ISSN: 2755-0192

Journal of Psychiatry Research Reviews & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

# Treatments to Combat Opiate Dependence

**Sidish S Venkataraman[1] and Nachum Dafny[2]***

[1]Wake Forest University School of Medicine, Department of Neurosurgery, Winston-Salem NC, 27157

[2]UT Houston McGovern Medical School, Department of Neurobiology and Anatomy, Houston TX, 77030

**SUMMARY**

The current opioid epidemic is a pressing public health concern that has been difficult to address because there is no generally accepted hypothesis to explain the underlying neurophysiological mechanism(s) that lead to tolerance and withdrawal, which in turn could serve as the basis for developing therapeutic interventions. As a step to developing such a unifying mechanistic hypothesis we studied both the electrophysiological firing patterns of individual neurons and behaviors indicative of tolerance and withdrawal in rats following chronic administration of morphine. Neuronal activity recordings from the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex (PFC), thalamus, hypothalamus, hippocampus (HIPP), Amygdala (AMYG) and caudate nucleus (CN) following exposure of repetitive (chronic) morphine produced a new baseline pattern of neuronal firing rates, which we refer to as an "opioid-induced pattern" in the mesocorticolimbic neuronal activity circuit, which is thought to be involved in mediating the "reward" effects of opioid and other drugs of abuse. These changes in neuronal firing rate was paralleled by behavioral changes indicative of the development of dependence such as tolerance and withdrawal suggesting a possible cause-effect relationship between the opioid induced pattern change of baseline neuronal firing and the development of opioid tolerance and withdrawal. Briefly, (i) morphine produces a new baseline pattern of neuronal firing (i.e., an "opioid-induced pattern"), (ii) there is an intrinsic neurophysiological mechanism that seeks to maintain newly established patterns of baseline neuronal firing once established, (iii) continued morphine administration maintains the new pattern of baseline neuronal activity so that withdrawal behaviors do not occur, but (iv) eventual discontinuation of the drug leads to opioid withdrawal symptoms. Consistent with this proposed hypothesis, co-administration of the immunomodulator such as interferon, cyclosporin and cortisol attenuated both the development of an altered baseline pattern of neuronal firing and the parallel behavioral changes. This observation suggests that immunomodifiers treatment to morphine dependence subject restore the neuronal firing rate to its pre-morphine baseline and thus alleviate the withdrawal symptoms that make is so difficult for addicts to discontinue opioid use. The studies in this review describe in more detail the findings that led to our proposed hypothesis for the underlying neurophysiological basis of the development of opioid tolerance and withdrawal and the possible use of immunomodulators to decrease the development of dependence and thereby attenuate withdrawal symptoms that make it so difficult for addicts to discontinue drug use.

Repetitive use of opioids results in dependence on the drug, a complex condition that is considered to be an opiate use disorder (OUD). The reduction or cessation of opioid consumption leads to severe withdrawal behaviors. The degree of opiate dependence can be assessed by the intensity of the withdrawal behavior. To prevent this devastating opiate withdrawal syndrome, the subject will continue to take the drug. Success in modifying the withdrawal behavior may shed light on the dynamics of OUD and help to curb the opiate epidemic. Classical therapeutic addiction research has focused on cellular and molecular alterations within neurons and their neuronal circuits. As such, most of the pharmacotherapies for opioid addiction are designed to target the neuronal processes known to be affected by drug intake. In addition to the pivotal role of neurons in the initiation, transition, and maintenance of opioid dependence, the glial cells within the central nervous system are also of particular importance. According to some studies, 60 to 80% of the cellular brain is composed of glial cells. Recent studies have shown that glial cells participate in synaptogenesis, neuronal excitability, and neurotransmission. Following opioid exposure, glial cells demonstrate robust changes in their morphology and physiology in key central nervous system regions known to contribute to drug dependence. They play a pivotal role in opioid-addiction like behaviors. Glial cells are also part of the immune system. This review summarizes studies demonstrating that the immune system participates in the expression of opiate withdrawal and that a single dose of immunological substances such as α-interferon, cyclosporine, or cortisol significantly attenuates the severity of the naloxone-induced withdrawal symptoms in opioid-dependent animals. These preclinical studies provide a new approach to treat opiate dependence using immunomodulators that do not belong to the opiate family. We hope that this review will encourage translational studies to use immunomodulators in combating the opioid epidemic and save lives.

***Corresponding author**

Nachum Dafny, UT Houston McGovern Medical School, Department of Neurobiology and Anatomy, Houston TX, 77030; E-mail: Nachum.Dafny@uth.tmc.edu

**Received:** June 14, 2020; **Accepted:** June 19, 2020; **Published:** July 02, 2020

**Significance Statement**

This review summarizes studies demonstrating that the immune system participates in the expression of opiate withdrawal and that a single dose of immunological substances such as α-interferon, cyclosporine, or cortisol significantly attenuates the severity of the naloxone-induced withdrawal symptoms in opioid-dependent animals. These studies demonstrate that non-opiate substances can be used to prevent and treat opioid addiction.

## Introduction

Everyday more than 115 people in the United States die as a result of opioid overdose [1]. In 2017, there were more than 47,000 American deaths from opioid overdose (National Institute on Drug Abuse, 2019). This is more deaths than from car crashes or guns (39,000/year each) and more than AIDS (42,000/year) during the height of its epidemic. In addition to the misuses and abuses of prescription opioids, a dynamic illicit drug marked is causing an increase in the number of deaths due to overdose [2-4].

Although opioids have been used for pain relief since the early 1800s (Courtwright, 2009), the opioid epidemic currently afflicting the US is thought to have occurred in three waves [5]. The first started around 1991 following an increase in the use of opioid medication for the treatment of pain in non-cancer patients. The second wave began around 2010 mainly as a result of widespread heroin abuse. The third wave began around 2013 due to the use of synthetic opioids such as fentanyl [6]. Opioid addiction is a chronic brain disease. Various methods have been used and continue to be developed in an effort to limit abuse of opioid medications [7]. Most therapies for addiction involve long periods of time in treatment with medications such as: Vivitol, Zubsolve, Probuphrine. Lofexidine Hydrochloride, Methadone, Buprenorphine, Sublocade, CAM 2038, Naltrexone, Buprenex, Modafinil, Mirtazapine, Vigabatrin, Baclofen, and Topiramate [7-13]. Many of these drugs are still under study to be verified as safe and beneficial. In addition, use of the above drugs should be combined with counseling and behavioral therapies [14]. Additionally, the effectiveness of current opioid treatments may be limited by risk of combination with other medications, potential for misuse and abuse, and/or induction difficulty. Moreover, many of the above drugs belong to the opioid family, in effect, combating the opioid addiction by giving patients opioids in a controlled fashion over extended periods of time [7, 14-17]. Further, for many patients there are issues with compliance related to these long-term treatment periods. A new therapeutic approach is desperately needed. This review summarizes pre-clinical research on the beneficial impact of immunomodulatory agents on the treatment of opioid addiction in the hopes of encouraging further research and clinical trials using immunomodulatory substance therapy. The use of immunomodulatory substances may allow for shorter treatment times with substances that do not belong to the opiate family. It is time for a novel therapy to be tested if we are to develop breakthrough therapies in the future.

## Morphine

Opioids are a medically necessary substance used for pain management and anesthesia [18]. About one-third of adults living in the US experience severe pain and receive prescription pain medication [19]. Morphine's are a naturally occurring pain medication of the opiate family found in a number of plants [20]. Morphine is the prototypical opioid and is the standard by which other opioids are compared [21]. The primary source of morphine is isolated from the poppy seeds of the opium poppy. Opioids are classified as narcotics and are considered to be a controlled substance for their abuse potential and addictive properties. Morphine is legally prescribed to patients in order to treat both acute and chronic severe pain [18, 22]. Morphine and other opioids act on the central nervous system to produce feelings of euphoria. They also act on the GI tract to decrease diarrhea and provide bowel relief and can also be used as a sedative [23].

