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Psychotherapeutic Benefits of Opioid Agonist Therapy

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Psychotherapeutic Benefits of Opioid Agonist Therapy

Peter L. Tenore, MD, FASAM

ABSTRACT. Opioids have been used for centuries to treat a variety of psychiatric conditions with much success. The so-called "opium cure" lost popularity in the early 1950s with the development of non-addictive tricyclic antidepressants and monoamine oxidase inhibitors. Nonetheless, recent literature supports the potent role of methadone, buprenorphine, tramadol, morphine, and other opioids as effective, durable, and rapid therapeutic agents for anxiety and depression. This article reviews the medical literature on the treatment of psychiatric disorders with opioids (notably, methadone and buprenorphine) in both the non-opioid-dependent population and in the opioid-dependent methadone maintenance population. The most recent neurotransmitter theories on the origin of depression and anxiety will be reviewed, including current information on the role of serotonin, N-Methyl d-Aspartate, glutamate, cortisol, catecholamine, and dopamine in psychiatric disorders. The observation that methadone maintenance patients with co-existing psychiatric morbidity (so called dual diagnosis patients) require substantially higher methadone dosages by between 20% and 50% will be explored and qualified. The role of methadone and other opioids as beneficial psychiatric medications that are independent of their drug abuse mitigating properties will be discussed. The mechanisms by which methadone and other opioids can favorably modulate the neurotransmitter systems controlling mood will also be discussed.

KEYWORDS. Methadone, psychiatric, co-morbidity, depression, anxiety, opioid.

INTRODUCTION

For centuries, opioids have been utilized effectively to treat a wide range of human disorders, including pain, cough, and diarrhea. Contemporary medicine still manages these conditions with various opioid preparations. A forgotten subject, however, is the use of opioids to treat psychiatric conditions such as depression and anxiety disorders. This article examines the evidence to support opioids' effectiveness in these instances. The neurotransmitter systems important to mood, including N-Methyl d-Aspartate (NMDA), glutamate, catecholamines, serotonin, and dopamine, are reviewed and the beneficial mood effect of methadone, buprenorphine, and other opioids is examined.The earliest record of opium use occurred in lower Mesopotamia in 3400 BC and documented poppy cultivation and the use of opioid-laden fluid, which was dried to a paste, and termed opium to treat a variety of conditions by the Sumerians. The antianxiety and antidepressant effect of opium was deemed so effective that the poppy was called "Hul Gil," or the "joy plant."[1] Hippocrates (460–377 BC), the historic father of medicine, and his successor Galen (AD 129–200) both prescribed opium for the treatment of numerous ailments, including depressin and anxiety disorders.[2]

British author Thomasy de Quincey (1785–1859) chronicled his 17-year addiction to opium

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in *Confessions of an English Opium Eater*.[3] De Quincey took opium primarily to relieve severe depressive symptoms, writing that opium was "the secret of happiness, about which philosophers had disputed for so many ages." He marveled at the psychiatric potency of such small dosages of opium, noting that "happiness might now be bought for a penny, and carried in the waistcoat pocket."[3]

With medications that are as rapidly effective as opioids in treating so many disorders and with unregulated over-the-counter availability of these agents, opioids were over-utilized and over-prescribed, resulting in thousands of people becoming unnecessarily addicted.[4] Restrictive legislation, including the Harrison Narcotics Tax Act,[5] dramatically limited the prescription of opioids. With the development of non-opioid medications to treat depression and anxiety in the early 1950s—the monoamine oxidase (MAO) inhibitors and tricyclic anti-depressants (TCDs)—opioids and their legislative restrictions became obsolete as psychiatric medications due to their addictive potential.[6]

STUDIES OF OPIOIDS AS ANTIDEPRESSANT MEDICATIONS

The antidepressive and anxyolytic effects of opioids have been studied extensively. Several of these trials are summarized below.

The Opium Cure

The opium cure was widely used during the latter 19th century up until the mid 20th century and was an effective treatment for refractory depression.[7] The opium cure utilized tincture of opium given daily in escalating dosages (which plateaued and then was weaned), with the average treatment lasting for 2 months. In virtually all reported cases, the "depressive symptoms disappear."[6] The efficacy of the opium cure was documented in several anecdotal reports and psychiatric texts of the time[7] and its use continued until the development of more modern non-opioid antidepressants in the 1950s.[6]

Endorphins: The Opium Cure Mechanism

Endorphins are a series of brain opioid-peptides, which play several critical roles in human physiology, including pain modulation, regulation of cortisol secretion, temperature control, stimulation of pleasure sensation and frank euphoria, mood stabilization, and generation of normal hedonic tone. Endorphins are active in the brain's pleasure-reward center and have been termed the "brain's own morphine."[8,9]

PLEASURE-REWARD CENTER

The meso-limbic dopaminergic neurons of the ventral tegmental area and their connections to rostral limbic nuclei and other structures are referred to as the pleasure-reward center, or the limbic system. This center is responsible for maintaining hedonic tone and generating normal sensations of pleasure, reward, joy, and euphoria, which are antidepressant effects. To do this, pituitary-released endorphins circulate and bind to endorphin mu-opiate receptors on the dopaminergic neurons of the ventral tegmental area, which then synthesize and release dopamine. Dopamine attaches to dopamine receptors in various areas of the pleasure-reward center (including the nucleus accumbens, prefrontal cortex, amygdala, caudate, and anterior cingulate), generating a sense of hedonic tone and contentment (i.e., antidepressant effects).[8,9] Dopamine levels fall if endorphin effects are muted or blocked or if endorphin levels are absolutely or relatively low, leading to anhedonia and a lack of pleasure or reward sensations (i.e., depressive symptoms).

In depression, a relative endorphin deficiency has been demonstrated, characterized by an increased number of endorphin receptors (up to a 700% increase vs. controls) on dopamine neurons, yet no matching increase in endorphin levels.[10,11] This mismatch results in lower endorphin stimulation and a low dopamine state, causing a lack of pleasure and the loss of hedonic tone, cardinal symptoms of depression. Further studies are needed to establish why endorphin receptors are increased in depression and

why endorphin levels do not increase to meet the expanded receptor pool; however, it is clear that the endorphin-dopamine system plays a critical role in generating and mitigating depression. In the Opium Cure, opium acts as endorphin to saturate a higher number of endorphin receptors on dopamine neurons, releasing dopamine and restoring hedonic tone and mitigating depression.

ENDORPHIN TREATMENT OF DEPRESSION

To evaluate the effect of endorphines on mood, intravenous infusions of beta-endorphin were used to treat depression in at least 5 clinical studies reported between 1977 to 1981. When examining these trials as a group, it was found that 20 of 24 patients experienced significant improvement in depressive symptoms in as little as 20 minutes following beta-endorphin infusions. The majority of test subjects experienced complete resolution of depressive symptoms within 4 hours. The rapidity of response contrasts current antidepressant therapy with serotonin (e.g., fluoxetine) and catecholamine (e.g., amitryptyline) modulators, which typically require 2 to 6 weeks for maximal effect.[12] Intravenous opioids (endorphins) demonstrate significant and rapid antidepressive effects, indicating that brain endorphins play an essential role in mitigating depression.[13] It is likely that infused endorphins stimulate a higher percentage of the expanded endorphin receptor pool resulting in enhanced dopamine output.

OPIOIDS AS ANTIDEPRESSANTS

Buprenorphine

From 1982 to 2001, at least five studies of buprenorphine in treatment-resistant depressed patients who were not dependent on opioids have been published. A total of 57 patients received buprenorphine in these trials. Each study demonstrated a positive and potent antidepressant effect of buprenorphine in a treatment-resistant population. Opioid administration significantly reduced depression (again, likely through increased stimulation of the endorphin system).[14] Because opioid treatment of severely depressed patients with buprenorphine resulted in a rapid and significant improvement with symptom resolution in most cases,[14–18] it seems clear that the endorphin-dopamine system is central to mood regulation and that administered opioids can be potent antidepressant medications.

