Endorphin Agonists for Severe Depression

Abstract
Endorphins and endorphin agonists play a crucial role in the neural modulation of mood, anxiety, pain and addiction. Recent studies have elucidated the crucial mechanism of enhancing prefrontal cortex influence and dampening limbic and sub cortical influences in depression and remission consistent with the biological profile of endorphin agonists. The historical, biological, experimental and clinical data strongly support the potential benefits of opiates for severe depression. Further research to study endorphin agonists for depression and possibly for other psychiatric disorders seems warranted.

Keywords: Endorphin agonists; Severe depression; Psychiatric disorders

Abbreviations: GABA: Gamma-Amino Butyric Acid; Ach: Acetylcholine; NMDA: N-Methyl D-Aspartate

Introduction
The treatment of depression is a difficult undertaking. Despite significant advances in psychiatry, annual suicidal deaths of some 37,000 in the USA and some 1 million worldwide suggest depression remains to be a major health concern [1]. Recent advances have offered new insights into the crucial influence of the governing influence of prefrontal cortex over sub cortical and limbic regions and in particular the mechanism of action of diverse antidepressant strategies: the ability to restore the predominance of prefrontal cortex over other brain regions [2]. There is also a growing body of behavioral and pharmacological evidence linking the opioid system to the pathophysiology of depression and the mode of action of antidepressant medications [3-7]. Abnormalities of mood and pain perception are common features of depression. It is noteworthy that opiates are known for the dual influence on the central nervous system with activating prefrontal cortex function and dampening the limbic influence consistent with the mechanism of action of many antidepressant strategies [8]. A number of studies have documented abnormalities of endorphin metabolism in patients or in postmortem brains of suicide victims consistent with the crucial role of opiates in the genesis of mood disorders [5,6,9]. From a number of different perspectives opiates influence almost all aspects of mood regulation. Although there have been no double blind prospective studies to support opiates as antidepressants they may offer new insights to treat depression. This study reviews antidepressant action of opiates. The major areas of review are

i. History of treatment with opiates
ii. Neurobiology
iii. Mechanism of antidepressant action
iv. Antidepressant effects of morphine like substances
v. Opiates and adverse events

Methods
We searched the MEDLINE data base from 1995 to July 2013 using the combined search terms depression, depressive disorders, morphine, morphine like substances, methadone, oxycodone, buprenorphine. Articles were also included by manual search of bibliography from all retrieved articles. Articles were included if they had primary data derived from clinical trials or review studies. Excluded studies were those addressing anecdotal reports.

History of opiate treatment
Since prehistoric times opiates have been used for medicinal purposes. The plant papaver has been known for its medicinal benefits. In the Odyssey, Homer refers to a curative substance which was administered to Helena as a remedy against grief and grudge. Similarly, the classical medical writings of Dioscurides [1st century] and Galen [129_199] have referred to the narcotic analgesic properties of opium. And it was Paracelsus [1493_1541] a Swiss German alchemist who observed that certain analgesic opium alkaloids are far more soluble in alcohol then water which led to tinctura laudanum, allowing for easy medicinal delivery. And thus paving the way for opioid’s regimented use in medicine. In the following century, Thomas Sydenham [1624_1689] recommended opium against hysteria and mania. Then, in general the 18th century witnessed opium as one of the more popular medications used in psychiatry. In 1988 Drs Weber and Emrich [10] published an extraordinary review of opiate treatment in psychiatric disorders [10].

Of significance was the role of the Engelken family in psychiatry. The family of Engelken living in northern Germany between 1750 and 1910 practiced psychiatry and developed the foundation of a new systematic pharmacotherapy of severe depressions and other psychiatric disorders. Their approach established opium as one of the more popular medications used in psychiatry. In 1988 Drs Weber and Emrich [10] published an extraordinary review of opiate treatment in psychiatric disorders [10].
treat severe depressions. In summary opiates have been known for antidepressant influence from ancient times to Emil Kraepelin and modern psychiatry.