## Opioid Addiction

While opioids are a legitimate medication used for treating pain, they should only be used and prescribed to select patients for a short amount of time as determined by a healthcare professional. Repetitive use of opioids may result in the development of tolerance and dependence on the drug. Once this occurs, more and more of the drug is needed to produce the same feelings of analgesia and euphoria, eventually leading to opioid addiction [24]. This is particularly dangerous as opioid overdose leads to loss of consciousness combined with respiratory depression, which may lead to death [25].

Opioid addiction is a condition classified as a substance use disorder (SUD) and is characterized by a powerful, compulsive urge to use the drugs when they are no longer needed medically. This leads to complex social misbehaviors and unwanted physiological consequences [26]. Further, opioid addiction is accompanied by a well-described physical dependence and a severe withdrawal syndrome characterized by flu-like symptoms, shakes, teeth chattering, loose stools, and nausea [27]. Long-term use of opioids causes changes in brain chemistry that lead to drug tolerance and addiction. Addiction is a primary, chronic, and relapsing brain disease characterized by an individual pathologically pursuing reward and/or relief by continuing use of opioids or other substances of abuse. Once patients are addicted to opioids, it takes much more than just will power to break free. A new therapeutic approach is desperately needed, such as proposed in this review.

## Cause of Opioid Addiction

When opioids are consumed, they bind to receptors located throughout the central nervous system (CNS) as well as in other organs such as those in the gastrointestinal tract. When opioids bind to CNS receptors, they trigger a series of chemical changes that produce feelings of euphoria and relieve pain [28]. These feelings of euphoria are caused by an increase in dopamine produced by the ventral tegmental area (VTA) and released into the nucleus accumbens (NAc), giving rise to feelings of pleasure [14]. After repetitive use, the body becomes tolerant to the drug such that the brain stops creating the same amount of dopamine, and more drug is needed to produce the same sense of analgesia and/or euphoria [29]. Molecular changes within CNS neurons occur that alter an individual's brain chemistry. No longer are they solely using the drug to feel pleasure, but they are dependent on the drug to avoid harmful withdrawal side effects. It is at this point that they are addicted.

## The Immune System and the Central Nervous System

The central nervous system (CNS) primarily consists of neurons with their dendritic fields and glial cells [30]. Dendrites are responsible for producing cytokines that serve as the chemical messengers and allow for communication between these two systems. Traditionally, the glial cell system was considered to be a passive accessory to neurons. However, it was demonstrated that these cells actively participate in synaptogenesis, neuronal excitability, and neurotransmission [31]. In fact, recent studies suggest that the CNS may be composed of 10 times more glial cells than neurons [32]. An increasing number of studies demonstrate that glial cells express receptors for most neurotransmitters and release neuroactive substances that have been shown to modulate neuronal activity and synaptic plasticity [30]. Synaptic plasticity consists of changes in synaptic strength that are believed to be the basis of learning and memory as well as addiction. This has been further substantiated by studies demonstrating that the glial system undergoes robust changes in their morphology and physiology in response to opioid exposure within key brain sites contributing to addiction [33,34]. For example, in animal models, several CNS areas have been shown to be responsible for opioid addiction,

namely the: periaqueductal gray matter, the nucleus accumbens, some thalamic nuclei, the hippocampus, and the spinal cord, and microglial cells in these areas have been shown to upregulate cytokines after opioid exposure [35]. Because glial cells are all around synapses and release a wide variety of neuroactive molecules during physiological and pathological conditions, glial cells have been shown to modulate synaptic plasticity in many different ways from changes in synaptic coverage to release of chemokines and cytokines [36, 37]. It has even been shown that there may be dedicated "glia" transmitter release. Glial cells were reported to affect synaptic scaling, homeostatic plasticity, metaplasticity, long-term potentiation, and long-term depression, critical changes to brain neurocircuitry that underlie drug addiction. Moreover, glial cells have also been shown to decrease morphine tolerance, morphine reward, and drug dependence strongly suggesting that glia may be the key neurological component responsible for opiate addiction. In fact, glial inhibitors such as the drug, Ibudilast, are currently being developed and investigated for their potential role in alleviating opioid withdrawal symptoms [38-42].

In addition to their role in addiction, glial cells are considered to be part of the immune system. The discovery of the glial system's role in immune activity led to the concept of the neuroimmune system. The neuroimmune system is primarily composed of glial cells and is structurally distinct from the peripheral immune system that consists of the complement system, macrophages, etc., many of which cannot cross the blood-brain barrier [43]. Neurons and glial cells work together to combat pathogens during brain injury. This interaction is mediated by chemokines and neurotransmitters [44]. It is believed that glial cells are also involved in the opioid addiction phenomenon as they have been shown to contain opioid receptors [45]. The activation of these receptors can be regulated by endogenous opioid production and when activated by endomorphins lead to IL-10 and IL-12 activation as well as IL-23 suppression [46, 47]. In fact, immature glial cells express low levels of opioid receptor mRNA and higher levels as they mature [48].

**Opioids and the Immune System**

Wybram group was the first group to produce experimental evidence demonstrating that opioids modulate the immune system [49]. Since then, studies have shown that opioids are found in many leukocyte subpopulations and in lymph nodes, and that opioid peptides, produced by leukocytes, are released in response to a stimulus leading to antinociceptive effects suggesting that there is an endogenous opioid effect on some immune functions [50-52]. Recently, many studies have been working towards connecting the immune system with opiate addiction and its analgesic properties [53, 54]. In other words, these studies have been investigating whether opioid's effects on the CNS immune system contribute to its euphoria and pain relieving properties [19, 50, 55, 56]. This idea was based on the observations that: 1) opiate receptors are present on immune cells; 2) morphine modulates the production of immune substances (cytokines); 3) cytokines are produced as part of the immunologic response (inflammation); 4) cytokines influence pain; and 5) opioids interfere with the immune system [57-61]. In this way, cytokines may be the logical target for analgesic development [57]. Many studies dating back to the 1980s, have demonstrated that opiate abuse can provoke other health conditions by breaking down the body's immune system [62]. Several clinical studies have suggested that opioid users are more susceptible to infection, including HIV, due to immune suppression [63-66]. In heroin users, specifically, it was shown that patients had lower levels of retrovirus transcription factors leading to increased HIV risk as well as higher levels of TNF-a, IL-8, and other immune suppressor genes [67, 68]. These effects were also seen in morphine withdrawal, which reduced cell-mediated immunity decreasing the body's capability of innate resistance to infection and leading to the reactivation of latent viruses [69]. Further, morphine was shown to reduce natural killer cell activity, mitogen induced lymphocyte proliferation, and cytokine production [70]. Morphine and fentanyl have been found to impair the function of macrophages, NK cells, and T cells. Further, Mao et al., demonstrated that morphine suppresses T-cell differentiation in a concentration-dependence manner, an effect inhibited by naloxone, an opioid antagonist [71].

Moreover, studies demonstrated that inflammatory changes occur after dopamine signaling, the neurotransmitter responsible for addiction, by inducing feelings of pleasure and reward [72]. This increase in dopamine signaling can be seen on fMRI and correlates with increased levels of immune system modulators such as interleukin-6 [73]. Additionally, morphine-induced activation of the central immune signaling system was shown to engage the mesolimbic dopamine neural circuit as well as withdrawal centers [33, 74-77]. In summary, there is reciprocal interaction between the immune system and opioids [56]. These findings were corroborated by Hutchinson and Watkins who went further to suggest that the immunopharmacology products (chemokines and interleukins) generated by the body upon morphine exposure are crucial targets for the future of addiction therapy [78].

**Studies Demonstrating that the Immune System Participates in Opiate Withdrawal**

Studies have shown that opioids have a direct effect on the immune system and this connection with the immune system was shown to influence its analgesic properties. There is hope that research into the use of drugs that modulate the immune system (immunomodulators) may be the treatment of choice in the prevention of opiate addiction and curing the opiate epidemic. However, first, it was necessary to establish that the immune system contributes to the opiate withdrawal syndrome.

