

# Opiates May Have Neuroprotective Properties against Neurodegeneration and Premature Death

## Abstract

Endorphins and endorphin agonists play a crucial role in the neuromodulation of mood, anxiety, pain and addiction. Review of clinical studies seem to elucidate possible protective role of opiates against neurodegeneration and premature death. The historical, biological, experimental, clinical and neuroimaging data strongly support the potential properties of opiates as neuro protectors.

## Review Article

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## Introduction

In general people with dual diagnosis-psychiatric and substance use disorders may represent a high risk of premature death [1]. There have been several recent publications consistent with premature deaths associated with discontinuation of opiates independent of withdrawal induced adverse events [2-4]. There is also compelling neuro imaging evidence of brain atrophy associated with chronic pain and depression [5-6]. 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 in psychiatric disorders [7]. This study reviews potential neuro protective properties of opiates against neurodegeneration and premature death.

The major areas of review are

- History of treatment with opiates
- Neurobiology
- Antidepressant effects of opiates
- Clinical studies
- Neuro imaging

## Methods

We searched Medline database from 1995 to February 2015 using the combined search terms morphine, morphine like substances, endorphins, endorphin agonists, methadone, buprenorphine, addiction depression premature death.

## History

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. Paracelsus (1493-1541) a Swiss German alchemist observed that opium alkaloids are far more soluble in alcohol than water which led to tincture laudanum allowing for easy medicinal delivery. Thomas Sydenham (1624-1689) recommended opiates against hysteria and mania. Then, in general the Asian century witnessed opium is one of the more popular medications used in psychiatry.

Of significance was the role of the Engelken family in psychiatry in Germany between 1750 and 1910 [8]. They established the foundation for a new systematic pharmacotherapy of severe depressions and other psychiatric disorders. Their approach established opium preparations is the most important method of psychiatric treatment for more than hundred years. After the Second World War the rise of newly developed antidepressants replaced the classical cure although even the introduction of electroconvulsive treatment and insulin shock treatment did not replace opiates as the supreme dominant intervention to treat severe depressions [8].

## Neurobiology

Neurobiology suggests brain function is region specific [9]. In general opiates and their receptors are central nervous inhibitors in sub cortex and limbic regions and act as activators of dopamine in prefrontal cortex consistent with their role in attainment of pleasure, pain control and rewarding addictive behavior [9]. Opiate receptor subtypes include  $\mu$ ,  $\delta$  and  $\kappa$ . Brain produces morphine like substances called endorphins enkephalins and dynorphines [9]. Acute effects of opiates include analgesia and euphoria. Analgesia occurs by acting as agonists at the 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 [9].

Animal studies suggest that despite morphine's significant reinforcing properties the increase in self administration is not infinite and correspond to a specific pattern. The animal self administers morphine just the amount to prevent discomfort associated with withdrawal symptoms [10].

## Antidepressant properties of opiates

The observation that the molecular changes associated with depression and remission share a common thread-sub cortical and limbic inhibition and in enhancement of dopaminergic activation of prefrontal cortex-is probably an important insight for the therapeutic benefits of opiates [11]. A recent review

has shown evidence of antidepressant efficacy of opiates [12]. Of significance is a small prospective study consistent with the efficacy of opiates in treatment refractory depressions unresponsive to electroconvulsive treatment [13]. Furthermore it has been shown that opiates have been therapeutic efficacy in treating pain depression and addiction consistent with the central role of opiates in common pathways of diverse brain disorders.

### **Neuroimaging and postmortem studies in chronic pain and depression**

Neuroimaging Studies have consistently shown a statistically significant correlation between chronic pain and depression with brain atrophy in specific brain regions [5,6]. A study by Iseroff et al. [7] demonstrated that brains of suicide victims were depleted of endorphins [7].

### **Clinical studies of premature deaths associated with discontinuation of opiates**

Several studies of diverse populations from different geographical areas and of diagnoses have shared a common observation: statistically significant rise in premature deaths following discontinuation of opiates unrelated to acute withdrawal effects [2-4]. Kakko et al. [2] and colleagues reported 20% death rate after discontinuation in one year follow-up versus zero death rate for people taking buprenorphine [2]. Two separate studies by Salerian also showed significantly high one year post opiate discontinuation rates among people treated with opiates [3,4].

### **Results**

Throughout history opiates have been utilized as therapeutic agents to treat diverse psychiatric conditions. Neurobiological, clinical and imaging studies are consistent with the protective properties of endorphins in combating neurodegeneration. Three studies show a statistically positive correlation between discontinuation of opiates and premature death.

### **Discussion**

The review of published literature seems to support the therapeutic benefits of opiates in diverse psychiatric conditions. Furthermore this review indicates possible Neuroprotective properties of opiates. In general chronic pain and depression-with compromised endorphin function-seem to precede neurodegeneration with brain atrophy seem to. Further support for a possible link between endorphin depletion and death and neurodegeneration has been made by Iseroff et al. [7] and colleagues thanks to their groundbreaking study of brains of suicide victims.

A major and obvious deficit of this review is the limited numbers of studies in support of potential neuro protective role of opiates. However it is also true that the largest epidemiological study of substance abuse in mood and anxiety disorders by Grant and colleagues had an ominous warning-observation about greater risk of premature death of patients not receiving opiates.

The studies by Kakko et al. [2] and Salerian [11,12] were of significance because, the observations of premature death were secondary and not the primary intent of these three investigations.

Noteworthy was to observe a significantly increased risk of death among non-geriatric patients without any known terminal illness. Collectively all of the above findings seem to support the conclusion that for yet unexplained reasons endorphin agonists may for some patients have a protective property against neurodegeneration and premature death.

### **Conclusion**

This review seems to support the observation that endorphin agonists may have Neuroprotective properties. Furthermore the findings are consistent to support a possible Neuroprotective role of opiates in reducing risk of premature death. The potential benefits of these findings may justify the need to investigate the validity of our observations by prospective double-blind studies.

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