From 1990 to 2005, there have been at least 6 studies of buprenorphine treatment of depression in the opioid-dependent population of methadone maintenance clinics. A total of 275 depressed patients received buprenorphine in these trials, with positive responses shown in 50% to 86% of patients, which again supports buprenorphine as a potent antidepressant. Seventy-five percent of responders showed a 91% drop in depression scores during the first week, demonstrating far more rapid improvement compared to conventional therapy. Depression was not related to opioid withdrawal symptoms. There was no difference in drug use in subjects versus controls. Authors concluded that buprenorphine exhibits an effective and rapid antidepressant effect, independent of drug use or opioid withdrawal symptoms.[19,20]

Methadone

Dean studied moderate to severely depressed patients entering methadone treatment. Thirty patients were randomized to receive methadone and 24 to receive buprenorphine. Depression significantly improved to the level of control in both groups within several weeks. Few were co-treated with conventional antidepressants, so favorable antidepressant effects were attributed to methadone and buprenorphine. Of note, the antidepressant effects of methadone and buprenorphine were not related to subjects' decrease in drug use, which remained unchanged. Thus, methadone and buprenorphine were shown to be significant and comparably effective antidepressants independent of drug use.[21]

In another trial, depressed patients were randomized to receive either methadone and a placebo or methadone and fluoxetine. Both

groups showed a significant positive response to treatment with equal reduction in depressive symptoms. Improvement in depression and psychosocial functioning was not related to a reduction in drug use. Methadone was a highly effective antidepressant medication, but adding fluoxetine confered no additional benefit, indicative of a potent antidepressant effect demonstrated by methadone in and of itself.[22]

In a study of mood and methadone, methadone blood levels were taken prior to the daily methadone dosage and then at frequent intervals for the 24-hour dosing interval. Mood scores were tightly correlated to blood methadone levels, with mood improving as methadone levels rose and mood deteriorating as methadone levels fell. The scores for all mood indicators—depression, anger, tension, confusion, fatigue, vigor, and Total Mood Disorder—were all best at the peak methadone blood levels and worst at the lowest levels.

Methadone had its most dramatic effect on depression. Methadone quickly and effectively alleviated depression and other mood disturbances, with most patients achieving complete resolution of depressive symptoms within 3 hours. In addition, mood alterations were responsive to relatively small changes in methadone blood levels, indicating that methadone exerts potent therapeutic effects on mood.[23]

PRESCRIBED OPIOIDS AUGMENT ENDORPHIN'S ANTIDEPRESSANT EFFECT

Though the brain is not synthesizing additional amounts of endorphin to meet the increased, unoccupied-endorphin-receptor load in depressed brains, exogenously administered opioids not subject to the synthesis limitations of endorphin can be given in sufficiently high dosages over appropriate periods of time to eventually occupy and stimulate the up-regulated, open receptors. Once a sufficiently high percentage of endorphin receptors are occupied by prescribed opioids, dopamine neurons will be stimulated to manufacture and release enough dopamine to restore hedonic tone and ameliorate depressive symptoms. In the treatment of depression, methadone, buprenorphine, and other opioids can be viewed as endorphin supplementation therapy, binding to and stimulating endorphin receptors on dopaminergic neurons and increasing dopamine. Endorphin-mediated dopamine release is essential to euthymia and can be augmented and maintained with exogenously administered opioids, such as methadone and buprenorphine, acting as endorphins.[13,14,19]

Taken together, these studies indicate that depression due to relative endorphin deficiency in brains with up-regulated numbers of endorphin receptors unmatched by up-regulated endorphin levels can be successfully treated by saturating open endorphin receptors with additional prescribed opioids. Depression can be relieved by administering the endorphin itself[13] or by administering prescription opioids (buprenorphine or methadone) that bind to the endorphin receptor (i.e., endorphin augmentation therapy).[22–24] In drug-using patients, improvement in depression and social functioning with methadone and buprenorphine is not related to decreases in drug use. The relief of depressive symptoms with methadone and buprenorphine in opioid-dependent and non-dependent patients is rapid and successful, arguing for their effectiveness as antidepressants in their own right. Augmentation of low relative endorphin levels with increased stimulation of dopamine seems to be the unifying mechanism. As will be discussed later in this review, favorable alterations in several mood-improving neurotransmitters are also affected by methadone and other opioids.

NON-ENDORPHIN PSYCHOTHERAPEUTIC MECHANISMS OF OPIOIDS

In addition to methadone and buprenorphine's saturation of endorphin receptors to increase dopamine and thus alleviate depression, these opioids have also been shown to favorably alter several other brain neurotransmitters important to mood regulation. The serotonin, catecholamine, dopamine, corticosteroid, glutamate, and NMDA systems are all essential

to mood regulation. Methadone, buprenorphine, and other opioids have a pronounced and favorable effect on all of these systems.

Depressed and anxious patients benefit from the following pharmacologic agents and mechanisms: (a) serotonin re-uptake inhibitors increase serotonin; (b) monoamine oxidase inhibitors increase serotonin, dopamine, and catecholamines; (c) tricyclic antidepressants increase catecholamines; (d) opioids decrease circulating cortisol; (e) opioids, acting as endorphins, increase dopamine output to limbic system structures; (f) NMDA receptor antagonists improve mood; and (g) glutamate reduction/antagonism improves mood. Methadone, buprenorphine, and other opioid agonists have been shown to be favorable and potent modulators of each of these mood enhancing and mood stabilizing mechanisms, discussed in the following sections.

Epinephrine/Norepinephrine

Tricyclic antidepressants (TCDs), including imipramine, amitryptyline, and nortryptyline, alleviate depression by blocking neuronal re-uptake of norepinephrine and epinephrine and, to a lesser extent, dopamine and serotonin. This decreased re-uptake makes these neurotransmitters available in extracellular fluid to act on their respective receptors to improve mood and relieve depression. Methadone has been shown to relieve depression by acting as a TCD, blocking re-uptake of catecholamines. Methadone displaced imipramine from norepinephrine re-uptake sites, indicating that mathadone would blockade re-uptake of norepinephrine as imipramine does. This blockade results in increased extra-cellular norepinephrine which improves mood. Methadone was shown to blind tightly to the imipramine receptor, suggesting a significant anti-depressant action similar to imipramine. The adjusted animal blood methadone levels were consistent with methadone blood levels achievable in patients receiving methadone for maintenance. With methadone functioning as a TCD, an "antidepressant action of methadone is suggested."[25]

Serotonin

Decreased cerebral serotonin effect plays an essential role in depression.[26,27] Decreased serotonin effect is due to two factors: (a) positron emission tomography scanning in depressed brains has demonstrated a mean decrease of 30% in the number of serotonin receptors;[26,28] and (b) depressed brains have been shown to have a 20% to 30% decrease in serotonin synthesis rates.[27] Treatment with selective serotonin re-uptake inhibitors (SSRIs), MAO inhibitors, TCDs, and NMDA-glutamate antagonists will increase brain serotonin and expose the limited number of receptors to higher levels of serotonin and stimulate maximal functioning, which moderates depression.[29]

METHADONE: A SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR

Methadone possesses SSRI capabilities and has been shown to raise brain serotonin levels. In a rabbit model, methadone inhibited serotonin re-uptake into brain neurons. Methadone was found to bind securely to the serotonin transporter, preventing re-uptake and increasing extracellular serotonin levels. Morphine had a similar effect but required higher dosages. Methadone exhibited "marked effects on serotonin re-uptake" and this process may be related to a methadone anti-depressant effect.[30]

To underscore methadone's ability to raise serotonin, it should be noted that if methadone is administered with other drugs that also elevate serotonin levels, excessively high (even toxic) levels of serotonin can result. Cases of methadone and tramadol causing serotonin excess when added to MAO inhibitors that resulted in serotonin-syndrome with fatality have been reported. This further demonstrates the ability of methadone to significantly raise brain serotonin.[31] The synthetic opioids—meperidine, tramadol, dextromethorphan, propoxyphene, and methadone—have all been shown to be serotonin re-uptake inhibitors and, to underscore their serotonin-elevating potency, have all been involved in serotonin toxicity reactions with MOA inhibitors.[31]

Methadone and tramadol are moderately potent SSRIs and, on this basis, have significant serotonin-raising ability. Methadone raises serotonin and, therefore, is expected to relieve depression and anxiety. In a drug–drug interaction, methadone can actually raise serotonin levels excessively high to induce a serotonin toxicity syndrome, underscoring methadone's function as an MAO inhibitor.[31]With the ability to augment serotonin levels, it is not surprising that methadone can be utilized as an effective antidepressant medication.

