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Endorphin agonists for psychiatric disorders

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Abstract

Endorphins and endorphin agonists play a crucial role in the neural modulation of mood, anxiety, pain and addiction.

Historical, experimental and clinical data strongly support the potential benefits of opiates for severe depression, addictive disorders, pain and psychosis. Recent studies have also elucidated a crucial mechanism of treating depression- enhancing prefrontal cortex influence and dampening limbic and sub cortical influences- similar to the neurobiological actions of endorphin agonists.

Despite much publicity of an alleged causal association between prescription pain medications and an epidemic of overdose deaths, no scientific evidence exists to support a causal link between prescription opiates and the overdose deaths.

Despite concerns of addiction and misuse potential further research to study endorphin agonists for diverse psychiatric disorders seems warranted.

Introduction

Endorphins and endorphin agonists play a crucial role in the neural modulation of mood, anxiety, pain and addiction [1,2].

Since prehistoric times opiates have been used for medicinal purposes for diverse conditions including depression, psychosis, pain, addiction and other psychiatric conditions [3].

There is also a growing body of behavioral and pharmacological evidence linking the opioid system to the pathophysiology of depression, addiction, chronic pain, psychoses and other psychiatric disorders [4-8].

It is also true that- partly due to the imperfections of our current controlled substance classification system - the unique therapeutic benefits of endorphins have been shadowed by concerns of dependence misuse and diversion.

This study reviews therapeutic actions of opiates in the treatment of diverse psychiatric conditions. The major areas of review are:

A. History

B. Neurobiology

C. Mechanism of action

D. Dopamine – endorphin relationship

E. Antidepressant effects

F. Common pathways of pain, depression, addictive behavior and psychosis

G. Opiates and adverse events

H. Do we have an epidemic of deaths from prescription pain medications?

Methods

We searched the MEDLINE data base from 1995 to July 2014 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.

Results

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 Paracelcus [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 opiums 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 published an extraordinary review of opiate treatment in psychiatric disorders [3]. Of significance was the role of the Engelken family in psychiatry.

The family of Engelkens living in northern Germany between 1750 and 1910 practiced psychiatry and developed the foundation of

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a new systematic pharmacotherapy of severe depressions and other psychiatric disorders. Their approach established opium preparations as the most important method of psychiatric treatment for more than hundred years. Moreover they initiated the general discussion concerning the value of and the indications for psychopharmacological therapies that ultimately led to an awareness and understanding of the complexity of the problem or dependence. In the second half of the 18th century Dr. Frederick Engelken founded a private hospital near Bremen for mentally ill [3].

After the Second World War, the rise of the newly developed antidepressants replaced the classical opium cure although even the introduction of electroconvulsive treatment and insulin shock treatment did not replace opiates as the predominant modality to 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 [1,2]. 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 [9]. Therefore a change in a single transmitter may induce major or minor changes in brain function. Wilder Penfield demonstrated that specific brain regions govern motor and sensory function [1,2]. Paul Broca and Carl Wernicke identified brain regions associated with language and auditory function [1,2]. Korbinian Brodman described the histological structure of diverse and distinct brain regions [1,2]. Evidence suggests amygdala and. play central roles in memory and learning [1,2]. Thalamus has been identified as a central switch forward. A filter that blocks out information to perform a specific task. The prefrontal 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 [1,2]. Amygdala plays a key role in our response to threatening stimuli.

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 [2,3]. Opiate receptor subtypes include mu, delta, and kappa. The opiates 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 [1,2]. Acute effects of opiates include analgesia and euphoria. Analgesta 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 produces dopaminergic activation of the mesolimbic pathway consistent with conditioned placed preference and reduction of threshold for intracranial electrical self-mutilation [10]. 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 [11]. 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 [11].

Another study by Basile and colleagues showed that bioengineered mice that had become dependent on a morphine like substance may still benefit from the analgesic effect yet not experience any withdrawal symptoms upon the stoppage of the substance [12]. Animal studies also suggest big difference between heroin and cocaine self-administration [13]. In general those animals self-administering heroine 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% [13].

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 antidepressant action

A reason scientific observation suggests, 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 [14,15]. This observation-the molecular changes associated with depression share a common thread- is probably an important insight for the potential benefits of opiates in depression. This is because opiates have dual influence of brain function with dampening influence on sub cortical and limbic regions and with activation of the prefrontal cortex function.