**Neurobiology:** Region specific brain function, neurotransmitters and opiates

Neurobiology suggests brain function is region specific [8,11]. Biology also suggests synaptic transmission is crucial for brain function. Any change in brain homeostasis may activate a cascade of dynamic changes with regionally defined neurobiological consequences [12]. Therefore a change in single transmitter may induce major or minor changes in brain function. Wilder Penfield demonstrated that specific brain regions govern motor and sensory function. Paul Broca and Carl Wernicke identified brain regions associated with language and auditory function. Korbinian Brodmann described the histological structure of diverse and distinct brain regions. Evidence suggests amygdala and play central roles in memory and learning. Thalamus has been identified as a central switch forward. A filter that blocks out information to perform a specific task. The prefrontal cerebral cortex mediates a variety of executive function such as abstract thought, learning, strategic thinking and problem solving. The limbic system monitors promotions and basic survival instincts such as thirst, hunger, sex drive and energy [8,11]. Amygdala plays a key role in our response to threatening stimuli.

Projections from locus coeruleus activate the entire cortex, the hypothalamus, the brainstem with norepinephrine. Projections from the ventral tegmental area extend to caudate and putamen represent neuro stratal pathway with dopamine as the primary neurotransmitter. Meso cortical and meso limbic tracks project to the prefrontal cortex and the limbic system and projections from the hypothalamus extend to the pituitary with dopamine as the primary neurotransmitter. Serotonergic neurons arise in the raphe nuclei and project to the entire neo cortex, the basal ganglia, temporal limbic region, the hypothalamus, the cerebellum and the brainstem. Glutamate is an excitatory amino acid neurotransmitter which is produced throughout the cerebral cortex and hippocampus. Gamma amino butyric acid (GABA) is an inhibitory transmitter in the cerebral cortex and limbic brain [8,11]. In general, it is true that neurotransmitters have activating or inhibitory properties. For instance, dopamine, norepinephrine, glutamate and histamine are activators and serotonin, endorphins and GABA have inhibitory influence. It is also true that multiple chemicals including neurotransmitters and other neuro-modulators such as brain derived neurotrophic factor, G protein and others coexist in neurons and synaptic systems and are of great importance for neurotransmission. It is also true that anatomical and functional interactions exist between the noradrenergic neurons originating in the locus coeruleus and the serotonergic nucleus in the raphe nuclei. The cholinergic system and acetylcholine (ACh) seem to be particularly important in memory formation. In general (ACh) increases excitability of cortical neurons. N Methyl D Aspartate [NMDA] is a glutamate receptor that allows sodium and calcium into the cell. NMDA receptors have a common role in experience induced neural changes by many addictive substances. NMDA antagonists seem to induce both tolerance and withdrawal symptoms associated with addictive substances. For instance acomprosat reduces alcohol withdrawal symptoms and drinking urges and dizocilpine reduces morphine tolerance without interfering with analgesia [8,11].

Opiates and their receptors are in general central nervous system inhibitors which play a major role in attainment of pleasure and pain control rewarding addictive behavior. Opiate receptor subtypes include mu, delta, kappa. The opiate receptors have a high affinity for opiates. Brain produces morphine like substances called endorphins, enkephalines and dynorphines. These endogenous morphine like substances form from precursor proteins, pro opiomelanocortin [pomc], proenkephaline, prodynorphine. Through opening of potassium and calcium channels opiates in general have an inhibitory influence in the central nervous system [8,11]. Acute effects of opiates include analgesia and euphoria. Analgesia occurs by acting as agonists at opiate receptor subtypes primarily in the sub cortical and limbic regions. In contrast animal studies suggest that euphoric effects are mostly due to the prefrontal cortex dopaminergic activation.

Morphine micro injections into the ventral tegmental area of the midbrain produce dopaminergic activation of the mesolimbic pathway consistent with conditioned placed preference and reduction of threshold for intracranial electrical self mutilation [13]. Using the drug self administration technique one striking finding that is that the reinforcement value and the pattern of use in animals suggests that animals learn to regulate with some accuracy the amount of morphine they require. Of significance is the observation that despite morphine’s significant reinforcing properties the increase in self administration is not infinite and correspondence to a specific pattern. The animal self administers morphine just the amount to prevent discomfort associated with withdrawal symptoms [14]. Another study by Basile and colleagues showed that bioengineered mice that had become dependent on morphine like substance may still benefit from the analgesic effect yet not experience any withdrawal symptoms upon the stoppage of the substance [15]. Animal studies also suggest big difference between heroin and cocaine self administration. In general those animals self administering heroin maintained grooming behavior pre testing body weight and a good state of general health whereas rats self administering cocaine lose up to 47% of the pretesting body weight and showed profound deterioration in general health. The mortality rate for 30 days for animals self administering cocaine was 90% [16]. With repeated exposure to morphine like substances notable adaptation tolerance to some of the effects of morphine like substances may develop. Desensitization ligand induced closure and unresponsiveness to the receptor is believed to play a role in tolerance and clinical evidence is consistent with the observation that mostly the withdrawal and euphoric effects are influenced by tolerance.