The capacity of the immune system to participate in the processes primarily considered to be CNS phenomena, (i.e. addiction and withdrawal) has been suggested by several studies demonstrating that injection of morphine into the periaqueductal grey area alters immune system function as well as that an intact immune system is essential to the expression of opiate withdrawal [79, 80]. In two different studies, the immune system was ablated after chronic morphine exposure. Animals were then treated with naloxone to induce opiate withdrawal. All of these animals with immune system ablation failed to express opiate withdrawal behaviors as compared to control (without ablation), see Fig 1A. In another group of animals, following immune ablation by selective irradiation, the immune components were reconstituted from donor animals. Following immune reconstitution, chronic morphine was administered followed by naloxone (Fig 1B). All of the rats in this experiment expressed withdrawal behaviors [60, 62, 80-82]. These studies provide scientific evidence linking the immune system to the opiate withdrawal syndrome.

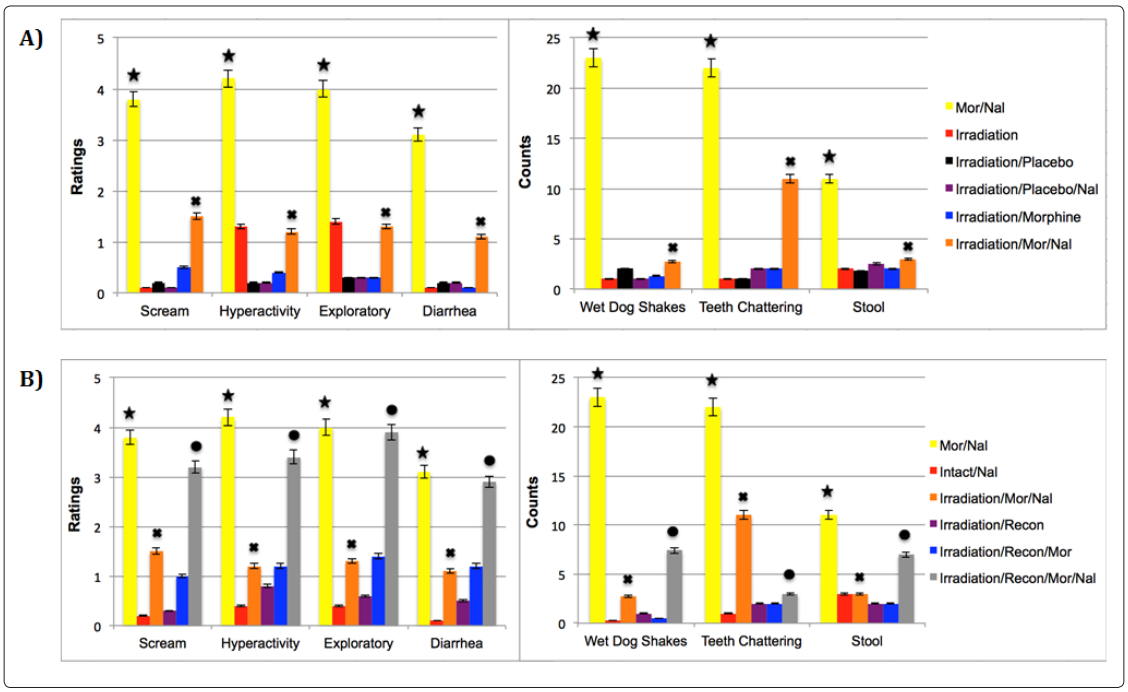


**Figure 1:** The figure summarizes two experiments (A and B) each with six groups of N=8 animals. In A), group 1 (Fig 1A left side, yellow) summarizes the group with the morphine pellet (75mg/kg) implanted for 72hrs followed by naloxone (Nal) 1.0mg/kg administration - showing the withdrawal behaviors as compared to the next 4 groups. The next four groups (red, black, purple, and blue) are control groups showing that the destruction of the immune system by irradiation did not alter the animals' behavior. The last group (orange) showed that destruction of the immune system significantly ($p<0.05$) attenuated the seven behavioral withdrawal symptoms as compared to the intact morphine naloxone group (yellow). In B), six similar groups were used. On the left (yellow) is the group with the implanted morphine pellet (75mg/kg) – showing the expression of behavioral withdrawal symptoms following precipitated withdrawal from naloxone (1.0mg/kg) as compared to the red group. The second group (red) is a control group showing that naloxone (1.0mg/kg) by itself did not elicit withdrawal behaviors. The third group (orange) showed that immune destruction by irradiation significantly ($p<0.05$) attenuated the seven behavioral expressions indicating withdrawal. The fourth (purple) and fifth (blue) groups showed that reconstitution of the immune system after its destruction by irradiation did not modulate the animals' behaviors as compared to group 2 (red, intact/Nal). The last group (grey) showed that immune reconstitution followed by morphine pellet implantation and then naloxone treatment expressed significant ($p<0.05$) withdrawal behaviors as compared to group 5 (blue). All the behavioral measures were obtained about 72hrs after morphine pellet implantation. indicates a significant ($p<0.05$) difference from the control groups. indicates a significant ($p<0.05$) difference from the morphine/naloxone groups. indicates a significant ($p<0.05$) difference from the intact/naloxone groups.

**Studies Aiming to Treat the Opiate Withdrawal Severities**

Since the discovery of endogenous opiates, the question that arose was: what prevents the development of tolerance and/or dependence to these endogenous opioids? It was postulated that endogenous production of a protein, peptide, or immune system product such as a cytokine in the central nervous system (CNS) could prevent the development of tolerance and/or physical dependence to these circulating endogenous opiates [61, 83-86]. Bertolini et al., suggested that some endogenous substances are produced and released along with the endogenous opioids in order to prevent the organism from developing tolerance to, or dependence on, its own endogenous opioids [61, 87]. It was reported that circulating endogenous α-interferon was reduced dramatically in opiate addicted animals. This was the rationale for a series of experiments to test if treatment with α-interferon to opiate addicted animals would reduce the severity of withdrawal symptoms. These experiments showed that treatment with α-interferon significantly reduced the severity of opiate withdrawal behaviors (Fig 2A) [58, 59, 83, 85, 88-94] . These studies were followed by the use of another two immunomodulators: cyclosporine and cortisol injected after chronic morphine exposure followed by naloxone administration. This experiment is summarized in Figure 2B and 2C. Figure 2 demonstrates that a single injection of each of the three immunomodulatory substances: α-interferon, cyclosporine, and cortisol to opiate-dependent rats prior to naloxone injection significantly attenuates and, in some animals, eliminates the severity of opiate withdrawal expression completely [58, 59, 61, 88-91, 95-100].