Dopamine – endorphin relationship

Endorphins and endorphin agonists enhance prefrontal cortex function, executive function mood, joy. Naloxone a morphine antagonist neutralizes dopamine specific joy [16]. Naltrexone a morphine antagonist seems to contribute to panic attacks and depression [17,18].

Because the prefrontal cortex is specifically wired to provide highly sophisticated intellectual and emotional functions even minute shifts in prefrontal cortex may cause executive dysfunction, anhedonia diminished initiative, and decreased metabolism in the orbital frontal and dorsolateral prefrontal cortex. All of these symptoms represent the core symptoms of depression.

Depletion of dopamine in a circumscribed area of association

cortex in rhesus monkeys produces an impairment in spatial delayed alternation performance nearly as severe as that caused by surgical ablation [19]. 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 mnnemonic, attentional and a 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 [19].

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 the antidepressant effects of opiates by modulating influence of dopamine.

Antidepressant effects of endorphin agonists: animal and clinical studies

Activation of the Delta opioid receptor produces robust antidepressant like effect in preclinical essays [20]. Beneficial effects of electroconvulsive treatment is associated with elevations of plasma beta endorphine level in depressed patients [21,22].

Cyclazocine a mixed opiate agonist antagonist was found to be effective in the treatment of 10 depressed patients [23].

Bodkin *et al.* reported 10 patients who had previously failed to respond to traditional treatments but had a positive response to buprenorphine [4]. In this study three patients dropped out of because of side effects. Four 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.

Nyhuis reported three patients who had failed electroconvulsive treatment but had a robust response to buprenorphine and oxycodone [5,6]. The study results were consistent with the observation that in some cases of treatment refractory depression opiates were more effective than ECT. Anecdotal reports can be of limited scientific power yet may offer 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 [24].

Common pathways of pain depression addiction psychosis

There is neuroimaging evidence of abnormal endogenous opioid neurotransmission in people with impulsiveness [25]. There is also evidence of dysregulation of endogenous endorphines in major depression and women [26]. There is also high comorbidity between addiction and depression [27] and also between pain and depression [27]. Furthermore, three major medications to treat addiction, methadone, buprenorphine and heroine intramuscular [28] are opiates.

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 suggest common pathways in the genesis of pain addiction and depression.

Endorphin function is involved in responses to diverse input such as exercise, pain, music and cocaine.

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 [14,15]. The chronic exposure to music, exercise, pain, and cocaine seem to have paradoxical results. Music and exercise seem to promote the prefrontal cortex function [16,29]. Noteworthy is the observation that naltrexone a morphine antagonist can block the effects induced by music [16] and opiates dampen pain [8]. The opposite is true for pain and cocaine. Neuroimaging evidence shows neurotoxicity and atrophy [30,31].

All of the above summarized findings are consistent with the mediating influence of endorphin agonists in the prefrontal cortex function. Hence opiates may be of benefit to mediate adverse influences on prefrontal cortex and normalize biological deficits.

Endorphin agonists -consistent with their dampening influence on dopamine in limbic and sub cortical brain regions -may have potential benefits for psychotic disorders yet scientific research of this potential therapeutic benefit has been limited partly because of concerns about addiction dependence and regulatory challenges. The published data has consistently supported the need for further investigation of opiates in psychotic disorders [32-36].

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 [37,38]. In contrast cognitive and brain atrophy have been associated with chronic pain [30,31]. 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 [1]. 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 an opiate. Of clinical significance is that, the onset of withdrawal does not always coincide with the onset of terminal effects. For instance, for opiates, 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.