In summary, it seems that opiates unlike cocaine and LSD, PCP and other substances with psychosis inducing properties have a calming influence. Note that, there is a clear trend toward progressive brain dysfunction with cocaine in contrast to behavior consistent with maintaining a homeostasis to prevent withdrawal symptoms with heroine. Furthermore, although opiates elicit euphoria an important influence in addictive behavior based upon animal studies and clinical observations it seems that withdrawal symptoms have a predominant influence in the genesis of addictive behavior.
Mechanism of action of antidepressant strategies

A recent neuroscientific discovery has been that the therapeutic efficacy of antidepressants strategies may depend less on their presumptive molecular mechanisms of action and more on their ability to restore the predominant metabolic and executive functions. This observation that the molecular changes associated with depression share a common thread is probably an important insight for the potential benefits of morphine like substances in depression [2]. This is because morphine like substances has dual influence of brain function with dampening influence on sub cortical and limbic regions and with activation the prefrontal cortex function. Because of the crucial influence of paradoxical influence on brain function inhibitory effect on limbic region with enhancement and activation of frontal cortex it would be helpful to review the core findings of mechanism of action for antidepressant effect.

**Diminished executive function in depression:** Executive function, a domain of prefrontal cortex, is compromised in unipolar depression [17,18], late life depression [19], obsessive compulsive disorder [20] and treatment resistant depressed patients [21] Importantly executive function improves when unipolar depression remits. Conversely, depressed patients with the greatest improvements and executive function are less likely to remit [22]. Stress and depression decrease frontal cortex dominance of sub cortical and limbic areas. Childhood stress reduces prefrontal cortex function and volume when measured in adolescence and adult hood, and even when adjusted for total brain volume [23-25]. Stresses in early life and beyond greatly increase the vulnerability for depression and anxiety in adulthood if stress reemerges [26,27] brain atrophy and decreased metabolism in frontal and dorsolateral prefrontal cortex contribute to this vulnerability [28,29] Like adult depression [30] pediatric depression [31] is associated with increases amygda size and patients with the largest amygda show the greatest levels of anxiety and impairments in learning emotional facial expressions [32,33].

The reciprocal nature of pre frontal and sub cortical limbic metabolism and depression is further documented at the two extremes of the depression spectrum, notably, dysthymia and severe depressive illness. Each illness is characterized by decreases in the flow of blood to the dorsal neo cortex including the frontal lobes and increases in ventral paralimbic areas including subgenual and interior cinguclate cortex [34-37]. Depression lessens prefrontal function through the enhanced sub cortical limbic activity. A wealth of clinical observations suggest that when activated a robust prefrontal cortex promotes cognitive processing, moderates emotional responses to sensory input and suppresses sub cortical limbic activity. And decline of cognitive and emotional functions, diminished prefrontal cortex function and activated sub cortical and limbic functions are well documented in major depression [34,35]. Human decision making abilities during emotional situations are impaired when there is damage to the medial and ventral prefrontal cortex and prefrontal abnormalities predispose people to develop fear and anxiety disorders [36]. Greater activation of the rostral anterior cinguclate cortex occurs in depressed patients exposed to people facial expressions and the magnitude of this increase is correlated with gray matter loss in the orbitofrontal cortex [37]. These and many other findings Figure 1 indicate that depression can be predicted by the extent of metabolic decreases in the prefrontal cortex and increases in sub cortical and limbic regions [2].

**Figure 1:** Endorphins: Morphine like substances and their dual influence.

**Depression remission and relapse varied with pre frontal and sub cortical limbic activity:** prefrontal dopamine and norepinephrine neurotransmision influences creativity, executive function, initiative, mood, attention and concentration.