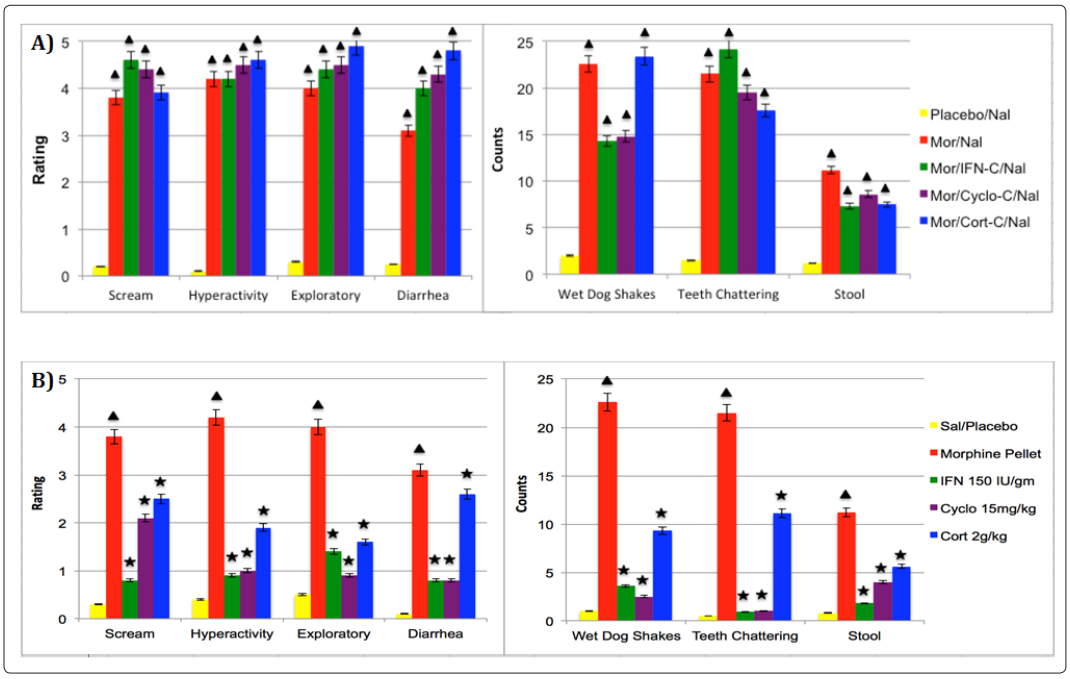


**Figure 2:** A) The left most histogram (yellow) summarizes the effect of placebo pellet, "Placebo" (control), followed by naloxone, "Nal" (1.0mg/kg) injection, i.e. naloxone did not elicit withdrawal behaviors in the group treated with the placebo pellet. The second histogram (red) summarizes the group of animals group implanted with morphine pellet ("Mor", 75mg/kg) followed by naloxone injection – showing that naloxone induced withdrawal behaviors. The next three morphine dependent groups (green, purple, and blue) were treated prior to naloxone with α-interferon (IFN), cyclosporine (cyclo), and cortisol (cort) carriers, respectively. They demonstrate that naloxone injection in the placebo pellet group has no effect, while naloxone administration in all the other animal groups that were treated with IFN, cyclo, and cort carriers expressed behavioral withdrawal. These findings are similar to the group treated with chronic morphine and naloxone without the carrier, i.e. demonstrating that the immunomodulator carriers did not reduce the severity of opiate withdrawal. B) Histograms showing the effects of α-interferon (IFN, 150 IU/gm/bw), cyclosporine (cyclo, 15mg/kg), and cortisol (cort, 20mg/kg) injection to morphine dependent animals 72hrs after morphine pellet (75mg/kg) implantation and one hour prior to naloxone (1.0mg/kg) administration. The figure demonstrates that all three neuromodulators attenuated significantly ($p<0.05$) the severity of opiate withdrawal precipitated by naloxone injection in morphine dependent animals with some animals exhibiting total elimination of opiate withdrawal behaviors modified from [88-91, 99]. Morphine dependence was obtained by implanting morphine pellets (75mg/kg) for 72hrs prior to naloxone (Nal) 1.0mg/kg injection. All recordings were performed about 74hrs after morphine pellet injection. indicates a significant ($p<0.05$) difference from the placebo control group. indicates a significant ($p<0.05$) difference from the morphine/naloxone group.

**Immunomodulators: α-interferon (IFN), cyclosporine (cyclo), and cortisol (cort)**

The following three immunomodulators were used in a series of experiments designed to reduce the severity of opiate withdrawal symptoms, thereby eliminating opiate cravings and relapse:

1). α-interferon (IFN) is an endogenous protein found in vertebrae animals including homosapiens. This endogenous substance has been show to be a biological regulator of cell function. IFN are the most rapidly produced defense against foreign macromolecules, with non-specific, potent immunomodulatory activity [101-104].

Studies have demonstrated that recombinant human IFN introduced to morphine-addicted rodents reinstated morphine conditioned place preferences (CPP), and that naloxone inhibited this reinstatement of morphine CPP, thus establishing IFNs potential to eliminate opioid dependence [105]. The mechanism by which this occurs is hypothesized to be two-fold. Firstly, IFN may have a direct affect on CNS cells, which have opioid receptors. This has been supported by neurophysiological studies recording from single neurons showing that IFN modulates opiate mediated phenomenon by directly acting on specific brain areas that participate in pain, temperature regulation, and food intake [61, 96, 97, 106, 107]. Secondly, IFN modulates the immune system possibly resulting in the modulation of morphine's analgesic effects. This has been supported by studies showing that IFN engages neurons initiating an immune response through the activation of inducible protein 10 (IB-10), a chemokine that promotes a Th1 inflammatory response, suggesting that there are specific immune system products, i.e. interferon, that are involved in cell signaling that affect brain activity to control craving and withdrawal [61, 98, 108]. It should also be noted that IFN possesses endocrine activities in addition to immunologic and neuromodulatory properties by eliciting corticosteroid secretion and affecting ACTH and endorphin release [85, 109, 110].

2). Cortisol: Numerous studies have shown that there is a close connection between the neuroendocrine and the immune systems [19, 111]. Cortisol is a steroid hormone, one of the glucocorticoids, whose release is stimulated by ACTH. It is made in the outer cortex of the adrenal glands and then released into the blood stream and transported throughout the body. Almost every cell contains receptors for cortisol and thus, cortisol has many different actions depending on the tissue it is acting upon [112]. These effects include controlling the body's blood sugar levels and thus regulating metabolism, acting as an anti-inflammatory, influencing memory function, controlling salt and water balance, influencing blood pressure, and helping with the development of the fetus [113,

114]. In many species, cortisol is also responsible for triggering the processes involved in giving birth [115-118]. It should also be noted that corticosteroids are nonspecific immunosupressors that modulate the immune system by affected T-cells and B-cells and hence cell-mediated and humoral-mediated immunity [119]. In addition, macrophages and monocytes appear to be greatly affected by cortisol. Furthermore, aside from inducing a lymphopenia by redistributing circulating lymphocytes to other lymphoid compartments glucocorticoids also may directly suppress the synthesis of IL-2 [120, 121]. Moreover, morphine was reported to modulate the hypothalamic-pituitary-adrenal (HPA) axis and cortisol administration may restore the HPA axis. Opioids activate the downstream pathway of the HPA axis suggesting that glucocorticoids modulate the immune system and may explain why cortisol treatment attenuates the opiate withdrawal symptoms [53, 65, 99, 122, 123].

3). Cyclosporine A: Cyclosporine is an immunosuppressive, cyclic polypeptide (substance), consisting of 11 amino acids [124]. It is obtained from a fungus and used in organ transplant surgery [125]. Cyclosporine has long been known as an immunodulator and is used clinically for its preferential action on helper T-lymphocytes [126, 127].

Recently, cyclosporine has been gaining attention for its effects on the central nervous system [128]. Rashki et al. demonstrated that cyclosporine, when given to rodent animal models, inhibited the development of morphine-induced tolerance [128]. While the mechanism for its action on the brain is not well understood, one commonly proposed hypothesis for how cyclosporine modulates morphine tolerance is through the nitric oxide synthesis pathway as studies have shown that increased nitric oxide formation, a freely diffusible compound through the blood-brain barrier that affects neural transmission, cell to cell communication, and neuronal survival, leads to antinociceptive properties [129, 130].

Cyclosporine activity is also known to influence the endocrine system. One example is that it has been demonstrated that cyclosporine induces a change in serum prolactin levels [131]. This may be significant since prolactin levels show marked alteration during morphine withdrawal behaviors [132]. Further, studies demonstrate that the sensitivities to the antinociceptive effects of morphine in diabetic mice were the same as sensitivities in non-diabetic mice after 14 days of cyclosporine implying that cyclosporine's ability to attenuate morphine withdrawal may be related to its activity on the endocrine system rather than on immunomodulation [133].

In a previous study, the cyclosporine levels in rat brain tissues were directly measured following intra-peritoneal (i.p.) injection. One hour after i.p. injection, significant levels of the drug (80.9ng) as compared to the control group (10.8ng) were observed [97]. This indicates that the drug does reach the brain area where it conceivably may have a direct effect on the central nervous system (CNS). Moreover, this is a level associated with the bioactivity of cyclosporine in immune cells and therefore, may indicate the potential for cyclosporine to act directly on the brain [93].

