sensitivity following nicotine exposure during early life has been reported. One study showed that maternal smoking during pregnancy increases the risk of musculoskeletal pain in offspring during adolescence [34]. Additionally, another study showed that nicotine exposure during adolescence increases pain-related behaviors in rat model of formalin test later in life, indicating changes in the pain modulatory system due to adolescent nicotine exposure [35]. Therefore, exposure to nicotine during early life can have a long-lasting effect on the nociceptive system and induces hypersensitivity to pain.

Although further research is necessary to fully comprehend the long-lasting effects of drug abuse during the early stages of life on pain sensitivity, it is clear from current evidence that such abuse has a significant impact and increases sensitivity to pain, which lasts for a significant period. This is due to the fact that crucial periods in development, such as prenatal, neonatal, or adolescence periods, have a lasting influence on brain systems, particularly those involved in pain perception. This suggests that drug exposure during early life is a crucial factor in pain sensitivity later in life. As a result, it is important to raise awareness among the community about the potential consequences of drug abuse during fetal and adolescent stages. Additionally, when examining, diagnosing, and treating patients

with chronic pain, it is essential to take into account their history of drug exposure during early life in order to ensure accurate diagnosis and appropriate treatment.

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