SSRI-Methadone Drug Interaction

An additional contributing factor to stabilization of dually diagnosed patients may be the slightly increased methadone exposure caused by the SSRI–methadone drug interaction, which increases methadone blood levels in co-treated patients. A majority of anxious or depressed dually diagnosed patients in methadone maintenance clinics are treated with SSRIs.[32] Due to liver enzyme inhibition by SSRIs—especially fluoxetine, paroxetine, and sertraline—a mild-to-moderate (10% to 26%) increase in blood methadone levels is expected.[33–35] Barring excessive serotonin (more of a fluvox issue) blood methadone levels increased by SSRI in dually diagnosed patients can further enhance methadone exposure and increase beneficial psychiatric effects. More recent SSRIs, including citalopram and escitalopram, have little to no effect on methadone bleed levels.[36]

MAO

MAO is a brain enzyme that degrades the mood enhancing mono-aminergic neurotransmitters serotonin, epinephrine, norepinephrine, and dopamine. Low levels of these monoamine neurotransmitters, especially serotonin, engender depression.[45,46] In 1952, MAO inhibitors were found to be significant antidepressant medications. Althogh effective as antidepressants, the increased side effect profile and availability of well-tolerated SSRIs has markedly limited widespread use of MAO inhibitors.[12]

As discussed above, depressed brains have been shown to have 20% to 30% lower levels of serotonin than non-depressed control brains.[27] To explain this serotonin depletion, Meyer et al.[37] postulated that depressed brains may have increased MAO levels, degrading serotonin and, thus, lowering serotonin levels. Using positron emission tomography scanning in untreated patients with major depression, the authors found enzyme levels to be a mean of 30% higher compared to the control patients. This marked MAO level elevation was found throughout the brain and is a compelling explanation for decreased serotonin in depression.[37] If MAO level elevation engenders depression, MAO inhibitors become a logical management strategy. Anti-depressant treatment with MAO inhibitors (e.g., phenylzine) is designed to hinder MAO function and decrease serotonin degradation. The resulting increase in serotonin levels can mitigate depressive symptoms.[12]

As an antidepressant, methadone has also been shown to be a potent MAO inhibitor. Methadone produced a pronounced brain MAO inhibition of 20% to 60% in the hippocampus, caudate, hypothalamus, and cerebral cortex of rodents. Because these areas are important in mood experience and regulation, increasing available serotonin, catecholamine, and dopamine levels by inhibiting MAO levels with methadone should contribute to relieving depressive symptoms.[38]

Other opium alkaloids, including papaverine and ethaverine, have also proven to inhibit brain MAO by 40% to 60%.[39] Inhibiting MAO and raising monoamine neurotransmitter levels have significant antidepressant effects. Methadone and other opium alkaloids have been shown to be potent MAO inhibitors. As such, methadone is expected to exert an antidepressive action based on its ability to inhibit MAO and elevate brain catecholamine and serotonin levels.

Cortisol

A cardinal biochemical finding in depression and anxiety is an elevation in serum cortisol.[40] Decreasing excessive cortisol can have a beneficial effect on mood, and endorpins play a key role in decreasing cortisol secretion. In a study of depressed patients, small dosages of intravenous methadone was

shown to induce a rapid and lasting fall in serum cortisol with depressive symptoms correspondingly mitigated. The hypothalamic-pituitary axis' role in depression—manifested by elevated cortisol—can be rapidly corrected with intravenous methadone for prolonged periods.[41]

In a study of anxiety patients, 10 mg of methadone administered intramuscular rapidly decreased blood cortisol and mitigated manic symptoms.[42] Elevated cortisol levels are contributory to depression and anxiety disorders, which improve when cortisol levels are decreased. In small dosages (5 to 10 mg), methadone decreases cortisol levels rapidly and significantly for a prolonged period. Methadone's ability to decrease cortisol likely contributes to its antidepressant and antianxiety effects.

NMDA

NMDA receptors are located throughout the brain and are stimulated by the brain's major excitatory neurotransmitter—glutamate. NMDA receptors are responsible for the modulation of learning and memory, excitation of neuronal impulses, oxidative tissue damage, and pain regulation. The NMDA system also plays a major role in mood regulation, specifically modulating depression and anxiety.[43,44] When activated by glutamate, NMDA receptors located on serotonin neurons exact distinct "anti-serotonin" effects and inhibite serotonin synthesis and release and increase serotonin degradation. All of these factors contribute to depression and anxiety. Methadone and buprenorphine are NMDA antagonists[45–47] and can be expected to counteract the "anti-serotonin" effects of the NMDA–glutmate system and benefit these disorders on this basis.

Because the NMDA system is a significant cause of depression, antagonists of the NMDA receptors are expected to exert antidepressant effects. In one study, single low dosages of intravenous ketamine (a powerful NMDA antagonist) were shown to dramatically improve depression in 60 minutes and continue maximal improvement for several days. Beneficial effects of NMDA antagonism were long-lasting, taking 1 to 2 weeks to diminish to baseline. Ketamine effected a potent, rapid, and sustained decrease in depressive symptoms.[48]

In another study, 71% of depressed patients demonstrated a positive response to ketamine and 29% achieved complete remission in 110 minutes and the beneficial effects lasted a week. Because NMDA antagonists relieve refractory depression rapidly and in a durable manner, future development of NMDA antagonists for the treatment of depression should be an important initiative.[46]

METHADONE: ANTIDEPRESSANT NMDA ANTAGONIST

Methadone has caused a marked decrease in NMDA receptor activity and is 8 to 16 times more potent than morphine.[45,47] Methadone demonstrates potent, non-competitive NMDA antagonism[49,50] that is achievable, with methadone blood levels easily attained in the methadone maintenance population.[45] As a potent NMDA receptor antagonist like ketamine, methadone is capable of exerting significant antidepressant effects. Psychiatric patients have repeatedly required higher dosages of methadone for stabilization (Table 1) and it is likely that they are experiencing, in part, benefits from the NMDA antagonism effect of methadone and are maximizing this effect in requiring higher

TABLE 1. Selected Studies Demonstrating the Need for Higher Methadone Doses in Dually Diagnosed Patients

Author	Year	DD† dosage – SD†† dosage	n
Treece[82]	1980	87.4 mg – 35.7 mg	31
Maremanni[52]	1993	0.60 mg – 30 mg	17
Pani[53]	1997	34 mg – 31 mg	46
Tenore[79]	2000	110 mg – 91 mg	160
Maremanni[72]	2000	154 mg – 99 mg	90
Bleich[83]	2002	145 mg – 90 mg	107
Pani[51]	2003	70 mg – 40 mg	78
Matteo[80]	2005	PB mg – PB mg + 45 mg	114
Trafton[78]	2006	82 mg – 69 mg	222
Peles[68]	2006	>120 mg – <120 mg	90
Tenore[84]	2007	149 mg – 99 mg	276

†DD = Dual Diagnosis patients.
††SD = Single Diagnosis patients.

dosages of methadone than non-psychiatric patients for stabilization.[32,51–53]

As an antidepressant, buprenorphine has also proven to be an NMDA antagonist roughly equivalent in potency to morphine.[54] Methadone and buprenorphine are expected to, and have been shown to, exert antidepressant effects consistent with an NMDA-blocking mechanism.