**Current Treatments for Opioid Addiction**

Non-medical abuse of opioids has been a concern since the 1990s, but rates of abuse have been increasing exponentially in recent years. Various methods have been used and continue to be developed in an effort to limit abuse of opioid medications [5, 7]. Currently, the only consistently utilized method to combat opioid addiction is medical management with formulations of the following drugs: methadone (an opioid agonist), buprenorphine (a partial opiod agonist), and naltrexone/naloxone (opioid antagonists) [134]. Additional medications include: Zubsolve, Probuphrine, Sublocade, CAM2038, Lofexidine Hydrochloride and Buprenex [7-13]. They vary from each other based on half-life, mode of delivery (injection vs. oral vs. sublingual), and degree of opioid receptor agonism/antagonism. While maintenance therapy with methadone, buprenorphine, or one of its cousin formulations has been shown to reduce opioid-related deaths, these medications are, in effect, combating opioid addiction by giving patients opioids in a controlled fashion over long periods of time [15,16]. These drugs do not address the underlying neurochemical adaptations leading to opioid addiction, nor do they target the inflammatory and/or dopaminergic pathways responsible for addiction phenomenon. Additional drugs are in the pipeline and are still under study to be verified as safe and beneficial (NIDA Update, 2018). It is time for an innovative therapy to be tested if we are to develop breakthrough therapies in the future. The current climate of opioid addiction research focuses on neuroinflammatory approaches that may directly address the underlying mechanisms behind opioid addiction and opioid withdrawal [135]. We hope to encourage the further study of neuromodulators (α-interferon, cyclosporine, and cortisol) that have shown promise in preclinical trials with the hopes of testing the efficacy of these drugs in human subjects. Using immunomodulatory substance therapy as proposed in this review may allow for shorter treatment time with substances that do not belong to the opiate family.

**Summary**

The opioid epidemic has claimed the lives of more than 700,000 people since 1999 to 2017 (Centers for Disease Control and Prevention, 2018). As of 2017, the Department of Health and Human Services declared the opioid epidemic a public health emergency [136]. This review presents preclinical studies demonstrating that the immune system participates in the expression of opiate withdrawal and that the use of immunological substances such as α-interferon, cyclosporine, and cortisol significantly attenuate the severity of the naloxone-induced withdrawal symptoms in opioid-dependent animals.

Recently, it has been observed that the immune system may be responsible for opioid addiction as endogenously released immune system substrates contribute to analgesia and morphine modulates the immune system [137]. For example, morphine acts on the periaqueductal gray matter (PAG), an area of the brain involved in drug addiction, to alter natural killer cell activity, an effect antagonized by the direct administration of naltrexone, an opioid antagonist, into the PAG [70]. Further, studies have begun to link glial cells with opioid addiction noting that glia contain opioid receptors and may be responsible for the synaptic plasticity underlying drug addiction. This hypothesis has been further substantiated by studies demonstrating that morphine enhances activation of microglia, an effect blocked by Naltrexone [138]. Moreover, central nervous system (CNS) dopaminergic mechanisms that are responsible for the feelings of euphoria that direct drug addiction, may also contribute to morphine-induced immunomodulation. Taken together, these findings support the interaction between opioids, the central nervous system, and the immune system, and encourage the use of immunomodulators in the treatment of opiate addiction.

The opiate abstinence syndrome represents a fundamental feature of the addictive process with tolerance, physical dependence, and withdrawal being characteristics of its repetitive (chronic) use, and the degree of addiction being directly correlated to the intensity

of the behavioral withdrawal expression [139-141]. The degree of opiate dependence can be assessed by injecting animals treated with chronic morphine with the opiate antagonist, naloxone. Dependence is measured by quantifying the various behavioral signs associated with naloxone-induced withdrawal (see Fig 2). Behavioral studies have demonstrated that the immunomodulators: α-interferon, cyclosporine, and cortisol significantly attenuate the naloxone-induced morphine withdrawal behavior, and that even a single dose can help alleviate the morphine withdrawal syndrome. [98, 142-149].

Ultimately there are several morphological and physiological substrates that provide the circuitry for reciprocal communication between the immune system and the central nervous system. Thus, the administration of immunomodulators such as α-interferon, cyclosporine, and/or cortisol may affect the activities of the CNS and immune systems in response to opioid exposure in order to eliminate relapse and dependence on opioids [108]. We hope that this review will encourage clinical studies to use immunomodulators in combating the opioid epidemic and save lives.

**Conclusion**

Morphine addiction is considered a central nervous system (CNS) phenomenon. The involvement of the immune system in modifying CNS phenomena has been suggested for at least 175 years and more recently by various groups [150]. This review presents several studies demonstrating that the immune system is involved in the opioid withdrawal syndrome (Figure 1) and that immunomodulatory therapy using α-interferon, cyclosporine, and cortisol treatment in morphine dependent rats was able to significantly attenuate the severity of the opiate withdrawal syndrome precipitated by naloxone injection (Figure 2). This review calls for further investigation and clinical trials in order to solve the opioid epidemic that is responsible for the deaths of thousands across the world.

By taking advantage of the interaction between the immune system and the central nervous system and investigating the role of immunomodulators as a treatment for opioid dependence, possible pharmacological treatments for opioid addiction may be discovered. Since behavioral studies demonstrated that the immunomodulators: α-interferon, cyclosporine, and cortisol significantly attenuate morphine abstinence withdrawal behavior, it is possible to conclude that opiate addiction is mediated at least in part via modulation of the immune and endocrine systems, and that the immune, endocrine, and CNS systems communicate with one another to produce opiate dependence and opiate withdrawal phenomenon [98, 142-149].

**Acknowledgements**

Support in part by NIH grant DA 00803. Morphine and naloxone were generously donated by DuPont and Penick Corp., respectively. Dr. J Sacks is appreciated for her help with editing the manuscript.

**Disclosures**

No conflict of interest, financial or otherwise, are declared by the authors.

**References**

1. Breehl N (2018) The immune system: A new hope for opioid addiction? Trending Immunology.
2. Berge KH, Dillon KR, Sikkink KM, Taylor TK, Lanier WL (2012) Diversion of drugs within health care facilities, a multiple-victim crime: patterns of diversion, scope, consequences, detection, and prevention. May Clin Proc 87: 674-82.
3. Lyden J, Binswanger IA (2019) The United States opioid epidemic. Semin Perinatol S0146-0005.
4. McDonald DC, Carlson KE (2013) Estimating the prevalence of opioid diversion by "doctor shoppers" in the United States. PLoS One 8: e69241.
5. National Institute on Drug Abuse. "Opioid Overdose Crisis." NIDA, 22 Jan. 2019, www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis.
6. Centers for Disease Control and Prevention (2018) Opioid Overdose.
7. Fudala PJ, Johnson RE (2006) Development of opioid formulations with limited diversion and abuse potential. Drug Alcohol Depend 83: S40-47.
8. Aschenbrenner DS (2018) New route for buprenorphine administration. Am J Nurs 118: 23.
9. Gowing L, Ali R, White JM, Mbewe D (2017) Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev 2: CD002025.
10. Haasen C, Linden M, Tiberg F (2017) Pharmacokinetics and pharmacodynamics of a buprenorphine subcutaneous depot formulation (CAM2038) for once-weekly dosing in patients with opioid use disorder. J Subt Abuse Treat 78: 22.
11. Itzoe M, Guarnieri M (2017) New developments in managing opioid addiction: impact of a subdermal buprenorphine implant. Drug Des Devel Ther 11: 1429-1437.
12. Pawar A, Rajalakshmi AK, Upadhvay RP (2015) Pentazocine use among people who inject drugs in Insia. Asian J Psychiatr 16: 3-6.
13. Webster L, Hjelmström P, Sumner M, Gunderson EW (2016) Efficacy and safety of a sublingual buprenorphine/naloxone rapidly dissolving tablet for the treatment of adults with opioid dependence: A randomized trial. J Addict Dis 35: 325-338.
14. Kosten TR, George TP (2002) The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect 1: 13-20.
15. Mattick RP, Breen C, Kimber J, Davoli M (2014) Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 6: CD002207.
16. Schwartz RP, Gryczynski J, O'Grady KE, Sharfstein JM, Warren G, et al. (2009) Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009 Am J Public Health 103: 917-922.
17. Yokell MA, Zaller ND, Green TC, Rich JD (2011) Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. Curr Drug Abuse Rev 4: 28-41.
18. Greco A, Faris J, DeLapp V, Hoffman J (2018) Multimodal pain management and effect on opioid use postoperatively in non-ICU patients. Crit Care Med 46: 775.
19. Liang X, Liu R, Chen C, Ji F, Li T (2016) Opioid system modulates the immune function: a review. Transl Perioper Pain Med 1: 5-13.
20. Rosenblum A, Marsch LA, Joseph H, Portenoy RK (2008) Opioids and the treatment of chronic pain: controversies, current status, and future directions. Exp Clin Psychopharmacol 16: 405-416
21. Pathan H, Williams J (2012) Basic opioid pharmacology: an update. Br J Pain 6: 11-6.
22. Vallejo R, Barkin RL, Wang VC (2011) Pharmacology of opioids in the treatment of chronic pain syndromes. Pain Physician 14: E343-360.
23. Leppert W (2012) The impact of opioid analgesics on the