At profound and selective deficit in delay that alternation performance is produced by at 90% depletion of dopamine in the prefrontal cortex of rhesus monkeys [38]. To deficit is so significant that it is hard to distinguish it from that produced by cross surgical ablation, however, the attention and cognitive deficits induced by dopamine depletion can be reversed by moderate doses of l dopa or apomorphine, but not high doses, which compromise improvement. The inverted U shaped response to catecholamine stimulation reinforces the need for optimal predominant roles of prefrontal cortex dopamine and norepinephrine for optimal executive function and mood control. Indeed, the predominant auto receptors that regulates catecholamine release, the alpha-2 receptor, produces only have to signal in the prefrontal cortex of medicated or unmedicated depressed suicide cases, compared to controls [39] and likely a result of this deficit, excessive catecholamine release, is associated with the stress induced distraction of cognitive functions. Low doses of alpha-2 adrenergic agonists can improve this cognitive decline by lessening the excessive baseline noradrenergic firing which enhances prefrontal cortex responses to salient information and attenuates catecholamine overload during stress [40] the role of prefrontal catecholamines in optimizing executive function and metabolism is supported by PET imaging with C-glucose. This tracer reveals rapid decreases in prefrontal metabolism of catecholamine depletion by tyrosine hydroxylase inhibition, which concomitantly invokes depression, anxiety and anhedonia. These behavioral responses occur to a greater extent in depression patients then in controls. While prefrontal cortex glucose utilization increases during remission from depression, it is decreased in the orbitofrontal gyrus and increased in mid cinguclate and subgenual anterior cinguclate, then from medial frontal cortex, temporal cortex and thalamic regions [41].

Antidepressant responses and enhanced prefrontal cortex function; the prefrontal locus of dopamine metabolism in explaining therapeutic effects on executive function and mood has

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Furthermore dopamine and or diminished initiative. All of these indicate executive dysfunction, anhedonia and decreased metabolism in the dorsal lateral prefrontal cortex [42,43]. Long term efficacy approximately coincides with increased dorsolateral prefrontal cortex metabolism and decreased hippocampus and amygdala metabolism [44,45].

The evidence is consistent with the observation that a metabolic decline of prefrontal cortex function promotes depressive disorders associated with executive dysfunction [46-49]. In many cases, this is associated with a diminished inhibitory sub cortical or limbic influences by the prefrontal cortex. Many effective and diverse strategies for treating depression, including ECT, TMS, rTMS, antidepressants of the SSRI, SNRI, tricyclic or monoamine Oxidase inhibitor types and ketamine, activate prefrontal cortex metabolism [2] (Figure 2). Other antidepressant approaches that have not been evaluated for effects human brain metabolism include mianserin, mirtazapine and agomelatine. Each of these facilitate frontal cortical dopamine projections albeit by different mechanisms and are predicted to show an antidepressant effect in proportion to their ability the normalize prefrontal cortex function and restore the ratio of healthy normal homeostasis.

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Dopamine-endorphin relationship: Furthermore dopamine morphine like substance relationship is worthy of special attention. Morphine like substances enhances prefrontal cortex function, executive function mood, joy. Naloxone a morphine antagonist neutralizes dopamine specific joy [50]. Naltrexone and morphine antagonist seems to contribute to panic attacks and depression [51,52]. Because the prefrontal cortex is specifically wired to provide highly sophisticated intellectual and emotional functions even minute shifts in the brain’s prefrontal cortex may cause executive dysfunction, anhedonia and decreased metabolism in the orbital frontal and dorsolateral prefrontal cortex contribute to this vulnerability [2] and or diminished initiative. All of these symptoms represent the core symptoms of depression.

Depletion of dopamine in a circumscribed area of association cortex in rhesus monkeys produces impairment in spatial delayed alternation performance nearly as severe as that caused by surgical ablation [30]. This behavioral deficit can be pharmacologically reversed with dopamine agonists. These provide direct evidence that dopamine plays an important role in a specific cortical function. In primates including humans the dorsolateral convexity of the prefrontal cortex plays a selective role in mediating mnemonic, attentional and spatial capacities. In subhuman primates this region over the cerebral neocortex has high catecholamine levels and metabolic rates particularly for dopamine whereas serotonin content and activity in the same cortical tissue is relatively low [38]. The finding that dopamine depletion can be restricted to a circumscribed area of the prefrontal cortex producing behavioral deficit in a selective function over that area suggests that dopamine in the prefrontal cortex may work as a neurotransmitter independent of its precursor role. The reversal of dopamine action in the prefrontal cortex by morphine antagonist naloxone supports morphine like substances antidepressant effects or modulating influence of dopamine.