ANXIETY DISORDERS

NMDA

The NMDA–glutamate system is a major contributor to the generation of anxiety.[55] Animal studies have demonstrated the potent antianxiety effects of NMDA receptor antagonists andagents that decrease glutamate. Tatarczynska et al.[55] examined a rodent model of anxiety with a powerful NMDA receptor antagonist and noted significant decreases in anxiety and depression reflective behaviors in all tested individuals. The authors concluded that NMDA receptor antagonists play a major role in ameliorating anxious and depressive behavior and that NMDA antagonists should, logically, be developed as antianxiety medications in the future.[55]

Glutamate

As discussed previously, the NMDA receptor system is a major cause of depression and is a major factor in generating anxiety, both due to glutamate binding to NMDA receptors and to decreasing brain serotonin levels.[43,44] Lamotrignine (Lamictal) decreases brain glutamate production, which decreases neuronal excitability, and is approved for the management of bipolar disorder and seizure disorders.[12] In an animal model, lamotrignine demonstrated a potent anxyolytic effect by decreasing the subjects' brain glutamate. The antianxiety effect was equivalent to that of benzodiazepines.[56] Klodzinska et al. showed such a powerful antianxiety effect of glutamate antagonism that the authors called for accelerating the clinical development of glutamate antagonists as potential antianxiety agents for use in humans.[57]

Glutamate (and it's cofactor, glycine) exerts multiple "anti-serotonin" effects that include increased serotonin metabolism (degradation), decreased serotonin synthesis, and decreased serotonin release, all of which are mediated through glutamate binding to and activating NMDA receptors on serotonin cells. All anti-serotonin effects of glutamate are reversed by the NMDA receptor antagonists, which can be viewed as serotonin "enhancers."[58] Methadone and buprenorphine, as potent NMDA receptor antagonists, can also be classified as serotonin enhancers.

Glutamate excess increases neuronal excitation globally and contributes to neuronal oxidative stress and nerve injury. These deleterious effects contribute to seizure activity, anxiety disorders, obsessive compulsive disorder, and pain disorders. Lamotrignine decreases central nervous system glutamate production and is effective in treating these conditions. The importance of the NMDA–glutamate system in anxiety should not be underestimated and additional glutamate antagonists (e.g., ketamine and methadone) or glutamate reducing agents (e.g., lamotrignine) should be developed for future clinical use in anxiety disorders.[59]

OBSESSIVE COMPULSIVE DISORDER

Glutamate Excess

Rosenberg et al. measured glutamate levels in obsessive compulsive disorder patients and found caudate glutamate levels to be much higher than those in the control subjects. With paroxetine SSRI treatment, glutamate concentrations returned to normal in weeks with a dramatic symptom improvement seen. Increasing serotonin levels with paroxetine inhibits glutamate synthesis and release, normalizing anxious symptoms.[60]

Using direct brain serotonin measuring techniques and injecting a glutamate-blocker directly into rodent amygdala, animal models have confirmed that increasing serotonin with a glutamate-blockade will rapidly resolve anxiety symptoms.[61,62] Decreasing glutamate via enhanced serotonin is beneficial to anxiety disorders. Methadone has proven to increase serotonin and can be expected to decrease glutamate on that basis.

OPIOIDS AS NMDA ANTAGONISTS IN ANXIETY DISORDERS

Methadone, buprenorphine, morphine, and tramadol have been shown to be significant NMDA–glutamate antagonists. As NMDA antagonists, it is expected that methadone and tramadol have serotonin-enhancing, antianxiety effects. In one report, a 27-year-old woman with a 10-year history of poorly controlled obsessive compulsive disorder noticed that her anxiety symptoms ceased entirely for several hours after taking a single dosage of oxycodone. Noting this, the authors prescribed 50 to 100 mg of tramadol, an opioid-receptor agonist, orally as needed up four times a day. The patient's symptoms resolved rapidly with each dosage. At 6 weeks, fluoxetine took its maximal effect and the patient no longer needed tramadol for symptom control, which was complete. The authors concluded that opioids decrease glutamate and block NMDA receptors, allowing for increased serotonin more rapidly than SSRIs. As such, opioids can be utilized in obsessive compulsive disorder for early symptom control until SSRIs can manifest their full clinical effects.[63]

In another trial, refractory anxiety patients treated with tramadol responded rapidly with symptoms decreasing a mean of 26%. Half of the patients responded within 1 week, which is remarkable in a disorder that usually requires 4 to 6 weeks of SSRI treatment to respond. Tramadol decreasing glutamate (mu-mediated glutamate inhibition as well as serotonin-enhancing via MAO inhibition) is the likely explanation for the findings.[64]

Given the high concentration of opiate receptors in the caudate, Koran et al. studied morphine for management of anxiety. Thirty percent of subjects treated with a single dosage of morphine responded, 17% responded to lorazepam, and none responded to a placebo. Morphine alleviated anxiety symptoms rapidly (within 24 hours) and this effect lasted for 2 to 5 days. Morphine directly stimulates serotonin neurons in the dorsal raphe nuclei and periaqueductal grey matter, thus increasing brain serotonin to alleviate symptoms. In addition, morphine decreases glutamate release from glutaminergic neurons in the prefrontal cortex and other areas. Lastly, morphine is a direct NMDA antagonist and is expected to increase serotonin on that basis.[45]

In another report, a methadone maintenance patient with no history of anxiety disorder who had been prescribed 60 mg methadone began elective tapering of methadone. Anxiety symptoms emerged and peaked at 12.5 mg, with a high anxiety score. When methadone dosage was increased to 25 mg, anxiety symptoms improved rapidly within 48 hours. Methadone seems to relieve anxiety through direct mu-mediated serotonin increase, blocking glutamate release and NMDA antagonism.[65,66]

METHADONE, NMDA, AND GLUTAMATE

As this review has shown, the NMDA-glutamate system is central to causing depression and anxiety disorders via inhibition of serotonin. Medications that block glutamate production (e.g., lamotrignine) and medications that directly block the receptors themselves (NMDA antagonists) can reverse serotonin inhibition and have beneficial psychiatric effects. Methadone and other opioids, such as buprenorphine, morphine, and tramadol, are potent NMDA receptor antagonists. NMDA antagonism causes rapid and durable relief of anxiety, as discussed above. Methadone and other opioids likely cause anxyolysys through several mechanisms and perhaps most significantly through the direct blockade or antagonism of NMDA receptors, disinhibiting serotonin elaboration. Also, both the mu-opioid receptor mediated decrease in brain glutamate levels and the direct mu-mediated stimulation of serotonin neurons will increase brain serotonin with methadone treatment. All of these actions will allow increased serotonin synthesis and release, alleviating depression and anxiety.[44]

PSYCHIATRIC DISEASE IN METHADONE MAINTENANCE POPULATIONIS

Psychiatric co-morbidity is common in opioid-dependent patients. Approximately 50% (range: 30% to 70%) of methadone maintenance

TABLE 2. The Mean Incidence of Selected Psychiatric Conditions Taken from Reviews

Bipolar Disorder	55%
Anxiety Disorder	52%
Depressive Disorder	46%
Posttraumatic Stress Disorder	42%
Borderline PD*	41%
Anti Social PD	51%
Histrionic PD	38%
Passive Aggressive PD	28%
Atypical Depression	12%
Psychotic Disorder	11%
Manic Disorder	0.1%

*PD = Personality Disorder.

patients will have one or more co-existing Axis 1 or Axis 2 psychiatric disorders.[32,51] Individuals with coexisting psychiatric disorders are referred to as dually diagnosed patients and those without psychiatric comorbidity are referred to as single diagnosis patients.[32,67] A substantial amount of research has been done on dually diagnosed patients in methadone clinics. Several predictors of beneficial outcome have been identified, including increased treatment retention, reduction in drug use, and higher methadone dosages.[32,51,52,68–70] The mean incidence of selected psychiatric conditions, taken from reviews[32,51,52,68–71] on this subject are described in the next setion (see Table 2).