gastrointestinal tract function and the current management possibilities. Contemp Oncol (Pozn) 16: 125-131.
24. Rudd RA, Seth P, David F, Scholl L (2016) Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep 65: 1445-1452.
25. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, et al. (2008) Opioid complications and side effects. Pain Physician 11: S105-120.
26. Nosyk B, Marshall BD, Fischer B, Montaner JS, Wood E, et al. (2012) Increases in the availability of prescribed opioids in a Canadian setting. Drug Alcohol Depend 126: 7-12.
27. Pan ZZ (2007) Mechanisms of Opioid Tolerance. In: Zhuo M. (eds) Molecular Pain. Springer, New York, NY.
28. Inturrisi C (2002) Clinical pharmacology of opioids for pain. Clin Journal of Pain 18: S3-13.
29. Van Ree JM, Gerrits MA, Vanderschuren LJ (1999) Opioids, reward, and addiction: an encounter of biology, psychology, and medicine. Pharmacol Rev 51: 341-396.
30. Ben Achour S, Pascual O (2010) Glia: the many ways to modulate synaptic plasticity. Neurochem Int 57: 440-445.
31. Watkins LR, Hutchinson MR, Johnston JN, Maier SE (2005) Glia: novel counter-regulators of opioid analgesia. Trends Neurosci 28: 661-669.
32. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ (2013) Principles of Neural Science. 5. New York: McGraw-Hill.
33. Coller JK, Hutchinson MR (2012). Implications of central immune signaling caused by drugs of abuse: mechanisms, mediators, and new therapeutic approaches for prediction and treatment of drug dependence. Pharmacol Ther 134: 219-245.
34. Miguel-Hidalgo JJ (2009) The role of glial cells in drug abuse. Curr Drug Abuse Rev 2: 72-82.
35. Hofford RS, Russo SJ, Kiraly DD (2018) Neuroimmune mechanisms of psychostimulant and opioid use disorders. Eur J Neurosci [Epub ahead of print].
36. Araque A, Navarrete M (2010) Glial cells in neuronal network function. Philos Trans R Soc Lond B Biol Sci 365: 2375-2381.
37. Magnaghi V (2007) GABA and neuroactive steroid interactions in glia: new roles for old players? Curr Neuropharmacol 5: 47-64.
38. Croft W, Dobson KL, Bellamy TC (2015) Plasticity of neuron-glial transmission: equipping glia for long-term integration of network activity. Neural Plast 2015:765792.
39. Fukagawa H, Koyama T, Kakuyama M, Fukuda K (2013) Microglial activation involved in morphine tolerance is not mediated by toll-like receptor 4. J Anesth 27: 93-97.
40. Zhang XQ, Cui Y, Cui Y, Chen Y, Na XD, et al. (2012) Activation of p38 signaling in the microglia in the nucleus accumbens contributes to the acquisition and maintenance of morphine-induced conditioned place preference. Brain Behav Immun 26: 318-325.
41. Hutchinson MR, Lewis SS, Coats BD, Skyba DA, Crysdale NY, et al. (2009) Reduction of opioid withdrawal and potentiation of acute opioid analgesia by systemic AV411 (ibudilast). Brain Behav Immun 23: 240-250.
42. Suzumura A, Ito A, Yoshikawa M, Sawada M (1999) Ibudilast suppresses TNFa production by glial cells functioning mainly as type III phosphodiesterase inhibitor in the CNS. Brain Res 837: 203-212.
43. El Khoury J (2010) Neurodegeneration and the neuroimmune system. Nat Med 16: 1369-1370.
44. Cui C, Shurtleff D, Harris RA (2014) Neuroimmune mechanisms of alcohol and drug addiction. Int Rev Neurobiol 118: 1-12.
45. Hutchinson MR, Bland ST, Johnson KW, Rice KC, Maier SF, et al. (2007) Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. Scientific World Journal 7: 98-111.
46. Li ZH, Chu N, Shan LD, Gong S, Yin QZ, et al. (2009) Inducible expression of functional mu opioid receptors in murine dendritic cells. Journal of neuroimmune pharmacology 4: 359-367.
47. Makarenkova VP, Esche C, Kost NV, Shurin GV, Rabin BS, et al. (2001) Identification of delta- and mu-type opioid receptors on human and murine dendritic cells. Journal of neuroimmunology 117: 68-77.
48. Benard A, Boue J, Chapey E, Jaume M, Gomes B, et al. (2008) Delta opioid receptors mediate chemotaxis in bone marrow-derived dendritic cells. Journal of neuroimmunology 197: 21-28.
49. Wybran J, Appelborn T, Famaey JP, Govaerts A (1979) Suggestive evidence for receptors for morphine and methionine-enkephalin on normal human blood T lymphocytes. J Immunol 123: 1068-1070.
50. Rittner HL, Brack A, Stein C (2008) Pain and the immune system. Br J Anesth 101: 40-44.
51. Labuz D, Berger S, Mousa SA, Zollner C, Rittner HL, et al. (2006) Peripheral antinociceptive effects of exogenous and immune cell-derived endomorphins in prolonged inflammatory pain. J Neurosci 26: 4350-4358.
52. Sacerdote P, Franchi S, Gerra G, Leccese V, Panerai AE, et al. (2008) Buprenorphine and methadone maintenance treatment of heroin addicts preserves immune function. Brain, behavior, and immunity 22: 606-613.
53. Eisenstein TK, Rahim RT, Feng P, Thingalaya NK, Meissler JJ (2006) Effects of opioid tolerance and withdrawal on the immune system. J Neuroimmune Pharmacol 1: 237-249.
54. McCarthy L, Wetzel M, Sliker JK, Eisenstein TK, Rogers TJ (2001) Opioids, opioid receptors, and the immune system. Drug Alcohol Depend 62: 111-123.
55. Moyano J, Aguirre L (2019) Opioids in the immune system: from experimental studies to clinical practice 65: 262-269.
56. Plein LM, Rittner HL (2018) Opioids and the immune system-friend or foe Br J Pharmacol 175: 2717-2725.
57. Clark JD, Shi X, Li X, Qiao Y, Liang D, et al. (2007) Morphine reduces local cytokine expression and neutrophil infiltration after incision. Mol Pain 3: 28.
58. Dougherty PM, Aronowski J, Samoraiski T, Dafny N (1986a) Opiate antinociception is altered by immunemodification: the effect of interferon, cyclosporine, and radiation-induced immune suppression upon acute and long-term morphine activity. Brain Res 385: 401-404.
59. Dougherty PM, Harper C, Dafny N (1986b) The effect of alpha-interferon, cyclosporine A, and radiation-induced immune suppression on morphine-induced hypothermia and tolerance. Life Sci 39: 2191-2197.
60. Dougherty PM, Dafny N (1987) Irradiation exposure modulates central opioid functions. Exp Neurol 98: 301-316.
61. Dafny N, Yang PB. Interferon and the central nervous system (2005) Eur J Pharmacol 523: 1-15.
62. Pellis NR, Harper C, Dafny N (1986) Suppression of the induction of delayed hypersensitivity in rats by repetitive morphine treatments. Exp Neurol 93: 92-97.
63. Budd K (2006) Pain management: is opioid immunosuppression a clinical problem? Biomed Pharmacother 60: 310-317.
64. Risdahl JM, Khanna KV, Peterson PK, Molitor TW (1998) Opiates and infection. J Neuroimmunol 83: 4-18.
65. Sacerdote P (2006) Opioids and the immune system. Palliat Med 20: S9-15.
66. Sacerdote P (2008) Opioid-induced immunosuppression. Curr