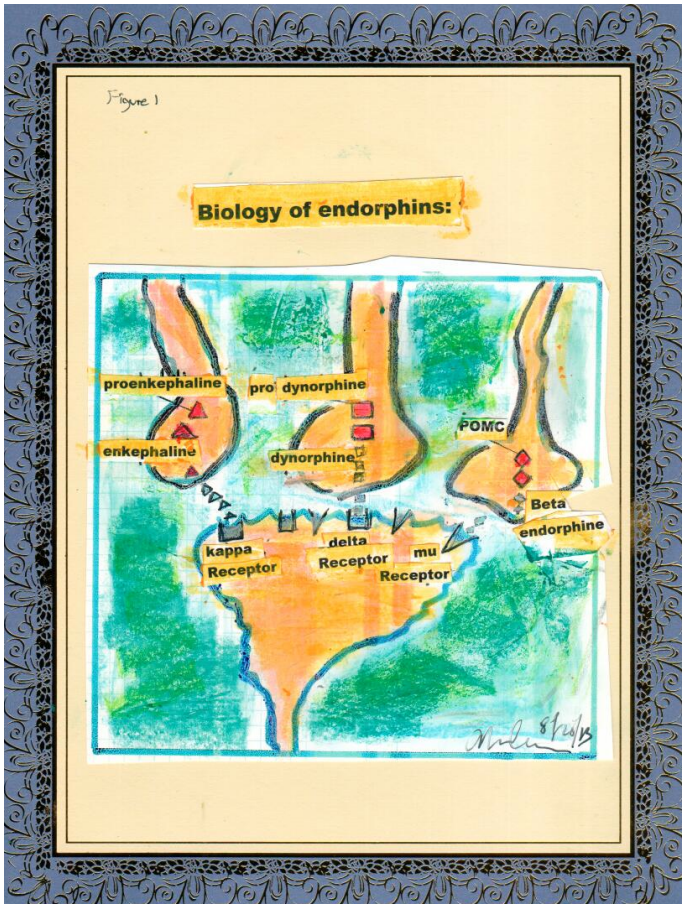

Figure 1. Biology of Endorphins.

From a clinical perspective, withdrawal associated symptoms are of crucial influence in addictive behavior. Animal studies suggest that addiction to opiates- unlike with cocaine, LSD, PCP or alcohol- is primarily driven by attempts to prevent withdrawal discomfort rather than to seek pleasure and reward.

Evidence of significantly diminished overuse potential of long-acting opiates

Clinical observations indicate that, the absence of an acute euphoric effect and the reduction of the unpleasant withdrawal associated symptoms are of crucial importance for the addictive potential of opiates. For instance heroine administered by intramuscular injection with a long-acting slow-release formula is an effective treatment for addiction [28].

It is also true that the overuse potential of many endorphin agonists (methadone, extended release opiate preparations with long elimination half-lives are significantly less than short acting opiates [38,39].

Also considerable evidence has accumulated to suggest the key mechanisms contributory to addictive potential: The crucial influence of brain dopamine firing rate associated with rate of intake and blood concentration of an addictive substance [40]. This means in general, slow-release endorphin agonists are void of euphoria reinforced addictive influence. This is consistent with the well-established safety and efficacy of long-term use of opiates or chronic pain.

The addictive property of an opiate is determined by its latency and elimination half-life [41]. Opiates with longer half-life elimination (methadone, im heroin and buprenorphine) have no all relatively very low addictive potential. Opiates with greater and faster euphoric effect have greater addictive potency [41]. Addictive potency may be calculated with an algebraic equation of A=E/T Max. T1/2 where A represents the addictive potency, E is euphoric potency, Tmax is the time to reach peak plasma concentration and T1/2 is the plasma elimination half-life [41].

Do we have an epidemic of overdose deaths from prescription pain medications?

During the past several years CDC has been warning the public about an epidemic of addiction to opiates and deaths from prescription pain medications [42].

CDC claims of a causal association between prescription pain medications and an epidemic of overdose deaths lack scientific validation primarily because no evidence has been offered to indicate that the association is causative. Also multiple reporting errors -such as not differentiating overdose deaths from suicides from accidental overdose deaths seem to distort and greatly exaggerate the number of accidental fatalities associated with opiates - make it impossible to reach scientifically valid conclusions.

From 2000 to 2014 total overdose deaths rose from 3 to 14.7 per 100.000 population. During the same time period deaths associated with opiate prescriptions rose from 1.4 to 5.6 per 100.000 population.