TREATMENT RETENTION

Methadone Dose

In studies of the methadone maintenance population, two commonly cited and easily quantifiable indicators of stabilization are treatment retention and decreased heroin use.[72] Dually diagnosed patients can achieve both goals with a higher dosage of methadone compared to single diagnosis patients.[52] Treatment retention has been extensively documented as a powerful indicator of stabilization and positive outcome in the methadone-maintained population.[72] Patients who remain in treatment for longer periods of time are those who are most satisfied with the treatment and those who benefit most from the treatment. Higher treatment retention is correlated with higher methadone dosages independent of psychiatric status. Many studies have shown higher dosages of methadone to be correlated with longer treatment retention and less heroin use.[68,73–77] Inherent in longer treatment retention, and what longer treatment retention actually demonstrates, is an improvement in psycho-social functioning.[51]

Dually Diagnosed Patients

At least 2 studies of the methadone-maintained population have shown higher retention rates in dually diagnosed patients compared to single diagnosis patients, which is indicative of better stabilization. Given a higher level of co-morbid psychopathology in dually diagnosed patients, the observation of higher retention may seem counterintuitive. To clarify this issue, Maremanni et al. reviewed the outcome data of dually diagnosed patients compared to single diagnosis patient controls over a 3-year (1,000-day) interval. After a short initial dropout period, dually diagnosed patients stabilized on substantially higher methadone dosages than the single diagnosis patients. Mean retention time in dually diagnosed patients was 1,000 days (i.e., all cases were retained for the entire remainder of the study period, significantly longer than as single diagnosis patients) (mean = 840 days). The authors concluded that "the general consensus that psychiatric comorbidity increases treatment resistance has not been confirmed by the present investigation" and that the significantly higher dosage of methadone required by dually diagnosed patients for stabilization versus the requirements of single diagnosis patients is central for stabilization.[72]

In a 24-month outcome study, dually diagnosed patients also required a higher mean dosage of methadone for stabilization. The treatment retention rate was higher for dually diagnosed patients for the first 20 months of the 24-month trial. The percent of positive urine opioid specimens from both groups showed similar approximate declines. Psychiatric patients respond well to therapy with higher dosage methadone, evidenced by longer treatment retention times and reduction in heroin use.

Methadone dosages are higher in dually diagnosed patients, indicating a psychiatric benefit to higher dosages. Dually diagnosed patients should be identified early in treatment to maximize methadone dosages for optimal psychiatric benefit, which is manifested in part by increased treatment retention.[51,78]

METHADONE DOSE AND PSYCHIATRIC PATIENTS

Higher methadone dosages are required to stabilize dually diagnosed patients. This theory has been extensively documented[32,39,51,67,68,72,79,80] and likely reflects methadone's beneficial modulation of multiple psychiatric neurotransmitter systems with regard to all patients; higher methadone dosages are clearly necessary to realize increased retention, decreased drug use, and improved psychosocial functioning independent of psychiatric co-morbidity.[32,81] However, if the dually diagnosed patients are analyzed separately, it becomes clear that even higher methadone dosages are required for stabilization compared to single diagnosis patients.[32] Levels of ongoing drug use do not differ between dually diagnosed patients and single diagnosis patients in most studies, indicating that improvement of dually diagnosed patients' psychosocial scoring and treatment retention is independent of drug use. Beneficial outcomes seem more closely correlated to the higher methadone dosages, which is noted repeatedly in dually diagnosed patients. Overall, heroin on admission compared to later dates in psychiatric methadone patients decreases to the same degree as non-psychiatric methadone patients.[81] In addition, the illicit use of benzodiazepams and cocaine generally remains similar throughout in both groups. With comparable and on-going non-heroin drug use in both groups and on-going decreased heroin use similar in both groups, the additional beneficial effect of opioids on psychiatric disease is not likely due to changes in drug use. Psychiatric patients seem to experience benefits from methadone and buprenorphine as psychiatric medications exacting beneficial effects on brain neurotransmitters (discussed below) and is independent from the ability of methadone or buprenorphine to reduce drug use.[21,22,51,81]

Several studies demonstrating the need for higher methadone dosages in dually diagnosed patients are summarized below. In one of the earliest observations of increased methadone dosages in dually diagnosed patients, Treece found a strong relationship between psychopathology and methadone dosage.[82] Schizoid disorders required a mean daily methadone dosages of 87.4 mg compared to a mean daily dosages of 35.7 mg for the control patients (a 145% increase for dually diagnosed patients). All patients were heroin-free. The author indicates a possibly favorable psychiatric effect of methadone that is independent of drug use.[82]

In another study, subjects with major psychopathology required higher methadone dosages for stabilization (mean 60 mg per day) compared to the control subjects (30 mg p day). The authors noted that the "best methadone dose" is not only that which stops heroin use, but also that which contributes to stabilization of psychiatric disease (i.e., a higher dose than control). The psychiatric effects of methadone are evident as being independent of methadone's ability to decrease heroin use.[52]

Mateo and Maremanni analyzed 55 methadone-maintained patients who were hospitalized for psychiatric decompensations. Patients were psychiatrically stabilized with a variety of psychotropic medications. A group of 30 patients remained on a personal baseline methadone dosage and were compared to 22 patients who received a mean increase in methadone dosage of 45 mg per day (personal baseline + 45 mg). The authors observed a significant decrease in psychiatric medications required in the group receiving augmented methadone dosages, with 22% fewer antidepressants, 54% fewer major sedatives, and 100% fewer anti-manic prescriptions. Methadone, exerting beneficial psychiatric effects, contributed significantly to the stabilization of mental health, thus diminishing the need for other psychiatric medications. Drug use was not an issue because patients were hospitalized, so the euthymic effects of methadone were not related to methadone's drug abuse attenuating effect but were likely related to psychiatric effects.[80]

Pani noted that dually diagnosed patients required a higher methadone dosage than single diagnosis patients, 70 mg per day for stabilization versus 40 mg per day, respectively, and noted higher retention in patients in the dually diagnosed patients group versus patients in the single diagnosis in the first 20 months of the 24-month study. The authors concluded that dually diagnosed patients should be clinically recognized expeditiously because they will require, and should receive, higher methadone dosages for psychiatric stabilization.[51]

In a study of 222 veterans, Trafton et al. also observed higher methadone dosages in drug-free dually diagnosed patients. The authors documented a statistically significantly higher daily methadone mean dosage of 81 mg for dually diagnosed patients with posttraumatic stress disorder, a mean dosage of 83 mg for those with depressive disorders. and a dosage of 69 mg for the control patients. Depression and posttraumatic stress disorder were strong predictors of a need for higher methadone dosages for stabilization independent of drug use. In addition, given the potential for early drop-out in the dually diagnosed patients population, it "may make sense to more aggressively titrate [higher dually diagnosed patients] dosages early in treatment in these patients."[78]

In our own institution, for recertification by the Commission on Accreditation of Rehabilitation Facilities (CARF) in 2006, we reviewed charts of 110 dually diagnosed patients and 176 single diagnosis patients to record medications prescribed. We noted a mean daily methadone dosage of 145.7 mg per day in dually diagnosed patients versus 99.8 mg per day in single diagnosis patients.[84] In this review, patients with psychiatric comorbidity required 46% higher methadone dosages for stabilization. A similar methadone dosage review for CARF completed in 2000 recorded that the dually diagnosed patients ($n = 72$) received a mean daily dosage of 110 mg and the single diagnosis patients ($n = 98$) received a mean daily dosage of 91 mg.[37] Maremmani noted a mean methadone dosage in dually diagnosed patients and single diagnosis patients of 154 mg per day and 99 mg per day, respectively. In addition, within the dually diagnosed patients patient population, patients with higher degrees of psychiatric patholgy required correspondingly higher methadone dosages. Notably, treatment retention after an initial fall-out was significantly higher in dually diagnosed patients than in single diagnosis patients.[72] Improvement from baseline in psychosocial scores was significant. Psychiatric patients can be well stabilized and glean benefits from methadone as a psychiatric medication. The authors call for recognition of psychiatric disease as early as possible in treatment to prevent initial drop-out. In addition, dually diagnosed patients will require expedient upward titration of methadone to minimize early drop-out and to provide maximal patient benefit of higher "psychiatric" methadone dosages.[72]

Higher methadone dosages in dually diagnosed patients reflect patients and providers appreciating progressive improvement in outcome as dosages increase and wishing to maximize and maintain beneficial psychiatric effects to the highest level safely possible. A common outcome measure is the Addiction Severity Index, a seven-domain global-functioning rating tool for addiction patients.[85] Despite psychiatric comorbidity and ongoing drug use, dually diagnosed patients showed improvement in all seven domains.[81] Because dually diagnosed patients scores on the Addiction Severity Index improve with methadone treatment at the same degree as single diagnosis patients compared to personal baselines independent of drug use, a beneficial psychiatric effect of methadone seems likely.[81]

As reviewed and referenced in this paper, methadone and other opioids exert potent psychotherapeutic effects based on favorable and potent modulation of several neurotransmitters. The mechanisms of action as reviewed in this paper are tabulated below.