Opin Support Pa 2: 14-18.
67. Zhu JW, Liu FL, Mu D, Deng DY, Zheng YT (2017) Heroin use is associated with lower levels of restriction factors and type I interferon expression and facilitates HIV-1 replication. Microbes Infect 19: 288-294.
68. Piepenbrink MS, Samuel M, Zheng B, Carter B, Fucile C, et al. (2016) Humoral dysregulation associated with increased systemic inflammation among injection heroin users. PLoS One 11: e0158641.
69. Jamali A, Soleimanjahi H, Moin M, Mahdavi M, Hashemi H, et al. (2012) Withdrawal from morphine reduces cell-mediated immunity against herpes simplex virus generated by natural immunization. Neuroimmunomodulation 19: 229-234.
70. Lysle DT, Hoffman KE, Dykstra LA (1996) Evidence for the involvement of the caudal region of the periaqueductal gray in a subset of morphine-induced alterations of immune status. J Pharmacol Exp Ther 277: 1533-1540.
71. Mao M, Qian Y, Sun J (2016) Morphine Suppresses T helper Lymphocyte Differentiation to Th1 Type Through PI3K/AKT Pathway. Inflammation 39: 813-821.
72. Chao J, Nestler EJ (2004) Molecular neurobiology of drug addiction. Annu Rev Med 55: 113-132.
73. Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD (2008) Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol Psychiatry 63: 1022-1029.
74. De Guglielmo G, Melis M, De Luca MA, Kallupi M, Li HW, et al. (2015) PPARgamma activation attenuates opioid consumption and modulates mesolimbic dopamine transmission. Neuropsychopharmacology 40: 927-937.
75. Ford CP, Mark GP, Williams JT (2006) Properties and opioid inhibition of mesolimbic dopamine neurons vary according to target location. J Neurosci 26: 2788-2797.
76. Tan H, Rosen LG, Ng GA, Rushlow WJ, Laviolette SR (2014) NMDA receptor blockade in the prelimbic cortex activates the mesolimbic system and dopamine-dependent opiate reward signaling. Psychopharmacology (Berl.) 231: 4669-4679.
77. Tanda G, Pontieri FE, Di Chiara G (1997) Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science 276: 2048-2050.
78. Hutchinson MR, Watkins LR (2014) Why is neuroimmunopharmacology crucial for the future of addiction research? Neuropharmacology 76: 218-227.
79. Weber RJ, Pert A (1989) The periaqueductal gray matter mediates opiate-induced immunosuppression. Science 245: 188-190.
80. Dafny N, Pellis NR (1986) Evidence that opiate addiction is in part an immune response. Destruction of the immune system by irradiation-altered opiate withdrawal. Neuropharmacology 25: 815-818.
81. Dougherty PM, Pellis NR, Dafny N (1990) The brain and the immune system: an intact immune system is essential for the manifestation of withdrawal in opiate addicted rats. Neuroscience 36: 285-289.
82. Pellis NR, Kletzly NE, Dougherty PM, Aronowski J, Dafny N (1987) Participation of lymphoid cells in the withdrawal syndrome of opiate dependent rats. Life Sci 40: 1589-1593.
83. Dafny N (1984) Interferon: a candidate as the endogenous substance preventing tolerance and dependence to brain opioids. Prog Neuropsychopharmacol Biol Psychiatry 8: 351-357.
84. Dafny N (1985) Interferon as an endocoids candidate preventing and attenuating opiate addiction. Prog Clin Biol Res 192: 269-276.
85. Dafny N (1998) Is interferon-alpha a neuromodulator? Brain Res Brain Res Rev 26: 1-15.
86. McCain Hw, Lamster IB, Bozzone JM, Grbic JT (1982) Beta-endorphin modulates human immune activity via non-opiate receptor mechanisms. Life Sci 31: 1619-1624.
87. Bertolini A, Poggioli R, Fratta W (1981) Withdrawal symptoms in morphine-dependent rats intracerebroventricularly injected with ACTH1-24 and with beta-MSH. Life Sci 29: 249-52.
88. Dafny N (1983a) Interferon modifies morphine withdrawal phenomena in rodents. Neuropharmacology 22: 647-651.
89. Dafny N (1983b) Modification of morphine withdrawal by interferon. Life Sci 32: 303-305.
90. Dougherty PM, Dafny N (1988a) Cyclosporine affects central nervous system opioid activity via direct and indirect means. Brain Behav Immun 2: 242-253.
91. Dougherty PM, Dafny N (1988b) Neuroimmune intercommunication, central opioids, and the immune response to bacterial endotoxin. J Neurosci Res 19: 140-148.
92. Dougherty PM, Pearl J, Kraiewski KJ, Pellis NR, Dafny N (1987a). Differential modification of morphine and methadone dependence by interferon alpha. Neuropharmacology 26: 1595-1600.
93. Dougherty PM, Aronowski J, Drath D, Dafny N (1987b) Evidence of neuro-immunologic interactions: cyclosporine modifies opiate withdrawal by effects on the brain and immune components. J Neuroimmunol 13: 331-342.
94. Dougherty PM, Drath DB, Dafny N (1987c) Evidence of an immune system to brain communication axis that affects central opioid functions: muramyl peptides attenuate opiate withdrawal. Eur J Pharmacol 141: 253-260.
95. Dafny N (1982) The hypothalamus exhibits electrophysiologic evidence for morphine tolerance and dependence. Exp Neurol 77: 66-77.
96. Dafny N, Prieto-Gomez B, Reyes-Vasquez C (1985a) Does the immune system communicate with the central nervous system? Interferon modifies central nervous activity. J Neuroimmunol 9: 1-12.
97. Dafny N, Wagle VG, Drath DB (1985b). Cyclosporine alters opiate withdrawal in rodents. Life Sci 36:1721-1726.
98. Dafny N, Nelson J (2016) The role of interferons on the central nervous system in health and disease. Reference Module in Biomedical Sciences 2004: 53-59.
99. Montgomery SP, Dafny N (1987) Cyclophosphamide and cortisol reduce the severity of morphine withdrawal. Int J Immunopharmacol 9: 453-457.
100. Reyes-Vasquez C, Prieto-Gomez B, Dafny N (2012) Itnerferon modulates central nervous system function. Brain Res 1442: 76-89.
101. Gresser I (1977) Antitumor effects of interferon in cancer. Becker, F (ed.) A comprehensive treatise. Plenum Press 5: 521-571.
102. Lengyel P (1982) Biochemsitry of interferon and their actions. Ann Rev Biochem 51: 251-282.
103. Petska S, Baron S (1981) Definition and classification of the interferons. Methods in Enzymology 78: 3-14.
104. Dianzani F, Antonelli G, Capobianchi MR (1990) The biological basis for clinical use of interferon. J Hepatol 11: S5-10.
105. Lang JY, Wang JS, Zhai HF, Fang Q, Wu P, et al. (2009) Interferon-alpha reinstates morphine-conditioned place preference through opioid receptors in rats. Behav Pharmacol 20: 166-173.
106. Dafny N, Prieto-Gomez B, Dong WQ, Reyes-Vasquez C

(1996) Interferon modulates neuronal activity recorded from the hypothalamus, thalamus, hippocampus, amygdala, and the somatosensory cortex. Brain Res 734: 269-274.