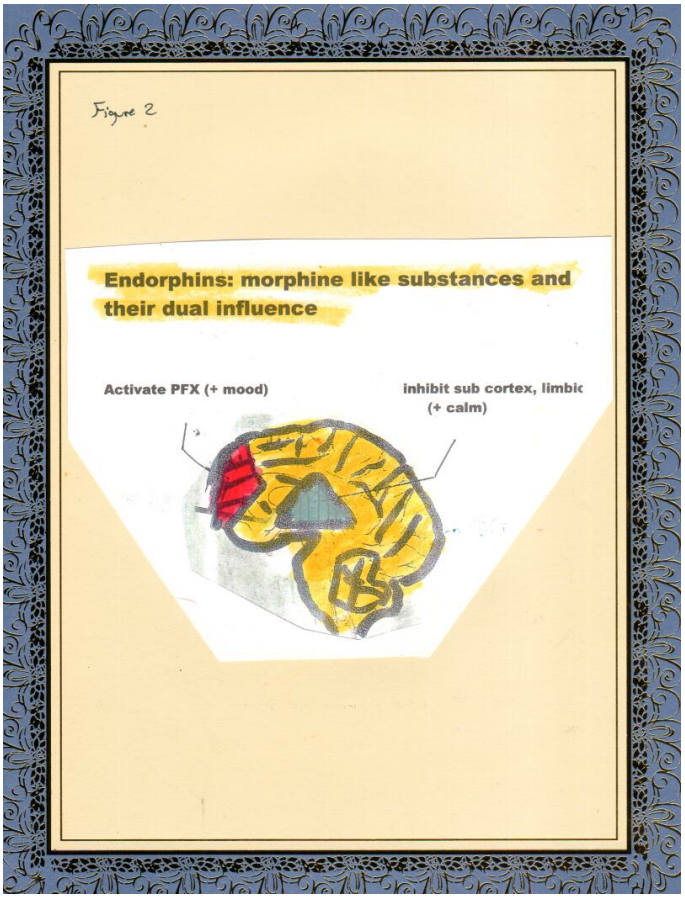

Figure 2. Endorphins: morphine like substances and their dual influence

From 2000 to 2014 the US annual suicide rates jumped from 10.1 to 12.9 per 100.000 (Tables 1 and 2).

The US suicide epidemic co-occurred as the annual suicide rates in Japan and Western Europe declined. The US unemployment figures were low and did not indicate any adverse impact on the suicide rates (Figure 4).

In 1984 the US Congress passed special legislation (title 21) to criminally prosecute psychiatrists and pain physicians and to confiscate physician wealth without due process for possibly overprescribing prescription pain medications [43]. Since then under title 21 some estimated 24,000 doctors lost their licenses and were rendered destitute [43,44]. A large number of patients endured disruption of stable treatment.

The increase in overdose deaths seems to be of multifactorial origin and may reflect recording errors, the increased numbers of people with chronic pain [45] and mental illness [46], the larger number of nonprescription pain medications etc. For instance the opiate related deaths include deaths from suicide and fatalities also associated with other medications and other possibly significant medical conditions. In California Dr. Frank Fisher was imprisoned with allegations of causing multiple deaths by methadone. Subsequently the charges were dismissed because of the scientific inconsistencies of the initial allegations [43].

Therefore, the dangers commonly attributed to the narcotic pain medications must not be assumed valid until scientific methods are used to ensure the collection, dissemination and evaluation of data related to opiate related fatalities (Tables 3 and 4).

Discussion

Our brains live and function with endorphins. Many of the processes that constitute mental function- *i.e.,* mood, anxiety, concentration, executive functions, empathy, creativity, sensitivity- are influenced by endorphins.

Table 1. US Deaths 2000 vs 2014 (Per 100.000 Population).

Overdose	3	14.7
Suicide	10.1	12.9
Prescription opiates	1.4	5.6
Heroin	0.4	3.4
PPM/OD %	↓↓↓16	38
Heroin /OD %	↑↑↑13	22

Observation: US has an epidemic of deaths by suicide and heroin overdose. The percentage of deaths from prescription pain medications in total overdose deaths declined from 46% to 38%.

CDC Vital Statistics
January 1, 2016 /64 (50); 1378 – 82
http://www. cdc.gov/mmwp Observation

Table 2. CDC false alarm due to human errors.