DISCUSSION

Methadone and other opioids reviewed in this paper have been shown to exhibit a remarkably broad range of rapid, potent, and favorable mood-regulating effects in dually diagnosed patients that is independent of drug use but

is seemingly dependent on higher methadone dosages. Numerous studies cited above (Table 1) have documented the need for higher methadone dosages in psychiatric patients to maximize these beneficial psychiatric effects. As antianxiety and antidepressant medications, methadone and the opioids reviewed here exert beneficial psychiatric effects independent of their substance abuse treatment effects. Even with ongoing drug use, the positive effect on depression and anxiety is still evident.[21,22,81] Nunez reviewed 6 double-blind, placebo-controlled studies of depression treatment involving 284 methadone patients. In 5 of 6 trials, antidepressant treatment had a positive outcome on depression but no significant effect on drug use. The author concluded that the psychiatric disease may be independent of the substance abuse disease and can be successfully managed independent of drug use in many cases.[86]

Opioid-dependent patients with psychiatric co-morbidity require substantially higher dosages of methadone for stabilization (Table 1) because they are appreciating the highly significant and highly beneficial antidepressant and antianxiety effects of methadone—as a psychiatric medication—as well as buprenorphine, tramadol, and morphine. It is clear that methadone is a potent psychiatric medication with multiple mechanisms of action that lead to mood improvement. Methadone, buprenorphine, and other opioids have been shown to increase serotonin to relieve depression and anxiety using SSRI and MAO inhibitor mechanisms,[25,38] to decrease glutamate to alleviate depression and anxiety via mu-opioid receptor glutamate inhibition and serotonin-mediated decreased glutamate synthesis,[66] to antagonize NMDA receptors to increase serotonin,[47] to decrease cortisol and depressive/manic symptoms by hypothalamic stimulation,[41,42] and to activate endorphin receptors in the pleasure center to enhance hedonic tone and pleasure sense to mitigate feelings of depression.[9] It may be said that methadone patients can benefit from the effects of many different and potent psychiatric medications with a single agent—methadone.

In recognition of multiple mechanisms, it is clear that methadone, buprenorphine, and other opioids are potent psychotropic medications in both the opioid-dependent and non-opioid-dependent populations. With methadone or buprenorphine treatment, dual diagnosis patients have been shown to improve psychiatric scores to the level of non-dual diagnosis controls,[14,15,19] to improve treatment retention to exceed that of single diagnosis patients,[72] and (given the presence pf psychopathology with added substance abuse) to counter-intuitively improve Addiction Severity Index scores compared to baseline in every domain.[81] Higher methadone dosages are required.

Depressed brains can have up-regulated numbers of endorphin receptors that are not matched by any increases in endorphin levels.[10] This relative endorphin deficiency creates depressive symptoms via sub-optimal stimulation of dopaminergic neurons with andhedonia and loss of pleasure sensation. Depressed individuals dependent on illicit opioids may have learned to increase endorphin receptor saturation with heroin and other opioids and are, in effect, self-treating or augmenting their limited endorphin levels with something that is effective—illicit opioids (read: endorphins). Unfortunately, illicit opioids are short acting and mood improvement is transient at best and behaviors associated with drug abuse are exceedingly dangerous to health and psychosocial functioning.[87] Given correctly, methadone is long acting and exceedingly safe.[88] Patients may experience long-acting mood benefits that they recognize and wish to maintain—evidenced by longer methadone treatment retention, improved Addiction Severity Index scores, and decreased heroin use.[52,53,72,81]

In addition, the significantly higher dosages of methadone required to stabilize dual diagnosis patients and the multiple mechanisms by which methadone, buprenorphine, and other opioids favorably and potently modulate mood-regulating neurotransmitters supports the notion that methadone is exerting beneficial psychiatric benefits. Patients appreciate and wish to appropriately maximize these beneficial psychiatric effects with increased dosages of methadone. Maremanni writes, “We hypothesize that the presence of psychiatric comorbidity may result in better compliance. Dual Diagnosis patients may associate the never previously experienced

TABLE 3. Mechanism of Opioid Psychiatric Effects

Effect	Neurotransmitter	Mechanism	Function/Model
a) Antidepressant	Serotonin	Block serotonin re-uptake	SSRI[30]
b) Antidepressant	Glutamate	Serotonin-mediated Glutamate Inhib	SSRI[60]
c) Antidepressant	Serotonin	Inhibit Monoamine Oxidase	MAO Inhibitor[38]
d) Antidepressant	Norepinephrine	Inhibit NE Re-uptake	Tricyclic AD[25]
e) Antidepressant	Epinephrine	Inhibit EPI Re-uptake	Tricyclic AD[25]
f) Antidepressant	Epinephrine/Norepinephrine	Inhibit Monoamine Oxidase	MAO Inhibitors[38]
g) Antidepressant	Serotonin/Dopamine	Inhibit Monoamine Oxidase	MAO Inhibitors[38]
h) Antidepressant	Glutamate	NMDA Antagonism	Ketamine[47]
i) Antidepressant	Glutamate	Mu-mediated Glut Release Inhib	Endorphin[66]
j) Antidepressant Restores Hedonic Tone	Dopamine	Mu-opiate Receptor Stimulation	Endorphin[8]
k) Antidepressant Pleasure/Reward Sense	Dopamine	Mu-stimulation	Endorphin[14]
l) Antidepressant	Cortisol	Cortisol Suppression	Endorphin[41]
m) Antianxiety	Serotonin	Block Serotonin Re-uptake	SSRI[58]
n) Antianxiety	Glutamate	Serotonin-Mediated Glutamate Inhib	SSRI[60]
o) Antianxiety	Glutamate	Mu-mediated Glut Inhib	Endorphin[66]
p) Antianxiety	Glutamate	NMDA Antagonism	Lamictal[47]
q) Antianxiety	Serotonin/Dopamine	Inhibit Monoamine Oxidase	MAO Inhibitors[38]
r) Antianxiety	Cortisol	Cortisol Suppression	Endorphin[42]

NMDA = N-Methyl d-Aspartate.

improvement in their mental health and emotional well-being with methadone, as a [psychiatric] medication, and they, correctly, fear discontinuing it."[72]

CONCLUSION

This review has attempted to highlight the prevalence and needs of dual diagnosis patients in methadone treatment and to understand why these individuals require higher "psychiatric" dosages of methadone for stabilization. Methadone, buprenorphine, and other opioids supply depressed and anxious brains with the serotonin, dopamine, and catecholamines that are lacking naturally and block deleterious NMDA–glutamate effects. In fact, in our experience, certain patients who repeatedly request increases in methadone dosages may be dual diagnosis patients whose diagnoses were missed by clinic staff; these patients are unknowingly self-treating, beneficially, in asking for increased dosages. Clinicians are encouraged to identify dual diagnosis patients at the earliest encounter and engage them in treatment, expeditiously titrating methadone dosage upward for earlier patient benefit.

Methadone, buprenorphine, and other opioids are effective, potent, durable, and rapid-acting psychotropic agents that favorably modulate multiple neurotransmitter systems as discussed above (Table 3). In our experience, many patients wish to minimize methadone dosages and minimize time in treatment. Patient comments such as "I can't stay on this stuff forever" and "I can't go over 100 milligrams" lead us to believe that patients do not understand the underlying psychiatric pathology related to low serotonin, low catecholamine, increased glutamate, and low endorphin effect. These are real pathologic issues that we can address and alleviate with appropriate dosages of methadone in the context of integrated medical and psychosocial care.