Common pathways of pain, depression, addiction: There is neuroimaging evidence of abnormal endogenous opioid neurotransmission in people with impulsiveness [53]. There is also evidence of dysregulation of endogenous endorphines in major depression and women [54]. There is also high comorbidity between addiction and depression [55] and also between pain and depression [56]. Furthermore, three major medications to treat addiction, methadone buprenorphine and heroine intramuscular [57] are morphine like substances. The cumulative evidence of high comorbidity of pain and depression and of addiction and depression and the observation that opiates are effective to treat pain and addiction [3,57] suggest common pathways in the genesis of pain addiction and depression. All of the above observations suggest that the endorphin metabolism in depression maybe altered.

Endorphin function or the influence of morphine like substances is involved in the responses to diverse input such as exercise, pain, music and cocaine. This interesting paradox can potentially be informative by investigating in which ways external input promotes or harms prefrontal cortex function. Music, exercise, pain and cocaine are influences that produce a lasting propensity for brain function to respond differently to sensory stimuli that persists for some time. The common final pathway seems to be dopamine action in the prefrontal cortex function. It seems that music, exercise, pain, cocaine, in the short run activate prefrontal cortex function [8]. The chronic exposure to music, exercise, pain and cocaine seem to have paradoxical results. Music and exercise seem to promote the prefrontal cortex function [50,58]. Noteworthy is the observation that naltrexone a morphine antagonist can block the effects induced by music [50] and morphine like substances dampen pain [8]. The opposite is true for pain and cocaine. Neuroimaging evidence shows neurotoxicity and atrophy [8,16]. All of the above summarized findings are consistent with the mediating influence of morphine like substances in the prefrontal cortex function. It is thus possible that the use of opiates may be of benefit to mediate adverse
influences and normalize biological deficits.

**Antidepressant effect of endorphin agonists**

Activation of the Delta opioid receptor produces robust antidepressant like effect in preclinical essays [58]. Beneficial effects of electroconvulsive treatment is associated with elevations of plasma beta endorphine level in depressed patients [59,60]. Cyclazocine a mixed opiate agonist antagonist was found to be effective in the treatment of 10 depressed patients [61]. Bodkin et al. [3] reported 10 patients who had previously been failed to respond to traditional treatments but had a positive response to buprenorphine [3]. In this a study three patients dropped out of because of side effects. For subjects achieved complete remission by the end of the trial. Three moderately improved. These findings were consistent with a possible therapeutic role for buprenorphine in treating treatment refractory depression.

Nyhus et al. [4] reported three patients who had failed electroconvulsive treatment but had a robust response buprenorphine and oxycodone [4,5]. The study results were consistent with the observation that in some cases of treatment refractory depression all appearance to be more effective than ECT. Anecdotal reports can be of limited scientific power yet manual for helpful insights that may play an important role in solving complex problems. In this context the wealth of data in support of potential antidepressant effects of opiates is worthy of mention. Among them The Morphine Cure by Dr. Robert Cochran has numerous success stories OF patients with pain and mood disorders with positive response to opiates [62].

**Opiates and adverse events**

The central inhibitory influence on the respiratory center merits special mention. Of concern is respiratory arrest especially when opiates are combined with other central nervous system depressants. Aside from the inhibition of respiration other side effects are, slowing down gastrointestinal motility and bladder emptying. Cognitive slowing or decline has been attributed to chronic use of opiates yet in general the great majority of studies are consistent with the observation that opiates do not cause cognitive decline [63,64]. In contrast cognitive and brain atrophy has been associated with chronic pain and depression [65-68]. Because opiates are addictive our knowledge of the pathophysiology of opiate induced addiction may be helpful. Upon the discontinuation of morphine like substances a constellation of symptoms defined as morphine abstinence syndrome develops. Most of the symptoms emerge in the first 24 hour gradually resolving in 7 to 10 days from the onset of withdrawal. The symptoms include increased anxiety, restlessness, irritability, dilated pupils, goose flesh, hot flashes, vomiting, diarrhea, fever, elevated blood pressure, increased heart rate and abdominal and generalized muscle cramps.

Morphine abstinence syndrome seems to represent increased noradrenergic parasympathetic and glutamatergic activity and the emergence of withdrawal symptoms coincide with plasma concentration half life and the final clearance of morphine like substance. Of clinical significance is that, the onset of withdrawal does not always coincide with the onset of terminal effects of a substance. For instance, for morphine like substances, a patient may remain pain free yet at the same time experience withdrawal symptoms. This is because the analgesic effect is determined by CNS effect and the withdrawal is triggered by the downward shift of the plasma concentration of the morphine like substance.