False alarm: Prescription pain medications are responsible for the epidemic of od deaths and heroin overdose deaths. 2014 CDC opiate deaths of 9 per 100.000 population include heroin reinforcing the public alarm about prescription pain medications.
Fact: Deaths from as a percentage of total overdose deaths have declined from 46% in 2000 to 38% in 2014.
False alarm: ***Pescription pain medications are responsible for an epidemic of heroin addiction and heroin od deaths.***
Fact: No causal link supports an association between prescription pain medications and the epidemics of heroin addiction and overdose deaths. Association is not causation. Heroin addiction and deaths have increased consistent with the rise of the rate of suicides – a reliable benchmark of mental health-possibly reflecting the adverse influences associated with the criminalization of psychiatry and pain medicine.

Table 3. CDC Alarm of an Epidemic of Prescription Pain Medication Overdose Deaths Lacks Scientific Integrity and Harms Millions of Americans with Chronic Pain Addiction and Psychiatric Problems.

No scientifically valid causal association between the epidemic of overdose deaths and prescription pain has been shown. Association is not causation.
The total number of people with addictive disorders and chronic pain who take prescribed opiates is estimated to be significant. 120 million Americans suffer from chronic pain, addiction and psychiatric disorders. 250 million prescriptions for opiates are prescribed annually .The suicide rates have steadily and consistently risen from 10.2 per hundred thousand population in 2000 to 12.9 in 2014 while the suicide rates in Japan and Western Europe have declined. This suggests not easily observable yet crucial psychiatric and psychosocial influences are significant contributors to the epidemic.
CDC vital statistics fail to distinguish deaths by accidental OD from suicides. Thus the actual numbers of overdose deaths from opiates may be exaggerated because deaths by suicides with opiates are included as opiate induced. This clinician bias may also lead to the possible underestimation of suicides.
The CDC vital statistics rely on death certificate diagnoses often unsubstantiated by clinical and laboratory data. This exaggerates the number of fatalities attributed to opiates for any death associated with history of opiate intake or even with not toxic and therapeutic blood levels may be registered as opiate related.

Table 4. Complex Evidence of the Therapeutic Benefits of Endorphin Agonists for Pain Addiction, Depression and Psychosis.

Since ancient times endorphins agonists have been used for depression and psychiatric disorders.
Postmortem examination of brains of suicide victims show endorphin depletion.
A group of patients with treatment refractory depression and unresponsive to electroconvulsive treatment had positive response to endorphinagonists.
The predominant influence of endorphin agonists are consistent with the clinical and neuroimaging evidence of classic antidepressant response: Dampening of sub cortical metabolism with enhancement of prefrontal cortex function.
Dampening (anti- dopaminergic) effect of endorphin agonists is consistent with the clinical evidence of antipsychotic properties of methadone.
Stress, pain, addiction and depression share common pathways with endorphins as the crucial mediating influence.
There is a very high rate of premature death and suicide among patients with addiction or pain after discontinuities of opiates.
Long- acting endorphin agonists (methadone, buprenorphine intramuscular heroin) have been the standard treatment for opiate addiction.

Furthermore historical, clinical and pathophysiological data show endorphin agonists have the crucial properties to treat depression addiction pain and possibly psychosis. 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 strongly support potential benefits of endorphin agonists to treat depression. Further research is necessary to investigate opiates as a consideration for treatment refractory depression.

Noteworthy is the evidence that in general endorphin agonists are neuroprotective and not neurotoxic like alcohol, cocaine, crack, LSD or PCP, a commonly held mistaken public perception. It seems not science but unscientific myths have limited potential research to adequately study possible benefits of endorphin agonists for treating conditions other than pain and addiction.

Many psychotropic substances classified as controlled substances – some legal and some illicit - cocaine, alcohol, tobacco, marijuana LSD and PCP are neurotoxic and may accelerate premature brain aging and death.

The unique therapeutic benefits of endorphin agonists have been shadowed by unscientific myths placing them in the same dirty bucket with many other controlled substances with neurotoxic properties.

The evidence does not support a causal link between the increasing overdose death rates and prescription pain medications. The observed increase in overdose deaths seems to be of multifactorial origin and may reflect recording errors, the increased numbers of people with chronic pain and mental illness, the larger number of nonprescription pain medications etc.

Conclusions

The benefits of opiates have been recognized since antiquity and well documented in modern history. The concerns about harm from addiction seem to be related to simplistic and erroneous misperceptions that all addictive substances are neurotoxic.

There is no aspect of human behavior that is outside of the domain of endorphins and further research to study opiates for diverse psychiatric disorders seems essential.

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