Proper patient education and thoughtful pharmacologic therapy, including optimal methadone dosages, should be our response. Dual diagnosis patients should be made aware of the multiple psychiatric benefits of methadone and other medications and not be fearful of increasing dosages or remaining in treatment for prolonged periods of time because patients

will benefit in both the short- and long-term. Methadone dosages for these individuals should be titrated upward in an expedient but not reckless manner to prevent early drop-out, allay psychiatric symptoms, decrease heroin use, and minimize human suffering.

AUTHOR'S NOTE

It should be noted that opioids do not have FDA approval for the treatment of psychiatric disorders. The intent of this paper was not to suggest that practitioners should prescribe opioids in a manner not approved by the FDA, but rather it was to explore the mechanisms and develop hypotheses that might explain the observation that opioid-dependent psychiatric patients in appropriately certified opioid replacement therapy programs (i.e., methadone treatment programs) stabilize on higher opioid dosages than those without psychiatric diagnoses.

REFERENCES

1. Hodgson B. Opium: A Portrait of a Heavenly Demon. San Francisco: Chronicle Books; 1999.

2. Bendick J. Galen and the Gateway to Medicine. Bathgate, ND: Bethlehem Books; 2002.

3. De Quincey T. Confessions of an English Opium Eater (1822). London: Penguin Classics; 2003.

4. White WL. Slaying the Dragon: The History of Addiction in America. Bloomington, IL: Chesnut Health Systems Publications; 1998.

5. Harrison Narcotic Tax Act. Public Law No. 223, 63rd Cong., approved December 17, 1914.

6. Varga E. The effect of codeine on involutional and senile depression. Ann N Y Acad Sci. 1982;398:103–5.

7. Kraepelin E. Einfu¨hrung in die psychiatrische Klinik: zweiunddreissig Vorlesungen. Leipzig: J.A. Barth; 1905.

8. Belluzzi J, Stein L. Enkephaline may mediate euphoria and drive-reduction reward. Nature. 1977;266(5602): 556–8.

9. Ikemoto S, Panksepp J. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res Rev. 1999;31(1):6–41.

10. Gross-Isseroff R, Dillon K, Israeli M, Biegon A. Regionally selective increases in mu opioid receptor density in the brains of suicide victims. Brain Res. 1990;530(2): 312-6.

11. Naber D, Pickar D, Post R, Van Kammen D, Waters R, Ballenger J, Goodwin F, Bunney W. Endogenous opioid activity and beta-endorphin immunoreactivity in CSF of psychiatric patients and normal volunteers. Am J Psychiatry. 1981;138(11):1457–62.

12. Sweetmen SC, Blake PS, McGlashan JM, Neathercoat GC, Parsons AV, eds. Martindale: The Complete Drug Reference. 35th Edition. London: Pharmaceutical Press; 2006.

13. Halbreich M, Endicott J. Possible involvement of endorphin withdraw in postpartum depression. Medical Hypotheses. 1981;7:1054–8.

14. Emrich H, Vogt P, Herz A. Possible antidepressive effects of opioids: Action of buprenorphine. Ann N Y Acad Sci. 1982;398:108–12.

15. Bodkin J, Alexander M, Zornberg G, Lukas S, Cole J. Buprenorphine treatment of refractory depression. Jour of Clin Psychopharm. 1995;15(1):49–57.

16. Resnick R, Falk F. Buprenorphine: Pilot trials in borderline patients and opiate dependence. In: Harris LB, ed. NIDA Research Monograph: Problems of Drug Dependence. Washington, D.C.: U.S. Government Printing Office; 1987.

17. Callawaye E. Buprenorphine for depression. Biological Psychiatry. 1996;39(12):989–90.

18. Morgan L, Callowaye E. Buprenorphine responders. Biological Psychiatry. 1990;28:1078–80.

19. Kosten T, Morgan C, Kosten T. Depressive symptoms during buprenorphine treatment of opioid abusers. J Subst Abuse Treat. 1990;7(1):51–4.

20. Maremmani I, Pacini M, Pani P. Effectiveness of buprenorphine in double diagnosed patients. Buprenorphine as a psychotropic drug. Heroin Add Rel Clin Probl. 2006;8(1):31–48.

21. Dean A, Bell J, Christie M, Mattick R. Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. Eur Psychiatry. 2004;19(8):510–3.

22. Dean A, Bell J, Mascord D, Parker G, Macdonald C. A trial of fluoxetine in methadone maintenance patients with depression. J Aff Disord. 72:1;85–90.

23. Dyer K, White J, Foster D, Bochner F, Memelaou A, Somogyi A. Mood state and methadone plasma concentrations. J Clin Psychopharm. 2001;21(1):78–84.

24. McNair DM, Lorr M, Droppelman LF. Profile of Mood States Manual. San Diego, CA: Educational and Industrial Testing Service; 1992.

25. De Montis, G, Devoto P, Tagliamonte A. Possible antidepressant activity of methadone. Euro J Pharm. 1892;79(1–2);145–6.

26. Drevets W, Frank E, Price J, Kupfer D, Holt D, Greer P, Huang Y, Gautier C, Mathis C. PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry. 1999;46(10):1375–87.

27. Rosa-Neto P, Diksic M, Okazawa H, Leyton M, Ghadirian N, Mzengeza S, Nakai A, Debonnel G, Blier P, Benkelfat C. Measurement of brain regional alpha-[11C]methyl-L-tryptophan trapping as a measure of

serotonin synthesis in medication-free patients with major depression. Arch Gen Psychiatry. 2004;61(6):556–63.

28. Neumeister A, Bain E, Nugent A, Carson R, Bonne O, Luckenbaugh D, Eckelman W, Herscovitch P, Charney D, Drevets W. Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci. 2004;24(3):589–91.

29. Williams J, Mulrow C, Chiquette E, Noel P, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann Intern Med. 2000;132(9):743–56.

30. Ciofalo F. Methadone inhibition of 5-hydroxytryptamine uptake. J Pharmacol Exp Ther. 1974;189(1):83–9.

31. Gillman P. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anaesth. 2005;95(4):434–41.

32. Maremmani I, Matteo P, Lubrano S, Lovreded M, Perugi G. Dual diagnosis heroin addicts: the clinical and therapeutic aspects. Heroin Add Rel Clin Probl. 2003;5(2):7–98.

33. Hamilton S, Nunes E, Janal M, Weber L. The Effect of sertraline on methadone plasma levels in methadone maintenance patients. Am J Addict. 2000;9:63–9.

34. Eap C, Gilles M, Powell K, Baumann P. Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of enantiomers of methadone. J Clin Psychopath. 1997;17(2):113–7.

35. Berge S, von Bardeleben U, Ladewig D, Jaquet S, Cosendai L, Golay K, Kosel M, Baumann P, Eap C. Paroxetine increases steady state concentrations of methadone. J Clin Psychopharmacol. 2002;22(2):211–5.

36. Waugh J, Goa K. Escitalopram: a review of its use in the management of major depressive and anxiety disorders. CNS Drugs. 2003;17:343–62.

37. Meyer JH, Ginovart N, Boovariwala A, Boovariwala A, Sagrati S, Hussey D, Garcia A, Young T. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. Arch Gen Psychiatry. 2006;63(11):1209–16.

38. VanderWende C, Spoerlein M. Effect of narcotics on monoamine oxidase activity of mouse brain. Res Chem Pathol Pharmacol. 1979;24(1):103–13.

39. Lee S, Lee J, Cheong M, Kim H, Kim Y, Yun Y, Lee C, Lee M. Inhibitory effects of ethaverine on monoamine oxidase activity in mouse brain. Biol Pharm Bull. 2001;24(7):838–40.

40. Sachar E, Hellman L, Roffwarg H, Halpern F, Fukushima D, Gallagher T. Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry. 1973;28(1):19–24.

41. Gold P, Extein I, Pickar D, Rebar R, Ross R, Goodwin F. Supression of plasma cortisol in depressed patients by acute intravenous methadone infusion. Am J Psychiatry. 1980;137(7):862–3.

42. Judd L, Parker D, Janowsky D, Segal D, Risch S, Huey L. The effect of methadone on the behavioral and neuroendocrine responses of manic patients. Psychiatry Res. 1982;7(2):163–70.