107. Reyes-Vasquez C, Mendoza-Fernandez V, Herrera-Ruiz M, Dafny N (1997) Interferon modulates glucose-sensitive neurons in the hypothalamus. Exp Brain Res 116: 519-524.
108. Dafny N, Lee JR, Dougherty PM (1988) Immune response products alter CNS activity: interferon modulates central opioid functions. J Neurosci Res 19: 130-139.
109. Roosth J, Pollard RB, Brown SL, Meyer WJ 3rd (1986) Cortisol stimulation by recombinant interferon-alpha 2. J Neuroimmunol 12: 311-316.
110. Smith SM, Morrill AC, Meyer WJ 3rd, Blalock JE (1986) Corticotropin releasing factor induction of leukocyte-derived immunoreactive ACTH and endorphins. Nature 321: 881-882.
111. Wybran J, Appelborn T, Famaey JP, Govaerts A (1979) Suggestive evidence for receptors for morphine and methionine-enkephalin on normal human blood T lymphocytes. J Immunol 123: 1068-1070.
112. Andrews RC, Herlihy O, Livingstone DEW, Andrew R, Walker BR (2002) Abnormal cortisol metabolism and tissue sensitivity to cortisol in patients with glucose intolerance. J Clin Endocrinol Metab 87: 5587-5593.
113. Hellhammer DH, Wust S, Kudielka BM (2009) Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology 34: 163-171.
114. Kudielka BM, Hellhammer DH, Wust S (2009) Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. Psychoneuroendocrinology 34: 2-18.
115. Dafny N, Phillips MI, Taylor AN, Gilman S (1973) Dose effects of cortisol on single unit activity in hypothalamus, reticular formation, and hippocampus of freely behaving rats correlated with plasma steroid levels. Brain Res 59: 257-272.
116. Feldman S, Papir-Kricheli D, Dafny N (1983) Single-cell and multiunit activity in freely moving rats after corticosterone administration. Exp Neurol 80: 427-438.
117. Feldman S, Dafny N (1970a) Changes in single cell responsiveness in the hypothalamus in cats following cortisol administration. Brain Res 20: 360-377.
118. Feldman S, Dafny N (1970b) Effects of cortisol on unit activity in the hypothalamus of the rat. Exp Neurol 27: 375-387.
119. Cupps TR, Fauci AS (1982) Corticosteroid-mediated immunoregulation in man. Immunol Rev 65: 133-155.
120. Fauci AS, Dale AC (1975) The effect of hydrocortisone on the kinetics of normal human lymphocytes. Blood 46: 235-243.
121. Winkelstein A (1984) The effects of cyclosporine and hydrocortisone on human T-lymphocyte colony formation. Cell Immunol 86: 413-420.
122. Ninkovic J, Roy S (2013) Role of the mu-opioid receptor in opioid modulation of immune function. Amino Acids 45: 9-24.
123. Flores LR, Hernandez MC, Bayer BM (1994) Acute imminosupressive effects of morphine: lack of involvement of pituitary and adrenal factors. JPET 268: 1129-1134.
124. Borel JF, Feurer C, Magnée C, Stähelin H (1977) Effects of the new anti-lymphocytic peptide cyclosporin A in animals. Immunology 32: 1017-25.
125. Milach PJ (1986) Cyclosporin A in organ transplantation. Med J Aust 145: 146-50.
126. Colombani PM, Robb A, Hess AD (1985) Cyclosporin A binding to calmodulin: a possible site of action on T lymphocytes. Science 228: 337-339.
127. Lafferty KJ, Borel JH, Hodgkin P (1983) Cyclosporin-A: models for the mechanism of action. Transplant Proc 15: 2242-2247.
128. Rashki A, Mumtaz F, Jazayeri F, Shadboorestan A, Esmaeili J, et al. (2018) Cyclosporin A attenuating morphine tolerance through inhibiting NO/ERK signaling pathway in human glioblastoma cell line: the involvement of calcineurin. EXCLI J 17: 1137-1151.
129. Grover VS, Sharma A, Singh M (2000) Role of nitric oxide in diabetes-induced attenuation of antinocipceitve effect of morphine in mice. Eur J Pharmacol 399: 161-164.
130. Džoljić E, Grbatinić I, Kostić V (2015) Why is nitric oxide important for our brain? Funct Neurol 30: 159-163.
131. Cardon SB, Larson DF, Russell DH (1984) Rapid elevation of rat serum prolactin concentration by cyclosporine, a novel immunosuppressive drug. Biochem Biophys Res Commun 120:614-618.
132. Jaffe JH (1980) Drug addiction and drug abuse. In The Pharmacological basis of therapeutics, 6th edition (eds Goodman LS, and Gilman A): 535-584.
133. Kamei J, Kawashima N, Suzuki T, Misawa M, Kasuya Y (1993) The effects of cyclosporine on morphine-induced antinociception in diabetic mice. Neurosci Lett 158: 213-216.
134. Noble F, Marie N (2019) Management of Opioid Addiction with Opioid Substitution Treatments: Beyond Methadone and Buprenorphine. Front Psychiatry 9: 742.
135. Rodriguez-Arias M, Aguilar MA, Minarro J (2015) Therapies in early development for the treatment of opiate addiction. Expert Opin Investig Drugs 24: 1459-1472.
136. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G (2018) Drug and Opioid-Involved Overdose Deaths – United States, 2013-2017. MMWR Morb Mortal Wkly Rep 67: 1419-1427.
137. Wan Q, Wang X, Wang YJ, Song L, Wang SH, et al. (2008) Morphine suppresses intracellular interferon-alpha expression in neuronal cells. J Neuroimmunol 199: 1-9.
138. Olin M, Oh S, Roy S, Peterson P, Molitor T (2012) Morphine induces splenocyte trafficking into the CNS. J Neuroimmune Pharmacol 7: 436-443.
139. Dafny N, Reyes-Vasquez C (1985) Three different types of alpha-interferon alter naloxone-induced abstinence in morphine-addicted rats. Immunopharmacology 9: 13-17.
140. Dafny N, Burks TF, Bergmann D (1983a) Dose effects of morphine on the spontaneous unit activity recorded from the thalamus, hypothalamus, septum, hippocampus, reticular formation, central gray, and caudate nucleus. J Neurosci Res 9: 115-126.
141. Dafny N, Zielinksi M, Reyes-Vasquez C (1983b) Alteration of morphine withdrawal to naloxone by interferon. Neuropeptides 3: 453-463.
142. Besedovksy HO, Del Rey A (2002) Introduction: immune-neuroendocrine network. Front Horn Res 29: 1-14.
143. Besedovsky HO, Del Rey AE, Sorkin E (1983) What do the immune system and the brain know about each other? Immunol Today 4: 342-346.
144. Bullock K (1985) Neuronatomy of lymphoid tissue: a review, in Neuromodulation of Immunity, Guillemin R, Cohn M, Melnechuk T, Eds., Raven Press, New York 111-128.
145. Dunn AJ (1989) Psychoneuroimmunology for the psychoneuroendocrinologist: a review of animal studies of nervous system-immune system interactions. Psychoneuroendocrinology 14: 251-274.
146. Fecho K, Maslonek KA, Dykstra LA, Lysle DT (1996) Assessment of the involvement of central nervous system and peripheral opioid receptors in the immunomodulatory effects of acute morphine treatment in rats. J Pharmacol Exp Ther 276: 626-636.

147. Felten DL, Felten SY, Bellinger DL, Carlson SL, Ackerman KD, et al. (1987) Noradrenergic sympathetic interactions with the immune system: structure and function. Immunol Rev 100: 225-260.
148. Friedman H, Eisenstein TK (2004) Neurological basis of drug dependence and its effects on the immune system. J Neuroimmunol 147: 106-108.
149. Solomon RE, Wasserman EA, Gebbart GF (1987) Tolerance to antinociceptive effects of morphine without tolerance to its effects on schedule-controlled behavior. Psychopharmacology (Berf) 92: 327-333.
150. Cohen M, Keats AS, Krivoy W, Ungar G (1965) Effect of actinomycin D on morphine tolerance. Proc Soc Exp Biol Med 119: 381-384.