From a clinical perspective it is evident that withdrawal associated symptoms are of great influence in addictive behavior. And if we follow the animal studies, we may predict that unlike with cocaine, LSD, PCP or alcohol, opiate addiction is primarily driven by behavior to maintain homeostasis by preventing withdrawal discomfort rather than personal pleasure and reward. In fact, clinical observations support the view that the absence of an acute euphoric effect and the reduction of the unpleasant withdrawal associated symptoms are of crucial importance for morphine like substances and their addictive potential. If, for instance heroine is administered by intramuscular injection with long acting slow release formula it can be an effective treatment for addiction in contrast to administration by intramuscular injection. It is also true that the addiction and overuse potential of many morphine like substances with long elimination half lives such as methadone and extended release oxymorphone are significantly less than short acting opiates. In an additional set of data considerable evidence has accumulated to suggest the key mechanisms contributory to addictive potential. The results of these findings are summarized in Figure 3. Although the details of these the studies R beyond the scope of this review it seems that they suggest the crucial influence the brain dopamine firing rate associated with rate of intake and blood concentration of an addictive substance. And as shown by previously discussed animal studies this means in general slow release, long acting morphine like substances are void of euphoria associated reinforcing influence. This is consistent with the well established safety and efficacy of long term use of long acting morphine like substances in the treatment of chronic pain [69].

**Figure 3: Antidepressant effects of opiates: Supporting evidence.**

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A brief comment on potential risk of death associated with morphine-like substances is also necessary. According to the vital statistics, the annual prescription pain medication associated fatalities were six deaths per population of hundred thousand in 2007 [70]. This number includes over the counter pain medications as well. In studying the risk of death from morphine-like substances, the vital statistics are essential. This approach is based upon the expectation that the recording methods are scientifically valid. The study by Drs. Webster and Dasgupta [71] describes the scientific unreliability of the current reporting systems [71]. This suggests, the results provided by the center of disease control of deaths from morphine-like substances are invalid. Therefore, dangers commonly attributed to the narcotic pain medications must not be assumed until it can be shown that scientific methods are used to ensure the collection, dissemination and evaluation of data related to mortalities to morphine-like substances. Recommendations made by Drs. Webster and Dasgupta [71] may help in securing scientifically reliable data.

In summary in terms of adverse effects, morphine-like substances are very different than LSD; PCP, cocaine and alcohol. Two major properties of opiates are the following.

i. Withdrawal associated discomfort is a predominant influence of addictive behavior.

ii. Long acting opiates have low abuse potential

What is the core message from the neurobiological data?

The simple answer is morphine like substances associated addictive behavior is very different then other addictions such as alcohol, cocaine, crack or PCP.

Discussion

Our brains live and function with morphine-like substances. Many of the processes that constitute mental function i.e. mood, anxiety, concentration, executive functions, empathy, creativity, sensitivity are influenced by endorphins. Furthermore, based upon historical, clinical and pathophysiological data we may state that morphine-like substances have the crucial properties to treat depression. Two unique observations about endorphin agonists, the biological profile to enhance the prefrontal cortex function and to dampen limbic sub cortical function and the wealth of historical data are compelling to support potential benefits of morphine-like substances to treat depression. Noteworthy is the evidence that in general endorphin agonists are neuroprotective and not neurotoxic like alcohol, cocaine, crack, LSD or PCP use, a commonly held mistaken public perception. It seems not science but unscientific myths have limited research to adequately study potential benefits of endorphin like substances for treating conditions other than pain.

Conclusions

Several key themes emerged from this review. First of all the need for more effective treatment for depression is obvious consistent with the number of people unresponsive to standard treatments. Second, the benefits of opiates have been recognized since antiquity and well documented in modern history. The concerns about addiction seem to be related to simplistic and erroneous misperceptions that all addictive substances are neurotoxic. It is well established that depression has many causes, including brain injury, neurodegenerative changes, environmental and genetic influences. In spite of the variety of the causes, dopamine and the prefrontal cortex function seem to be the final pathway. And endorphines are one of the major neurotransmitters with direct influence of dopamine in the prefrontal cortex. All of the above findings suggest that future research of opiates for depression with prospective placebo controlled double blind studies is both a reasonable and necessary next step. There is no aspect of human behavior that is outside of the domain of endorphinrs and this is my view as to why bypassing opiates in depression research is unwise.

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