43. Paul I, Skolnick P. Glutamate and depression. Ann N Y Acad Sci. 2003;1003:250–7.

44. Bergink V, van Megen H, Westenberg H. Glutamate and anxiety. Eur Neuropsychopharmacol. 2004;14(3):175–83.

45. Callahan R, Au J, Liu C, Yost C. Functional inhibition by methadone of NMDA receptors. Anesth Analg. 2004;98(3):653–9.

46. Zarate C, Singh J, Carlson P, Brutsche N, Ameli R, Luckenbaugh D. A randomized trial of NMDA antagonist in major depression. Arch Gen Psychiatry. 2006;63(8):856-64.

47. Gorman A, Elliott K, Inturrisi C. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett. 1997;223(1):5–8.

48. Berman R, Cappiello A, Anand A, Oren D. Antidepressant effects of ketamine in depressed patients. Biol Psych. 2000;47(4):351-4.

49. Ebert B, Andersen S, Krogsgaard P. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. Neurosci Lett. 1995;187(3):165–8.

50. Davis A, Inturrisi C. Methadone blocks morphine tolerance and NMDA induced hyperalgesia. Pharmacol and Exper Therap. 1999;289(2):1048–53.

51. Pani P, Trogu E, Carboni G, Palla P, Loi A. Psychiatric severity and treatment response in methadone programs. Heroin Add Rel Clin Probl. 2003;5(3):23–36.

52. Maremmani I, Zolesi O, Agueci T, Castrogiovanni P. Methadone doses and psychopathological symptons during methadone maintenance. J Psychoact Drug. 1993;25(3):253–6.

53. Pani P, Trogu E, Contu P, Agus A, Gessa G. Psychiatric severity and treatment response in a comprehensive methadone maintenance treatment program. Drug Alcohol Depend. 1997;48(2):119–26.

54. Lomas L, Picker M, Behavioral assessment of temporal summation in the rat: sensitivity to sex, opioids and modulation by NMDA receptor antagonists. Psychopharmacology (Berl). 2005;180(1):84–94.

55. Tatarczynska E. Potential anxiolytic effects of MPEP. Br J Pharmacol. 2001;132(7):1423–30.

56. Mirza N, Bright J, Stanhope K, Wyatt A, Harrington N. Lamotrignine has an anxiolytic-like profile in rats. Psychopharmacology. 2005;180(1):159–68.

57. Klodzinska A, Tatarczynska E. Anxiolytic effects of MTEP. Neuropharmacology. 2004 Sep; 47(3):342–50.

58. Becqet D, Hery M, Francois A, Giraud P, Deprez P, Faudon M, Fache M, Hery F. Glutamate, GABA, glycine and taurine modulate serotonin synthesis and release in rostral and caudal rhombencephalic raphe cells in primary cultures. Neurochem Int. 1993;23(3):269–83.

59. Rybakowski J. Long-term pharmacological treatment of bipolar disorders. Neuro Endocrinol Lett. 2007; 28(Suppl1):71–93.

60. Rosenberg D, MacMaster F, Keshavan M, Fitzgerald K, Stewart C, Moore G. Decrease in Caudate Glutamate in OCD. J Am Acad Child Adol Psych. 2000;39(9):1096-103.

61. Owen J, Whitton P. Chronic treatment with antidepressants reverses NMDA mediated regulation of 5-HT in rat brain. Brain Res Bull. 2006;70(1):62–7.

62. Stachowicz K, Chojnacka E, Klak K, Pilc A. Anxiolytic-like effect of group III mGlu receptor antagonist is serotonin-dependent. Neuropharmacology. Feb;52(2):306–12.

63. Goldsmith M, Shapira N, Keck P. Rapid remission of OCD with tramadol hydrochloride. Am J Psychiatry. 1999;156:660–1.

64. Shapira N, Keck P, Golsdmith T, McConville B, Eis M, McElroy S. Open-label pilot study of tramadol hydrochloride in treatment-refractory obsessive-compulsive disorder. Depress Anxiety. 1997;6(4):170–3.

65. Khazaal Y, Krenz M, Zullino D. Worsening of OCD symptome under methadone tapering. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(7):350-2.

66. Zhu W, Pan Z. Mu-opioid-mediated inhibition of glutamate synaptic transmission in rat central amygdala neurons. Neuroscience. 2005;133(1):97–103.

67. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders., 4th Edition, Text Revision. Washington, D.C.: Author; 2000.

68. Peles E, Schreiber S, Adelson M. Factors predicting retention in treatment: 10-year experience of a methadone maintenance treatment (MMT) clinic in Israel. Drug Alcohol Depend. 2006;82(3):211–7.

69. Mason B, Kocsis J, Melia D, Khuri E, Sweeney J, Wells A, Borg L, Millman R, Kreek M. Psychiatric comorbidity in methadone maintained patients. J Addic Diseas. 1998;17(3):75–89.

70. Peles E, Schreiber S, Naumovsky Y, Adelson M. Depression in methadone maintenance treatment patients. J Affect Disord. 2006; [Epub ahead of print].

71. Ross J, Teesson M, Darke S, Lynskey M, Ali R, Ritter A, Cooke R. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). Drug Alcohol Rev. 2005;24(5):411–8.

72. Maremmani I, Zolesi O, Agletti M, Tagliamonte A, Shinderman M, Maxwell S. Methadone dose and retention during treatment of heroin addicts with axis 1 psychiatric comorbidity. J Addic Dis. 2000;19(2):29–41.

73. Villafranca S, Mckellar J, Trafton J, Humphreys K. Predictors of retention in methadone programs: a signal detection analysis. Drug Alcohol Depend. 2006;83(3): 218–24.

74. Farre M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis. Drug Alcohol Depend. 2002;65(3):283–90.

75. Brady T, Salvucci S, Sverdlov L, Male A, Kyeyune H, Sikali E, DeSale S, Yu P. Methadone dosage and retention: an examination of the 60 mg/day threshold. J Addict Dis. 2005;24(3):23–47.

76. Maxwell S, Schinderman M. Optimizing long-term response to methadone maintenance treatment: a 152-week follow-up using higher-dose methadone. J Addict Dis. 2002;21(3):1–12.

77. Torres M, Castillo C, Perez V. Retention in a low-threshold methadone maintenance program. Drug Alcohol Depend. 1996;41(1):55–9.

78. Trafton J, Minkel J, Humphreys K. Determining effective methadone doses for individual dependent patients. PLoS Med. 2006;3(3):80–94.

79. Tenore P. CARF Review Data File, Oct 2000, Albert Einstein College of Medicine, Division of Substance Abuse, Division of Psychiatry, data on file.

80. Matteo P, Maremanni I. Methadone reduces need for psychiatric agents in heroin addicts hospitalized for panic and/or acute psychotic episodes. Heroin Add & Rel Clin Probl. 2005;7(4):43–8.

81. Cacciola J, Alterman A, Rutherford M, McKay J, Mulvaney F. The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. Drug Alcohol Depend. 2001;61(3):271–80.

82. Treece C, Nicholson B. Personalilty type and dose levels in methadone maintenance. J Nerv Ment Dis. 1980;168(10):621–8.

83. Bleich A, Gelkopf M, Weizman T, Adelson M. Benzodiazepine abuse in a methadone maintenance treatment clinic in Israel: characteristics and a pharmacotherapeutic approach. Isr J Psychiatry Relat Sci. 2002;39(2):104–12.

84. Tenore P. CARF Review Data File, Oct 2006, Albert Einstein College of Medicine Division of Substance Abuse, Division of Psychiatry, data on file.

85. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The Fifth Edition of the Addiction Severity Index. J Subst Abuse Treat. 1992;9(3):199–213.

86. Nunes E, Quitkin F, Brady R, Post-Koenig T. Antidepressant treatment in methadone maintenance patients. J Addict Dis. 1994;13(3):13–24.

87. O'Connor P, Selwyn P , Schottenfeld R. Medical care for injection-drug users. N Engl J Med. 1994;331(7): 450–9.

88. National Consensus Development Panel on Effective Treatment of Opiate Addiction. JAMA. 1998;280: 1936–43.